Basic Pharmacology and Advances in Emergency Medicine

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Pain is the most common reason patients seek care in emergency departments (ED), and emergency physicians treat many patients who have severe pain, ranging from shingles to long bone fractures to myocardial infarction. The volume and severity of pain-related problems make pain management a core skill in emergency medicine, yet there is ongoing evidence that pain is inadequately treated in the ED [1].

When pain is mild, simple analgesics alone may suffice. But the neurophysiology of pain is complex, involving the central and peripheral nervous system at biochemical, neural, cognitive and emotional levels [2,3]. Given the multiple processes, mediators, and receptors responsible for initiating and modulating pain, it is clear that no single agent will provide optimal analgesia in all cases. For more severe pain, it is often necessary to use potent analgesics and analgesic combinations, and it is logical to combine different drugs to capitalize on their complementary mechanisms of action.

Multimodal analgesia is a critical concept in pain management, and a practice that emergency physicians use on an hourly basis. Multimodal analgesia may involve diverse methods of pain control (eg, regional block, transcutaneous nerve stimulation, and analgesics) or diverse drug combinations. Acetaminophen, anti-inflammatories, opioids and other adjunctive...
agents (eg, tricyclics, anticonvulsants, sedating drugs) can be combined in fixed or variable combinations to provide additive or synergistic pain relief without additive side effects. Evidence suggests that multimodal drug combinations enhance analgesic activity, minimize adverse effects, and enable the use of lower doses of component analgesics (ie, opioid sparing strategy) [4]. Alternatively, a sustained-release analgesic can be used to manage baseline pain levels in conjunction with an as-needed analgesic for breakthrough attacks.

Fixed-dose combinations like acetaminophen (Tylenol #3) or acetaminophen and oxycodone (Percocet) are widely used and convenient, but offer limited flexibility and may preclude the optimal dosing of component drugs to meet patient needs. Wherever possible, clinicians should tailor the pharmaceutical cocktail to the nature of the pain and the patient’s specific needs, rather than adopting a “one size fits all” approach.

To provide optimal pain control for their patients, emergency physicians should have an in-depth understanding of analgesic drugs and how to use and combine them effectively. The purpose of this article is to describe the pharmacology and use of analgesic agents that are most useful in the management of acute pain in the ED.

**Acetaminophen**

*Description*

Acetaminophen is a synthetic nonopiate derivative of p-aminophenol that has analgesic and antipyretic effects, but no anti-inflammatory properties [5]. It is effective, alone or in combination with other agents (eg, acetylsalicylic acid [ASA], opioids), for the treatment of musculoskeletal injuries, headache, earache, back pain, and dysmenorrhea, and is considered the drug of choice for pain associated with osteoarthritis [6–9]. Acetaminophen is also considered the drug of choice for the management of fever in both children and adults.

*Pharmacology*

Acetaminophen’s analgesic mechanism is poorly understood, but though to be related to inhibition of prostaglandin synthetase. Its antipyretic effects are through actions on the hypothalamic heat-regulating center.

*Dosing*

Acetaminophen can be administered by the oral or rectal route. For adults and children older than 12, the usual dose is 325 to 1000 mg every 4 to 6 hours as necessary, not to exceed 4 g daily. Children under 12 years of age should take 10 to 15 mg/kg every 4 to 6 hours as necessary, not to exceed 75 mg/kg per day.
**Contraindications**

Acetaminophen should be avoided in patients who have a known hypersensitivity to acetaminophen.

**Precautions**

There is some evidence that chronic, excessive alcohol consumption may increase the risk of hepatotoxicity. Chronic alcoholics should avoid regular or excessive use of acetaminophen.

**Adverse effects**

Acetaminophen is well-tolerated when used at recommended doses. Minor dermatological reactions including pruritic maculopapular rash and urticaria have been reported. Neutropenia, thrombocytopenia, and, rarely, agranulocytosis have also been reported. Hepatotoxicity is rare at therapeutic doses, but can result from ingestion of a single toxic dose or multiple excessive doses of acetaminophen [5].

**Important drug interactions**

**Anticonvulsants**

Anticonvulsants that induce hepatic microbial enzymes, including phenytoin, barbiturates, and carbamazepine, may aggravate acetaminophen-induced hepatotoxicity because of increased conversion of the drug to hepatotoxic metabolites. Usually, no dosage reduction is required in patients taking concomitant therapeutic doses of acetaminophen and anticonvulsants; however, patients should limit acetaminophen use while receiving anticonvulsants.

**Oral anticoagulants**

Conflicting results have been reported regarding the likelihood of a drug interaction between acetaminophen and warfarin. In a case-control study of 289 patients [10], Hylek et al reported that in patients receiving warfarin, acetaminophen ingestion was independently associated in a dose-dependent manner with significant elevation of International Normalized Ratio (INR) greater than 6. For those in the highest acetaminophen dose category (>9100 mg/week), the odds of having an INR greater than 6 were increased 10 fold (95% confidence interval [CI] 2.6–37.9). These authors concluded that acetaminophen is an unrecognized cause of overanticoagulation, but the trial was limited by the possible presence of other confounding risk factors for overcoagulation and lack of causality assessment.

The mechanism of acetaminophen-warfarin interaction is not known, but may relate to acetaminophen inhibition of the cytochrome P-450 microsomal enzyme system, with a resulting increase in warfarin blood concentration.
Until the magnitude of this interaction is defined, acetaminophen remains preferable to nonsteroidal anti-inflammatories (NSAIDS) as a mild analgesic and antipyretic in patients receiving warfarin, because of the potential for serious bleeding complications when warfarin and NSAIDS are used concomitantly. It is recommended that patients receiving acetaminophen and warfarin receive more frequent INR monitoring until values have stabilized.

Comments and controversies

Acetaminophen is equipotent as an analgesic and antipyretic. It is the safest therapeutic option for mild to moderate pain in children and adults, and the agent of first choice for the management of fever. Its efficacy, favorable adverse effect profile, and lack of significant drug interactions relative to salicylates make acetaminophen an attractive choice for pain management in a variety of patients with and without comorbid medical conditions.

Nonsteroidal anti-inflammatories

Description

NSAIDS are one of the most commonly prescribed drug classes worldwide [11]. By inhibiting cyclooxygenase (COX), the enzyme responsible for prostaglandin biosynthesis, NSAIDS provide anti-inflammatory, analgesic and antipyretic properties. This makes them valuable agents for the ED treatment of acute headache, renal and biliary colic, gout, and other musculoskeletal complaints; however, although they are effective for inflammation, pain and fever, NSAIDS are associated with potentially limiting adverse effects.

Pharmacology

There are two types of COX enzymes—COX-1 and COX-2—that mediate prostaglandin generation [12]. COX-1 is present in all cells, producing prostaglandins that have important homeostatic functions. COX-2 has an insignificant presence in most tissues until induced by injury or inflammation. Once induced, it generates prostaglandins that mediate ongoing inflammation and pain [12]. NSAIDS inhibit both forms of COX enzyme, which explains their effect on inflammation, pain and fever. Unfortunately, this nonspecific COX inhibition contributes to undesirable adverse effects.

In the gastrointestinal tract, COX-1 mediates the generation of endothelial cell-derived prostacyclin, a vasodilator that enhances mucosal perfusion and integrity. In the stomach, COX-1 enhances mucosal perfusion, bicarbonate production, and mucus production, key gastric defense mechanisms. COX-1 inhibition compromises gastrointestinal (GI) mucosal integrity, predisposing to erosions and ulceration, and antiplatelet effects increase bleeding risk.
In the cardiovascular system, COX-1 generates platelet thromboxane $A_2$, which has prothrombotic and vasoconstrictive effects to facilitate thrombosis and hemostasis. COX-1 and COX-2 produce endothelial prostacyclin, which has balancing vasodilatory and antiplatelet effects that are protective during states of abnormal platelet activation. Consequently, anti-inflammatory agents that inhibit primarily COX-1 (eg, NSAIDS) have antiplatelet effects that may be cardioprotective, whereas agents that inhibit prostacyclin more than thromboxane (ie, COX-2 inhibitors) might have prothrombotic effects that increase the risk of cardiovascular events [13–15].

