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Acute Pain Management in the Emergency Department: Emphasis on NSAIDs

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Abstract

Millions of patients are treated every year for acute pain symptoms in the Emergency Department (ED), but pain control in this setting still remains suboptimal. This may be due to the logistical challenges in the ED, ED clinicians' limited education and training in pain control, regulatory and legal concerns, and other barriers to prescribing. The most common analgesics used in the ED are acetaminophen (paracetamol), Non Steroidal Anti-Inflammatory Drugs (NSAIDs), and opioids. All are effective in relieving pain, but are also associated with serious side effects. Thus, pain control in the ED becomes a balancing act of weighing potential benefits and risks. NSAIDs are often the appropriate choice for many of the common acute pain conditions encountered in the ED, but because of risks associated, administration is often limited. A review of the literature regarding current ED pain treatment practices and guidelines, patient and clinician barriers to pain treatment in the ED, and the pros and cons of current analgesic options for the ED is warranted and timely. The objectives of the current review are to: (1) provide healthcare providers with an overview of the current state of acute pain treatment in the emergency room setting, (2) describe the common drug treatments utilized in emergency medicine, (3) review advantages and disadvantages of these treatments, with a focus on NSAIDs, and (4) examine the potential value of novel "low dose" NSAID formulations for use in this setting.

Keywords: Emergency department; Body mass index; Oligoanalgesia

Introduction

In the United States, there were over 129 million Emergency Department (ED) visits in 2010, [1] with acute pain syndromes, including stomach pain, chest pain, musculoskeletal pain, headache, and earache, among the leading complaints [2]. Emergency care focuses on immediate, short-term (acute) analgesia in a hectic setting with little opportunity for follow-up. The pharmacological treatment of acute pain involves balancing its potential benefits against potential harms, but much of what is known about analgesic safety and efficacy has been derived from studies of mid- and longer-term use [3,4]. There are few guidelines that address pain management in the ED setting, although guidelines for specific conditions and populations exist [5-7]. In 1999, the Joint Commission on Accreditation of Healthcare Organizations declared pain as the "fifth vital sign" and required hospitals to make pain control a priority [8]. For reasons unique to the ED setting, pain is not as well managed in the ED as in the surgical setting [9].

About half of ED patients complaining of pain receive no analgesic, and of patients reporting severe pain, 63% receive no analgesic [10]. In a survey of 842 patients at 20 U.S. and Canadian hospitals, only 60% of ED patients received analgesics with a median delay of 90 minutes (range 0 to 962 minutes) and, most concerning, 74% were discharged in moderate to severe pain [11].

There are multiple barriers to adequate pain control in the ED. One is that patients may not request analgesia. In a survey, it was found that 42% of ED patients discharged without analgesics had wanted them, but 31% of that group did not specifically request them [11]. New emphasis on patient satisfaction may drive a change here, in that effective pain control significantly improved patient satisfaction scores of ED care (n=328) [12]. So while patients may not always ask for pain relievers, they may want or expect them. Emergency clinicians practice in a unique atmosphere that emphasizes triage and often relies on the rapid transfer of patients to other clinical departments for more specialized care. The nuances of pain management can be lost in an environment that emphasizes rapid and transient care. Another barrier is clinicians' generally inadequate training in acute pain management, reticence to use opioids, the "ED culture," as well as personal biases [13]. Moreover, many clinicians in and outside the ED are rightly concerned about potential adverse effects of analgesics and may hesitate to prescribe potentially harmful drugs to patients they are not going to follow. Such non-clinical factors have been shown to influence prescribing decisions. For example, in a study of opioid prescribing practices at a single center before and after the arrest of a physician for drug diversion, patients with moderate pain were significantly less likely to be prescribed an opioid immediately (<90 days) after the arrest than before (0.4 likelihood ratio, confidence interval, 0.2 to 0.7), although prescribing patterns for patients in mild and severe pain remained unchanged [14].

