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Exploring Opioid-Sparing Multimodal Analgesia Options in Trauma: A Nursing Perspective

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ABSTRACT

Challenges with opioids (e.g., adverse events, misuse and abuse with long-term administration) have led to a renewed emphasis on opioid-sparing multimodal management of trauma pain. To assess the extent to which currently available evidence supports the efficacy and safety of various nonopioid analgesics and techniques to manage trauma pain, a literature search of recently published references was performed. Additional citations were included on the basis of authors' knowledge of the literature. Effective options for opioid-sparing analgesics include oral and intravenous (IV) acetaminophen; nonsteroidal anti-inflammatory drugs available via multiple routes; and anticonvulsants, which are especially effective for neuropathic pain associated with trauma. Intravenous routes (e.g., IV acetaminophen, IV ketorolac) may be associated with a faster onset of action than oral routes. Additional adjuvants for the treatment of trauma pain are muscle relaxants and alpha-2 adrenergic agonists. Ketamine and regional techniques play an important role in multimodal therapy but require medical and nursing support. Nonpharmacologic treatments (e.g., cryotherapy, distraction techniques, breathing and relaxation, acupuncture) supplement pharmacologic analgesics and can be safe and easy to implement. In conclusion, opioid-sparing multimodal analgesia addresses concerns associated with high doses of opioids, and many pharmacologic and nonpharmacologic options are available to implement this strategy. Nurses play key roles in comprehensive patient assessment; administration of patient-focused, opioid-sparing, multimodal analgesia in trauma; and monitoring for safety concerns.

Key Words

multimodal, nursing, opioid sparing, pain management, trauma

Trauma-related injuries are common and burdensome. In 2011, injuries were responsible for more than 40 million visits to emergency departments (EDs) in the United States (National Center for Health Statistics & Ambulatory and Hospital Care Statistics Branch, n.d.). Pain is reported in at least 70% of trauma-related injuries (Berben, Schoonhoven, Meijs, van Vugt, & van Grunsven, 2011), and undertreated acute pain may contribute to delirium, particularly in geriatric patients (McKeown, 2015); prolonged need for mechanical ventilation; and delayed mobilization (Barr et al., 2013). Acute pain is cited as a predictor of chronic pain development (McGreevy, Bottros, & Raja, 2011; Trevino, Harl, Deroon-Cassini, Brasel, & Litwack, 2014). Even at 4 months after injury, 79% of trauma patients reported chronic pain, with positive correlations between pain severity and the level of interference with activities of daily life (Trevino, Essig, deRoon-Cassini, & Brasel, 2012). A study among veterans revealed that 73.4% experience persistent pain, possibly because of combat and blast injuries (Higgins et al., 2014). Effective acute pain management is expected to improve the patient experience and potentially prevent long-term effects.

Opioids have historically been the mainstay treatment for severe trauma pain (Aldington, McQuay, & Moore, 2011; Gausche-Hill et al., 2014; Keene, Rea, & Aldington, 2011). As an example of the reliance on opioid analgesics, a 2010 study indicated that 31% of all ED visits involved the administration of an opioid (Mazer-Amirshahi, Mullins, Rasooly, van den Anker, & Pines, 2014). However, opioids can cause adverse events (AEs) that limit their use in trauma pain management. These AEs are well known and include nausea, vomiting, and constipation (Keene et al.,

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2011). Of greatest concern is the risk of opioid-induced sedation and its progression to respiratory depression, which may lead to injury or death (Jarzyna et al., 2011). The concomitant use of sedating medications, especially benzodiazepines, increases the risk of sedation and of diminishing respiratory drive (Jarzyna et al., 2011).

Additional concerns with the use of opioids are related to the risks of misuse by patients and of substance abuse. *Misuse* is defined as the "use of a medication (for a medical purpose) other than as directed or indicated, whether willful or unintentional, and whether harm results or not," and *substance abuse* is defined as "any use of an illegal drug, or the intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness, for example, getting high" (Chou et al., 2009, p. 130; Katz et al., 2007, p. 650). Abuse may contribute to injuries, as suggested by a survey in which 38% of trauma populations displayed problematic/risky alcohol behavior and 44% of those with toxicology results tested positive for illicit drugs (Stroud, Bombardier, Dyer, Rimmele, & Esselman, 2011). An observational study showed that 42% of patients discharged with opioids from a level 1 trauma center ED misused these drugs (Beaudoin, Straube, Lopez, Mello, & Baird, 2014). Individuals who are opioid dependent as a result of substance abuse report lower quality of life than the general population (Griffin et al., 2015).

Opioids are often required for moderate to severe trauma pain, but they are increasingly used at lower doses as part of opioid-sparing and multimodal analgesic approaches (Figure 1). This shift is due to both the demonstrated effectiveness of multimodal pain management (American Society of Anesthesiologists Task Force on Acute Pain Management, 2012; Cho et al., 2011) and the widely recognized dangers associated with opioid use, misuse, and abuse (Beaudoin et al., 2014; Keene et al., 2011). Opioid-sparing strategies can mitigate the undesirable effects of opioids by facilitating the use of the lowest effective dose of opioids (Jarzyna et al., 2011). Multimodal regimens involve the use of multiple medications (e.g., opioids and nonopioids) with different mechanisms of action (Figure 2) as well as nonpharmacologic interventions to achieve more effective analgesia. Use of multiple analgesics allows for lower and safer doses of each drug (Jarzyna et al., 2011). This review aims to summarize evidence on pharmacologic and nonpharmacologic options that may be utilized in opioid-sparing, multimodal therapy for trauma pain. The main focus is the treatment of pain during hospitalization, with consideration for discharge planning.

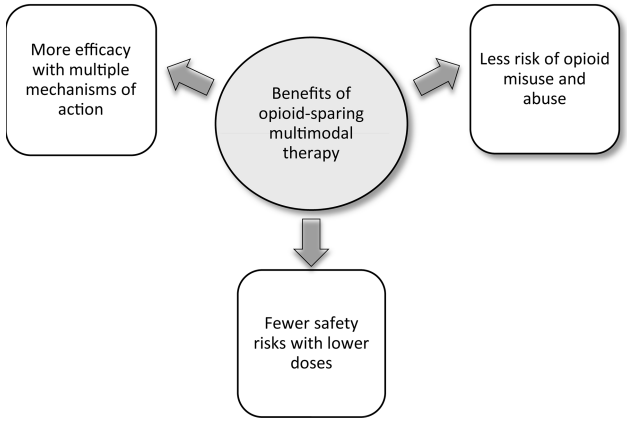

Figure 1. Potential advantages of opioid-sparing multimodal therapy.