In the kidney, COX-1 produces vasodilatory prostaglandins that maintain renal blood flow and glomerular filtration rate, especially in volume-depleted patients. NSAIDS block this COX-1 protective effect, causing renal ischemia and functional damage in some people. As a result, NSAIDS may cause renal sodium retention, edema, weight gain, hypertension, congestive heart failure, hyperkalemia, and rarely, acute renal failure [13]. Acute renal failure occurs at a rate of 2 per 100,000 person-years in the general population and 5 to 10 times more often in NSAIDS users. The risk of NSAID-related nephrotoxicity is dose-dependent, age- and comorbidity-related, and likely to occur during the first month of therapy [16].

**Dosing**

Table 1 outlines the usual and maximum daily doses of NSAIDS [5,17]. Although some agents have been advocated for specific indications (eg, indomethacin for gout), there is no compelling evidence that any one NSAID is superior to any other—for any indication. Consequently, NSAIDS should be selected based on convenience, cost, and availability rather than on theoretical efficacy advantages.

Ketorolac, unique as the only parenteral NSAID available in North America [18], has proven effective in the emergency department treatment of various acute pain states [19–26]. Parenteral administration results in a faster onset of action than oral or rectally-administered agents, offers an advantage in patients unable to tolerate oral medications, and in some cases reduces the need for opioids [27]; however, in patients able to tolerate oral agents, ketorolac has little advantage over orally or rectally administered NSAIDS [28–30].

**Contraindications**

NSAIDS are contraindicated in patients who have known hypersensitivity to NSAIDS.

**Precautions**

Conditions associated with dehydration increase the risk of renal toxicity, and may impair cardiac function in some patients. All NSAIDS should be
used with caution in patients who have impaired renal function, liver disease, or congestive heart failure—especially those already receiving angiotension-converting enzyme (ACE) inhibitors, angiotensin II receptors blockers (ARBs) or diuretics. NSAIDS should generally be avoided in patients who have a history of peptic ulcer disease or gastrointestinal bleeding; however, in some cases, potential benefits may outweigh risks. If this is judged to be the case, NSAID use should be limited to the lowest effective dose for the shortest treatment duration, and concurrent gastro-protection should be considered (see below). NSAIDS may cause asthma, urticaria, or severe hypersensitivity in ASA-sensitive patients; thus caution should be exercised in patients at risk. Although a clear causal relationship has not been confirmed, children who have varicella infection or influenza-like illnesses who are treated with salicylates have an increased risk of Reye’s syndrome [5].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose</th>
<th>Maximum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>325–650 po/pr every 4–6 hours</td>
<td>650 mg po every 4 hours (max 5 g/day)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>IR: 50–75 po/pr every 6–8 hours</td>
<td>IR: 50 mg po/pr every 6 hours</td>
</tr>
<tr>
<td></td>
<td>SR: 75–100 po every 8–12 hours</td>
<td>SR: 75 mg po every 8 hours (max 225 mg/day)</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>250–500 mg po every 8–12 hours</td>
<td>500 mg po every 8 hours (max 1.5 g/day)</td>
</tr>
<tr>
<td>Etodolac</td>
<td>200–400 mg po every 6–8 hours</td>
<td>400 mg po every 8 hours (max 1.2 g/day)</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>50–100 mg po every 12 hours</td>
<td>100 mg po every 12 hours (max 300 mg/day)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>200–800 mg po every 6–8 hours</td>
<td>800 mg po every 6 hours (max 3.2 g/day)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>IR: 25–75 mg po every 8–12 hours</td>
<td>50 mg po every 6 hours (max 200 mg/day)</td>
</tr>
<tr>
<td></td>
<td>SR: 75 mg po every 12–24 hours</td>
<td>75 mg po every 6 hours (max 300 mg/day)</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>IR: 50–100 mg po every 6–8 hours</td>
<td>50 mg po every 6 hours (max 40 mg/day)</td>
</tr>
<tr>
<td></td>
<td>SR: 200 mg po/pr every 12–24 hours</td>
<td>10 mg po every 6 hours (max 40 mg/day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–60 mg IV/IM load then 10–30 mg IV/IM every 6 hours</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>10 mg po every 6 hours</td>
<td>30 mg IV/IM every 6 hours (max 120 mg/day for ≤ 5 days)</td>
</tr>
<tr>
<td></td>
<td>30–60 mg IV/IM load then 10–30 mg IV/IM every 6 hours</td>
<td>10 mg po every 6 hours (max 40 mg/day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg IV/IM every 6 hours (max 120 mg/day for ≤ 5 days)</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>1–2 g po every 12–24 hours</td>
<td>1 g po every 12 hours (max 2 g/day)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250–500 mg po every 8–12 hours</td>
<td>500 mg po every 8 hours (max 1.5 g/day)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>10–20 mg po every 12–24 hours</td>
<td>20 mg every 12 hours (max 40 mg/day)</td>
</tr>
<tr>
<td>Sulindac</td>
<td>150 mg po every 12 hours</td>
<td>200 mg po every 12 hours (max 400 mg/day)</td>
</tr>
</tbody>
</table>

Abbreviations: IM, intramuscular; IR, immediate release; IV, intravenous; PO, per os; PR, per rectum; SR, sustained release.

The administration of NSAIDS late in pregnancy may prolong gestation and interfere with labor. In addition, NSAIDS have been associated with miscarriage and premature closure of the duct arteriosus, and are not recommended in pregnancy (Food and Drug Administration [FDA] category C) [31].

**Adverse effects**

NSAIDS’ most well documented serious adverse effects involve the GI tract, where they cause mucosal injury due to prostaglandin inhibition [11,32]. Rectal or parenteral administration reduces direct mucosal exposure and may mitigate mucosal damage, but NSAID systemic effects remain, and GI injury is possible regardless of the route of administration. Even without direct exposure, systemic COX-1 inhibition compromises gastrointestinal protective mechanisms, including mucosal perfusion, bicarbonate production, and mucus production, thus predisposing to peptic ulcer disease (PUD) and upper gastrointestinal bleeding.

Overall, 10% to 60% of NSAID users develop abdominal pain, dyspepsia, or nausea, and 2% to 4% of patients develop symptomatic ulcers after using NSAIDS for 1 year [32]. The 1-year likelihood of PUD-related hospitalization or death has been estimated at 1% in NSAID users [33,34]. Risk factors associated with NSAID-induced PUD include advanced age and concomitant use of warfarin, corticosteroids, or other NSAIDS (including acetylsalicylic acid) [32,35,36]. Other systemic diseases, such as congestive heart failure, diabetes, and coronary artery disease, also place patients at increased risk [32]. The risk of developing PUD is also correlated with NSAID dose and duration of therapy [35,37,38].

Cytoprotective agents reduce the risk of NSAID-induced PUD. Misoprostol and proton pump inhibitors (PPIs) have the best supporting evidence, whereas the prophylactic benefit of histamine-2 receptor antagonists is less clear [39]. The Misoprostol Ulcer Complications Outcome Safety Assessment (MUCOSA) trial demonstrated that, in patients receiving NSAIDS, prophylactic misoprostol reduced the development of serious upper gastrointestinal complications from 0.95% to 0.56% (absolute risk reduction [ARR] 0.39%; number need to treat [NNT] 256) [40]. Several trials have shown that PPIs reduce the risk of NSAID-induced PUD [41–43]. The Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT) trial showed that, at 6 months follow-up, 72% of NSAID users treated with omeprazole were ulcer-free, compared with 59% in the ranitidine group (ARR = 13%; NNT = 8) [40]. The Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) trial demonstrated that 61% of NSAID recipients treated with omeprazole versus 48% treated with misoprostol remained ulcer-free at 6 months (ARR = 13%; NNT = 8) [42]. Therefore, the best available
evidence suggests that high-risk patients receiving NSAIDS should receive prophylaxis with a proton pump inhibitor.

In the kidney, NSAIDS inhibit vasodilatory prostaglandins that maintain renal blood flow and glomerular filtration rate. This may result in renal ischemia and functional damage, especially in volume-depleted patients. NSAID renal effects may cause sodium retention, edema, weight gain, hypertension, hyperkalemia, and acute renal failure\[3,16,44\]. The risk of NSAID-related nephrotoxicity is dose-dependent, age- and comorbidity-related, and likely to occur during the first month of therapy [16]. Sodium and water retention may aggravate congestive heart failure in patients who have otherwise acceptable symptom control [45]; consequently, caution is warranted when initiating NSAIDS in patients who have congestive heart failure, hypertension, or renal dysfunction.