In New York state, I-STOP legislation passed in 2012 requires all prescribers of Schedule II, III, and IV controlled substances to consult the Prescription Monitoring Program in that state prior to prescribing drugs [15]. Since emergency medicine ranks third among all specialties for writing opioid prescriptions for 10-19 year olds and 20-29 years old and ranks fourth for 30-39 year olds, [16] emergency medicine serves a population at high risk for inappropriate opioid usen [17]. This may increasingly cause emergency room clinicians to hesitate to prescribe opiates. So common is misuse of opioids in the emergency setting that the term "oligoanalgesia" has been used to describe the situation [18].

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ED practices often only somewhat conform to recommended doses, regimens, or guidelines for analgesia [19]. Therefore, analgesia is often administered too little and too late to achieve optimal efficacy [10].

Methods

Using the PubMed and EMBASE databases, we searched articles from the past five years that addressed pain management in an emergency department setting. We excluded case reports, articles not in English, and articles that focused on other aspects of care (triage, diagnosis, cost-effectiveness). We supplemented this research by reviewing the bibliographies of selected articles and evaluating those articles. We also supplemented secondary topics by searching for recent articles using relevant keywords.

Overview of pain treatment for acute pain in ED setting

The analgesic agents that are most often used in the ED are typically grouped into two broad categories: opioids and nonopioids. The nonopioid agents include acetaminophen (paracetamol) and non steroidal anti-inflammatory drugs (NSAIDs). Opioids are used for higher steps of the World Health Organization's analgesic "ladder" [20]. Fixed-dose combination products that offer two drugs (typically acetaminophen or an NSAID plus an opioid) are another important analgesic category [21]. In total, about 100 million prescription analgesics were dispensed in American emergency rooms in 2010 [2].

Special populations

Racially-based, sex-based, and ethnic-based differences in analgesia have been reported in the literature [22-26]. There is also interpatient variability in how a patient perceives, describes, and considers pain. Add to this the variability of analgesic use in diverse populations, and it is important for ED clinicians to consider certain patient population segments who may present with acute pain syndromes.

Geriatric patients: Emergency services are frequently used by geriatric patients [27]. Geriatric patients account for about 15% of all ED visits, [28] and this number is expected to increase substantially in the next 20 years [29]. Such patients are at elevated risk for Cardio Vascular (CV) and renal effects of analgesics [30]. British guidelines recommend that seniors taking NSAIDs be routinely monitored for GI, CV, and renal side effects along with potential drug-drug interactions [31]. The National Health Service in Britain has found that the risk of NSAID-induced GI adverse events doubles with every decade of age after age 55 [32]. Furthermore, the concomitant use of such drugs as warfarin, oral corticosteroids, selective serotonin reuptake inhibitors, venlafaxine, and duloxetine may increase the risk of NSAID-induced GI side effects in older individuals, [32] because taking multiple agents can lead to competition for first-pass metabolic processes and set the stage for potential pharmacokinetic drug-drug interactions [33].

Many factors can affect drug metabolism in the elderly (Table 1). In particular, the use of NSAIDs in geriatric patients has been associated with an increased risk for peptic ulcer, [34] ulcer-related complications, and added costs for gastroprotective agents and healthcare utilization [35]. This increased risk is dose related, [34] and may be specific to the particular NSAID used [36]. For example, the risk for peptic ulcer is reported to be lowest with ibuprofen or diclofenac and highest with azapropazone or ketoprofen [36]. In the elderly, NSAID use has been associated with acute renal failure, likely owing to NSAID-induced reductions in renal perfusion [37]. Basic recommendations on the use of NSAIDs in geriatric patients are summarized in Table 2.

Pediatric patients: There is evidence that younger patients may be more likely to get inadequate pain control compared to adults [38]. This is complicated by the fact that many parents lack a fundamental understanding of the value of pain control. For example, in one study, 28% of parents withheld pain medication from their children because they believed that the analgesics were actually harmful [39]. To be sure, there are legitimate concerns about pediatric analgesia, because small children metabolize drugs differently than do adults, so efforts should be undertaken to decrease the anxiety of patients and other caregivers.