PATIENT ASSESSMENT AND COMMUNICATION

Pain assessment (e.g., intensity level, nature and quality, duration, location) is key to developing a pain management plan of care for trauma patients. Pain intensity scales can help patients communicate their pain. Appropriate scales should be selected on the basis of a patient's age and cognitive status. Patient self-report is the gold standard for determining pain intensity (Gélinas, 2016). Adults who are able to self-report their pain intensity should use a validated visual analog scale or a validated numeric rating scale (Gausche-Hill et al., 2014; Hjermstad et al., 2011). For patients aged 4–12 years, a validated self-report tool such as the Wong-Baker FACES® scale is suggested (Garra et al., 2010; Gausche-Hill et al., 2014).

Patients who are unable to communicate verbally are at particular risk for undertreatment of pain (Barr et al., 2013; Gausche-Hill et al., 2014; Pasero & McCaffery, 2011; Reavey et al., 2014). For these patients, a hierarchy of pain assessment techniques (Figure 3) has been recommended that involves assuming pain is present for conditions that are typically painful and includes both formal tools and practitioner observations (Pasero & McCaffery, 2011). In critically ill patients who cannot self-report, scales such as the Critical-Care Pain Observation Tool, which can be used for intubated and extubated patients, or the Behavioral Pain Scale should be utilized. For patients younger than 4 years, available scales include the Face, Legs, Arms, Cry, and Consolability scale and the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS). For patients younger than 3 months, the Neonatal Pain, Agitation, and Sedation Scale (N-PASS) is recommended. When using behavioral tools, practitioners should remember that the absence of pain-related behaviors does not always indicate the absence of pain.

Evaluating pain intensity with a valid and appropriate scale is only one component of a comprehensive pain assessment. In addition, assessments of the character of pain (e.g., sharp, dull, aching, cramping, burning), pattern (e.g., radiating, intermittent, constant), duration, location, and interventions that make pain better or worse are key to

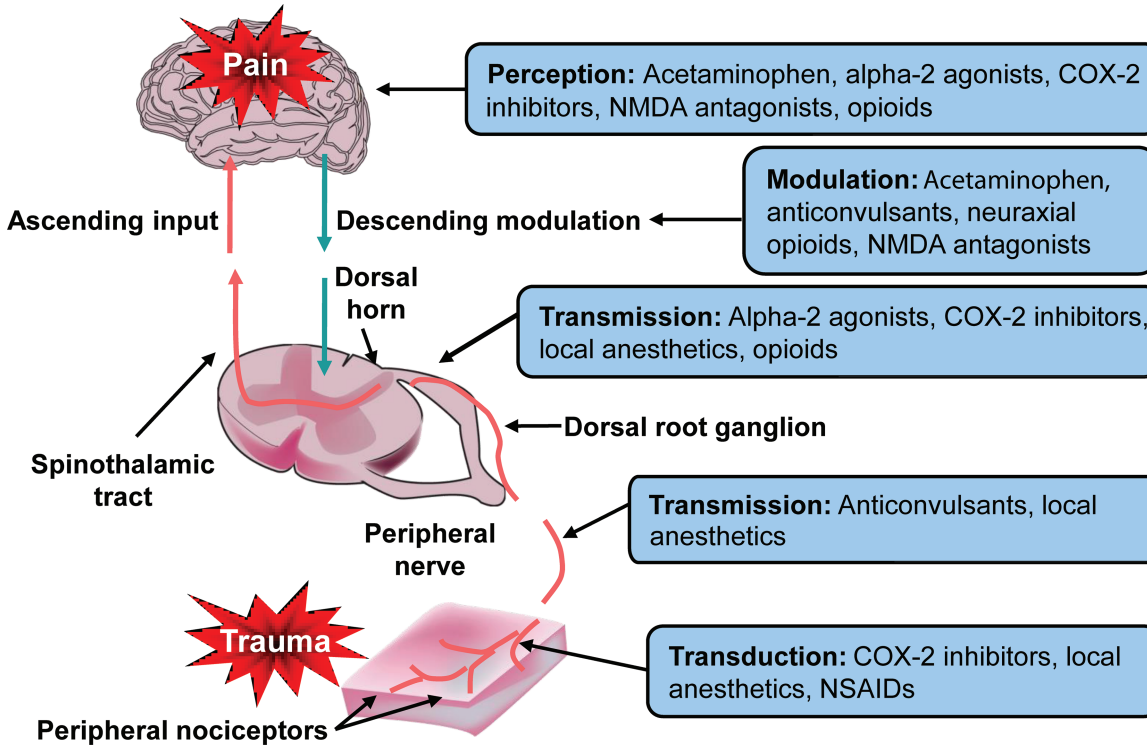

Figure 2. Diagram showing the location of action in the nervous system for analgesics used in multimodal therapy (De Kock & Lavand'homme, 2007; D'Mello & Dickenson, 2008; Gottschalk & Smith, 2001; Kehlet & Dahl, 1993; Ossipov, Dussor, & Porreca, 2010; Smith, 2009; Warner & Mitchell, 2004). COX-2 = cyclooxygenase-2; NMDA = *N*-methyl-D-aspartate; NSAID = nonsteroidal anti-inflammatory drug. From "The Value of 'Multimodal' or 'Balanced Analgesia' in Postoperative Pain Treatment," by H. Kehlet and J. B. Dahl, 1993, *Anesthesia and Analgesia,* Vol. 77(5), pp. 1048–1056. Copyright Wolters Kluwer Health. Adapted with permission.