Other adverse effects may include headache, tinnitus, dizziness, and drowsiness. Severe hepatic reactions, including jaundice, acute hepatitis, hepatocellular necrosis, cholestasis, and fatal fulminant hepatic failure, have been reported rarely in patients receiving NSAIDS. Mild dermatological reactions such as rash or pruritis have been reported, and more serious allergic reactions such as anaphylaxis can also occur. Leukopenia, thrombocytopenia, and agranulocytosis are extremely rare [5].

**Important drug interactions**

**Oral anticoagulants**

Concurrent use of NSAIDS and oral anticoagulants such as warfarin increases bleeding risk. NSAID antiplatelet effects compound the anticoagulant properties of warfarin, increasing the risk of bleeding complications; therefore concomitant use is not recommended.

**Angiotension-converting enzyme inhibitors**

Because of effects on glomerular filtration, concurrent use of ACE inhibitors and NSAIDS may result in impaired renal function and loss of antihypertensive effects.

**Diuretics**

Patients receiving diuretics are at increased risk of developing renal failure if given NSAIDS that reduce renal blood flow. In addition, NSAIDS may interfere with the natriuretic response to diuretics, whose activity depends in part on prostaglandin-mediated alterations in renal blood flow. Thus concomitant use should be avoided.

**Glucocorticoids**

NSAID therapy may increase the risk of PUD in patients using corticosteroids. The two agents should be combined cautiously if at all.
Lithium

NSAIDS alter the sodium balance at the level of the nephron. As a result, lithium reabsorption is enhanced and lithium levels rise. Some NSAIDS may also directly reduce lithium elimination. If coadministration is necessary, the lithium dosage should be reduced by 50% when a NSAID is added. Physicians should watch carefully for evidence of lithium toxicity involving the central nervous system (drowsiness, confusion, hand tremor, blurred vision, vertigo, and seizures), GI tract (nausea and vomiting) or cardiovascular system (arrhythmias and widening of the QRS complex).

Methotrexate

Concomitant chronic administration of NSAIDS and methotrexate have been associated with severe toxicity associated with prolonged blood concentrations of methotrexate. The exact mechanism of the interaction has not been established, but it has been suggested that NSAIDS may inhibit renal elimination of methotrexate, possibly by decreasing renal perfusion.

Comments and controversies

NSAIDS are effective analgesic and anti-inflammatory agents with low abuse potential. They do not cause sedation or constipation and, at least in short term use, have better side-effect profiles than opioids. Oral NSAIDS are as effective as oral opioids, and parenteral NSAIDS may be as effective as parenteral opioids. There is no good evidence to indicate that any particular NSAID is superior, in terms of analgesic efficacy, to the others, and no good evidence to suggest that parenteral NSAIDS are superior to orally administered NSAIDS. In clinical practice, different patients respond better to different NSAIDS, and experimentation is often necessary to determine the NSAID of choice for a given patient. NSAIDS should be avoided in patients who have gastritis or peptic ulcer disease, and must be used cautiously in the elderly, and in patients who have renal disease or those who have congestive heart failure. Concomitant administration with diuretics and ACE inhibitors may increase risk of adverse renal and cardiovascular effects, and concomitant administration with warfarin and corticosteroids predisposes patients to bleeding complications.

Cyclooxygenase-2 agents

Description

COX enzymes mediate prostaglandin generation in the body. The discovery of distinct COX isoforms—one associated with many important physiological processes and the other associated with pain and inflammation—generated hopes for a new class of analgesics that would control pain and inflammation while causing fewer adverse effects. In reality, COX
physiology is much more complex, and the functional distinction between
the two isoforms is less clear than initially hoped.

COX-2 inhibitors were designed around the hypothesis that selective
inhibition of the COX-2 isoform should reduce pain and inflammation
without compromising gastric mucosal integrity. In the ED, these agents are
likely to have an increasing role in patients who have acute musculoskeletal
pain, headache, and renal or biliary colic. They are somewhat promising,
relative to traditional NSAIDS, for patients prone to GI upset and those at
higher risk for adverse GI events. Physicians who treat acute pain should be
aware of the potential benefits and hazards of COX-2 technology.

Pharmacology

Gastrointestinal

As described in the previous section, traditional NSAIDS that inhibit
COX-1 may compromise GI mucosal integrity, predisposing to erosions and
ulceration, and may also increase bleeding risk by virtue of antiplatelet
effects [14]. Agents that selectively inhibit COX-2 would be expected to
cause fewer ulcerations and lower bleeding risk. COX-2 has, however, been
identified in normal gastric mucosa, and may have a role in gastroprotection
and GI mucosal healing [13].

Cardiovascular

As described in the previous section, anti-inflammatory agents that
inhibit primarily COX-1 (eg, NSAIDS) have antiplatelet effects that may
be cardioprotective, whereas agents that inhibit prostacyclin more than
thromboxane (ie, COX-2 inhibitors) might have prothrombotic effects that
increase the risk of cardiovascular events [14,15].

Renal

The beneficial effect of COX-1 on renal perfusion and function was
previously described. COX-2 has similar effects on renal prostacyclin
production and hence on renal function [44,46,47]. COX-2 inhibitors
increase renin activity and reduce sodium excretion by approximately 20%,
as do nonspecific NSAIDS [46,48,49]. Although it was hoped that COX-2
agents would have less effect on renal perfusion than traditional NSAIDS,
a large amount of existing data suggests that the renal effects associated with
COX-2 administration are similar to those reported with prototypical
NSAIDS. In addition, cases of acute renal failure (ARF) have occurred in
patients who have pre-existing renal disease and who were treated with
COX-2 agents [50].

Cyclooxygenase-2 selectivity

In theory, highly selective COX-2 inhibitors should reduce pain, fever, and
inflammation while preserving important homeostatic and protective COX-1
functions in the gastrointestinal, cardiovascular, and renal systems. The extent to which an agent inhibits COX-2 activity but not COX-1 activity is referred to as its selectivity. In-vitro selectivity assays suggest that there are large and important differences between agents (Table 2) [51]. Unfortunately, what happens in a test tube may not reflect what happens in a living human. Clinical selectivity—the ability to suppress pain and inflammation without causing COX-1 related adverse events—depends not only on the specificity of the drug for the enzyme, but on how distinct the functions of the two enzyme systems are. Because COX-2 has some physiological roles apart from inflammation, COX-2 inhibitors do in fact have effects on GI mucosa, renal function, and platelets. Clinical selectivity is assessed by clinical trials looking at patient outcomes [51].

**Efficacy**

COX-2 agents have been studied in several pain models; unfortunately, no studies have been conducted in ED patient populations; thus efficacy must be extrapolated from other settings. The bulk of the efficacy data come from trials comparing celecoxib (Celebrex) or rofecoxib (Vioxx) to various NSAIDS. These trials suggest that there are no clinically relevant efficacy differences between COX-2 agents and traditional NSAIDS for osteoarthritis or rheumatoid arthritis [52–54]. Other studies, more relevant to emergency medicine, showed that COX-2 agents are superior to placebo and as efficacious as naproxen, aspirin, diclofenac, and ibuprofen in acute postoperative dental pain, postoperative orthopedic pain, primary dysmenorrhea, and osteoarthritis [55–61]. It is important to note that COX-2 agents also have antipyretic effects [62]. As yet there are no published studies evaluating COX-2 inhibitors in renal colic, biliary colic, nonspecific abdominal pain, acute gout, headache syndromes, sickle cell crisis, or acute musculoskeletal and soft-tissue injury—conditions of greatest interest in the ED setting.

COX-2 agents have not been adequately studied in the ED setting, but evidence from other therapeutic areas suggests that there are no clinically meaningful efficacy differences between COX-2 inhibitors and traditional NSAIDS for the management of acute pain. Efficacy differences between

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**Table 2**

In-vitro COX-2 selectivity of selected NSAID and COX-2 agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>COX-1 IC$_{50}$</th>
<th>COX-2 IC$_{50}$</th>
<th>COX-1/COX-2 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin</td>
<td>0.1</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>38</td>
<td>117</td>
<td>0.14</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>0.03</td>
<td>0.01</td>
<td>3.0</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>15</td>
<td>0.04</td>
<td>375</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>140</td>
<td>0.005</td>
<td>28,000</td>
</tr>
</tbody>
</table>

*IC$_{50}$ = drug concentration necessary to reduce enzyme activity by 50%.

