CHAPTER 3

Pain Management

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PERSPECTIVE

Pain-related complaints represent as many as 70% of presenting concerns for patients in the emergency department (ED) setting.[1-5] Uncontrolled pain should be considered a medical emergency. The estimated degree of pain experienced by a patient should play a role in the determination of a patient's overall acuity and urgency for therapy. Pain estimations, from both provider- and patient-derived scales, should be obtained and recorded for patients as frequently as any vital sign or patient indicator. Although pain can be present in a wide variety of physical and psychosocial situations, it is almost always present in the context of tissue injury. Pain can therefore be assumed to be present in patients with physically apparent disease or injury, even in those who cannot effectively communicate their condition. Important terms relating to analgesic practices are listed in Box 3-1.

A wide variety of options are available for the treatment of pain. Despite having effective treatments available for both acute and chronic pain therapy, the treatment of pain can be difficult and is often one of the most challenging and frustrating aspects of the practice of emergency medicine.[6-10]

Patients' perceptions of their ED care are highly influenced by pain treatment. Satisfaction with emergency care often depends on the techniques and timeliness of analgesia as well as the discharge plans for pain relief.[11,12] In every interaction with a patient in pain, a balance should be achieved between relief of patient suffering and the diagnosis and treatment of the underlying medical condition.

A growing body of evidence supports the importance of pain management as a central aspect of disease treatment. Unrelieved pain is associated with a variety of potentially negative physiologic outcomes, including increases in sympathetic outflow, peripheral vascular resistance, myocardial oxygen consumption, and the production of carbon dioxide (CO_2). Other adverse effects of unrelieved pain appear to include hypercoagulability, decreases in gastric motility, and immune function impairment.

Poorly treated acute pain can promote the development of chronic pain syndromes and vegetative symptoms, as well as increase the need for pain management during any recovery period.[13-20] Pain during serial medical procedures may increase if successful analgesia was not provided during initial procedures.[21] It is also likely that a patient's experience of pain increases the ability to perceive pain from similar stimuli in the future.[22]

As an affirmation of the recognized importance of pain management in health care, The Joint Commission (TJC) requires hospitals to develop quality improvement efforts related to acute pain management in addition to comprehensive programs for the measurement, documentation, and treatment of pain. Improvements in pain management are occurring as a result of an enhanced interest in pain research, education, and regulatory efforts.[23-28]

PATHOPHYSIOLOGY

Pain can be generally described as *nociceptive or neuropathic*. Nociceptive pain results from the activation of sensory neurons that signal pain (nociceptors) in response to noxious stimuli. Neuropathic pain results from signal processing changes in the central nervous system (CNS). Neuropathic pain is usually described as burning, tingling, or shooting sensations and includes neuropathies and deafferentation. Both nociceptive and neuropathic types of pain involve peripheral and central sensitization with a complex array of mediators to sensitize peripheral nociceptors and perpetuate thalamic signals, shown in Figure 3-1. At each level in the physiologic process of pain production or transmission, interventions and therapeutic opportunities should be considered to alter the process and ultimately improve the patient's pain experience.

Pain Conduction Pathways

Pain perception can be divided into four separate processes (see Fig. 3-1): pain detection (transduction), pain transmission, pain modulation, and pain expression (perception). The transduction of painful sensory input is initiated by the activation of nociceptors, with subsequent depolarization of their axons. The axons then relay information (afferent input) to their cell bodies located in the dorsal root ganglion, lateral to the spinal cord.[29] Central dendrites of these first-order neurons synapse in the dorsal horn, where sensory input is modulated. These sensory signals travel through the CNS spinothalamic tracts and posterior columns to synapse in the reticular system and the thalamus. Thalamic and reticular signals are then projected to the cerebral cortex (Fig. 3-2).

Pain Detection

The somatosensory system is responsible for the detection of pain as well as tactile, proprioceptive, and thermal sensations. Receptors responsible for the detection of pain are termed *nociceptors*. Nociceptors include sensory nerves that are capable of detecting mechanical, thermal, or chemical stimulation. Several different subtypes of nociceptors are present in cutaneous tissues, including mechanoreceptors, polymodal nociceptors (PMNs), and a variety of thermoreceptors.[29] Most nociceptive input is derived from inflammatory mediators through PMNs, in response to intense chemical, thermal, and mechanical stimuli.

The threshold of activation of a nociceptor can be modulated, increased or decreased, by a variety of chemical mediators including prostaglandin, cyclic adenosine monophosphate, leukotrienes,

Box 3-1 Definitions for Terms Related to Analgesia

Allodynia—pain from a stimulus that does not normally provoke pain
Amnestic—an agent the suppresses the formation of memories
Local anesthesia—an area of insensibility to pain created by the injection of a local anesthetic agent
Analgesia—relief from pain
Hypnotic—an agent that promotes the onset of sleep
Narcotic—a term with legal implications describing opioid agents together with various central nervous system depressant drugs of abuse
Nociceptor—a receptor that is sensitive to and responsible for transmitting pain stimuli
Noxious stimulus—a stimulus that is damaging or potentially damaging and results in sensation of pain
Opiate—a naturally occurring derivative of opium alkaloid that binds opiate receptors and produces effects similar to those of the endogenous endorphins
Opioid—a naturally occurring or semisynthetic derivative of opium alkaloid (includes all opiates) that binds opiate receptors and produces effects similar to those of the endogenous endorphins
Pain—an unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage
Procedural sedation—pharmacologic induction of a state of sedation or dissociation with amnesia for pain control during a painful procedure
Sedative—an agent that decreases a patient's level of awareness

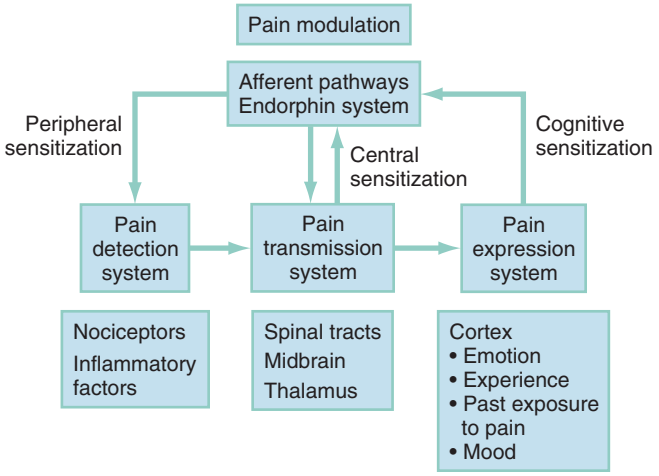

Figure 3-1. The pain system algorithm.

bradykinins, serotonin, substance P, thromboxanes, platelet-activating factor, and endorphins. This change in nociceptor activation thresholds is termed *peripheral sensitization.* Trigger points, for example, are areas of frequent or constant low-level sensory stimulation (e.g., scar tissue or a degenerative joint) that have developed peripheral sensitized nociceptors that perceive pain from otherwise innocuous stimuli.

Information Transmission

Peripheral Nerve Fibers

All sensory neurons are composed of a cell body located in the dorsal root ganglion. The dorsal root ganglia are connected by nerve axon fibers with sensory receptors located in a number of body sites, including dermatomes (cutaneous input), sclerotomes

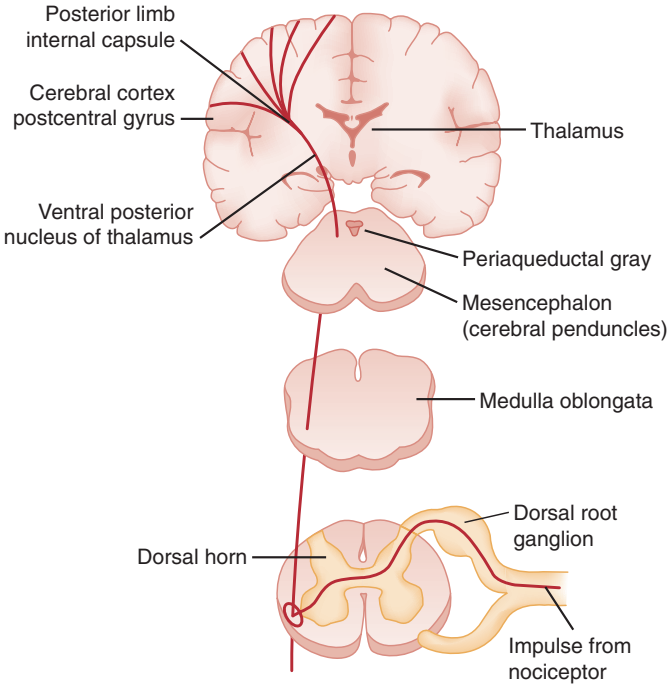

Figure 3-2. Spinal tracts.

(input from bones), and myotomes (input from muscle). The discrete areas covered by each nerve provide a sensory map of the body surface.

Peripheral nerve fibers can be classified by the roles of each fiber group (Table 3-1). A-δ and C fibers are responsible for the transmission of pain. A-δ fibers transmit sharp, initial pain. C fibers, in contrast, transmit dull, aching, or burning pain. The pain transmitted by A-δ fibers persists only as long as the initial stimulus is in effect, whereas C fiber pain persists longer than the initial stimuli, rendering a prolonged pain sensory experience.

The relative concentration of nerve fiber types, both C and A-δ, varies by body tissue. Muscles, for example, are high in C fiber concentration and create pain sensations that are aching and poorly localized in response to violent contractions, stretch, ischemia, or inflammation. Bones and joints, in contrast to muscle, possess afferents with thresholds sensitized by chemicals present during inflammation (accounting for the pain associated with arthritis). Bone periosteum has the lowest pain threshold of all deep tissues and is supplied by both A-δ and C fibers, whereas bone cortex and marrow have very few nociceptors.

Pain Transmission

Dorsal Horn

The dorsal horn is the gray matter of the posterior aspect of the spinal cord (Fig. 3-3). The dorsal horn acts as an integration system where sensory input is filtered, attenuated, or amplified before being relayed to other spinal segments or the cortex (Fig. 3-4).

The dorsal horn is a processing center for incoming information and is extensively involved in the modulation of nociceptive input. Afferents from visceral, muscle, bone, and cutaneous areas converge in the dorsal horn and likely account for the cutaneous allodynia associated with painful visceral, muscular, or bony stimuli.