Consideration	Geriatric Body Changes	Prescribing Concerns
Water-soluble drug	Decrease in body water mass	These drugs are more concentrated; reduce dose
Fat-soluble drug	Increase in body fat proportion	These drugs have a longer half-life because of their slow release from adipose tissue
Hepatic metabolism	Decline in hepatic blood flow	Slower clearance rates
	Liver size decreases and number of functional hepatocytes decrease	
Renal clearance	Glomerular filtration rate decreases with age after about age 20 and is substantially reduced in seniors	Slower clearance rates
Polypharmacy	May exist in any patient at any age but is more likely in seniors	Potential pharmacokinetic drug-drug interactions [33,136,137]

Table 1: Analgesic prescribing considerations in the elderly [134,135].

NSAIDs in Geriatric Patients with Acute Pain Syndromes
Do not use in patients with Gastro Intestinal (GI) disorders or with peptic ulcer disease
Do not use in patients with renal insufficiency
Do not use at supratherapeutic doses
Do not use extended period of time
Prescribe lowest effective dose for shortest period of time

Table 2: Guidance for use of NSAIDs in geriatric patients who present with acute pain syndromes in the ED.

Pregnant women: The use of NSAIDs in pregnancy is not recommended by the FDA; however the reproductive risk associated with NSAIDs has not been systematically evaluated. It is not known whether NSAIDs are excreted in human milk.

Morbidly obese: Obesity, defined as a body mass index (BMI) ≥ 30 kg/m^2, is prevalent in the United States and other countries [40]. Class III, or "morbid" obesity, defined as BMI ≥ 40 kg/m^2, poses special problems for emergency care: the need for special equipment (e.g., longer catheters for peripheral venous lines, oversized blood pressure cuffs, larger sized beds and robust wheelchairs) and logistical challenges involving moving and transporting patients [41]. Pain is prevalent among the obese, who report higher functional pain levels than normal-weight individuals [42]. For example, obesity is an independent predictor of postsurgical pain following total hip arthroplasty [43].

Further, adipose tissue may affect pharmacokinetic factors such as drug metabolism [44]. Excess fat may also modify the distribution of highly lipophilic drugs. Although weight loss is generally thought to reduce most pain syndromes in the obese, a retrospective study of 11,719 bariatric surgery patients found that of the 8% on chronic opioid therapy before weight-loss surgery, 77% continued with opioid therapy one year after surgery (mean daily morphine equivalents 45.0 mg, 95% CI, 40.0 to 50.1 before surgery versus 51.9 mg, 95% CI, 46.0 to 57.8 after surgery) [45]. Moreover, opioid consumption patterns did not vary with relative weight loss (that is among those who lost 50% excess

BMI versus those who lost less) [45]. This suggests that pain is not well managed in obese patients and that there might be further factors influencing analgesic efficacy. The obese have greater sensitivity to pain and lower pain thresholds than normal-weight individuals [46] and certain genetic polymorphisms have been associated with both obesity and altered analgesic pharmacodynamics [47].

The morbidly obese have greater muscle mass, more total body water, and greater plasma volumes than normal-weight patients [48,49]. Cardiac output, kidney and liver size, and blood volume all increase with weight. The increased plasma and water volumes can affect a drug's pharmacokinetics; enlarged organs and increased cardiac output can affect its clearance [50]. Thus, morbid obesity is associated with hypertension, increased renal plasma blood flow, increased glomerular filtration, and a higher rate of albumin excretion [51,52]. At the same doses, morphine clearance tends to be higher in obese than normal-weight patients, because morphine is metabolized via the UGT2B7 pathway. On the other hand, fentanyl, a lipophilic agent metabolized via CYPP3A4, should be dosed lower in obese than normal-weight patients. Dose adjustments for obese patients based solely on weight can be misleading, and might lead to overdose [50]. Further study is warranted for a better understanding of managing acute pain in morbidly obese patients in the ED.

Drug-seeking patients: Most EDs are open round the clock primarily to deal with life threatening cardiovascular and neurological disorders and trauma, provide only fleeting contact with prescribers, treat patients quickly despite limited access to their histories and medical records, and generally are hectic environments focused on rapid triage and patient throughput [53] ED clinicians are concerned about drug-seekers and may err on the side of caution by denying analgesics to those who ask for it, an attitude related to "opiophobia" [54]. Complicating the situation is that opioid-experienced patients who present at the ED may require relatively large doses of opioid analgesics, due to the development of tolerance, in order to achieve reasonable levels of pain relief. Thus, differentiation between patients seeking genuine pain relief from those who want to abuse opioids is important.