COX-2 agents may exist, but further research is required to identify and quantify these [12].

Cyclooxygenase-2 interactions with other drugs

Nonsteroidal anti-inflammatory drugs and acetylsalicylic acid (ASA)

Because of pharmacological similarity and the likelihood of additive toxicity, COX-2 agents should rarely be combined with NSAIDS. COX-2 agents can be combined with cardioprotective doses of ASA (in fact it is important not to discontinue cardioprotective ASA when a selective COX-2 inhibitor is prescribed); however, the risk of GI hemorrhage appears to be similar in patients receiving NSAIDS and in patients receiving a COX-2 agent with cardioprotective ASA.

Angiotension-converting enzyme inhibitors and antihypertensives

Because of effects on glomerular filtration, concurrent use of ACE inhibitors and NSAIDS may result in loss of antihypertensive effects and impaired renal function. For the same reason, COX-2 agents may reduce the effects of prescribed loop diuretics.

Anticoagulants

Some NSAIDS are known to displace anticoagulants from plasma protein binding sites, and this effect may occur with COX-2 agents. Celecoxib has been shown not to affect coagulation parameters in healthy subjects, but increased INRs and bleeding episodes have been reported in patients receiving concurrent therapy with warfarin and celecoxib or rofecoxib. If these agents are prescribed for patients on anticoagulants, close INR monitoring is recommended—especially soon after initiation or discontinuation of the COX-2 inhibitor.

Lithium

By reducing glomerular filtration, celecoxib and other COX-2 agents can decrease renal clearance of lithium, which may lead to increased serum lithium concentrations. Patients receiving lithium and a COX-2 agent should be monitored for signs of lithium toxicity, and should have appropriate dosage adjustments when these agents are initiated or discontinued.

Antacids

Magnesium- or aluminum-containing antacids reduce COX-2 plasma concentrations and interfere with clinical effects.

Fluconazole

Fluconazole inhibits cytochrome P450-2C9 isoenzyme activity, and may reduce the metabolism of COX-2 agents. Concurrent use of fluconazole with
celecoxib, valdecoxib, or parecoxib may result in increased levels of and side effects from these agents.

**Sulfonamide allergy**

Celecoxib is structurally similar to the sulfonamides, and hypersensitivity reactions have occurred in patients who have sulfonamide allergy. This effect has not been described with rofecoxib or other COX-2 agents.

**Precautions**

COX-2 agents should generally be avoided in patients who have a history of ulcer disease or GI bleeding, particularly the elderly and debilitated, who are at higher risk of GI hemorrhage. Because of effects on glomerular filtration, these drugs may exacerbate edema, hypertension, or heart failure, especially in elderly or volume-depleted patients (eg, those who are dehydrated or receiving diuretics), and in those taking ACE inhibitors or ARBs. There are limited data from patients who have severe renal or hepatic impairment, and COX-2 inhibitors are not recommended in such patients.

Agents that modify prostaglandin activity may cause asthma, urticaria, or severe hypersensitivity in aspirin-sensitive patients. Celecoxib and rofecoxib have not been studied in children under 18 years of age or in pregnancy. The administration of prostaglandin inhibitors (including COX-2 agents) late in pregnancy may prolong gestation and interfere with labor. In addition, prostaglandin inhibitors have been associated with miscarriage and premature closure of the duct arteriosus, and are not recommended in pregnancy (FDA category C).

**Safety and adverse effects**

**Tolerability**

Adverse reactions to COX-2 agents are usually mild, and most often involve the GI tract, although neurological symptoms including headache, dizziness, and fatigue are reported by 2% to 5% of patients. An analysis of five 3-month trials comparing naprosyn, celecoxib, and placebo found that 12% of naprosyn recipients, 7.8% of celecoxib recipients, and 8.5% of placebo recipients developed moderate to severe abdominal pain, dyspepsia, or nausea (NNT = 25) [63]. Diarrhea, constipation, nausea, heartburn, dyspepsia, or abdominal pain occur in 3% to 10% of COX-2 recipients, but this is statistically similar to rates seen in patients receiving placebo or traditional NSAIDS.

**Endoscopic ulcers**

The incidence of endoscopic ulcers, defined as mucosal lesions 3 mm or more in diameter, is significantly higher in patients receiving traditional NSAIDS than in patients receiving placebo or COX-2 agents; however,
these lesions may be clinically unimportant because they are asymptomatic, not associated with bleeding, and usually detected by endoscopic examinations that are mandated within the study protocol. In an endoscopic study of 742 patients randomly assigned to rofecoxib (25 or 50 mg daily), ibuprofen (800 mg three times a day), or placebo, the incidence of gastroduodenal ulcers 3 mm or larger (at 12 weeks) was 9.9% in the placebo group, 4.1% in the low-dose rofecoxib group, 7.3% in the high-dose rofecoxib group and 27.7% in the ibuprofen group (NNT = 5) [64].

In a 12-week gastroscopy study [65], 537 patients who have osteoarthritis (OA) or rheumatoid arthritis (RA) were randomized to treatment with celecoxib 200 mg twice daily (n = 270) or naproxen 500 mg twice daily (n = 267). Endoscopic ulcer rates were lower with celecoxib at all time intervals: After 12 weeks of treatment, the cumulative incidence of gastroduodenal ulcers was 9% with celecoxib and 41% with naproxen. Efficacy was similar in both treatments, and the incidence of clinical adverse events and withdrawal rates did not differ between treatments.

Significant gastrointestinal events

The manufacturers of rofecoxib pooled 8 trials of 5435 patients [66]. Symptomatic ulcer, perforation, or bleeding occurred in 1.3% of rofecoxib patients compared with 1.8% of NSAID patients per year of exposure (NNT = 200). Fewer rofecoxib patients than NSAID patients (3.5% versus 4.8%) discontinued the study drug due to an adverse GI effect. Most studies show that clinically important upper GI events (perforations, symptomatic ulcers, and bleeding) are less common with COX-2 agents than with prototypical NSAIDS. The best safety data come from the CLASS (Celecoxib Long-term Arthritis Safety Study) and VIGOR (Vioxx GI Outcomes Research) trials, which are discussed below.

Renal effects

In a 6-week trial, 810 patients taking antihypertensives were randomized to celecoxib 200 mg/day or rofecoxib 25 mg/day. The primary endpoints were the development of edema and blood pressure changes. Overall, 9.5% of rofecoxib-treated patients and 4.9% of celecoxib-treated patients reported edema (P < .05). At 6 weeks, the change in mean systolic blood pressure was +2.6 mmHg for rofecoxib and -0.5 mmHg for celecoxib. Other trials suggest that the effects of COX-2 inhibitors on renal function are similar to those of nonselective NSAIDS [46,67]. The most common events reported after celecoxib—edema (2.1%), hypertension (0.8%), and exacerbation of preexisting hypertension (0.6%)—were not time- or dose-related.

The cyclooxygenase-2 safety megatrials

It is impossible to discuss COX-2 agents without mention of the COX-2 safety megatrials: CLASS and VIGOR. The CLASS randomized 8059
patients who had osteoarthritis or rheumatoid arthritis to celecoxib 400 mg twice daily (four times the recommended dose), diclofenac 75 mg twice daily, or ibuprofen 800 mg three times daily. The primary outcome was a composite end point incorporating perforation, gastric-outlet obstruction, or upper GI bleeding and referred to as “clinically significant upper GI event” (CSUGIE). Because of controversy around the reporting of the CLASS outcomes in the journal publication [53], we chose to present data from the more comprehensive set submitted to the FDA [68,69].

The CLASS data show that, after a mean treatment duration of 6 months, patients receiving celecoxib had a lower rate of clinically significant upper GI events (0.28%) than those receiving diclofenac or ibuprofen (0.45% and 0.55%, respectively), but the differences were not statistically significant. At 6-month follow-up, celecoxib recipients also had lower rates for the secondary combined outcome measure of CSUGIE or symptomatic gastroduodenal ulcer (0.75%, 1.0%, and 1.5%, respectively; \( P = 0.02 \) for celecoxib versus pooled NSAIDS). It is important to note, however, that in the 20% of CLASS patients using cardioprotective ASA, there were no significant differences in any of these key outcomes. Although this study was not designed to measure efficacy, these outcomes were also similar between groups: 14.8% of NSAID recipients and 12.6% of celecoxib recipients withdrew due to unsatisfactory treatment effect [69].