Differentiation between innocuous stimuli and nociceptor input occurs in the dorsal horn by stimuli received in cells referred to as wide dynamic range neurons (WDRNs). WDRNs receive

Table 3-1 Peripheral Nerve Fibers

FIBER	FUNCTION	MYELIN	MEAN DIAMETER (μm)	ASCENDING TRACT	CONDUCTION VELOCITY (m/s)
A-α	Skeletal muscle motor	Deep	12-20	Ipsilateral dorsal column	70-120
A-β	Light touch and pressure	Superficial	5-15	Contralateral spinothalamic tract	30-70
A-γ	Motor	Superficial	6-8	Ipsilateral dorsal column	15-30
A-δ	Sharp pain (mechanoreceptors, thermoreceptors, PMNs)	Superficial	1-4	Contralateral spinothalamic tract	12-30
B	Sympathetic		1-3	Preganglionic	3-15
C	Long-lasting burning pain	Superficial	0.5-1.5	Contralateral spinothalamic tract	0.5-2

Adapted from Paris PM, Uram M, Ginsburg MJ: Physiological mechanisms of pain. In: Paris PM, Stewart RD, eds. Pain Management in Emergency Medicine. Norwalk, Conn: Appleton & Lange; 1988.
PMNs, polymodal nociceptors.

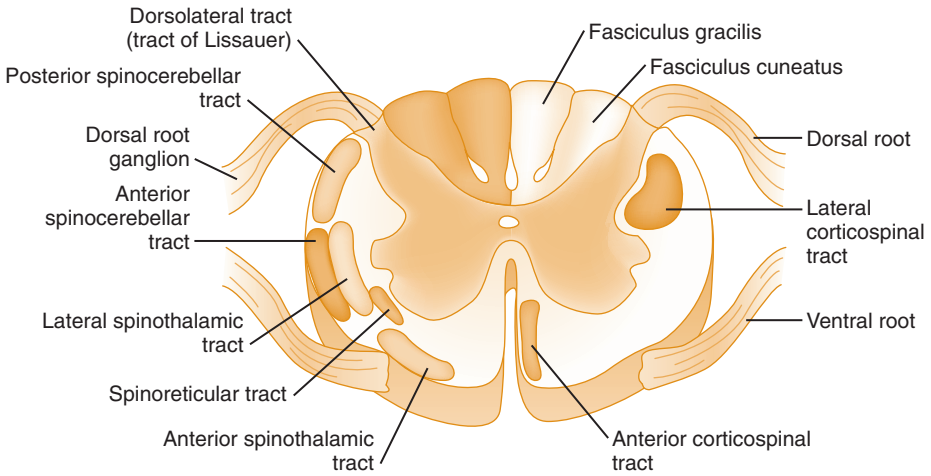

Figure 3-3. Spinal cord.

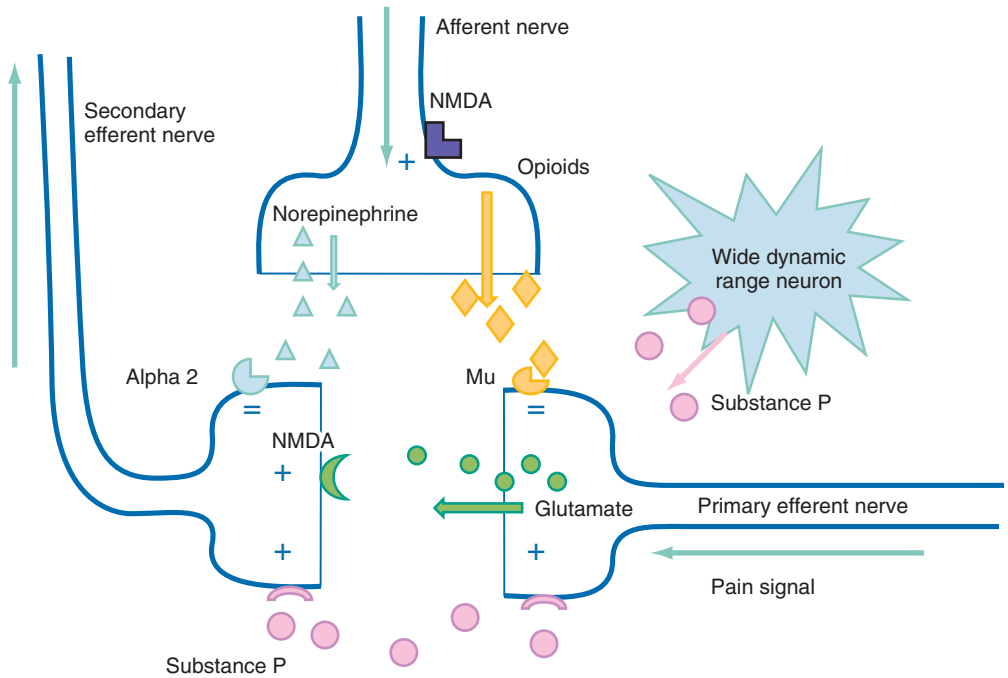

Figure 3-4. Neurotransmitters and receptors at the dorsal root ganglion. *Mu,* opioid receptor; *NMDA, N*-methyl-D-aspartate.

modulating input from a variety of chemical pathways, such as opioids, substance P, or inflammatory factors. These cells also receive modulating input from efferent and afferent neuronal pathways.

Visceral Pain

The quantity and type of stimuli that produce pain vary among visceral structures. The myocardium, for example, is sensitive to ischemia but not mechanical stimulation. Tissues in the intestine may be severed, crushed, or burned without pain; however, traction or distention produces pain sensations.

The quality of visceral pain is unique from that of somatic pain. Somatic pain is initially sharp and later becomes burning or throbbing in nature as the response is modulated. Visceral pain in contrast tends to start as poorly localized, dull, and aching, with pronounced autonomic activation relative to somatic pain. These sensations may then develop into sharp, localized, referred pain. This progression is likely a result of the varying ratios of A to C fibers, which are 1 : 10 in visceral nerves and 1 : 2 in cutaneous nerves.

Visceral pain often produces referred pain. For example, periumbilical pain is often associated with appendicitis. This referred pain sensation occurs because of visceral afferents supplying the small bowel and traveling through the celiac ganglia and splanchnic nerves to enter the spinal cord at T10. This input sensitizes the dorsal horn at T10, leading to sensitization of all the dorsal horn nociceptive neurons, and ultimately leading to the perception of pain in the T10 dermatome. As appendicitis progresses, the pain localizes to the right lower quadrant as the inflammation extends to the parietal peritoneum with the same nerve supply as the overlying dermatome.

Ascending Tracts Associated with Pain

Fibers carrying pain impulses exit the dorsal horn and ascend the spinal cord to the brain. The predominant pathways for pain conduction through the spinal cord are the spinothalamic tract, the spinomesencephalic tract, and the spinoreticular tract, located in the anterolateral aspect of the spinal cord (see Fig. 3-3).

The spinothalamic tract is the most important pathway for pain transmission. Lesions in this tract (the anterolateral portion of the spinal cord) cause a loss of pain sensation in the contralateral side below the lesion. Axons cross the midline within two spinal segments of their origin and then ascend the tract. The axons synapse in the ventroposterolateral nucleus of the thalamus and the posteromedial thalamus, where they then project to the cortex.[29] As these tracts ascend, fibers are added to the anteromedial border, producing an organization with sacral segments located dorsolaterally and cervical segments located anteromedially.

The spinoreticular tract ends in synapses in the reticular formations of the medulla, pons, midbrain, and intralaminar thalamic nuclei. These locations ultimately project to the limbic forebrain. The spinoreticular tract is an important part of the suprasegmental reflex responses to pain and serves as a direct link between the reticular arousal centers and the dorsal horn. Spinomesencephalic tract fibers synapse in the periaqueductal gray matter and other midbrain nuclei. These fibers likely activate a system of descending pain inhibitory signals that project from the periaqueductal gray matter.

The dorsal columns of the spinal cord primarily transmit innocuous sensory information. These columns, however, may also play a role in pain through modulation of the spinothalamic tract. In addition to providing discriminatory information to localize pain, sensory input may activate cortical descending pathways that modulate the dorsal horn response to nociceptive input. The spinothalamic tract then provides precise localization of the nociceptive data, whereas the spinoreticular and spinomesencephalic tract input serves to arouse the body to ongoing tissue damage. This sequence activates the neuroendocrine, emotional, and autonomic reflexes associated with pain.[30]

Pain Modulation

Impulses from nociceptors are modulated by descending tracts in the spinal cord. The two primary descending pathways appear to be primarily serotonergic and noradrenergic. These pathways originate in the midbrain (periaqueductal gray matter and locus ceruleus) and medulla (nucleus raphe magnus and nucleus reticularis gigantocellularis) and are transmitted to the spinal cord via the dorsolateral funiculus.

Electrical stimulation of descending pathways produces analgesia comparable to that produced with opioids. Stimulation of the thalamus can also produce analgesia.[31] Inputs to this system come from the frontal cortex, the limbic system, the hypothalamus, the reticular system, the locus ceruleus, and the spinal cord. Multiple neurotransmitters are involved in these pathways, including serotonin, norepinephrine, and substance P. It is believed that the activation of this system is responsible for effects achieved by placebo, acupuncture, and transcutaneous electrical nerve stimulation (TENS) units.

Central Sensitization

Central sensitization involves the amplification of nociceptive signals. Central sensitization is mediated by multiple substances such as nitric oxide, glutamate, substance P, aspartate, prostaglandins, leukotrienes, norepinephrine, and serotonin. It can occur in the presence of chronic pain or as a result of damage at any point along the pain transmission system. Central sensitization is described in the setting of traumatic and degenerative conditions of the spinal cord and brainstem and can be associated with thalamic strokes, multiple sclerosis, Parkinson's disease, Arnold-Chiari formation, and cervical stenosis.

Pain Expression

The transduction, transmission, and modulation of pain stimuli develop the perception of the subjective emotional experience of pain. Many factors other than the stimulation of nociceptors influence the final perception of pain. The discrete cognitive processes and pathways involved in the interpretation and experience of painful stimuli remain a mystery and are affected by factors such as cultural expectations, personality, experiences, and the underlying emotional state. Many of these factors, and therefore the subsequent perception of pain, can be greatly influenced by both pharmacologic and nonpharmacologic interventions.