The problem grows increasingly complex because emergency clinicians are increasingly faced with acute pain in patients who may be under opioid maintenance treatment with buprenorphine or methadone. Further study is needed to establish guidelines for acute pain management in this population [55]. The same holds true for known substance abusers, including intravenous street drug users, who present in the ED with pain. When the pain complaint is verifiable, such patients need be taken seriously and their pain treated appropriately, [53] but when their complaints are more nebulous or suspicious, opioid therapy. Indeed, opioids are not recommended unless there is clear understanding of the etiology of the pain and the nature of the painful condition [56]. It is a particular conundrum to prescribe opioid therapy for a patient known to have an existing pain treatment contract [57].

Common ED analgesics

Acetaminophen: Acetaminophen has been shown to be effective for many acute pain syndromes [58-60]. However, acetaminophen alone may not always be effective, particularly in the control of moderate to severe pain. Despite its ubiquity, however, the mechanism of action of acetaminophen remains incompletely understood [61]. An aniline analgesic, it differs from NSAIDs and may rely on multiple, interconnected mechanisms of action for its effect. Cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) are enzymes that catalyze the metabolism of arachidonic acid to Prostaglandin H2 (PGH2). COX enzymes possess two active sites: a COX site and a prostaglandin or POX site [62]. COX enzymes must be oxidized to be effective, and it is speculated that acetaminophen reduces the amount of oxidized forms by its action at the POX site. Some selectively at COX-2, [63] or even a third isozyme, the so-called COX-3 isoform, [64] have been speculated, [62] but only COX-1 and COX-2 have been definitively identified [63] and preclinical evidence does not support a COX-3 mechanism of action [64]. A predominant central mechanism of action is likely [61].

Acetaminophen is metabolized via the Cytochrome (CYP) P450 metabolic pathway to a toxic electrophilic metabolite, N-acetyl-p-benozquinone imine (NAPQI), which normally is detoxified by glutathione and eliminated from the body in the urine or bile. At appropriate doses, the body can rid itself of NAPQI efficiently, including tiny residual amounts which fail to be detoxified. At higher doses, however, NAPQI causes potentially life-threatening liver damage[65]. Acetaminophen toxicity is a leading cause of poisoning and liver damage in the U.S. [66] Albeit rare, idiosyncratic drug-induced liver injury can occur unpredictably even in therapeutic dose ranges, implying that environmental and/or genetic factors may influence individual susceptibilities [67]. In the U.S., the Food and Drug Administration (FDA) has required new warning labels on acetaminophen products to alert consumers about the risks of acetaminophen [68].

Although known for its potential hepatoxicity, acetaminophen might also be implicated in hypertension. It had been thought that the association between NSAIDs and hypertension would not apply to acetaminophen. However, acetaminophen inhibits prostaglandin synthesis, which regulates vascular tone and sodium excretion [69]. Men who used acetaminophen six or more times per week had a relative risk for incident hypertension of 1.34 compared to non-users (study of 1,968 cases, 95% Confidence Interval (CI), 1.00 to 1.79, p=0.01 for trend) [70]. Among women who consumed >500 mg of acetaminophen daily, the relative risk of hypertension was 1.93 (95% CI, 1.30 to 2.88) for older and 1.99 (95% CI, 1.39 to 2.85) for younger women compared to those who did not take acetaminophen [71]. This relative risk was similar to that for NSAIDs (1.38, 95% CI, 1.09 to 1.75, p=0.002 trend) [70]. However, the body of evidence associating acetaminophen with hypertension is mixed. A prospective study (n=80,020 women) found a significant association between acetaminophen use and high blood pressure, [72] whereas a retrospective study of 2,754 hypertensives ≥ 65 years of age found no such association [73].