Table 3, a summary of GI events seen in the CLASS study (compiled from FDA data), shows that adverse events were relatively common in all three study groups, and that celecoxib recipients suffered fewer events at all time intervals, but that the differences seen were very small. This table also suggests that, for the treatment durations of 7 to 28 days that emergency physicians are likely to prescribe, differences between groups were negligible.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Gastrointestinal (GI) adverse events in the CLASS trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>Celecoxib 400 bid</td>
</tr>
<tr>
<td>Any GI AE</td>
<td>17.5%</td>
</tr>
<tr>
<td>GI AE causing withdrawal</td>
<td>7.5%</td>
</tr>
<tr>
<td>CSUGIE within 7 days</td>
<td>0%</td>
</tr>
<tr>
<td>CSUGIE within 28 days</td>
<td>0.03%</td>
</tr>
<tr>
<td>CSUGIE within 6 mo</td>
<td>0.28%</td>
</tr>
<tr>
<td>CSUGIE within 1 yr</td>
<td>0.43%</td>
</tr>
<tr>
<td>Ulcer(^a) or CSUGIE within 6 mo</td>
<td>0.75%</td>
</tr>
<tr>
<td>Ulcer(^a) or CSUGIE within 1 yr</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; bid, twice daily; CSUGIE, clinically significant upper GI event (perforation, obstruction, bleeding); mo, months; tid, three times daily; yr, years.

\(^a\) ulcer symptomatic.

Table 4 shows that there were no clinically relevant differences between the three treatment groups for renal effects, changes in blood chemistry (blood urea nitrogen [BUN], creatinine, electrolytes), or cardiovascular adverse events.

In the VIGOR trial [54], 8076 RA patients were randomized to rofecoxib (50 mg/d) or naproxen (500 mg twice a day) over a treatment period of 9 months. Most were older women, 60% were on long-term steroids, and 8% had prior peptic ulcer disease. Patients who had renal failure, recent coronary artery bypass surgery, or myocardial infarction were excluded, as were those taking ASA. The primary outcome measure was the incidence of confirmed upper GI events.

The VIGOR data suggest that effectiveness was similar for the two drugs, and that the same proportion of patients in each group withdrew from the study because of adverse effects or lack of efficacy [54]. Table 5 shows that rofecoxib caused fewer symptomatic ulcers and GI bleeds, but that it was associated with a higher rate of serious vascular events, including acute myocardial infarction, unstable angina, pulmonary embolism, transient ischemic attack, stroke, and vascular death. It is interesting that the absolute reduction in the rate of complicated ulcers (0.5%) was similar to the absolute increase in the rate of serious vascular events (0.6%).

Cyclooxygenase-2 inhibitors and serious vascular events

NSAIDs and COX-2 agents differ in their antiplatelet effects. Platelet aggregation inhibition is approximately 93% with naproxen, 92% with ASA, 80% with ibuprofen, 40% with diclofenac, and 15% or less with COX-2 agents [15]. COX-2 agents clearly lack a beneficial antiplatelet effect in patients at risk, and may have a prothrombotic effect based on differential inhibition of prostacyclin compared with thromboxane. In the VIGOR trial, 45 (1.1%) of 4047 rofecoxib recipients and 20 (0.5%) of 4046 naproxen recipients suffered serious vascular events, as described above (relative risk [RR] = 2.38; 95% CI, 1.39–4.0), whereas in the CLASS study, no

| Table 4 Renal adverse events occurring during entire CLASS study period |
|----------------|--------|---------|---------|-----|
| Adverse event  | Celecoxib | Diclofenac | Ibuprofen | NNT |
| Hypertension   | 2.0%      | 2.0%     | 3.1%*    | 200 |
| Generalized edema | 0.5%    | 0.6%     | 1.0%*    | 300 |
| Peripheral edema | 3.7%    | 3.5%     | 5.2%*    | 150 |
| Cardiac failure | 0.3%     | 0.2%     | 0.5%     | 667 |
| Increased BUN  | 1.1%     | 1.7%     | 0.9%     | 500 |

* P < 0.05 versus celecoxib.

cardiovascular hazard was apparent. Mukherjee and associates [15] suggested that acute myocardial infarction (AMI) rates in VIGOR and CLASS were higher than those seen in a large cardiovascular risk meta-
analysis, and therefore that COX-2 agents posed a potential cardiovascular hazard; however, no adjustment was made for age or comorbidity, and it is not clear that the patient populations compared are in fact comparable. It is possible that COX-2 agents may increase cardiovascular event rates. If so, the mechanism, the level of increased risk, and the differential toxicity of specific COX-2 agents remain unclear. Physicians should be aware of this potential effect, and assure that patients who have indications for antiplatelet prophylaxis receive an appropriate antiplatelet agent whether or not they are treated with a COX-2 inhibitor.

Specific agents

The best studied COX-2 inhibitors currently available are celecoxib and rofecoxib. Newer, highly selective COX-2 agents include valdecoxib and parecoxib (see Table 2). Trials in dental, gynecologic, and orthopedic pain suggest that these newer highly selective drugs have a similar efficacy to NSAIDS, but fewer GI adverse effects and a prolonged action duration that enables once-daily dosing [69,70]. Like NSAIDS, all of the COX-2 agents have additive effects with morphine and show morphine-sparing effects in acute pain models.

Parecoxib, an intravenous prodrug that is metabolized to valdecoxib, is the first COX-2 agent available in North America that can be given by the IV and intramuscular (IM) routes, providing an opportunity for IV-to-oral progression. In dental, gynecologic, and orthopedic pain, parecoxib (20 mg IV or IM) provided a similar degree and duration of analgesia to intravenous ketorolac (30–60 mg), and more prolonged analgesia than IV morphine (4 mg). Parecoxib (40 mg IV) provided a longer duration of analgesia than morphine or ketorolac [70–73].
Dosing

Celecoxib

Celecoxib is administered orally as a single daily dose or two divided doses. In osteoarthritis trials, daily and twice-daily regimens were equally effective, but this may or may not be true in acute pain. Dosing should be adjusted according to the patient’s response, starting at 100 mg twice a day, titrating to effect, and using the lowest effective dose, up to 400 mg twice daily in rare instances.

Rofecoxib

Rofecoxib is available in 12.5 mg, 25 mg, and 50 mg tablets, as well as 12.5 mg/5 mL and 25 mg/5 mL oral suspension. It is administered orally as a single daily dose—most often 25 or 50 mg. Dosage should be adjusted based on individual pain response, using the lowest effective dosage.

Meloxicam

Meloxicam is available as 7.5 and 15 mg tablets. The initial and typical maintenance dosage in adults is 7.5 mg once daily, although doses up to 15 mg/day may provide additional analgesia. As with other agents, the lowest effective dosage for the shortest feasible duration should be used.

Valdecoxib

Valdecoxib is available as 10 and 20 mg tablets. The recommended dosage in adults is 10 to 20 mg once daily. As with other agents, the lowest effective dosage for the shortest feasible duration should be used.

Parecoxib

Parecoxib can be administered as an IM or IV injection in doses of 20 to 40 mg.

Comments and controversies

Unfortunately, COX-2 agents have not been studied in the ED setting. Existing studies from diverse settings use different drugs, different doses, different end points, and different end-point detection methods in diverse patient populations. In addition, they tend to describe adverse events that occur over time periods that are much longer than emergency physicians are likely to prescribe for. Given these limitations, the evidence suggests that COX-2 agents are effective in acute pain, and that they have similar efficacy to NSAID comparators. They are well-tolerated, but cause similar rates of minor GI side effects as traditional NSAIDS. They cause significantly fewer endoscopic ulcers than nonselective NSAIDS, but the clinical importance of these lesions is uncertain. As the selectivity hypothesis predicts, COX-2 agents cause fewer symptomatic ulcers (NNT ~ 100) and slightly fewer
bleeding ulcers than nonselective NSAIDS, although the incidence of the latter is very low and the NNT (to prevent one GI bleed) is very high: between 200 to 1000. COX-2 agents are equally likely to cause serious (GI + cardiovascular) adverse events, but these events are uncommon with short treatment durations.