For drugs such as nitrous oxide and low-dose opioids, much of their analgesic effect is on the cognitive interpretation and emotional reaction to pain rather than on the transmission of the pain stimulus. Noninvasive techniques (e.g., distraction and hypnosis) can limit pain perceptions and increase tolerance. Changes in the manner in which a person experiences pain, based on previous experiences and learned behaviors, are referred to as *cognitive sensitization*.

Reflex Responses to Pain

There are two types of reflex responses to nociceptor input: spinal segmental (or suprasegmental) and cortical. Spinal reflexes are generated by the transmission of nociceptive impulses from the dorsal horn to motor and autonomic neurons in the spinal cord, provoking a range of responses, including tachycardia, vasoconstriction, paralytic ileus, and muscle spasm (Box 3-2).[32]

Box 3-2 Reflex Responses to Pain

Increased Sympathetic Tone
Vasoconstriction producing increased peripheral resistance
Increased cardiac output from increased stroke volume and heart rate
Increased blood pressure
Increased metabolic rate and oxygen consumption
Decreased gastric tone and gastric emptying (may progress to ileus)
Decreased urinary tract tone (may lead to urinary retention)

Endocrine Responses
Decreased insulin production
Increased cortisol
Increased antidiuretic hormone
Increased growth hormone
Increased renin, angiotensin II, aldosterone
Increased glucagon
Increased catecholamines

Respiratory Responses
Hyperventilation

Cortical Responses
Anxiety and fear

Table 3-2 Opioid Receptors

OPIOID RECEPTOR CLASS	EFFECTS	ASSOCIATED ENDOGENOUS ENDORPHIN
Mu 1	Euphoria, supraspinal analgesia, confusion, dizziness, nausea, low addiction potential	Beta-endorphin
Mu 2	Respiratory depression, CV and GI effects, miosis, urinary retention	Beta-endorphin
Delta	Spinal analgesia, CV depression, decreased brain and myocardial oxygen demand	Enkephalin
Kappa	Spinal analgesia, dysphoria, psychomimetic effects, feedback inhibition of endorphin system	Dynorphin, beta-endorphin
Epsilon	Hormone	Beta-endorphin
Gamma	Dysphoria, psychomimetic effects	Beta-endorphin

CV, cardiovascular; *GI,* gastrointestinal.

Suprasegmental reflexes are transmitted through ascending tracts to the brainstem, hypothalamus, and cortex, where withdrawal reflexes and autonomic responses occur in conjunction with conscious responses. The autonomic reflex responses to pain are variable and cannot be used to quantify pain in an individual.[33,34]

Endorphin System

The endorphin system is a neuroendocrine system that serves to modulate responses to pain and stress. The endorphin system consists of widely scattered neurons that produce three types of opioids: beta-endorphin, met- and leu-enkephalins, and dynorphins. These opioids act as neurotransmitters and neuromodulators at three major classes of receptors—mu, delta, and kappa—and produce analgesia and counter the stress response (Table 3-2).

Under normal circumstances the endorphin system serves to decrease pain and stress after a person has adequately dealt with the inciting noxious stimuli. The endorphin system normally is a responsive system that can have an increased or decreased effect to produce the appropriate response to a painful event. As with other neuroendocrine systems, increasing stimulation by endorphins produces feedback inhibition on their own circulating levels. During prolonged periods of pain with high levels of stimulation, the system can become less responsive and less effective at modulating the pain response.

Like their endogenous counterparts, opiates act at chemical receptors to produce both analgesia and undesirable side effects.[35] As these drugs are given over a prolonged period, they inhibit the endogenous endorphin system, blunting the response to pain and stress and decreasing the overall endorphin effect. As these drugs are withdrawn, the normal effects of the endorphin system resume.

Table 3-3 Acute versus Chronic Pain

	ACUTE PAIN	CHRONIC PAIN
Inciting factor	Associated pathology present and recovery is expected.	Associated pathology either not identifiable or not expected to improve; recovery either unpredictable or not expected.
Relation to healing	Pain improves as the injury heals; limitation of activity because of pain assists healing.	Neither pain nor injury expected to improve; pain may limit activities that could improve condition.
Psychosocial effects	Limited to acute stress reaction.	Negative effects a prominent feature of disease.
Treatment	Analgesics, immobilization.	Psychosocial aspects must be addressed; analgesics play a smaller role.

Acute versus Chronic Pain

Acute pain is usually associated with an identifiable pathologic condition and serves an adaptive function by warning the individual that an illness or injury exists. This sequence will motivate the person to cease the activity that is causing the pain, look for a cause, seek help, and avoid the stimulus in the future.

Acute pain becomes chronic pain when the pain pattern persists, in changed or unchanged form, after the original physiologic insult has apparently resolved. All chronic pain starts as acute pain, but only small subsets of patients with acute pain develop chronic pain (Table 3-3). The physiologic transition from acute to chronic pain is a complex process with both physiologic and psychosocial components. In many circumstances the development of chronic pain is likely related to the treatment of acute pain.

Acute pain serves an important purpose in that it stimulates a person to protect the injured area and seek help. In addition, the neurochemical factors that contribute to acute pain acknowledgement will generally initiate and support recruitment of tissue repair mechanisms.[36] As an injury heals, these adaptive responses may become maladaptive if the pain persists, as this cycle can lead to a decreased range of motion and decreased function of the area and ultimately an increased susceptibility to injury and pain. Pain also causes a stress response that is initially adaptive in the face of injury. A prolonged stress response, however, causes immune system impairment, a hypercoagulable state, sleep disturbances, anxiety, and depression.[15,16,37]

Chronic pain is very common, and a large number of patients with chronic pain are seen in the ED.[5,38] It can be difficult to determine the point at which an adaptive pain response becomes maladaptive and the progression from acute pain to chronic pain occurs. Chronic pain can have a wide range of inciting events

Figure 3-5. Pain scales.

including persistent tissue injury or even factors unrelated to tissue injury.

MANAGEMENT PRINCIPLES

Pain Assessment

The early, accurate recognition and assessment of a patent's pain are the most important aspects of effective acute pain management.[39] When pain is inadequately treated, inaccurate assessment is very likely the root cause of the problem.[7]

The degree to which a person experiences pain is a complex and subjective interaction between the physical stimulus and the patient's cognitive and emotional state. It is clear, however, that the degree of pain a patient perceives is not directly determined by the degree of physiologic injury. Patients in the ED with relatively identical injuries may report completely different amounts of pain.[39] Therefore pain treatments, analgesic requirements, and the manner in which a patient describes pain cannot be uniformly described based on the nature of a patient's injury.

The assessment of pain depends on the patient's ability to communicate the nature of the painful experience to the physician and the physician's ability to obtain this information. Unfortunately, there is no objective test or physiologic index to measure pain reliably.[40-47] Objective observations, such as hypertension, diaphoresis, or tachycardia, do not correlate well with the degree of pain present.[9,44,48]

Pain assessment is made through an indirect estimation by the patient's caregivers. Because pain cannot be objectively measured, a physician's assessment depends on communication with the patient, both verbal and nonverbal. Barriers to communication between patients and physicians, including linguistic, socioeconomic, and cultural differences, limit the ability to effectively assess pain. Because effective treatment is based on the assessment of pain, patients who have difficulty communicating are at particular risk of undertreatment of their pain (oligoanalgesia). Groups at particular risk for oligoanalgesia include infants and children, patients whose cultural background differs significantly from the treating physician's, and patients who are developmentally delayed, cognitively impaired, under severe emotional stress, or mentally ill.[5,9,39,49-52]

Oligoanalgesia

Oligoanalgesia, the inadequate treatment of pain, is described in most studies of pain in ED patients.[5,53-66] The National Hospital Ambulatory Medical Care Survey evaluated all isolated closed fractures of extremities and clavicles and demonstrated that only 64% of patients received an analgesic, with only 42% receiving an opioid.[53] Children, the elderly, and patients from social and ethnic minorities exhibit oligoanalgesia the most frequently.[5,52,67,68]

Even when analgesia is administered in the ED, there frequently is a long delay before therapeutic actions. When opioids are used, they are often given in subtherapeutic doses. One study of trauma centers demonstrated that of the 38% of patients who received an analgesic, the average time to administration of the first dose of analgesic was 109 minutes after arrival.[65]

There are a variety of reasons why patients do not receive adequate analgesia from health care providers. These include the ineffective assessment of pain. Other issues are prohibitive, including misconceptions about the safety and efficacy of various treatments as well as the effect of analgesic interventions on a patient's evaluation.

Pain Measurement

The use of numeric rating scales employing a verbal 0 to 10 score ("none to worst imaginable") is ubiquitous in the ED and other settings where acute pain is managed or inflicted.[68] Visual analog scales, usually consisting of a 10-cm straight line with anchors at both extremes, are frequently used in research to provide continuous data for analysis. These scales offer little practical advantage over verbal reports in the clinical setting.[40,45,67,69,70] Including a pain scale as a part of vital sign assessment is now mandated by TJC (Fig. 3-5).[70] Routine verbal or visual pain scale assessment encourages clinicians to communicate with patients to assess their pain and to evaluate responses to analgesic intervention attempts.[55,71]

Patient-derived pain scales are useful only if the patient understands the scale as communicated by the health care provider. Pain scale use also requires the patient to be able to assign a concrete value to the abstract concept of pain. In general, children younger than 7 years are unable to successfully relate to pain scale

processes. As a consequence, children require alternate communication venues to both acknowledge and relate pain. The FACES pain scale is designed for children younger than 7 and is an example of a pain assessment tool to be used by children to describe their pain.[72] This scale has a series of cartoon faces expressing a range of emotions from happiness to severe distress. The child is asked point to the face that corresponds to how he or she feels. The FACES pain scale and others like it require less of an abstract reference than numeric and verbal scales and are useful in pain assessment for toddlers and cognitively impaired adults.[73]

In preverbal children, observer-derived scales may be used. These include scales such as the Modified Pre-Verbal, Early Verbal Pediatric Pain Scale (M-PEPPS),[74] the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS),[75] and the CRIES scale for neonates.[76] These scales use a scoring system for observed criteria that is reproducible between trained observers, making them useful for research. These scales appear to have little clinical utility over the physician's or parents' overall impression of the child's pain.[77]

Numeric rating scales can be used as communication tools between the patient and the physician to describe pain. Care must be taken, however, in using the scores derived from the scale as an absolute indicator of pain. The score a patient uses to describe pain may have as much to do with how the patient desires the health care provider(s) to respond to the pain complaint as it does a description of the pain relative to previous experiences. As a patient undergoes treatment, changes in the pain scores may represent a number of factors, including satisfaction from analgesic interventions and a desire for further treatment, as well as actual changes in experienced pain.