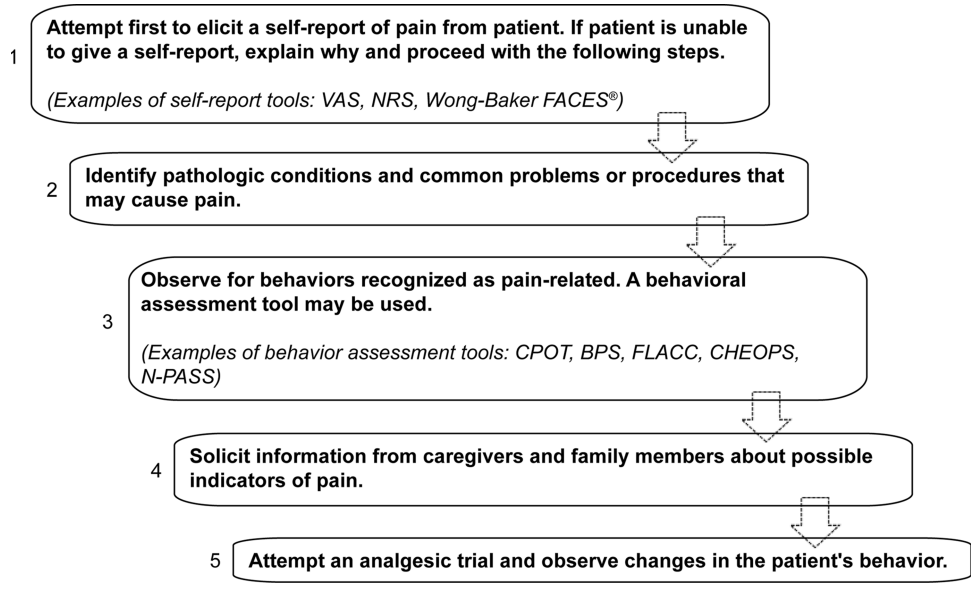

Figure 3. Hierarchy of pain assessment techniques, including assessment tools discussed in this review within the relevant steps. BPS = Behavioral Pain Scale; CHEOPS = Children's Hospital of Eastern Ontario Pain Scale; CPOT = Critical-Care Pain Observation Tool; FLACC = Face, Legs, Arms, Cry, and Consolability; N-PASS = Neonatal Pain, Agitation, and Sedation Scale; NRS = numeric rating scale; VAS = visual analog scale. From *Pain Assessment and Pharmacologic Management* by C. Pasero and M. McCaffery, Eds., 2011, St. Louis, MO: Elsevier. Copyright Elsevier. Adapted with permission.

identifying the most appropriate and effective treatments for the type of pain, such as somatic, visceral, and neuropathic (Vadivelu, Urman, Hines, & Kunnumpurath, 2011). In the trauma patient, somatic pain is typically the result of a fracture or a muscular injury that is well localized and described as aching, sharp, or stabbing. Deep injuries of the liver, pancreas, or bowel are examples of trauma that causes visceral pain, which is more diffuse than somatic pain and is typically described as a pressure, cramping, aching, or sharp pain. Neuropathic pain, often the most difficult to treat, can result from injury to nerves; this type of pain is classically described as burning, tingling, electric, or lancinating.

Communication between health care providers and patients is important to establish positive relationships and rapport and may reduce patient anxiety, support patients' sense of security, increase patient satisfaction, and enhance treatment efficacy. Discussing realistic expectations for pain management enables patients to participate in treatment decisions and improves the likelihood of satisfaction with the plan of care (Georgy, Carr, & Breen, 2011). Focusing on the patient's ability to meet functional goals instead of reaching an arbitrary pain rating score reinforces the concept of having realistic expectations. Nonjudgmental communications (especially if alcohol or drug abuse was implicated in the injury) and advocating for multimodal analgesia that targets the source of the pain can improve nurse-patient relationships and patient care.

To mitigate risks of opioid abuse and dependency, assessing patients for risk of opioid abuse with a screening tool, reducing the dose as the pain abates, and educating patients that opioids will be administered for a limited period are suggested (Macintyre, Huxtable, Flint, & Dobbin, 2014). Appropriate weaning from opioids (Chou et al., 2016; Washington State Agency Medical Directors' Group, 2015) could prevent withdrawal symptoms and therefore misuse, because patients may administer opioids to prevent the experience of withdrawal when pain is no longer present. Discussions of patient expectations and assessing the risk of opioid abuse have the potential to improve patient satisfaction and safe care (Browne, Andrews, Schug, & Wood, 2011; Georgy et al., 2011; Macintyre et al., 2014).

METHODS

A PubMed literature search was performed on September 3, 2015. To obtain studies in trauma populations, the following search terms were included: *trauma*, *injury*, *fracture*, *combat trauma*, and *amputation*. To focus on end points of interest, the search terms *analgesic effect*, *pain management*, *safety*, and *opioid-sparing* were also used. Studies on specific interventions requested by the authors were obtained through inclusion of the following search terms: *intravenous acetaminophen*, *oral acetaminophen*, *oral NSAID*, *topical NSAID*, *topical local anesthetic*, *gabapentin*, *pregabalin*, *amitriptyline*, *ketamine*, *regional techniques*, *nonpharmacological*, *distraction techniques*, *relaxation techniques*, *touch therapy*, *cognitive behavioral therapy*, *acupuncture*, *massage*, *biofeedback*, *cryotherapy*, and *TENS*. To focus on high-quality data and evidence-based recommendations, the search terms *clinical trial*, *prospective study*, *review of utilization*, and *guideline* were included.

The following terms were excluded to omit articles outside the scope of this review: *survival*, *death*, *chronic*, *cancer*, *stroke*, *case*, and *feasibility study*. Articles from the initial literature search were required to be published in the last 5 years (September 5, 2010, to September 3, 2015), be in English, and have human subjects. In total, 166 citations were obtained through the literature search; 58 additional citations were included at the discretion of the authors (Table, Supplemental Digital Content 1 [available at: http://links.lww.com/JTN/A0], which shows additional citations). The additional citations were not required to adhere to the restrictions of the original literature search (e.g., articles could be published >5 years ago) to address gaps and allow for inclusion of older landmark studies. After the citations were filtered for appropriateness of topic, 91 remained (Figure 4). To indicate the scientific rigor and possible biases in each study, the brief summaries in the Results section specify whether blinding was part of the study design. Uncited recommendations and observations are expert opinions of the authors.