Opioids: While the World Health Organization (WHO) categorizes opioids as "weak" versus "strong", [20] it is also common to group opioids into short-acting (sometimes known as immediate-release) versus long-acting (sometimes called extended-release or controlled-release) formulations. Immediate- Release (IR) opioids are characterized by a relatively rapid increase in serum blood levels and subsequent relatively rapid decrease, resulting in a relatively rapid onset of analgesia and relatively short duration of action [74]. These formulations are considered appropriate for the management of acute pain, postsurgical pain, and other transient pain syndromes [75]. Some commonly used short-acting opioid formulations available in the United States include codeine, fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, and oxymorphone. Long-acting opioids include some that are inherently long acting (methadone, levorphanol) and those with special extended-release formulations (such as oxymorphone, fentanyl, and morphine). Long-acting opioids offer more stable and longer-lasting drug plasma concentrations with fewer peak-to-trough fluctuations and may result in fewer analgesic gaps when consistently dosed. However, with careful dosingand good compliance, long-acting and short-acting opioids can offer similar total systemic opioid serum

concentrations and similar levels of pain control [76,77]. In the ED setting, where most pain is nociceptive and acute, short-acting opioids are often more commonly used.

Opioids have well-known adverse events, which can be mild to severe and in some cases limit treatment. The most common opioid-associated adverse events include, but are not limited to, nausea, vomiting, constipation, dry mouth, and sedation [78]. Guidelines for opioid use state that clinicians prescribing opioids must anticipate opioid-associated side effects and, when possible, treat them [79]. There is no unequivocal evidence in the literature that short-acting opioids have a more or less favorable side effect profile than long-acting opioids.

Both long-acting and short-acting opioids can be the subject of inappropriate use and abuse [80,81]. Tampering with some long-acting opioid formulations allows them to be converted into immediate-release formulations; [74] since long-acting opioids contain more active agent per tablet, they may be particularly appealing to abusers. New tamper-resistant opioid formulations attempt to deter this kind of abuse [82].

The hectic atmosphere of the ED makes it a potential target for some drug-seeking patients. For instance, patients may report to the ED complaining of pain and state that they are under the care of a pain specialist who for some reason is unavailable to refill the prescription [83]. Some drug-seeking patients may present with conditions that are difficult to refute, such as migraine, renal colic, or low back pain. In fact, low back pain, which accounts for 2.6 million ED visits annually, [5] is a presenting complaint associated with patients at high risk for opioid misuse [84]. EDs have developed practical methods to help manage potential opioid abuse, such as keeping records of suspicious patients ("frequent fliers") or contacting other institutions or clinicians regarding patients requesting opioid analgesics [83].

It is, however, important to note that opioid addiction is different from opioid physical dependence, the latter of which is an expected and normal physical condition characterized by physical symptoms (withdrawal) uponabrupt discontinuation. All addicts have physical dependence, but only a minority are addicted. Patients on long-term opioid therapy who abruptly discontinue their drugs will experience symptoms that are distressing and unpleasant, although not life threatening. Tapering off the opioid reduces potential of experiencing withdrawal. Patients in withdrawal can receive symptomatic treatment ora formal detoxification protocol [83].

Non Steroidal Anti-Inflammatory Drugs (NSAIDs): NSAIDs are a class of drugs known to inhibit the arachadoniccascade, reducing pro-inflammatory and pro-nociceptive prostaglandins. NSAIDS work via inhibition of COX, either selectively (inhibiting only COX-1 or COX-2) or non selectively (inhibiting both COX-1 and COX-2). COX enzymes are responsible for catalyzing the conversion of arachidonic acid to prostaglandins and thromboxane, which act as messengers in many processes. The arachidonic cascade produces a variety of metabolites, including prostaglandins, thromboxanes, and leukotrienes [85]. Prostaglandins are associated with pain, inflammation, localized vasodilation, and swelling, but also have certain housekeeping functions with respect to regulation of gastric mucosa and fluid and electrolyte balances [86]. While NSAID-induced prostaglandin inhibition can reduce pain and inflammation, it may have adverse effects on the GI system. COX-1 is the more prominent enzyme in the Gastro Intestinal (GI) tract, kidney, and platelets, while COX-2 is expressed at inflammatory sites by leukocytes and activated mesenchymal cells [87]. Some commonly-used NSAIDs are listed in Table 3.