Pain scores have gained acceptance as the most accurate and reliable measure of assessing a patient's pain as well as response to pain treatment. Pain treatment should be targeted to a goal of reducing the pain score (e.g., by 50%, to below 3/10, or to "mild" from "moderate or severe") rather than a specific (maximum) analgesic dose.

Treatment

The approach to patients in pain should use a division of pain patients into four specific treatment groups:

1. acute pain
2. chronic pain
3. recurrent pain
4. chronic pain of malignancy

Therapy for groups other than those with acute pain should focus on a long-term, multidisciplinary approach to treat the multiple manifestations of these diseases. In addition, the approach should address the role of the emergency physician and ED as part of a patient's ongoing comprehensive strategy. Acute and chronic pain have different physiologic causes and thus require different treatment approaches (Fig. 3-6).

Chronic Pain

The assessment of pain in the absence of acute or obvious physical injury requires a great deal of communication skill on the part of the physician and the patient. Many patients with chronic pain develop a great deal of experience, some of it adaptive and some maladaptive, in describing their pain and interacting with physicians to receive pain treatment.[78] Many behaviors such as exaggerating symptoms or attempting to manipulate providers are developed around the patient's expectations for receipt of pain therapy and/or pain relief. These behaviors, combined with the negative psychosocial effects and sense of futility associated with chronic pain, can complicate the evaluation process and the care of chronic pain patients.

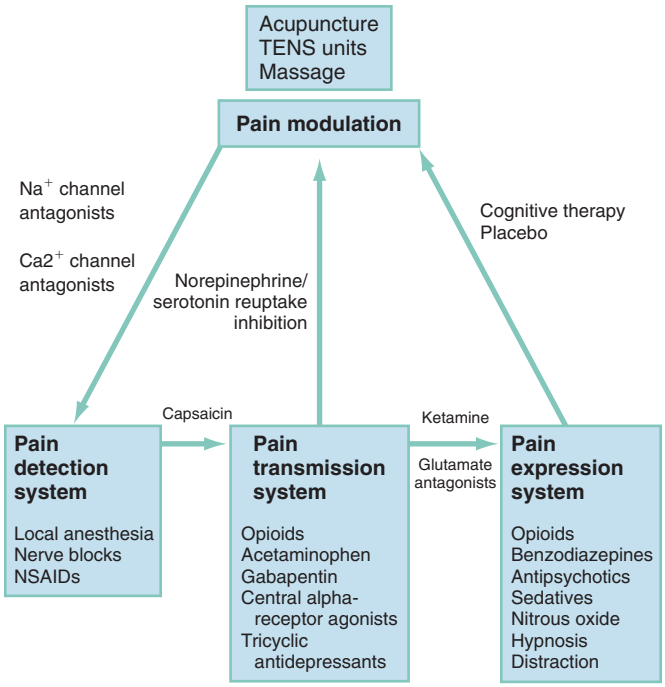

Figure 3-6. Sites for pain treatment algorithm.

The assessment of chronic pain can be one of the most challenging situations in which to obtain an accurate clinical history. Patients who are having a difficult time describing their pain should be encouraged with detailed questions about the pain, combined with multiple examples, comparisons, and summarizing statements, to facilitate accurate communication. Assuring the patient that the questions are intended to aid understanding and to enable treatment of symptoms as effectively as possible can facilitate the development of a common goal and help establish the trust necessary to develop an effective treatment strategy.

Presentation of patients with chronic pain can be either an exacerbation of their chronic pain in the setting of ongoing therapy or untreated chronic pain resulting from a gap in, or a lack of, appropriate treatment. These scenarios require different treatment approaches. For chronic pain patients with an exacerbation in their pain exceeding the pain control of their usual treatment strategy, treatment can be approached in a fashion similar to that for acute pain. The goal in these patients should be to control the exacerbation and return the patient to baseline function.

Many patients with chronic pain are in comprehensive treatment programs, most of which involve a "contract" with respect to the location for their pain management (e.g., not in an ED) and specific medications. For such patients, a review of the pain management plan in the medical records, or contact with the physician who typically manages the patient's pain, is desirable before embarking on a short-term treatment strategy in the ED.

Patients with chronic pain who have a gap in their baseline treatment, or who have never established appropriate treatment for chronic pain, require an approach that addresses the need for establishment of a chronic, consistent treatment plan. Patients with no ongoing treatment plan who are identified as having chronic pain should have a basic chronic pain treatment plan implemented during their ED visit. This should consist of acetaminophen, if not contraindicated, and a nonsteroidal anti-inflammatory drug (NSAID) if tolerated. Tramadol may be helpful in certain cases. Adjuvants appropriate for neuropathic or central pain may be added if appropriate. Opioids should not be

prescribed until these other treatments have been maximized and should be added in addition to these other therapies rather than as an alternative.[79] In general, opioids for chronic pain management are best managed through ambulatory pain centers or through a primary care physician who can follow the patient's therapy and response.

Recurrent Pain

Recurrent pain is a subset of chronic pain and is a condition in which patients have repeated episodes of similar pain. Recurrent pain can include such disorders as back pain, myofascial pain syndrome, migraine syndrome, sickle cell disease, and inflammatory bowel disease. The approach to the treatment of recurrent pain in the ED is similar to that of acute pain, except that prevention of recurrent pain events are considered as part of the treatment strategy. These therapies may integrate nonpharmacologic approaches, such as physical therapy for back pain, in addition to preventive medication agents.

Chronic Pain of Malignancy

Chronic pain from malignancy is approached differently than other causes of chronic pain. Chronic malignant pain is similar to acute pain in its relation to ongoing nociceptive stimulation and similar to chronic pain in its duration and psychobehavioral effects. The medications used, for the most part, are similar to those used for acute pain. Similarly to chronic pain, the psychosocial effects of the pain of malignancy must also be addressed as part of an effective treatment strategy.

Patients with a significant change in the pattern of their chronic pain caused by cancer or a terminal illness, as with other chronic pain patients, should be evaluated for a new process to account for the pain. Opioids, especially in long-acting or transdermal preparations, should be used liberally to bring pain relief in patients with terminal illnesses.[80]

Neuropathic Pain

Activation of the sympathetic system does not typically result in pain. Acute nerve injury appears to modulate the development of hyperalgesia and allodynia, however, and is associated with a wide variety of neuropathies. *Complex regional pain syndrome* (CRPS) is a term that includes most sympathetically maintained pain.[81] CRPS type 1 (often referred to as *reflex sympathetic dystrophy*) develops after an injury and typically follows the distribution of a peripheral nerve.[80] It is associated with hyperalgesia, allodynia, changes in skin blood flow, and sympathetic dysfunction. CRPS type 2 (commonly referred to as *causalgia*) is associated with burning pain and allodynia in the distribution of an injured nerve with no association with sympathetic symptoms.[80-82] Opioids are ineffective in preventing CRPS after the injury has ocurred.[83] Clonidine, *N*-methyl-D-aspartate receptor antagonists, and γ-aminobutyric acid (GABA) receptor agonists are more effective in the treatment of CRPS than opioids.[81]

Antidepressants have effects on neuropathic pain that appear to be distinct from mood effects.[84] A meta-analysis of 39 placebo-controlled trials involving first-generation tricyclic antidepressants demonstrated benefits in a variety of chronic pain syndromes.[85,86] For patients with chronic pain that is thought to be unrelated to central or neuropathic origins, other antidepressants such as serotonin reuptake inhibitors may be safer and more effective.

Several anticonvulsants, including gabapentin, phenytoin, carbamazepine, and valproic acid, have been used for neuropathic pain with lancinating or burning properties. Carbamazepine is used most frequently for trigeminal neuralgia, postherpetic neuralgia, and diabetic neuropathy. Gabapentin is described for both types of CRPS, postherpetic neuralgia, and diabetic neuropathy.[87-89]

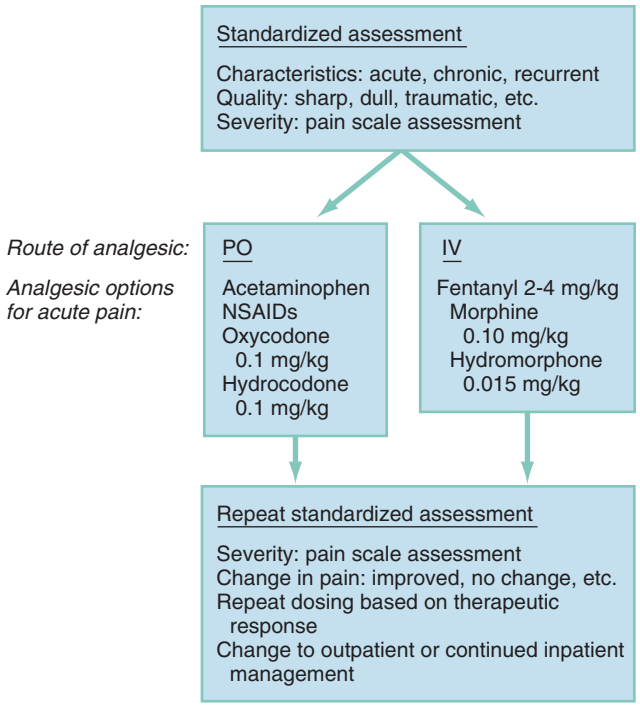

Figure 3-7. Emergency department pain therapy algorithm.

Acute Pain

Symptomatic treatment of pain should be initiated promptly, titrated to an acceptable level of relief, and continued while the investigation for a cause is proceeding (Fig. 3-7). When the cause of acute pain is uncertain, immediate relief of pain occurs in parallel with initial efforts to establish the diagnosis. It is inappropriate to delay analgesic use until a diagnosis has been made. There is no evidence that the administration of adequate doses of opioid analgesia to establish patient comfort impairs the physician's ability to diagnose the cause of an acutely painful condition. To the contrary, administration of analgesia may enhance the accuracy of physical examination and patient assessment.[90,91]

Analgesic Agents

Opioid Analgesic Agents

In 1680 Sydenham wrote, "Among the remedies it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."[92] Centuries later, this statement is still accurate, and titrated opioids are the mainstay of therapy for acute pain.