RESULTS

Overview

The following sections summarize data on pharmacologic and nonpharmacologic options for opioid-sparing and multimodal treatment of trauma pain. Extensive discussion of systemic opioids is beyond the scope of this article because it focuses on strategies to move beyond overreliance on these agents, which have been the mainstay of treatment. In addition, a detailed analysis of opioids in the trauma environment was deemed redundant with previous reviews (Dijkstra, Berben, van Dongen, & Schoonhoven, 2014; Gausche-Hill et al., 2014). The summarized studies primarily focus on the acute treatment of trauma pain, though data from the postsurgical environment are sometimes included because opioid-sparing and multimodal therapy have demonstrated efficacy in this clinical setting (Laskowski, Stirling, McKay, & Lim, 2011; Melemeni, Staikou, & Fassoulaki, 2007) and trauma patients may require surgery. It should be noted that the search terms *amitriptyline*, *massage*, *biofeedback*, *transcutaneous electrical nerve stimulation (TENS)*, and *touch therapy* did not return any relevant recent studies. As such, these techniques are not reviewed. A summary of key advantages and disadvantages of each type of therapy discussed is included in Table 1.

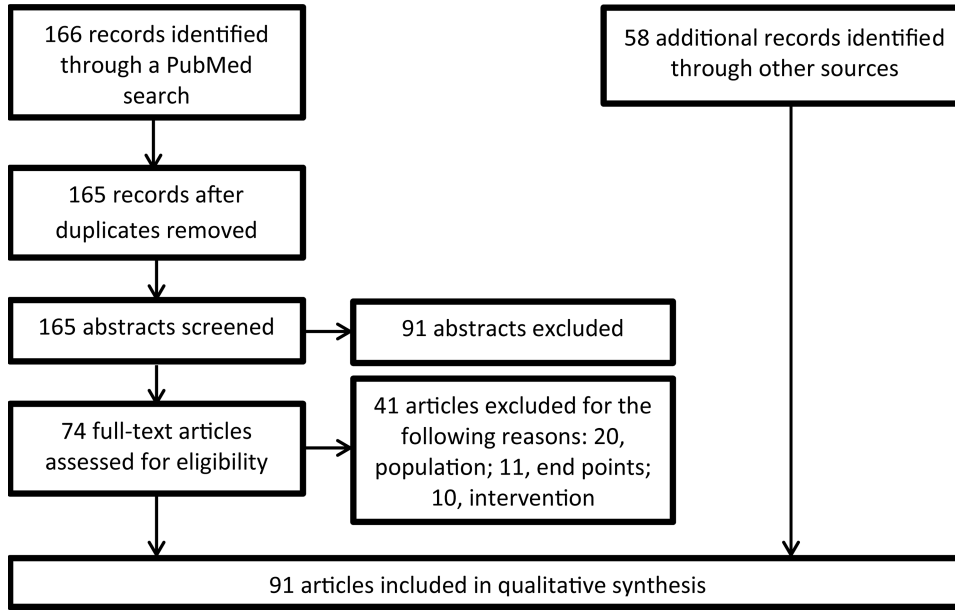

Figure 4. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the literature search process for obtaining articles on medications and techniques for pain relief.

TABLE 1 Summary of the Key Advantages and Disadvantages Associated With Each Type of Analgesic Discussed in the Review

Analgesic Type	Key Clinical Advantages	Key Clinical Disadvantages
Acetaminophen	Long history of safety and efficacy in oral and IV routes; IV route may be opioid sparing and have faster onset of action and less hepatotoxicity than oral route	Can be hepatotoxic at high doses or in at-risk populations
NSAIDs	Effective across multiple routes (e.g., oral, IM, IV)	Nonsystemic administration is associated with local AEs
Topical local anesthetics	May be locally effective for neuropathic pain associated with trauma	Several studies did not show significant pain relief for various types of trauma pain
Gabapentinoids	Some evidence for efficacy for neuropathic pain associated with trauma; opioid sparing	Not all studies support efficacy for trauma pain
Muscle relaxants	Can reduce painful muscle spasms	Caution is warranted because of AEs such as dizziness and drowsiness
Alpha-2 adrenergic agonists	Sedative and anxiolytic properties; opioid sparing	Should be used with caution in hemodynamically unstable patients
Ketamine	May decrease incidence of pain hypersensitivity and opioid tolerance; opioid sparing	Requires provider training and patient monitoring
Regional techniques	A variety of effective techniques are available to target pain at various locations; opioid sparing	Require provider training; caution should be exercised if the patient is receiving anticoagulation therapy
Nonpharmacologic options	May be safe and simple to implement; opioid sparing	Are considered complementary to and not a substitute for analgesics; studies supporting their efficacy are typically not double-blind

Abbreviations: AE, adverse event; IM, intramuscular; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug.

Standard Oral and Intravenous Medications

Oral Acetaminophen

Oral acetaminophen has a long history as an analgesic, and its mechanism of action involves the inhibition of prostaglandin synthesis (Oyler et al., 2015). A study of osteoarticular injuries in the ED showed significantly improved pain intensity with oral acetaminophen over time (Viallon et al., 2007). At doses higher than 4,000 mg/day, the limit set by the U.S. Food and Drug Administration, acetaminophen is associated with hepatotoxicity (U.S. Food and Drug Administration, 2011). In patients with compromised liver function, including many elderly patients and those abusing alcohol, the use of any level of acetaminophen requires caution (Oyler et al., 2015). Because an estimated 16.4% of injuries in EDs are attributable to alcohol, the safety risk of acetaminophen products related to alcohol should be considered when creating an analgesic plan (Cherpitel et al., 2015).

Intravenous Acetaminophen

The mechanism of action of oral and intravenous (IV) acetaminophen is the same (Oyler et al., 2015). Although IV acetaminophen was approved in the United States in 2010, it has a longer history of efficacy and safety because of its availability in Europe since 2002 (Viscusi, Singla, Gonzalez, Saad, & Stepanian, 2012). Pain relief with IV acetaminophen was similar to that with IV morphine in a double-blind study of traumatic limb pain (Craig, Jeavons, Probert, & Benger, 2012). Comparable pain scores for IV acetaminophen plus oral oxycodone versus IV morphine were also observed in a double-blind trial in patients with acute bone fracture (Zare et al., 2014). In a pharmacokinetics study, IV acetaminophen achieved earlier and higher peak plasma levels than an equivalent dose of oral acetaminophen, which may contribute to faster pain relief (Singla et al., 2012). According to analyses of a pharmacokinetic first-pass model, IV acetaminophen results in one-half of the peak hepatic concentration of the oral formulation (Royal, Gosselin, Pan, Mouksassi, & Breitmeyer, 2010). This suggests that IV acetaminophen may carry a reduced risk of hepatotoxicity compared with oral acetaminophen (Royal et al., 2010). No evidence of hepatotoxicity was observed with IV acetaminophen after administration of 5 g across 24 hr, a higher dosage than recommended (Gregoire et al., 2007).