The most frequently reported dose-dependent NSAID adverse events [88] include GI symptoms, CV events, renal complications, and hypertension [89-91]. These effects may vary by specific agent. For example, celecoxib has a relatively low risk of clinically significant upper and lower GI events than nonselective NSAIDs [92] but greater CV events [93].

The American Geriatric Society recommends the use of opioid pain relievers rather than NSAIDs for chronic pain conditions in the elderly because of NSAID risks, [94] and the FDA urges prescribers to carefully weigh risks and benefits of NSAID therapy and to use NSAIDs only at the lowest effective dose for the shortest possible time [95]. Guidelines for NSAID use recommend the same [96-99].

Some NSAIDs have been linked with increased rates of cardiac morbidity and mortality [100-104]. For example, rofecoxib has been taken off the market due to CV safety concerns [105]. Both long-term [102,103] and short-term [106,107] use of NSAIDs have been associated with CV risk. While more pronounced with selective COX-2 inhibitors, some non selective NSAIDS have also been linked with cardiac risk [108,109].

Preclinical studies suggest that NSAIDs reduce the cardioprotective effect normally produced by COX-2 associated prostaglandins [110,111]. Various guidelines address these safety concerns, including guidelines published by the American Heart Association (AHA), which recommends that if NSAIDs are indicated, a non selective NSAID should be considered as first-line therapy, then a partially selective NSAID before a coxib [112]. Updated AHA guidelines add that selective COX-2 inhibitors should only be used in the lowest-risk patients for the shortest-possible durations at the lowest doses [113].

Renal side effects include electrolyte imbalances, fluid retention, nephrotic syndrome, interstitial nephritis, renal papillary necrosis, and renal insufficiency [114]. Patients receiving the highest doses of NSAIDs (≥ 90th percentile) have a 26% increased risk for chronic kidney failure [115]. In contrast, in a study of small-volume diclofenac bolus injections for postsurgical pain (n=971), less than 1% of patients had nausea, dyspepsia, decreased urine output, or acute renal failure [116]. This was a study of patients having different types of surgery (38% were ≥ 64 years of age, 62% were on anticoagulation therapy, and 6% suffered from pre-existing renal insufficiency).

NSAIDs are associated with GI toxicity, [117] including a five-fold increased risk of peptic ulcer disease and associated complications, including perforation and hemorrhage [118]. NSAIDs limit mucosal blood flow, impair the secretion of mucus and bicarbonate, and adversely affect hydrophobic mucosal surfaces [119]. NSAIDs impede the healing of pre-existing ulcers and have been linked to reduced epithelial proliferation [119]. This is likely related to inhibition of COX-1, since selective COX-2 inhibitors have a lower risk for clinically significant upper and/or lower GI events than non selective NSAIDs [92]. Patients may be stratified for the risk of GI side effects (e.g., female sex, prior history, age) and other factors can be taken into account (e.g., dose and duration of treatment) to minimize risk [120].

Inhibition of platelet cyclooxygenase results in blocking of formation of thromboxane A2, a key lipid in platelet aggregation. Adverse events associated with NSAIDs therefore have been increased bleeding and prolonged bleeding time. NSAIDs inhibition is reversible and thus the duration of bleeding ultimately depends on specific NSAID and dose. In addition, patients who concomitantly use alcohol or anticoagulants as well as those with comorbidities such as liver disease or coagulopathies are at greater risk to experience these adverse events [121].