Rofecoxib has been associated with a higher rate of AMI and major vascular events. This may or may not be a class effect; therefore patients eligible for cardiovascular prophylaxis should receive low-dose ASA, recognizing that it reduces thrombotic risk and increases ulcer and bleeding risk.

COX-2 inhibitors have renal effects similar to nonspecific NSAIDS. Both types of drugs should be used with caution in patients who have renal compromise, heart failure, and hypertension. These agents should be considered part of a pain strategy that involves acetaminophen, traditional NSAIDS, COX-2 agents, opioids, and perhaps other analgesics. When used for acute pain, all agents should be prescribed in the lowest effective dose for the shortest time necessary, particularly in elderly and debilitated patients.

**Opioid analgesics**

*Description*

Opioids are an essential component of severe pain management and the most important class of analgesics for emergency physicians to be familiar with [74]. Titrated intravenous opioids remain the treatment of choice for most patients who have acute severe pain [75,76], and oral opioids are a mainstay for outpatient management of moderate to severe pain. In recent years, increasing physician awareness of pain management principles has led to increasing use of potent opioids such as fentanyl, oxycodone, hydro-morphone, and morphine, yet ED studies continue to suggest that emergency physicians undertreat acute pain [1].

*Pharmacology*

Opioids bind to receptors in the central nervous system and suppress neuronal pain transmission. In addition, they alter thalamocortical processing of pain signals to modify the subjective experience of pain [2]. The three primary opioid receptors are mu, kappa, and delta receptors. Mu receptors, named for morphine, mediate analgesia, respiratory depression, euphoria, and dependence; kappa receptors mediate analgesia, sedation, and dysphoria; and delta receptors mediate analgesia and mood effects. In addition to their analgesic properties, opioids suppress the medullary cough center (antitussive effects) and decrease the CO2 responsiveness of the medullary respiratory center. This impairs respiratory drive and relieves the sensation of breathlessness (antidyspnea effects). Opioids also activate
the chemoreceptor trigger zone and cause nausea and vomiting. In the GI and urinary tract, opioid receptors inhibit bowel motility (antidiarrheal effect) and may cause urinary retention. Opioids produce differing degrees of histamine release, with resultant pruritus, urticaria, and postural hypotension. The ability of opioids to produce euphoria and dependence generates concerns about abuse and addiction. Many patients fear becoming addicted to opioids, and many physicians avoid opioids out of concern about drug abuse. Unfortunately, these legitimate concerns, coupled with limited pharmacological awareness, have led to underprescribing and underdosing, and are a significant roadblock to the appropriate use of opioids for pain management [74].

Opioids provide dose-dependent central analgesia with variable sedation and anxiolysis. Because they lack the “ceiling” effect of other analgesics, opioid titration can relieve any level of pain; hence, the correct opioid dose is not a standard dose or a weight-based dose; it is the dose that relieves the pain. In terms of analgesic efficacy, there is little difference between the different mu receptor agonists. Any of the opioids discussed below can relieve severe pain if they can be tolerated in adequate doses; however, with some agents, notably codeine, limiting side effects appear at relatively low doses. Consequently, when determining the best drug for a specific patient, physicians should consider individual differences, patient experience, and adverse effect profile [77–79].

Mixed opioid agonist-antagonists such as pentazocine, butorphanol, and nalbuphine are not recommended. Their efficacy is limited by a ceiling effect, they have a high rate of adverse effects, and they may cause withdrawal syndromes in patients already using pure agonist opioids [80]. The pure agonist opioids (codeine, hydrocodone, hydromorphone, morphine, and oxycodone) are preferred for acute pain management. These are considered short- or intermediate-acting drugs, and their clinical effects correspond with peak serum levels: Maximal analgesia occurs 60 to 90 minutes after oral dosing, 30 minutes after IM injection, and 6 minutes after IV injection. Significant first-pass metabolism means that oral doses must be substantially higher than parenteral doses to achieve equivalent analgesia (Table 6). In general, the pure opioid agonists are first conjugated in the liver, then the (generally active) metabolites are excreted by the kidneys [80].

Maximum pain control for any given drug and dose is achieved when serum levels reach steady state—at about five half-lives if the drug is dosed regularly. The most effective way to relieve acute continuous pain is therefore to administer short acting opioids on the half-life (ie, every 4-hours rather than merely “as needed”) [80]. Using the immediate-release pure opioids listed above, administered on the half-life, steady state can be achieved within 24 hours. As a general rule, shorter-acting strong opioids should be prescribed initially to rapidly control pain and to estimate the daily opioid requirement; then, if ongoing treatment is required, a switch to a longer acting (slow-release) agent is appropriate. When treating acute
severe pain, it is best to avoid transdermal or delayed release oral formulations, because delayed onset may lead patients to take additional doses before appreciating the effect of the first dose, and prolonged action duration may cause dangerous-dose “stacking” effects [76]. Table 7 lists equivalent doses of opioids for acute pain management.

**Specific agents**

**Morphine**

Morphineline opioids are the foundation of effective pain management [75]. Based on effectiveness, relative lack of toxicity, and longer duration of analgesia—approximately 4 hours compared with meperidine’s 2 to 3—morphine is the opioid of first choice for acute severe pain in the ED. Oral morphine preparations are an effective option for moderate and severe outpatient pain, but for acute dosing, it is important to remember that morphine is largely eliminated by first-pass metabolism, with only about 20% of the ingested dose reaching the tissue level. Consequently, oral doses are approximately five times parenteral doses. Table 8 compares standard parenteral doses of morphine to other drugs.

### Table 6
Analgesic equivalence table

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose equivalent to 10 mg morphine (IM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parenteral</td>
</tr>
<tr>
<td>Morphine sulphate</td>
<td>10 mg</td>
</tr>
<tr>
<td>Meperidine</td>
<td>100 mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>120 mg</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>15 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1 mg</td>
</tr>
</tbody>
</table>

<sup>a</sup> For chronic dosing, morphine’s oral/IM ratio is approximately 3/1, not 6/1.


### Table 7
Equivalent doses of opioids for acute pain management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intramuscular dose</th>
<th>Oral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 milligrams</td>
<td>60 milligrams</td>
</tr>
<tr>
<td>Meperidine</td>
<td>100 milligrams</td>
<td>300 milligrams</td>
</tr>
<tr>
<td>Hydromorphone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 milligrams</td>
<td>8 milligrams</td>
</tr>
<tr>
<td>Codeine</td>
<td>60 milligrams</td>
<td>180 milligrams</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>20 milligrams</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20 milligrams</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.15 milligrams</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> 2 mg hydromorphone po is equivalent to 10 mg morphine solution orally.
Morphine is mainly metabolized by hepatic glucuronidation to several metabolites, including morphine 6-glucuronide (M6G) and morphine 3-glucuronide (M3G), which are eliminated in the urine (Fig. 1). M6G is a more potent analgesic than morphine, and contributes to therapeutic and opioid effects. M3G, known to cause significant central nervous system (CNS) toxicity, including tremors, myoclonic jerks, delirium, and seizures, actually antagonizes morphine’s analgesic effects [76]. With repeated administration, particularly in elderly patients and those who have limited renal function, M6G and M3G may accumulate, producing enhanced opioid effects and CNS toxicity.

Like other opioids, morphine causes pruritus, nausea, constipation, and dizziness. Morphine is one of the stronger histamine releasers, and may cause transient urticaria. It is common to see localized urticaria tracking along forearm veins after intravenous morphine administration, but this finding usually resolves quickly without treatment, and by itself should not be construed as an allergic reaction.