A guideline on the treatment of patients in medical, surgical, and trauma intensive care units (ICUs) recommends IV acetaminophen, among other analgesics, as an adjunctive pain medication to reduce opioid requirements (Barr et al., 2013). A study of patients with hip fracture showed that less IV morphine was required for breakthrough pain in the group that received scheduled IV acetaminophen with as-needed oral opioids than in the control group that received oral acetaminophen plus scheduled oral opioids (Tsang, Page, & Mackenney, 2013). In summary, data suggest that IV acetaminophen effectively relieves pain, may have a faster onset of action than oral acetaminophen, is theoretically less hepatotoxic than oral acetaminophen, and is opioid-sparing; these properties may be advantageous in trauma populations, including military patients with combat-related injuries (Vokoun, 2015). Overall, acetaminophen is considered an effective analgesic that can be included in a multimodal analgesic plan when contraindications and safety issues are considered (Barr et al., 2013; Oyler et al., 2015).

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) produce their opioid-sparing analgesic effects through inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) (Oyler et al., 2015) and have been recommended as adjunctive analgesics in the ICU (Barr et al., 2013). Oral ibuprofen demonstrated similar efficacy as orally administered morphine in a double-blind trial of children with fractures (Poonai et al., 2014). Oral ibuprofen has also shown analgesic efficacy similar to that of acetaminophen, and no difference in efficacy was observed for the combination of NSAID plus acetaminophen versus either alone in a double-blind trial of adult ED patients with acute musculoskeletal pain (Bondarsky et al., 2013). However, a systematic review suggests that the combination of acetaminophen and an NSAID may improve analgesia versus each drug alone (Ong, Seymour, Lirk, & Merry, 2010). The effect of NSAIDs on bone healing is controversial (Dodwell et al., 2010; Pountos, Georgouli, Calori, & Giannoudis, 2012), but a meta-analysis showed no increased risk of failed bone healing (nonunion) for oral, IV, and intramuscular NSAIDs (Dodwell et al., 2010).

Various routes for NSAIDs may have different advantages, limitations, and effects. Intramuscular formulations may be appropriate for patients who are unable to receive oral medications and do not yet have IV access. Intravenous administration is believed to provide the fastest relief, but additional study is needed (Tramèr et al., 1998). Regarding safety, local AEs such as site dermatologic reactions have been most commonly reported with topical, intramuscular, and rectal administration (Kuehl, Carr, Yanchick, Magelli, & Rovati, 2011; Tramèr et al., 1998). Systemic NSAIDs can cause gastrointestinal bleeding and renal issues, but serious events are rare with short-term use for trauma pain (Jones & Lamdin, 2010). Cyclooxygenase-2 selective inhibitors (e.g., celecoxib, meloxicam) are associated with an even lower risk of gastrointestinal AEs than other NSAIDs (Jones & Lamdin, 2010). In addition, COX-2 selective inhibitors showed minimal effects on platelet function in a physician-blinded study (Graff et al., 2007), which suggests a reduced risk of bleeding with

these drugs. Nonsteroidal anti-inflammatory drugs have proven efficacy, are opioid sparing, and are versatile analgesics because of their multiple routes of administration.

Topical Local Anesthetics

Topical local anesthetics (e.g., lidocaine, tetracaine) are hypothesized to block local pain signals (Desai et al., 2014; Gimbel, Linn, Hale, & Nicholson, 2005). Evidence suggests that topical application is at least as effective as injection of local anesthesia in patients with lacerations (Jenkins, Murphy, Little, McDonald, & McCarron, 2014). A lidocaine emulsion formulation and an aqueous solution were equally effective at reducing pain during dressing changes in a double-blind trial of burn patients (Desai et al., 2014). Lidocaine patches and plaster have shown efficacy for low back pain (Gimbel et al., 2005) and neuropathic pain related to disk herniation (Likar, Kager, Obmann, Pipam, & Sittl, 2012). Topical lidocaine did not show efficacy for pain associated with traumatic rib fracture (Ingalls, Horton, Bettendorf, Frye, & Rodriguez, 2010), and topical tetracaine did not significantly reduce pain associated with corneal abrasions (Waldman, Densie, & Herbison, 2014); both studies with negative results were double-blind. The rib fracture study may have been underpowered (Fabricant, Ham, Mullins, & Mayberry, 2013), and a more recent trial showed efficacy of the lidocaine patch in patients with rib fractures (Zink, Mayberry, Peck, & Schreiber, 2011). Thus, topical anesthetics can be effective in trauma pain.

Gabapentinoids

Gabapentinoids are anticonvulsants that modulate sodium and calcium channels (Guy, Mehta, Leff, Teasell, & Loh, 2014) and are used to treat acute and chronic neuropathic pain. These medications are recommended as adjunctive analgesics by ICU guidelines (Barr et al., 2013). According to a systematic review, oral gabapentin and pregabalin successfully relieve chronic neuropathic pain after spinal cord injury (Guy et al., 2014). Furthermore, in a pooled analysis of two double-blind trials, pregabalin was associated with superior pain reduction versus placebo in patients with chronic neuropathic pain related to spinal cord injury (Parsons, Sanin, Yang, Emir, & Juhn, 2013). Gabapentin and pregabalin led to decreased pain versus placebo in two double-blind studies of patients with burns (Gray et al., 2011; Rimaz et al., 2012). In addition to analgesic effects, data in the postoperative setting from reviews and a meta-analysis strongly demonstrate the opioid-sparing effects of gabapentin and pregabalin (Gilron, 2007; Melemeni et al., 2007; Zhang, Ho, & Wang, 2011).

Gabapentinoids have not shown analgesic efficacy in all studies, including two double-blind trials (Pfizer, 2015a; Wibbenmeyer et al., 2014). Although the U.S. Department of Veterans Affairs and the U.S. Department of Defense (2007) recommend gabapentin and pregabalin as options for the treatment of neuropathic pain associated with amputation, gabapentin did not significantly reduce postamputation pain in a double-blind study (Nikolajsen et al., 2006).