Agent	Classification	COX inhibition	Selected brand names	Formulations	Note
Celecoxib	Coxib	S	Celebrex, Belebra, Onsenal	Oral	
Dexibuprofen	Propionic acid derivative	NS		Oral	This is the active dextrorotatory enantiomer of ibuprofen
Dexketoprofen	Propionic acid derivative	NS	Keral, Enantyum, Dolmen	Oral	Contrandicated in patients <18 years
Diclofenac	Acetic acid derivative	NS	Aclonac, Cataflam, Voltaran	Oral, transdermal, topical, suppository, eye drops	One of most potent NSAIDs
Diflunisal	Salicylate	NS	Dolobid	Oral	Duration of action ≥ 12 h
Etodolac	Acetic acid derivative	NS	Lodine, Etopan, Etofree, Haipen	Oral	Preferentially COX-2 selective
Fenoprofen	Propionic acid derivative	NS	Nalfon, Fenopron	Oral	
Flurbiprofen	Propionic acid derivative	NS	Ansaid, Froben, Ocufen	Oral, active ingredient in throat lozenges	
Ibuprofen	Propionic acid derivative	NS	Motrin, Nurofen, Advil, Nuprin	Oral, topical gel, parenteral	
Indomethacin	Acetic acid derivative	NS	Indocin	Oral, suppository, syrup, parenteral, spray, topical gel, transdermal patches, topical liquid	
Ketoprofen	Propionic acid derivative	NS	Orudis, Oruvail, Ketoflam	Oral, topical	
Ketorolac	Acetic acid derivative	NS	Toradol, Acular, Sprix	Oral, intramuscular, parenteral, eye drops, intranasal spray	
Lornoxicam	Enolic acid derivative	NS	Lorcam, Xefo	Oral, parenteral	
Loxoprofen	Propionic acid derivative	NS	Loxonin, Oxeno, Loxomac	Oral, transdermal	Prodrug which converts to its trans-alcohol metabolite
Meloxicam	Enolic acid derivative	NS		Mobic	Oral
Nabumetone	Acetic acid derivative	NS	Relafen, Relifex, Gambaran	Oral	
Naproxen	Propionic acid derivative	NS	Aleve, Midol Extended Release	Oral	Lowest overall cardiovascular risk
Oxaprozin	Propionic acid derivative	NS	Daypro, Dayrun, Duraprox	Oral	
Parecoxib	Coxib	S	Dynastat	Intravenous, intramuscular	Prodrug of valdecoxib; not approved in USA
Piroxicam	Enolic acid derivative	NS	Feldene, Roxam, Dolonex	Oral	
Rofecoxib	Coxib	S	Vioxx, Ceoxx, Ceeoxx	Oral, oral suspension, parenteral	Withdrawn from US market in 2004
Salsalate	Salicylate	NS	Mono-Gesic, Salflex, Disalcid	Oral	Being studied as diabetes treatment [138]
Sulindac	Acetic acid derivative	NS	Clinoril	Oral	
Tenoxicam	Enolic acid derivative	NS	Mobiflex	Oral	
Tolfenamic acid	Fenamate	NS	Clotam Rapid, Tufnil	Oral	Used for migraine
Tolmetin	Acetic acid derivative	NS	Tolectin	Oral	
Valdecoxib	Coxib	S	Bextra	Oral	Withdrawn from US market in 2001
Zaltoprofen	Propionic acid derivative	Preferential COX-2 inhibitor		Oral, transdermal	

NS=nonselective
S=selective

Table 3: Some commonly-used NSAIDs.

Novel NSAID preparations

The manifestation of side effects of NSAIDs can vary with product formulation. For example, topical NSAIDs have equivalent efficacy, but a lower rate of adverse events, than do oral NSAIDs [96,99]. Indeed, topical NSAIDs can be both effective and well tolerated in geriatric patients who are a high risk for adverse events from oral NSAIDs [122]. Thus, NSAID formulations are of great clinical interest, particularly for the ED. But not all forms are appropriate or convenient for the ED setting. Oral administration of NSAIDs remains the norm.

The history of oral NSAIDs has been an ongoing story of drug development. Modern NSAID use began in the 19th century with the development of aspirin by the Bayer Company. By the mid 20th century, ibuprofen was introduced. As concerns grew over the GI tolerability of these early nonselective NSAIDs, selective NSAIDs (coxibs) were introduced in the 1990s. Development continues today both in the discovery of new molecules [123,124] and in the creation of improved formulations. Among the new technologies are topical formulations [125], aerogels [126], transdermal patches [127], microparticle technologies [128] and drug-loaded nanofibers [129].