Although by itself morphine is a potent and extremely effective analgesic, there is evidence that it can be combined with simple analgesics in an effective multimodal approach to pain. In a double-blind randomized trial, Schug and coworkers [3] compared morphine patient-controlled analgesia (MPCA) with and without acetaminophen in a cohort of postorthopedic surgery patients. Patient satisfaction was significantly higher and mean pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parenteral</th>
<th>Dose (IM or SC)</th>
<th>PR dose</th>
<th>Dose frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>200 mg</td>
<td>120 mg</td>
<td></td>
<td>every 4 hours</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Percocet (Acet.)</td>
<td>10–15 mg</td>
<td></td>
<td></td>
<td>every 4 hours</td>
</tr>
<tr>
<td>- Percodan (ASA)</td>
<td>(2–3 tabs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>4 mg</td>
<td>2 mg</td>
<td>3 mg</td>
<td>every 4 hours</td>
</tr>
<tr>
<td>- Dilaudid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sustained Release</td>
<td></td>
<td>2 × 6 mg</td>
<td></td>
<td>every 12 hours</td>
</tr>
<tr>
<td>Capsule</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- solution (MOS)</td>
<td>20–30 mg</td>
<td></td>
<td></td>
<td>every 4 hours</td>
</tr>
<tr>
<td>- MS Contin/MOS-SR</td>
<td>60–90 mg</td>
<td>10, 20 or 30 mg</td>
<td></td>
<td>every 6–8 hours</td>
</tr>
<tr>
<td>- suppository</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- injectable</td>
<td>10 mg</td>
<td></td>
<td></td>
<td>every 4 hours</td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoid:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merperidine</td>
<td>300 mg</td>
<td>75 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Demerol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations:* SC, subcutaneous; Acet, acetaminophen; MOS-SR, morphine sulphate-slow release; PO, per os; PR, per rectum.
scores lower when acetaminophen was added to the MPCA regimen. In addition, patients receiving acetaminophen used 16% less self-administered morphine, although the latter difference did not achieve statistical significance.

Some physicians tend to avoid morphine because of historic teaching that it causes more biliary and ureteral spasm than meperidine. Evidence suggests, however, that all opioids cause some smooth-muscle spasm, and that equianalgesic doses of morphine and meperidine have similar effects on renal and biliary smooth muscle. This evidence reduces the “biliary spasm” concept to the level of a medical myth, and mitigates morphine’s main perceived disadvantage [81].

**Morphine formulations and dosing**

There are a large range of morphine preparations available. Those most relevant to acute ED pain management include morphine oral solution, morphine immediate-release tablets (10, 20, and 30 mg) and parenteral morphine for subcutaneous, IM, or IV administration. MS Contin and MOS-SR, or M-ESLON sustained-release preparations are available in strengths of 15, 30, 60, 100, and 200 mg. These are convenient in that they can be given every 12 hours, but they are more appropriate for chronic pain involving prolonged administration. An average oral morphine (immediate release) starting dose in adults is 10 mg orally every 3 to 4 hours as needed, but doses of 20 to 30 mg every 4 hours may be reasonable, depending on patient characteristics and pain severity. An average adult subcutaneous or IM dose is 10 mg (0.15 mg/kg) every 3 or 4 hours. The treatment of choice for acute severe pain in the emergency department is 2.5 to 5 mg IV every 5 to 10 minutes, titrated to effect.
**Meperidine (Demerol)**

Historically, meperidine is one of the most commonly used agents for the ED treatment of acute pain; however, in recent years, meperidine has fallen from favor and its use has decreased significantly, whereas the use of other opioids has increased [74]. This move away from meperidine may reflect an increasing awareness of its many shortcomings, which include poor bioavailability, a brief duration of analgesia (only 2–3 hours), and toxic side effects [75]. In addition, meperidine is poorly absorbed from the GI tract, and variably absorbed after IM injection, making its effects unpredictable and often inadequate. There is some evidence that meperidine is a less effective analgesic than morphineline opioids [82]. In addition, oral meperidine is poorly absorbed, and the most commonly prescribed oral dose—50 mg—is no more effective than 650 mg of aspirin or acetaminophen.

When scientists first synthesized meperidine, their intention was to produce an anticholinergic agent; hence meperidine blocks muscarinic receptors and has significant anticholinergic effects, notably visual blurring, constipation, tachycardia, and dry mouth. Central manifestations may include agitation, confusion, delirium, disorientation, and visual hallucinations [83]. In addition, meperidine or its breakdown product normeperidine blocks the reuptake of serotonin and norepinephrine, potentially leading to an over-abundance of these neurotransmitters and to clinical consequences related to CNS excitation. As a result, meperidine has been associated with serotonin syndrome [84], and it is contraindicated in patients receiving monoamine oxidase inhibitors, in whom it may precipitate severe hypertensive crises.

In the liver, meperidine is metabolized by the cytochrome P-450 system to normeperidine, a neurotoxic nonopioid metabolite that has weak analgesic effects and potent CNS excitatory effects. These are manifested by anxiety, confusion, dysphoria, hallucinations, hyperreflexia, myoclonus, and occasionally seizures [75,81,85]. Because first-pass metabolism converts much of the active drug to its toxic metabolite, normeperidine blood levels are higher in patients using oral meperidine than in those on parenteral therapy [86]. Although meperidine has a relatively short elimination half-life of 3 to 4 hours, normeperidine has a prolonged half-life of 24 to 48 hours; therefore repeated dosing leads to accumulation and increasing neurotoxicity, particularly in the elderly and in patients with renal dysfunction. The combination of anticholinergic, serotonergic, and adrenergic effects explains why meperidine is the only opioid that causes mydriasis rather than miosis, and why it is perhaps the most neurotoxic opioid—a suboptimal therapeutic choice at the best of times and a particularly bad option in older patients. The major cause for concern with meperidine is the rapid accumulation of the neuroexcitatory metabolite, normeperidine. Although all opioids can cause some degree of CNS excitation, most require prolonged use at high doses. Meperidine can produce subtle changes in a matter of hours and significant toxicity within 1 to 2 days. Because normeperidine is not an opioid, opioid antagonists such as naloxone do not reverse neurotoxic symptoms.
It is a long-held medical myth that meperidine is preferable to morphine in patients who have colicky pain, particularly cholelithiasis [76]. This conclusion is not supported by scientific evidence; in fact, when used in equianalgesic doses, meperidine has as much effect on GI smooth muscle as do other opioids. When the neurotoxic side effects are taken into consideration, it is clear that meperidine has several disadvantages, but no advantages, relative to other opioids; therefore meperidine should rarely if ever be considered the opioid of choice for acute pain.

Meperidine formulations and dosing

Meperidine should generally be avoided, and is rarely the drug of choice for acute pain in the ED. It is available in 50 mg tablets, which should not be prescribed because of the many preferable options, and parenteral formulation for IM and IV administration. An average adult subcutaneous or IM dose is 100 mg (1.5 mg/kg) every 2 to 3 hours as needed. Intravenous doses range from 10 to 50 mg IV every 5 to 10 minutes, titrated to effect.

Codeine

Codeine is the most commonly prescribed opioid, usually given in fixed combination with acetaminophen (eg, Tylenol #3). It is a moderately effective analgesic used for mild and moderate pain, but it causes frequent gastrointestinal adverse effects at doses that have limited euphoric and analgesic effect. These adverse effects reduce both its abuse potential and its therapeutic potential. Codeine’s analgesic effects are dose-related, but pushing the dosage above 60 mg produces relatively less pain relief and incrementally more constipation, nausea, and sedation [87]. Codeine is absorbed more completely than morphine (roughly 60% bioavailable); however, it is a prodrug with minimal analgesic effect until it metabolized by hepatic enzymes to morphine and other active metabolites. Unfortunately, 10% of the population are genetically poor metabolizers and experience toxicity, but not pain relief, with codeine. Common side effects include pruritus, nausea, constipation, and dizziness.

Codeine acts additively with acetaminophen, and acetaminophen-codeine combinations are more effective than either drug used alone; however, the evidence is less convincing for codeine-ASA combinations, in which the addition of codeine provides only a small improvement in analgesia relative to ASA alone [87].

In a meta-analysis of 40 trials of moderate to severe dental and postsurgical pain, Moore et al [88] compared the analgesic efficacy of several acetaminophen codeine combinations, presenting their results in terms of the number needed to treat to achieve one additional patient with greater than 50% pain relief. In this analysis, acetaminophen (1000 mg) was more effective than placebo, with an NNT of 4.6, meaning that it is necessary to treat 4.6 patients (with acetaminophen instead of placebo) to have one more patient with at least 50% pain relief. In a similar comparison of
acetaminophen-codeine (650 mg/60 mg) versus placebo, the NNT to achieve one additional patient with 50% pain relief was 3.6. These authors concluded that increasing codeine doses up to 60 mg increased pain relief, but that increasing the dose beyond this level led to a disproportionate increase in adverse effects.