Gabapentin and pregabalin vary in their pharmacokinetic properties and therapeutic effects. Pregabalin is absorbed more quickly than gabapentin (Gilron, 2007), and patients may experience improved neuropathic pain relief when switching from gabapentin to pregabalin (Toth, 2010). Transitions between the two drugs should be gradual across 7 or more days because of potential withdrawal symptoms (Pfizer, 2015b, 2016). Gabapentin and pregabalin may be appropriate for neuropathic pain associated with trauma, and the choice of gabapentinoid varies on the basis of patient characteristics and goals.

Muscle Relaxants

Muscle relaxants are a broad category of drugs, but many (e.g., tizanidine, cyclobenzaprine) act to reduce painful muscle spasms (van Tulder, Touray, Furlan, Solway, & Bouter, 2003). Muscle relaxants effectively relieve nonspecific low back pain, including that from injuries (van Tulder et al., 2003). High-quality evidence suggests that tizanidine plus analgesics is more effective at pain relief than placebo plus analgesics in patients with acute low back pain (van Tulder et al., 2003). However, a double-blind trial did not show benefit for routinely adding cyclobenzaprine to NSAIDs in ED patients with acute cervical strain (Khwaja, Minnerop, & Singer, 2010). Muscle relaxants are effective analgesics, but caution is advised because of the associated AEs of dizziness and drowsiness (van Tulder et al., 2003).

Alpha-2 Adrenergic Agonists

The alpha-2 adrenergic agonist activity of clonidine and dexmedetomidine contributes to their opioid-sparing analgesia as well as their sedative and anxiolytic effects, which may be achieved without respiratory depression (Bernard, Hommeril, Passuti, & Pinaud, 1991; Keating, 2015; Oyler et al., 2015; Panzer, Moitra, & Sladen, 2011). In a double-blind study of spine surgery patients, both low-dose ketamine and dexmedetomidine infusions provided good analgesia and decreased rescue opioid use compared with saline (Garg et al., 2016). However, oral dexmedetomidine is not as strong an analgesic as oral ketamine according to a double-blind study of patients undergoing burn wound dressing changes (Kundra, Velayudhan, Krishnamachari, & Gupta, 2013). Clonidine, which is available for multiple routes of administration including oral, has long been used to treat hypertension and may be an opioid-sparing addition to multimodal analgesia (Oyler et al., 2015). A review highlighted sedative and opioid-sparing analgesic properties of oral clonidine that support its use in critically ill military patients

with trauma as well as in civilian patients with trauma (Malchow & Black, 2008). Alpha-2 adrenergic agonists may cause hypotension and bradycardia and therefore should be used with caution in hemodynamically unstable patients (Keating, 2015; Oyler et al., 2015). Because of these AEs, clonidine and dexmedetomidine require increased monitoring and should be administered only by experienced providers. Alpha-2 adrenergic agonists may also reduce hyperadrenergic states and provide comfort for patients experiencing opioid withdrawal (Gowing, Farrell, Ali, & White, 2014; Panzer et al., 2011).

Techniques Requiring Additional Support

Ketamine

Ketamine inhibits neuropathic and nociceptive pain signaling and promotes anesthesia (at higher doses) by binding to the *N*-methyl-D-aspartate receptor (Arendt-Nielsen et al., 1995; Jennings, Cameron, & Bernard, 2011; Oyler et al., 2015). The drug may decrease pain hypersensitivity and windup pain (i.e., the continuation of pain sensation despite the absence of a stimulus) (Kundra et al., 2013) as well as opioid tolerance (Subramaniam, Subramaniam, & Steinbrook, 2004) and so might be particularly appropriate for patients with long-term opioid use (Goltser, Soleyman-Zomalan, Kresch, & Motov, 2015).

According to reviews, IV ketamine can be safe and effective in the prehospital setting for patients presenting with pain from causes including bone fractures (Jennings et al., 2011), for burn patients (McGuinness et al., 2011), and for analgesia during intubation of patients with acute head injury (Sih, Campbell, Tallon, Magee, & Zed, 2011). Data from two trials, one of which was double-blind, showed similar trauma pain relief for ketamine and morphine (Miller, Schauer, Ganem, & Bebarta, 2015; Tran et al., 2014). A meta-analysis demonstrated that ketamine reduced the amount of opioid used versus placebo after surgery (Laskowski et al., 2011), and an open-label study showed superior analgesia for out-of-hospital trauma pain when IV ketamine was added to IV morphine therapy compared with IV morphine therapy alone (Jennings et al., 2012). In addition, a double-blind study demonstrated a benefit of oral ketamine and midazolam versus oral acetaminophen, midazolam, plus codeine in pediatric burn patients (Norambuena et al., 2013).

Ketamine requires monitoring and nursing support to address potential postdose agitation and hallucinations as well as elevations in heart rate and blood pressure (Miller et al., 2015; Polomano et al., 2013; Tran et al., 2014), and administration is best performed by providers familiar with its use. In summary, ketamine can play an important role in multimodal therapy if the required medical and nursing support is available.

Regional Techniques

The application of local anesthetics (e.g., for multiple types of nerve blocks) or a low dose of an opioid (e.g., for epidurals or spinals) near the nerves that transmit a pain signal can be a well-tolerated and effective method of pain control that limits doses of systemic opioids (Choi, Lin, & Gadsden, 2013; Oyler et al., 2015) and is recommended by ICU guidelines (Barr et al., 2013).

Nerve blocks placed near the brachial plexus can provide analgesia for the upper extremity and shoulder, whereas epidurals and transversus abdominis plane (TAP) blocks have been shown to provide effective analgesia after abdominal procedures (Argoff, 2014; Oyler et al., 2015). For patients with traumatic rib fractures, a thoracic epidural is suggested (Barr et al., 2013). If an epidural is contraindicated (e.g., because of infection, coagulopathy, or hemodynamic instability), a paravertebral block may be a similarly effective alternative (Chelly, 2012; Mohta, Ophrii, Sethi, Agarwal, & Jain, 2013; Winters, 2009). Paravertebral blocks have been associated with fewer AEs such as hypotension and respiratory depression than epidurals (Chelly, 2012). Intercostal blocks also have effectively relieved pain after rib fracture (De Cosmo, Aceto, Gualtieri, & Congedo, 2009), and continuous infusion intercostal blocks have been shown to reduce hospitalization time versus continuous epidural infusion (Britt, Sturm, Ricardi, & Labond, 2015).