One of the better known of these novel technologies is microencapsulation, which serves to protect the encapsulated agent, control its rate of release, or help target its delivery [130]. Microencapsulation is intended to improve efficacy, reduce adverse events, improve compliance, and make the product more convenient to patients. Aerogels are nanoporous materials that have large and highly-porous surface areas that can entrap agents in such a way as to better modulate their release [131]. Drug-loaded beads may be produced using a microencapsulation technique known as prilling, in which a nozzle is used to separate a laminar jet of polymer solution into drops

NSAID	Novel formulation or technology	Goal	Intended to
Celecoxib [139]	Silica-lipid hybrid microparticles	Improve bioavailability of oral agent	Improve effectiveness
Diclofenac [116]	Parenteral	Small volume bolus injections	Reduce bleeding and renal effects
Diclofenac [128]	Microencapsulation	Controlled release	Improve dosing and tolerability
Ibuprofen [127]	Drug-loaded electrospun fibers for transdermal patch	Improve release of drug while preserving adhesion	Improve effectiveness
Indomethacin [140]	Biodegradable injectable *in-situ* gel-forming delivery system	Drug encapsulation for sustained release	Improve effectiveness, possibly reduce side effects
Ketoprofen [126]	Alginate-based aerogel	Modulate release kinetics (faster delivery), increase bioavailiabity	Improve effectiveness
Ketoprofen [141]	Prilling	Improve drug solubility and increase bioavailability	Improve effectiveness, onset of action
Ketoprofen [142]	Lipid microparticles	Deliver drug directly to the small intestine	Reduce GI side effects
Piroxicam [143]	Transdermal	Optimize existing transdermal gel formulation for greater permeation	Improve effectiveness
Zaltoprofen [144]	Transdermal	Avoids first-pass metabolism	Reduce GI effects

Table 4: Selected examples of new NSAID formulations (some are only in the early stages of development).

which are immediately brought into contact with a gelling solution, creating uniform-sized hydrated beads [132]. A few specific examples of novel NSAID formulations are listed in Table 4.

Over the years, multiple products (those mentioned above) have been developed to reduce risks for GI toxicity in NSAIDs, including enteric coating, COX-2 selective agents, and combination products with GI protective agents. Though these products have the potential to reduce the risk associated with NSAID use, there is still room for improvement. For example, enteric coating and pro-drugs (e.g., nabumetone) potentially reduces upper GI events, but does not protect against lower GI, cardiovascular or renal events. Similar reduction in risk has been reported for combination products such as NSAIDs with Gastro-protective agents. In addition, topical NSAIDs provide adequate localized pain relief, but have limited utility depending on the location of the pain. Another logical step would be to research ways to lower the required dose yet maintain efficacy.

Clinical Perspective and Conclusion

The ED is a novel clinical environment that may be viewed as a "front-line" for trauma and acute syndromes. Pain is a frequent complaint, but may not always be the focus of the emergency team's efforts. To some extent, this is understandable- triage may dictate the care paradigm- nevertheless, patients in pain should be quickly treated with safe and effective analgesics. Emphasis on patient satisfaction is on the rise and patient satisfaction involves pain control. ED clinicians will increasingly be asked to adequately relieve pain. However, unlike pain specialists who typically form long-term relationships with their patients, ED clinicians may never see their patients again. Without follow-up and no way to manage the patient beyond the ED, ED prescribers often focus on short-acting analgesics and assume that those patients who need it can receive mid-term or longer-term analgesia through other caregivers.

In sum, the ED has typically not provided optimal pain control to its patients, but under-treating pain is not limited to the ED. As we continue to regard pain as the "fifth vital sign" and a fundamental human right, [133] pain control will become increasingly important. The shift in our healthcare system toward more patient-centric practices will further underscore analgesic relief. Thus, there is now an urgent need for more and better analgesic options, particularly for acute pain relief. NSAIDs are an important agent in the armamentarium against acute pain, but their use has been limited by concerns about GI tolerability and other risks. It is clear that NSAIDs are effective and that certain NSAID formulations are substantially better tolerated than others. For these reasons, novel NSAID formulations could provide needed and important contributions.

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