**Codeine formulations and dosing**

Codeine is available as codeine syrup (5 mg/ml), codeine tablets (15, 30, and 60 mg) and codeine phosphate injection (15, 30, and 60 mg/ml). Tylenol 1, 2, and 3 tablets contain 300 mg acetaminophen and 15 mg caffeine, as well as 8, 15, and 30 mg of codeine, respectively. Atasol 15 and 30 tablets contain 300 mg acetaminophen and 30 mg caffeine, as well as 15 and 30 mg of codeine, respectively. Empracet 30 and 60 contain 300 mg acetaminophen with 30 and 60 mg of codeine, but Empracet contains no caffeine, thus may be preferable if insomnia is a concern. Usual codeine dosing is 30 to 60 mg of codeine orally, every 4 to 6 hours as needed. Codeine dosage is limited by GI side effects, and by the acetaminophen content of combination products.

**Hydrocodone**

Hydrocodone, also a prodrug, is hepatically metabolized to hydromorphone. This drug is often used as an antitussive, but it offers better analgesia with fewer GI adverse effects than codeine. Like codeine, hydrocodone is often combined with simple analgesics such as acetaminophen and ibuprofen, because the combination provides better pain relief than the component analgesics \[4,89\]. In studies of acute musculoskeletal pain and dental surgery, a hydrocodone-acetaminophen (5 mg/500 mg) combination provided comparable pain relief to a codeine-acetaminophen (30 mg/500 mg) \[4,89\]. In these studies, hydrocodone caused more drowsiness and dizziness, but fewer GI side effects. In postoperative abdominal surgery studies, hydrocodone-ibuprofen combinations (7.5 mg/200 mg and 15 mg/400 mg) provided better and faster analgesia than corresponding doses of the component drugs used alone \[90,91\].

**Hydrocodone formulations and dosing**

Hydrocodone-acetaminophen and hydrocodone-ibuprofen combinations are available as described above. The usual hydrocodone dose range is 5 to 20 mg orally every 4 to 6 hours as needed. Hydrocodone-acetaminophen combinations are limited by adverse effects and acetaminophen content. These compounds are usually prescribed as one or two tablets orally every 4 hours as needed.

**Hydromorphone (Dilaudid)**

Like codeine, hydromorphone is a prodrug that is metabolized in the liver to morphine. It is effective for moderate and severe pain. Analgesic effects and side effects are dose-related, and its adverse effect profile is similar to
other potent mu receptor agonists. Nausea, drowsiness, and pruritus are the most frequent adverse effects, and hydromorphone causes relatively little GI upset [77]. Elderly patients and those who have renal impairment tend to tolerate hydromorphone better than morphine, with less drowsiness and cognitive impairment [92]. Ironically, its euphoric effects and favorable adverse effect profile contribute to a higher abuse potential [77].

With respect to analgesic efficacy and adverse effects, hydromorphone is similar to oxycodone and morphine [77]. A systematic review of 32 acute pain studies comparing hydromorphone and morphine in patients who had postoperative pain, acute trauma pain, burns, biliary colic and ureteral colic concluded that there are no significant differences in terms of efficacy, adverse effects, and patient preference when the two drugs are administered in equianalgesic doses. Conversely, four studies using meperidine as a comparator suggested that hydromorphone provided better analgesia without a increase in adverse effects [77].

Hydromorphone formulations and dosing

Hydromorphone is available in 1, 2, 4, and 8 mg tablets, 3 mg suppositories, and injectable solution. Sustained-release hydromorphone capsules (3 mg and 6 mg) and long-acting Hydromorph Contin are available, but are less appropriate for acute ED pain management. Usual hydromorphone doses are 4 to 8 mg orally every 3 to 4 hours, 1 or 2 mg IM every 3 to 4 hours as needed, or 1 mg IV every 10 minutes titrated to effect.

Oxycodone

Oxycodone is a strong opioid agonist, available in short- or long-acting formulations, and in combination with acetaminophen (Percocet) or ASA (Percodan). Oxycodone preparations are useful for the management of moderate and severe pain. At equianalgesic doses, they cause relatively fewer GI adverse effects than codeine, but it is important to remember that overuse of combination products may result in significant ASA or acetaminophen toxicity. Oxycodone’s favorable adverse effect profile, along with its euphoric effects, give it a higher abuse potential.

Analgesic effects are very dose-dependent: A Cochrane meta-analysis [81] showed that, although oxycodone 5 mg is not statistically better than placebo, doses of 10 to 15 mg, with or without acetaminophen, have similar efficacy to IM morphine and NSAIDS. Pooled studies of oxycodone 15 mg versus placebo, in patients who had moderate to severe postoperative pain, show an NNT of 2.4 to achieve one additional patient with 50% pain relief. Oxycodone-acetaminophen (10 mg/650 mg) showed similar superiority over placebo in postabdominal surgery and dental pain patients, with an NNT of 2.2. A dose-response analysis by Edwards and colleagues [78] indicated that oxycodone 15 mg, oxycodone-acetaminophen (5 mg/325 mg), and oxycodone-acetaminophen (10 mg/650 mg) have similar efficacy, which suggests that, in the presence of acetaminophen, oxycodone dosage can be lowered...
without loss of efficacy. Oxycodone’s most common adverse effects are nausea, headache, dizziness, and drowsiness, which are dose-related and rarely severe. At a dose of 5 mg, oxycodone has a similar rate of adverse effects as placebo, but oxycodone 10 mg or 15 mg caused significantly more drowsiness, nausea, and vomiting (RR = 1.8–2.8) [78]. In a recent study of osteoarthritis patients who had NSAID-resistant pain [93], controlled-release oxycodone provided similar analgesia to but less nausea than an immediate-release oxycodone/acetaminophen combination. Both of these active treatments were superior to placebo.

**Oxycodone formulations and dosing**

Typical oxycodone dosing is 5 to 20 mg every 4 hours as needed. Oxycodone-acetaminophen preparations include Percocet 2.5/325 (5 mg oxycodone/325 mg acetaminophen), Percocet-5/325, Percocet-7.5/500, and Percocet-10/650. Oxycodone-ASA is available as Percodan (5 mg oxycodone/325 mg ASA).

Percocet and Percodan dosing are limited by acetaminophen and ASA content, and they are usually prescribed as one or two tablets every four hours as needed. OxyContin is the sustained release form of oxycodone. It is available in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths, and is usually administered on a twice-daily basis. Because of problems with dependency, misuse, and diversion, this formulation has generated a great deal of controversy.

**Fentanyl**

Fentanyl is a synthetic opioid that is highly lipid soluble, giving it a rapid onset within 2 to 3 minutes. Because of rapid redistribution from the CNS into tissues, its clinical duration of action is only 30 minutes, and its elimination half-life is 3 hours, slightly longer than that of morphine. Consequently, after prolonged fentanyl infusions or repeated dosing, when tissue sites are saturated, drug accumulation and toxicity may occur, but this is unlikely after acute dosing in the emergency department. Fentanyl causes less histamine release than morphineline opioids, and hence produces fewer hemodynamic effects and less hypotension. This makes it a good choice for rapid titration analgesia in ED patients who may be volume-depleted or hemodynamically unstable. The recommended dose is 1 ug/kg given slowly every 3 to 5 minutes, titrated to effect.

Transdermal fentanyl patches (Duragesic) are available for patients who have GI absorption problems or poor compliance with oral regimens. These are a long-acting formulation that takes days to reach steady state after initiating or discontinuing, hence they are rarely appropriate for acute ED pain management [94].

The most appropriate formulation and dosing of fentanyl for acute ED pain management is rapid IV titration, as described above.
Nurse-initiated opioid protocols

Traditionally, ED patients who have acute painful conditions wait for physician assessment before receiving potent analgesics. In settings with experienced ED nurses, nurse-initiated IV morphine protocols for stable adult patients who have acute painful conditions are associated with more rapid and satisfactory pain control, with a low and acceptable rate of complications. Protocols involve IV morphine given as 2.5 mg boluses every 5 minutes until the patient is comfortable, up to 0.1 mg/kg [95].

References