Nerve blocks placed along the femoral and sciatic nerve distribution can reduce pain in the lower extremities (Oyler et al., 2015). Patients with hip fractures may benefit from femoral nerve blocks, as evidenced by a trial showing reduced pain intensity for ultrasound-guided 3-in-1 femoral nerve blocks in addition to IV morphine versus IV morphine plus placebo (Beaudoin, Haran, & Liebmann, 2013). Fascia iliaca blocks are a type of nerve block for femoral injuries that can be easily performed by emergency medical service personnel (McRae, Bendall, Madigan, & Middleton, 2015; Slagt & van Geffen, 2015). Prehospital patients randomized to a fascia iliaca block achieved greater pain relief than those randomized to IV morphine only (McRae et al., 2015). In a double-blind study of hip fractures in an ED, similar long-term efficacy (up to 8 hr) was achieved for a fascia iliaca block versus an IV NSAID injection (Godoy Monzón, Vazquez, Jauregui, & Iserson, 2010).

Interventional techniques are important additions to multimodal analgesia, but caution must be used with neuraxial procedures in the setting of anticoagulation because of bleeding risk (Choi et al., 2013; Oyler et al., 2015). Use of regional blocks for extremity fractures in patients at risk for compartment syndrome is controversial because of the potential masking of signs associated with this condition; however, there is no definitive correlation between the use of peripheral nerve blocks and

delay in the diagnosis of compartment syndrome (Choi et al., 2013). In summary, various effective regional techniques are available for multiple locations of pain. The placement and management of regional blocks/catheters require the expertise of trained professionals who may not be available at all institutions.

Nonpharmacologic Options

Overview

Nonpharmacologic approaches may complement drug therapy as part of a multimodal plan to relieve pain (Barr et al., 2013). These approaches tend to be easy to implement and relatively safe (Barr et al., 2013). Nonpharmacologic approaches also assist patients in feeling more involved in their pain management. Many of the studies described below demonstrate the efficacy of nonpharmacologic approaches, but as a caveat, none were double-blind. One rationale for lack of blinding is that appropriate controls such as placebos or sham treatments have not yet been developed for these therapies.

Cryotherapy

Ice packs are used to reduce swelling/edema and associated pain in a variety of trauma injuries (Berben et al., 2011; Rana et al., 2013). Circulating cold water therapy reduced postoperative fracture pain more than conventional cooling (Rana et al., 2013), and a cold pressure system reduced opioid consumption versus epidural after knee arthroplasty (Holmström & Härdin, 2005). In summary, cryotherapy is a widely accepted adjunctive treatment for trauma injuries.

Distraction Techniques

Distraction techniques (e.g., movies, virtual reality) focus patient attention and limit the nervous system's ability to process pain stimuli (Jeffs et al., 2014). These techniques have been shown to effectively relieve pain in adults (Drahota et al., 2012), and other studies have focused on their efficacy in children and adolescents. Trials during laceration repair for children in the ED (Ha & Kim, 2013) and during physical therapy for children and adolescent burn patients (Schmitt et al., 2011) showed improved pain relief with distraction versus no distraction. Sophisticated multimodal distraction (e.g., educational device, virtual reality) decreased pain intensity relative to standard distraction (e.g., television, videos, stories, toys, soothing) in studies of children or adolescents with burns (Brown, Kimble, Rodger, Ware, & Cuttle, 2014; Jeffs et al., 2014; Kipping, Rodger, Miller, & Kimble, 2012; Miller, Rodger, Kipping, & Kimble, 2011). An abundance of evidence supports the use of distraction techniques for reducing pain and potentially reducing the need for anxiolytics and opioids, particularly after burns (Drahota et al., 2012; Jeffs et al., 2014).

Breathing and Relaxation

Relaxation techniques such as breathing exercises can be effective at decreasing pain and reducing reliance on opioids (Barr et al., 2013; Wong, Chan, & Chair, 2010). A study of patients with bone fractures showed greater pain reduction for the yogic prana energization technique (involving controlled breathing, chanting, and visualization) versus control (Oswal, Nagarathna, Ebnezar, & Nagendra, 2011). Another study demonstrated decreased pain with activity for a mind-body skills–based intervention plus standard of care versus only standard of care (Vranceanu et al., 2015). In a trial of patients with musculoskeletal trauma, an educational intervention involving training on breathing relaxation decreased pain levels more than usual care involving no educational intervention (Wong et al., 2010). Relaxation techniques are simple and effective nonpharmacologic options to complement pharmacologics.

Acupuncture

Acupuncture is hypothesized to provide analgesia via central mechanisms by stimulating high-threshold, small-diameter nerves that modulate endogenous opioid pathways (Wong, Cheuk, Lee, & Chu, 2013). However, a systematic review concluded that the efficacy and safety of acupuncture (including scalp, body, auricular, tongue, injection, and electroacupuncture) for traumatic brain injury are not strongly supported on the basis of the quality of the studies identified (Wong et al., 2013). Variations of the technique may be appropriate for rib fractures; in one trial, pain relief was more effective with filiform needles than with thumbtack intradermal needles during deep breathing, coughing, and turning (Ho et al., 2014). Acupuncture is a nonpharmacologic technique with a long history of use to relieve pain, requires specialized practitioners, and has limited recent evidence of its efficacy.

DISCUSSION

Trauma-related injuries are commonly associated with pain and are often treated with opioids as first-line therapy. Because of the safety concerns associated with opioids, particularly those relating to respiratory depression and misuse and abuse with long-term use, there is a need for opioid-sparing, multimodal therapy for trauma pain. In multimodal analgesia, opioid and nonopioid medications are administered to achieve the safest, most effective pain therapy with additive and synergistic effects; opioid-sparing strategies minimize the dose of opioids administered to reduce safety concerns. This review summarizes results from a literature search of various pharmacologic and nonpharmacologic options for use in opioid-sparing, multimodal trauma pain management. The literature search

was limited to the last 5 years, though older articles were included at the authors' discretion; the information and recommendations are not meant to be exhaustive. The review focuses primarily on pain management during hospitalization, with a plan for appropriate weaning or tapering of analgesics at discharge, after which the analgesic regimen will be managed by the primary care physician or surgical team.