The beneficial effects of opioids have been well documented for centuries, as have their toxicity and potential for abuse.[93] Unfortunately, opioids are often poorly used in clinical practice.[56] Concerns regarding opioid toxicity or dependence and a poor understanding of the pharmacokinetics of the drugs lead to inadequate dosage and excessively infrequent dosage intervals. The safety of the short-term use of opioids for acute pain, in terms of both toxicity and likelihood of causing future dependence, is demonstrated.[90,91] Opioids should be the first-line agents in the management of acute severe pain (Table 3-4).

Mechanism of Action and Toxic Effects. Opioids bind to specific endorphin system receptors located throughout the nervous

Table 3-4 Opioid Analgesics

NAME	INITIAL PARENTERAL DOSE	INITIAL ORAL DOSE	DURATION OF ACTION	EQUIPOTENT INTRAVENOUS DOSE	EQUIPOTENT ORAL DOSE	COMMENTS
Morphine	0.1 mg/kg	0.5 mg/kg	3-4 hr	10 mg	50 mg	Standard opioid for comparison
Hydromorphone	0.015 mg/kg	0.075 mg/kg	2-4 hr	1.5 mg	7.5 mg	Inactive metabolites are an advantage to patients with renal or hepatic disease.
Methadone	0.1 mg/kg	0.2 mg/kg	4-8 hr	10 mg	20 mg	Used for opioid addiction therapy and chronic pain; half-life longer than duration of action.
Fentanyl	1.5 µg/kg	3 µg/kg	0.5-1.5 hr	100 µg	NA	Oral dose actually transmucosal absorption; metabolites inactive; transcutaneous patches used for chronic pain.
Oxycodone	0.1 mg/kg	0.15 mg/kg	3-4 hr	10 mg	15 mg	Excellent bioavailability renders an effective oral agent for acute pain.
Codeine	1.3 mg/kg	2.5 mg/kg	2-4 hr	130 mg	200 mg	Side effect to analgesia ratio is undesirable. Pronounced peripheral effects: constipation, nausea and vomiting, cough suppression.
Hydrocodone	NA	5-15 mg	3-4 hr	NA	30 mg	Commonly used in preparations with acetaminophen; more potent than codeine.
Meperidine	0.75 mg/kg	3 mg/kg	2-3 hr	75 mg	300 mg	Toxic metabolite normeperidine accumulates at normal doses; generally should not be used for acute analgesia.
Oxymorphone	0.01 mg/kg	0.1 mg/kg (rectal)	3-4 hr	1 mg	10 mg	Rectal administration more predictable than with other agents.
Alfentanil	10-20 µg/kg	NA	8-12 min	1 mg	NA	Short duration because of redistribution; duration of action increases with the size of the dose.
Sufentanil	0.1 µg/kg	NA	1-1.5 hr	10 µg	NA	Minimal cardiovascular side effect.
Remifentanil	0.5-1 µg/kg	NA	4-6 min	50 µg	NA	Used as a continuous infusion.
Nalbuphine	0.4 mg/kg	0.1 mg/kg	3-4 hr	40 mg	NA	Mixed agonist/antagonist; decreased respiratory depression relative to other opioids; limited analgesic effect; used in perinatal period.

NA, not applicable.

system. These receptors suppress pain detection peripherally, modify pain transmission in the spinal cord and thalamus, and alter the perception of pain at the level of the cortex. A variety of endorphin receptors are defined (see Table 3-2). The unique actions of opioids are determined by the specific binding properties of the agent to the various receptors.

Side effects sometimes can limit the success of opioid therapy, particularly in the acute treatment setting. The occurrence of these side effects varies among individual patients and opioid agents. Tolerance of many side effects develops shortly after the initiation of therapy.

The most common side effect of opioids is constipation. Constipation is attributed to opiate binding of receptors located in the antrum of the stomach and proximal small bowel.[94] Parenteral and transdermal administration routes may be superior to oral methods owing to decreased exposure of the gut to the opioids.[95,96] Constipation can be anticipated with long-term (more than a few days) opioid use. An active laxative, such as senna, lactulose, or bisacodyl, should be prescribed as needed.

Nausea and vomiting can occur with the administration of opioids, especially in opioid naïve patients.[97] It is often difficult to distinguish whether nausea and vomiting are caused by the opioid or the acute pain for which it is administered. Routine coadministration of an antiemetic with the opioid, once an almost universal practice, has largely been discontinued in clinical practice. Nausea and vomiting in the context of persistent, acute pain after opioid administration may require additional opioid and an antiemetic, such as promethazine, droperidol,[98] prochlorperazine, or one of the 5-HT_3 receptor antagonists (e.g., ondansetron).

True immunoglobulin-mediated allergies are rare for morphine and other opioids. Many patients will experience mild pruritus of the trunk and face after parenteral administration. This side effect is related to histamine release from opioid receptors on mast cells and does not constitute an allergy. To a varying degree, opioids destabilize mast cells in a dose-dependent fashion, causing histamine release and resultant urticaria, pruritus, and orthostatic hypotension This reaction may appear as localized urticaria tracking up a vein after intravenous administration of an opioid, especially morphine. Rarely, bronchospasm may be seen in patients with reactive airway disease or atopy. This effect usually subsides rapidly, with no treatment required, although the symptoms can be controlled with administration of an antihistamine.

Sedation and respiratory depression can occur with opioid administration for acute pain. Opioids decrease medullary sensitivity to CO_2 via central stimulation of the mu receptor, resulting in respiratory depression. The combination of opioids with other sedating agents, such as benzodiazepines, will increase the likelihood of respiratory depression. Patients with underlying hepatic or renal dysfunction are also at increased risk because of inability to clear opiates normally, resulting in the accumulation of active metabolites.

Pain is a very effective stimulant of respiratory drive, rendering respiratory depression rare in the context of acute, severe pain. Fear of respiratory depression should not deter the clinician from adequately treating pain. It should be noted that patients who previously tolerated a dose of an opioid may develop respiratory depression if the source of acute pain is removed, such as by local anesthesia or the reduction and stabilization of a fracture.[99] Transient respiratory depression from opioids usually responds to simple verbal or tactile stimulation and uncommonly requires more aggressive interventions.

Tolerance and physical dependence are common effects of the prolonged use of opioids. Physical dependence is defined as the occurrence of an opioid withdrawal syndrome after abrupt cessation, rapid dose reduction, or administration of an antagonist. Tolerance is a phenomenon that occurs after prolonged exposure to opioids and is characterized by the diminution of an opioid's effect over time. Normal expected results of the prolonged use of opioids should be accounted for in planning their use for extended periods, and do not represent addiction.

Addiction is a potential risk associated with prolonged opioid use and often limits their use.[100] The term *addiction* refers to a neurobiologic disease, with many factors influencing its development and manifestations. Addiction is characterized by compulsive drug use, continued use despite harm, and craving. The iatrogenic creation of opioid addiction, a new addiction where one did not previously exist, is a relatively rare phenomenon.[101] In one trial, the Boston Drug Collaborative Study, only 4 in 11,892 hospital inpatients treated with opioid analgesic agents developed new opioid abuse behaviors.[102]

Pseudoaddiction describes patient behaviors that may occur when pain is undertreated.[103] Patients with unrelieved pain may become focused on obtaining medications and otherwise seem inappropriately "drug-seeking." Behaviors such as illicit drug use and deception can occur in the patient's efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that it resolves when pain is effectively treated.

Suggestion of Drug-Seeking Behavior. Some patients feign or exaggerate pain to receive opioids.[104] A physician's impression that a patient is drug-seeking is associated with a reduction in the treatment of the patient's pain. These perceptions are often complicated by differences between the health care provider and patient in characteristics such as socioeconomic class, ethnic background, age, and race. These elements are frequent sources of bias in the treatment of pain.[39] Care should be taken to recognize such factors and consider their impact on treatment behaviors. Unless or until a thorough evaluation of the patient, usually including medical records related to prior visits and sometimes including telephone contact with other providers (other hospitals, primary care physician), establishes a working diagnosis of drug-seeking behavior, a patient should be given the benefit of the doubt and should be treated as though the pain is legitimate. Primary providers, chronic pain specialists, and others should note patient contracts, prescription details, and patterns of possible nontherapeutic drug-seeking in the medical record, using objective terms and descriptions.[105] Patients with repetitive episodes of drug-seeking events may benefit from a multidisciplinary review to establish specific recommendations for their care when they are seen by anyone other than their primary pain management provider.

Administration. The goal of the administration of opioids is to attain and maintain effective analgesia with minimal adverse effects. The effects of opioids vary widely among individuals. There is no "ceiling effect" to their potency. There is also no standard, fixed, or weight-related dose that can consistently produce a given clinical effect. The correct dose a particular patient requires at a particular time can be determined only by repeated assessment of the degree of pain relief and adverse effects. The use of opioids therefore requires titration based on frequent and accurate assessments.[90] The most effective and safest way to achieve pain relief is to use a deliberate intravenous titration.

Box 3-3 Disadvantages of Intramuscular Opioid Administration

Pain on injection
Delayed onset of action
Inability to predict therapeutic effect
Inability to titrate dosage
Diurnal variation in level achieved
Disease state may affect level achieved
Level dependent on intramuscular injection site

The intramuscular route of administration of opioids has several disadvantages and is not advised for treatment of acute pain (Box 3-3). The principal limitation of the intramuscular route is that it does not allow effective titration. The time to achieve significant pain relief from an intramuscular injection varies substantially for each patient—from 20 to 60 minutes—and the intramuscular route offers no therapeutic advantage over the oral route. If an intramuscular injection dose is inadequate, the patient will require another painful injection to achieve effective analgesia. If too large a dose is given, the patient is at risk of side effects without the added safety of an intravenous line for reversal agents or drugs to counter side effects.

Most patients with mild to moderate pain are best treated with oral opioids. If pain is severe or if the patient is expected to require multiple doses of an agent for management, then an intravenous route of administration is desirable. If an intravenous line cannot be established and the patient cannot tolerate oral medications, the subcutaneous route is preferable to the intramuscular route. Subcutaneous injection is less painful than intramuscular injection, with a similar onset of pain relief.