Many pharmacologics reviewed have broad indications for the treatment of pain, but several drugs have more limited indications. To disclose potential off-label discussions in this review, meloxicam is indicated for types of arthritis but not pain in general (Boehringer Ingelheim, 2012), gabapentin for postherpetic neuralgia but not other neuropathic pain (Pfizer, 2015b), pregabalin for spinal injuries but not other sources of trauma (Pfizer, 2016), clonidine for hypertension but not pain or opioid withdrawal (Boehringer Ingelheim, 2011), dexmedetomidine for sedation but not pain (HQ Specialty Pharma, 2015), ketamine for burn dressing changes but not other trauma applications (JHP Pharmaceuticals, 2012), and opioid epidural for postsurgical pain but not broader trauma indications (EKR Therapeutics, 2008).

On the basis of its long history of efficacy and safety (Oyler et al., 2015; Viscusi et al., 2012), acetaminophen may be considered a first-line analgesic in trauma patients. Pharmacokinetic data imply a more rapid onset of action as well as a potentially decreased risk of hepatotoxicity for IV acetaminophen versus the oral route, though the clinical relevance of this difference has yet to be clearly established. Available data and clinical experience support the use of the drug for initial trauma pain. Nonsteroidal anti-inflammatory drugs are also first-line agents for trauma pain with demonstrated efficacy across multiple routes of administration (e.g., oral, intramuscular, IV). The relationship between NSAIDs and bone healing is controversial; therefore, the lowest effective dose of NSAIDs should be administered for the shortest amount of time in patients with fractures. Intravenous acetaminophen and NSAIDs may be especially useful for patients who are nauseated or unable to receive medication by mouth (e.g., in the perioperative period or ICU setting), though these are not the only trauma patients likely to benefit from nonoral routes.

Beyond acetaminophen and NSAIDs, additional nonopioids are important options for trauma pain management. Topical local anesthetics are effective for targeted pain relief, especially for neuropathic pain associated with trauma. Gabapentinoids should be considered for opioid-sparing therapy to treat neuropathic and postoperative pain. Muscle relaxants are used to reduce pain associated with muscle spasms, and alpha-2 adrenergic agonists are opioid-sparing analgesics that also have sedative and anxiolytic properties. Institutions with personnel trained to administer ketamine and regional techniques (e.g., epidural; paravertebral, femoral nerve, and fascia iliaca blocks) can also utilize these effective interventions to reduce the need for systemic opioids.

Nonpharmacologic options complement drug therapy to achieve the most comprehensive multimodal analgesia. Cryotherapy, distraction techniques, breathing and relaxation, and acupuncture may be appropriate as safe adjunctive therapy for pain associated with many traumas. Further studies are needed on methods for safely and effectively combining pharmacologic and nonpharmacologic analgesics in multimodal therapy.

Patients who are receiving long-term opioid therapy for chronic pain may particularly benefit from multimodal therapy. Guidelines on postoperative pain management (Chou et al., 2016) suggest that providers conduct a preoperative evaluation to document opioid use, provide education regarding opioids before surgery, and recognize that postoperative pain may be challenging to treat and may require increased doses of pain medications in patients who receive long-term opioid therapy. To achieve sufficient analgesia in postoperative patients with chronic pain, these guidelines propose considering the following measures: consultation with a pain specialist (and perhaps a behavioral/addiction specialist) for complex cases, nonopioid systemic medications, nonpharmacologic interventions, local anesthetic–based analgesic techniques, and patient-controlled analgesia. Instructions on tapering opioids after discharge are recommended. As a caveat, these guidelines were developed for postoperative pain instead of trauma pain, but the authors believe that the principles may also apply to the trauma setting.

If one multimodal treatment plan does not effectively relieve pain, another may be warranted. As drivers of patient assessment and intervention, nurses are in a unique position to advocate for appropriate analgesia as a patient's needs change over time. The authors also encourage nurses to involve patients in treatment decisions and manage patient expectations to enhance satisfaction. Nurses who stay informed of current pain management strategies and are aware of evidence and resources that support multimodal treatment options are best prepared to provide effective patient care. Nurses can educate staff and patients who may be unaware of the benefits attributable to opioid-sparing multimodal therapy, such as reducing the side effects of opioids (e.g., sedation, nausea, constipation) as well as mitigating the risks of opioid abuse and dependence. Nurses are encouraged to initiate, participate in, and share results from quality improvement projects related to pain management strategies. The future of trauma pain management involves comprehensive, opioid-sparing, patient-focused analgesic strategies, with nurses playing a key role.

CONCLUSIONS

The management of trauma pain by multimodal and opioid-sparing therapy (i.e., including both opioids and

nonopioids) is increasingly supported by clinical studies and recommended by pain specialists. On the basis of a literature search of recent trauma studies and the authors' clinical experience, oral acetaminophen, IV acetaminophen, and NSAIDs appear to be safe and effective analgesics for trauma pain when contraindications are considered. Topical local anesthetics show limited evidence of efficacy. Gabapentinoids are appropriate to treat neuropathic pain associated with trauma, muscle relaxants can address painful spasms, and alpha-2 adrenergic agonists can be used to treat pain and opioid withdrawal. Ketamine and regional techniques should be considered in institutions that support their use. Nonpharmacologic techniques (e.g., cryotherapy, distraction techniques, breathing and relaxation, acupuncture) may also contribute to a comprehensive approach to trauma pain management. Reviewed data support the opioid-sparing properties of acetaminophen, NSAIDs, gabapentinoids, alpha-2 adrenergic agonists, ketamine, regional techniques, and nonpharmacologic techniques. Nurses play an important role in managing patient expectations as well as optimizing and individualizing pain management in trauma patients.

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KEY POINTS

- Traditionally, trauma pain management has relied heavily on opioids, which are associated with safety concerns. Therefore, emerging treatment strategies should minimize the dose of opioids and involve the administration of other analgesics to optimize safe and effective pain control.
- Medications that can be used to minimize the dose of opioids and enhance pain relief include acetaminophen, NSAIDs, anticonvulsants, muscle relaxants, and alpha-2 adrenergic agonists. Ketamine and regional techniques are also effective for pain management but require special education and training of physician and nursing staff as well as additional patient monitoring. Nonpharmacologic treatments that can be used with pain medications to improve pain relief include cryotherapy, distraction techniques, breathing and relaxation, and acupuncture.
- Nurses play critical roles in assessing patients' trauma pain, administering agents and techniques to relieve pain, monitoring for side effects/safety concerns, and researching improvements in pain management.

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