Opioids can be delivered via an oral transmucosal or intranasal mucosal route.[106-108] Buprenorphine can be given by the sublingual route, and fentanyl is available in an impregnated, sweetened matrix called a Fentanyl Oralet (oral transmucosal fentanyl citrate). Nasal fentanyl, butorphanol, and sufentanil also produce rapid clinical effects via nasal mucosal absorption.[33,77,109]

The optimal use of intravenous opioids requires the administration of an initial loading dose, followed by assessment of the analgesic effect. Frequent (every 5-15 minutes) repeated doses should be administered until analgesia is achieved, followed by doses at regular intervals to prevent the return of significant discomfort. The best method to assess the need to administer repeat doses of an analgesic agent is to use the patient's subjective impression. Patient-controlled analgesia uses a computerized delivery system that allows patients to self-administer a prescribed dose of opioid based on self-assessment. Patient-controlled analgesia is safe and effective in a number of therapeutic settings, including sickle cell pain crisis in a pediatric ED.[110]

Specific Agents

Morphine. Intravenous morphine is often the first choice for treatment of acute, severe pain in ED patients. Morphine is the opioid analgesic agent with which all other opioids are compared. When administered intravenously (IV), morphine reaches a peak of action in 15 to 20 minutes; it has a half-life of 1.5 to 2 hours in healthy, young adults and slightly longer in the elderly. Its duration of action is 3 to 4 hours. An appropriate loading dose of morphine for acute severe pain is 0.1 mg/kg IV, augmented by repeated doses of approximately half the initial dose every 5 to 15 minutes, depending on the severity of the pain and patient response. Administration is continued until pain is relieved

according to a predetermined goal, such as achievement of 3 or less (of 10) on the pain scale.

Morphine also is effective by oral administration; however, only 20% of the ingested dose reaches the tissues after first-pass metabolism, requiring a dose adjustment of 5× from an equipotent intravenous dose. There is no validity to the perception that morphine causes more smooth muscle spasm than other opioids, rendering it compatible for treatment of patients with biliary or renal colic.

Morphine is primarily metabolized by conjugation into a 3-conjugate and 6-conjugate form in the liver. The 3-conjugate form (normorphine) has no opioid analgesic activity and rarely has been associated with CNS side effects (e.g., tremors, myoclonus, delirium, or seizures). This risk is greatest in elder patients and those with renal insufficiency, although it is rarely an issue in the ED. The 6-conjugate form morphine metabolite is a strong mu- and delta-receptor agonist. This form plays an important role in the efficacy and duration of clinical effects.

Meperidine. Meperidine (Demerol), although once widely used, has several disadvantages compared with morphine and other parenteral opioids. Given these limitations, meperidine should not be used in the ED management of acute pain. The duration of action of meperidine, less than that of morphine, is only 2 to 3 hours. The greatest disadvantage of meperidine, however, is that it is metabolized by the cytochrome P_{450} system to the active metabolite normeperidine. Normeperidine is produced in much larger quantities than the toxic metabolite of morphine at a therapeutically equivalent dose. In addition, normeperidine can cause CNS toxicity at therapeutic meperidine doses.

Normeperidine has a half-life of 12 to 16 hours and blocks muscarinic receptors, resulting in significant anticholinergic effects including agitation and delirium. These effects may lead to seizures, hallucinations, and psychosis as the metabolite accumulates. Normeperidine is excreted through a renal mechanism with a subsequently longer half-life in patients with decreased renal function. Repeated administration of meperidine should be avoided.

Of particular concern with meperidine use is the potentially lethal interaction of meperidine with monoamine oxidase inhibitors as a result of serotonin accumulation. Meperidine is also associated with serotonin syndrome in patients taking a selective serotonin reuptake inhibitor or other serotonin agonist. Meperidine is no longer a formulary drug at many hospitals.

Hydromorphone. Hydromorphone is a semisynthetic derivative of morphine that is a potent analgesic agent, increasingly used in the management of acute pain in the ED. Hydromorphone is the P_{450} metabolite of hydrocodone and is seven times more potent than morphine with parental administration. Hydromorphone has a duration of action similar to that of morphine. Although 7 mg of morphine is equivalent to 1 mg of hydromorphone, nursing staff are more likely to administer "low" milligram doses of hydromorphone to patients with acute pain than "higher" equipotent doses of morphine.[111,112]

Pruritus, nausea, and vomiting may occur less frequently with hydromorphone administration than with morphine at equianalgesic doses. Hydromorphone is primarily conjugated into hydromorphone-3-glucuronide (H3G) in the liver and is excreted renally. H3G is primarily an inactive metabolite. As a result, hydromorphone is better tolerated than morphine, particularly in elderly patients and those with hepatic impairment. Patients with renal insufficiency may be at some risk of neurotoxicity after prolonged exposure owing to H3G accumulation.

Patients allergic to morphine do not consistently have cross-reactivity with hydromorphone. Hydromorphone can be given via intravenous, subcutaneous, or oral routes. A rectal preparation is available in the form of 3-mg rectal suppositories.[92]

Fentanyl. Fentanyl is a synthetic opioid that is highly lipophilic and produces analgesia within 1 to 2 minutes after intravenous infusion. Fentanyl redistributes rapidly, and its duration of therapeutic action is approximately 30 to 60 minutes.

Fentanyl is metabolized by the P_{450} system into inactive metabolites. Drug accumulation and toxicity may occur after tissue saturation following a prolonged infusion, but this is unlikely to happen during acute therapy. The short duration of action of fentanyl makes it highly titratable and ideal for use in patients who require serial examinations, such as trauma patients with possible occult head injury.

Fentanyl causes less histamine release than morphine and is associated with fewer peripheral effects at an equianalgesic dose. Fentanyl is therefore an excellent choice for treating pain in patients with bronchospastic lung disease. Fentanyl is more frequently associated with respiratory depression, however, than morphine, and patients receiving fentanyl infusions should be monitored with direct observation, supplemented by pulse oximetry or capnography.

The ED use of fentanyl is associated with a very low (1.1%) incidence of serious complications.[77,113-115] High or repeated fentanyl doses may produce muscle rigidity. This side effect, "rigid chest syndrome," usually occurs with anesthetic doses greater than 15 μg/kg and may be so severe that it interferes with respiration. Rigid chest attributed to fentanyl is exceedingly rare at doses typically used for acute analgesia. This rigidity, when observed to occur, does not uniformly respond to naloxone but is abolished by neuromuscular blockade.

Fentanyl can be administered IV, transmucosally, or transdermally.[115] Nebulized or intranasal fentanyl is described for the treatment of acute pain in patients without intravenous access at doses of 3 μg/kg.[33,77,82,116]

Oxycodone. Oxycodone is a strong opioid agonist that is highly bioavailable in an oral form. Oxycodone is widely available in combination with acetaminophen or aspirin as well as by itself, and is also available in long-acting oral formulations. Oxycodone bioavailability is 0.60 to 0.85, which is much higher than that of other opioids. It is quickly and efficiently absorbed, which may lead to its associated abuse potential.[117]

Oxycodone is not available in a parenteral form in the United States, although studies have demonstrated its intravenous form to be equianalgesic to morphine. As with other opioids, the analgesic effects of oxycodone are dose dependent. A 15-mg oxycodone dose has an efficacy similar to 10 mg of intravenous morphine. The onset of action of oral oxycodone is approximately 20 to 30 minutes.[106]

Oxycodone undergoes hepatic metabolism into oxymorphone, a strong opioid agonist that principally accounts for its analgesic effects. The inactive metabolite, noroxycodone, is also a product of oxycodone hepatic metabolism. As with codeine, approximately 10% of patients do not metabolize oxycodone well and are unable to generate the functional metabolite oxymorphone. This defect in metabolism renders these patients unable to achieve clinically meaningful pain relief with typical administration strategies and may require very large doses to achieve analgesia. This effect can also be caused by agents that compete with oxycodone for CYP2D6 metabolism, such as neuroleptics, tricyclic antidepressants, and selective serotonin reuptake inhibitors. Cases of serotonin syndrome are reported when serotonin reuptake inhibitors and oxycodone are given together, likely because of this metabolic interaction.[118,119]

Hydrocodone. Hydrocodone is metabolized in the liver to hydromorphone and is typically given orally (PO). Hydrocodone provides greater pain relief when combined with acetaminophen or NSAIDs than either component does alone. In two small studies, hydrocodone-acetaminophen (5 mg/500 mg) provided analgesia similar to that achieved with codeine-acetaminophen (30 mg/500 mg) in patients with acute musculoskeletal pain or undergoing dental surgery.[120,121] Hydrocodone may cause more

drowsiness and dizziness but relatively less nausea than codeine. Hydrocodone combinations are less effective than oxycodone-acetaminophen combinations.[122] Hydrocodone clinical analgesia effects typically last 4 hours with typical administration of 5 mg to 20 mg.

Codeine. Codeine is a commonly prescribed opioid, usually in combination with acetaminophen, but is a weak opioid-receptor agonist and has little role in the modern ambulatory treatment of pain. Codeine is thought to exert its effects through metabolism into morphine and other active hepatic metabolites.

Approximately 10% of the population metabolizes codeine poorly. The effect of this genetic trait is a reduction in active analgesic metabolites and an enhancement in deleterious side effects including nausea, constipation, and pruritus. Although often prescribed for mild to moderate pain, codeine is a poor choice for analgesia owing to its tendency to cause side effects, especially nausea, cramping, and constipation, at doses that provide minimal analgesia.

Propoxyphene. Propoxyphene has limited indications for the treatment of acute pain. Many studies demonstrate its analgesic efficacy to be no better or only marginally better than placebo.[123] The propoxyphine metabolite, norpropoxyphene, can accumulate with repeated or large doses and cause refractory seizures, respiratory arrest, and significant risk of death as a result of torsades de pointes.[124] There is little evidence to support propoxyphene use alone or combined with acetaminophen for acute pain. As a consequence, propoxyphene generally should not be used in the ED or prescribed for the outpatient management of pain.[125]

Methadone. Methadone has several unique features that distinguish it from other opioids. It has no known neurotoxic or active metabolites and has high bioavailability. In addition to being a strong opioid agonist, methadone also has *N*-methyl-D-aspartate antagonist and serotonin reuptake–blocking properties. Methadone has a slow elimination half-life of 27 hours owing to its lipophilicity and tissue distribution. This slow clearance of methadone is the basis for its use in maintenance therapy, given that it can delay the onset of opioid withdrawal symptoms for up to 24 hours. The duration of its analgesic effects, however, is closer to 6 to 8 hours. The discrepancy between the duration of action of analgesia and the duration of the prevention of withdrawal symptoms is a result of the biphasic elimination of the drug and its redistribution.[126]

Naloxone. Naloxone is an opioid antagonist that can be given IV, intramuscularly (IM), subcutaneously (SC), or via endotracheal tube. Naloxone reverses the effects of opioids and is usually used in the setting of severe adverse events or opioid overdose. Naloxone can precipitate physiologic withdrawal in patients who are opioid dependent.

The duration of action of naloxone is approximately 45 minutes, which is shorter than that of most opioids. Therefore care should be taken to monitor for the recurrence of the opioid adverse events after this time period. Naloxone is typically given in repeat, titrated doses of 0.2 mg IV until reversed of any adverse opioid effect. In the setting of adverse events from opioid treatment, most commonly respiratory depression, careful titration allows for the smallest dose possible to be administered in order that the analgesic effect of the opioid can be maintained.

Tramadol. Tramadol is a synthetic oral compound that is a weak mu agonist with some serotonin and norepinephrine reuptake qualities. Its analgesic properties are thought to be primarily a result of mu-receptor agonism. Tramadol-induced analgesia, however, is only partially reversed by naloxone, suggesting other properties play a role in its therapeutic effects.

Tramadol, as a selective mu agonist without kappa agonist effects, should not cause physiologic dependence. Although tramadol use is associated with abuse and withdrawal similar to those of other opioids, their occurrence is sufficiently infrequent that the drug remains unscheduled.

Tramadol is metabolized in the liver by the cytochrome P_{450} system. One of its metabolites, M1, has an even greater mu-receptor affinity than tramadol and has an elimination half-life of 9 hours. Tramadol appears to have effects on GABA, norepinephrine, and serotonin receptors and the reuptake of the neurotransmitters, which may serve to activate descending pain modulation pathways.

Compared with traditional opioids, low-dose tramadol has a more favorable side effect profile and may present a lower risk of addiction with chronic use. The most common tramadol side effects are nausea, vomiting, dizziness, orthostatic hypotension, and sedation. These side effects are seen in as many as 17% of patients using the drug for chronic pain, with slightly lower rates occurring in patients receiving controlled-release versions.[127]

The occurrence of tramadol therapy side effects increases dramatically with increasing doses. Owing to reports of overdose and fatalities, a past or present history of addiction to opioids is a contraindication for the drug. The use of tramadol with other serotonergic medications (selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and serotonin norepinephrine reuptake inhibitors) is associated with serotonin syndrome.[128]

Tramadol is effective at low doses. At increasing doses it is associated with nausea and vomiting, which limits its use to low doses and effectively creates a therapeutic ceiling to its clinical use. Tramadol 37.5 mg combined with acetaminophen 325 mg appears to have similar efficacy to hydrocodone 5 mg combined with acetaminophen 325 mg.[129]

Tapentadol. Tapentadol is a mu opioid agonist and a norepinephrine reuptake inhibitor and is thought to control acute pain via both of these pathways. Tapentadol has similar efficacy to oxycodone for the treatment of acute pain with less frequent nausea and vomiting.[130-133] Its dual mechanism of action makes it a potentially effective drug for use in chronic pain, although it has not been studied for this use.

Opioid Agonist-Antagonist Analgesic Agents. The agonist-antagonist group of opioids was synthesized in an attempt to provide analgesia with little or no respiratory depression or abuse potential. It is believed that the analgesia provided by these agents is caused by agonist action at the kappa receptors, whereas the ceiling on respiratory depression is created by mu-receptor antagonism. Agonist-antagonist agents have rates of abuse similar to those for standard opioids and a ceiling effect to their analgesia that limits their use. Clinical application of these drugs is typically in situations in which brief, limited analgesia is needed and respiratory depression is the principal adverse concern, such as in the perinatal period.

Nalbuphine is a commonly used agonist-antagonist. The half-life of nalbuphine is 3.5 hours, and the effects of renal or hepatic disease on metabolism are not completely known. The usual therapeutic parenteral dose is 10 mg. As with all other opioids, the dose is individualized for the specific patient and clinical needs.

Opioid Use in Acute Abdominal Pain. Historically, pain treatment was withheld from patients with abdominal pain, to avoid confounding the diagnosis. This recommendation dates from the turn of the 20th century, predating modern diagnostic techniques, and has no place in modern emergency care. Multiple studies have confirmed the safety of providing effective opioid analgesia to patients with undiagnosed abdominal pain.[134-142]

Nonopioid Analgesic Agents

Acetaminophen. Acetaminophen is the first-line agent for the treatment of both acute and chronic pain and is the safest pharmacologic option for pain in children and adults. It has a high

toxic-to-therapeutic ratio and lacks significant drug interactions compared with other pain medications.

Although acetaminophen has been in use since the 1880s, its pharmacologic mechanism of action is unknown. Acetaminophen has known analgesic and antipyretic activity, with no known peripheral anti-inflammatory effects. Its activity may be a result of the inhibition of prostaglandin endoperoxide H_2 synthase and a cyclooxygenase (COX) isoenzyme centrally.[143] It may also effect the activation of beta-endorphin centrally.[144] The analgesic actions of acetaminophen are comparable in magnitude to those of NSAIDs,[145] and the analgesic effects of the combination of acetaminophen with an NSAID are additive.

Acetaminophen is metabolized in the liver primarily through conjugation to sulfate or glucuronides. A minor pathway for the oxidative metabolism of acetaminophen produces the toxic metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI). NAPQI requires glutathione for detoxification and elimination. Hepatic toxicity can occur when glutathione pathways are overwhelmed by an increase in NAPQI or a decrease in glutathione. Hepatic toxicity is rare with ingestions less than 10 g in a 24-hour period unless underlying liver disease exists or there is concomitant ethanol abuse. In such cases, therapeutic doses can cause clinical hepatotoxicity.[146]

Acetaminophen is generally well tolerated when used at therapeutic doses. Mild rashes are reported, as is bone marrow suppression, manifested by neutropenia, thrombocytopenia, and agranulocytosis. Its use is associated with several important drug interactions. Many anticonvulsants, including phenytoin, barbiturates, and carbamazepine, induce hepatic microsomal enzymes. Increased conversion of acetaminophen to its toxic metabolite may occur in patients who are taking anticonvulsants, but this is rarely of clinical significance in the context of the usual doses for pain management.

Although uncommon, drug interaction resulting in an increased international normalized ratio (INR) is reported for patients taking both acetaminophen and warfarin, particularly among patients taking high doses of acetaminophen (>9100 mg/week).[147,148] Chronic use of acetaminophen should be avoided in patients with hepatic or renal disease. Renal failure can worsen with acetaminophen use, but the mechanism is unknown.[149] Patients with a history of salicylate hypersensitivity characterized by urticaria have an 11% cross-reactivity to acetaminophen, and the agent should be used with caution in this group.[150]

For mild analgesia and fever reduction, acetaminophen is the first-line agent, and it is a first choice for use in combination with other agents, usually opioids, in the treatment of patients with more severe pain. The recommended dose of acetaminophen for an adult is 650 to 1000 mg every 4 to 6 hours, not to exceed 4000 mg/day.

Nonsteroidal Anti-inflammatory Agents

NSAIDs inhibit COX and, as a result, the synthesis of prostaglandin, a key mediator of inflammation. The analgesic effect of NSAIDs is peripherally mediated by decreasing prostaglandin and effectively raising the threshold of activation of nociceptors. NSAIDs have synergistic effects with opioids and can reduce the amount of opioids needed to achieve pain relief.

Two COX isoenzymes mediate prostaglandin synthesis. COX-1 is present in all cells and plays an important role in homeostatic functions. COX-2 is induced by injury or inflammation and generates prostaglandins as part of the inflammatory process. Nonselective NSAIDs inhibit both COX-1 and COX-2, which results in multiple beneficial effects (reduction of inflammation, pain, and fever) but also some important undesirable effects.

As a group, and because of their common use, NSAIDs are responsible for more serious drug-related side effects than any other class of analgesic drugs.[151] The major side effects of NSAID analgesic agents are gastrointestinal (GI) bleeding, renal failure, anaphylaxis, and platelet dysfunction. The majority of these side effects occur in patients who are taking NSAIDs for chronic conditions. It is estimated that more than 100,000 hospital admissions and approximately 16,500 deaths each year from GI bleeding are related to NSAID use for osteoarthritis and rheumatoid arthritis.[152] One survey estimated that for every 100,000 people taking NSAIDs each year, there are 300 GI-related deaths, 5 hepatic-related deaths, 4 renal-related deaths, and some congestive heart failure–related deaths.[153]

Bone healing and repair during NSAID use is a concern in patients with acute fractures. There is limited evidence to suggest that prostaglandins promote bone formation and that NSAIDs might inhibit the process. This question has not been thoroughly pursued, nor its answer established, through properly conducted studies.[154] There is no evidence that short-term use of NSAIDs for analgesia after fracture is deleterious to healing.

In addition to prostaglandin, COX helps generate prostacyclin, a vasodilator that increases GI mucosal perfusion. In the stomach, COX-1 increases bicarbonate and mucus production, important for protecting the mucosal lining. Inhibition of COX-1 compromises these protections, predisposing patients to ulcerations and bleeding, which are then exacerbated by concomitant NSAID-induced platelet dysfunction.[155]

COX-1 and COX-2 affect the cardiovascular system through the production of endothelial prostacyclin (vasodilatory) and thromboxane (platelet aggregation). Inhibition of COX-1 produces antiplatelet activity that may be cardioprotective by inhibiting thromboxane production more than prostacyclin production. Inhibition of COX-2 inhibits prostacyclin production more than thromboxane production and may produce prothrombotic effects, increasing the risk of cardiovascular events. In the case of nonselective COX inhibitors, these two effects appear to balance each other out, resulting in few changes in cardiovascular risk in studies of these drugs. In the case of selective COX-2 inhibitors, this may result in an increase in cardiovascular risk.[156-158]

Prostaglandin produced by COX-1 causes renal vasodilation that maintains renal blood flow and the glomerular filtration rate (GFR). Inhibition of COX-1, especially in volume-depleted patients, can result in decreased GFR and even acute renal insufficiency. Sodium and water retention, hypertension, hyperkalemia, and acute renal failure may also ensue, particularly in patients with congestive heart failure.

The most common adverse effect of NSAIDs is GI mucosal injury. In patients taking NSAIDs continuously for 1 year, 10 to 60% will develop abdominal pain, dyspepsia, or nausea and 2 to 4% will develop symptomatic ulcers.[159] Risk factors include age, concomitant use of warfarin or corticosteroids, congestive heart failure, diabetes, and coronary artery disease. There is evidence that cytoprotective agents such as misoprostol and proton pump inhibitors reduce this risk.[159,160] The relative risk of GI side effects varies with the various NSAID agents and treatment strategies (Table 3-5).

Drug Interactions

Aspirin. NSAIDs may impair the cardioprotective effect of aspirin, although the available evidence is unclear and the use of daily aspirin for cardiac prophylaxis should not deter the prescribing of an NSAID for acute pain or inflammation.[161,162]

Oral Anticoagulants. The antiplatelet effects of NSAIDs add to the anticoagulant properties of warfarin, compounding the risk of significant bleeding complications, especially from GI ulcers. Furthermore, NSAIDs displace protein-bound warfarin and cause subsequent increases in prothrombin times at a constant warfarin dose.[160] NSAID use is generally avoided in patients who are taking warfarin.

Table 3-5 Risk of Serious Gastrointestinal Effects of Nonselective Nonsteroidal Anti-inflammatory Drugs (NSAIDs)[152,153]

NSAID	RELATIVE RISK OF SERIOUS GI TOXICITY
COX-2 inhibitor	0.6
Ibuprofen	1.0
Diclofenac	1.8
Sulindac	2.1
Naproxen	2.2
Indomethacin	2.4
Tolmetin	3.0
Piroxicam	3.8
Ketoprofen	4.2
Ketorolac	24.7
Risk Reduction When Added to Ibuprofen[166]	
Proton pump inhibitor	0.09
Misoprostol	0.57

COX, cyclooxygenase; *GI,* gastrointestinal.

Box 3-4 Patients at Risk for Adverse Events during Nonsteroidal Anti-inflammatory (NSAID) Therapy

1. Patients with dehydration, hypovolemia, or impaired renal function are at increased risk for decreasing renal function or renal failure.
2. In patients with liver disease or congestive heart failure—in particular, those already taking ACE-inhibitors, ARBs, or diuretics—liver or heart conditions may worsen.
3. Elder patients are at enhanced risk for GI and renal events.
4. Patients with asthma and known aspirin hypersensitivity have an increased risk of bronchospasm.
5. In women in the third trimester of pregnancy, NSAIDs may prolong gestation or prematurely close the ductus arteriosus.
6. Patients who use tobacco or ethanol and have a history of gastritis or peptic ulcer disease are at increased risk for peptic ulcer or GI bleed.

ACE, angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *GI,* gastrointestinal.

Angiotensin-Converting Enzyme Inhibitors. Concurrent use of NSAIDs with angiotensin-converting enzyme (ACE) inhibitors may impair renal function and impair the antihypertensive effects of ACE inhibitors.

Diuretics. Patients who are taking diuretics have a greater risk of developing renal failure caused by NSAID-mediated decreased renal blood flow. Also, the natriuretic response to diuretics depends in part on prostaglandin-mediated vasodilatation.

Glucocorticoids. Patients on corticosteroids have an increased risk of peptic ulcer disease. NSAIDs should generally be avoided in patients concurrently taking glucocorticoids unless closely supervised by an ambulatory care physician.

Lithium. NSAIDs enhance lithium reabsorption and may directly reduce lithium excretion, leading to increased lithium levels. CNS symptoms (drowsiness, confusion, vertigo, convulsions, or tremors), cardiac dysrhythmias, and QRS widening are warning signs of lithium toxicity. The lithium dosage should be reduced when an NSAID is prescribed.

Methotrexate. Chronic coadministration of NSAIDs and methotrexate has resulted in prolonged, elevated blood levels of methotrexate, resulting in severe toxicity. A possible mechanism for this effect may be decreased renal perfusion caused by NSAIDS, decreasing the elimination of methotrexate.

Nonselective Cyclooxygenase Inhibitors. NSAIDs combine analgesia and anti-inflammatory effects with low abuse potential and many different side effects compared with opioid agents. Oral NSAIDs can be as effective as oral opioids for mild to moderate pain. Parenteral NSAIDs offer little advantage over their oral forms.[160,163] Different patients respond differently to both the beneficial effects and the side effects of different NSAIDs. Therefore some experimentation may be necessary for determination of the best NSAID choice for a particular patient. No particular NSAID has been proven to be superior for any indication. Drug selection should depend on availability, side effect profile, convenience, and cost. Patients at risk for adverse events with use of NSAIDs are listed in Box 3-4.

Ketorolac Tromethamine. Ketorolac is the first nonopioid analgesic agent available for parenteral use in the United States. For acute pain management, ketorolac is rarely indicated, given that 60 mg of ketorolac administered IM is not clinically superior to 800 mg of oral ibuprofen. In addition, NSAID agents can be administered at a fraction of the cost of drugs administered via parenteral routes.[163-165] The main indication for ketorolac use is in the early treatment of renal colic (accompanied by a loading dose of intravenous morphine), a pain mechanism for which NSAIDs are particularly effective.

Ibuprofen. Ibuprofen is the most widely used agent in the NSAID class. It is available over the counter in a variety of preparations, including tablets, liquid suspension, and suppository. Ibuprofen is rapidly absorbed from the upper GI tract and has minimal interaction with other medications. The adult analgesic dose is 400 mg, with an anti-inflammatory dose of 600 to 800 mg. No NSAID is more effective as an analgesic than ibuprofen 400 mg, including ibuprofen 800 mg.[165-167]

Cyclooxygenase-2–Specific Inhibitors. The discovery of two distinct COX isoenzymes (COX-1 and COX-2) raised expectations that an effective new class of analgesics could be developed. COX-2–specific agents were expected to control pain and inflammation with fewer adverse effects (particularly GI mucosal injury) than traditional NSAIDs.

Despite great initial promise, a dramatic pricing differential, and intensive marketing, the two classes of NSAIDs (nonselective COX inhibitors and selective COX-2 inhibitors) appear to perform similarly in clinical use, with similar side effect profiles. Agents that selectively inhibit COX-2 are expected to cause less ulceration and are associated with a lower risk of bleeding. COX-2 has been identified in normal gastric mucosa, however, and selective inhibitors may not confer any GI-protective advantage.

COX-2 inhibitors may have prothrombotic effects from greater inhibition of prostacyclin than thromboxane, thus increasing the risk of cardiovascular events. COX-2 inhibitors also decrease renal perfusion, thereby decreasing renin activity and reducing sodium excretion by the same amount (approximately 20%) as NSAIDs.

Given the higher relative price, a potential for adverse cardiovascular events related to long-term use, and the lack of superior safety or efficacy when compared with nonselective NSAIDs, there appears to be little or no role for COX-2 inhibitors in the ED or for acute pain management after discharge.

Skeletal Muscle Relaxants. Skeletal muscle relaxants are advocated as an adjunct to analgesics in the management of musculoskeletal pain with a spasm component, principally back pain. Despite the common use of skeletal muscle relaxants, relatively few data exist regarding their role in the treatment of pain. Studies demonstrate that muscle relaxants, such as cyclobenzaprine, are indistinguishable from ibuprofen in analgesic effect but have an increased side effect profile. Although a Cochrane systematic review claims that skeletal muscle relaxants are more effective than

placebo with respect to relieving acute low back pain, it is not possible to discern any differential or additive effect to that of NSAIDs when the primary trials are reviewed.[168]

Skeletal muscle relaxants are not of benefit in the treatment of chronic low back pain, which is their most common use.[169] Skeletal muscle relaxants should not be used in the management of acute musculoskeletal pain as a substitute for proper doses of effective analgesics unless there is a high degree of anxiety accompanying the pain and it is believed that an anxiolytic might be helpful. In that case a benzodiazepine, such as diazepam 5 mg three times daily or lorazepam 1 mg twice daily, may be an effective adjunct for pain control.

Benzodiazepines have hypnotic, anxiolytic, antiepileptic, and antispasmodic properties. Muscle relaxation with these agents is probably caused by GABA-mediated presynaptic inhibition at the spinal cord level.[169]

Nitrous Oxide and Oxygen Mixtures. Nitrous oxide–oxygen mixtures can be used in the ED or the out-of-hospital care setting to reduce anxiety in patients and to manage mild to moderate pain states. The analgesic and anesthetic properties of nitrous oxide were discovered more than 200 years ago. A mixture of nitrous oxide and oxygen in a 50:50 ratio is safe when self-administered by the patient. This technique is one of the original forms of patient-controlled analgesia.

Nitrous oxide and oxygen administered by nasal mask have long been used by dentists for the treatment of pain and anxiety. Experience in emergency medicine with nitrous oxide–oxygen mixtures is greatest in the ratio of 50:50 mixtures with self-administered hand-held masks.[170,171]

The mechanisms of analgesia and anxiolysis with nitrous oxide are not fully delineated. The agent's analgesic effect appears to be similar in nature to that of low-dose opioids and is probably mediated by a variety of neuromodulators.

Some of the anxiolytic effects of nitrous oxide appear to have more in common with benzodiazepines than opioids. It has been postulated that nitrous exerts an effect on GABA receptors.[172]

Nitrous preparations are often administered in a two-tank system, with a fixed-ratio nitrous oxide–oxygen mixture delivered to the patient through a demand-valve activated with inhalation through a face mask or mouthpiece. A negative pressure of 3 to 5 cm H_2O should be produced within the mask or mouthpiece to activate the flow of gas, limiting the use of these devices in very small children. This patient administration element provides safety for the patient-controlled aspects of the system, given that patients are required to initiate a breath while holding a mask to the face to receive the medication. This delivery mechanism also may serve to minimize the amount of nitrous oxide released into ambient air.

In 10 to 15% of patients, nitrous oxide is ineffective.[170] It is much more potent as an anxiolytic than as an analgesic agent. As with all analgesic agents, nitrous oxide administration success should be determined by the patient's subjective feedback. When necessary, nitrous oxide can be supplemented with other analgesics.

Nitrous oxide is a folate antagonist and is strictly contraindicated in pregnant patients. Nitrous oxide–oxygen mixtures are relatively or absolutely contraindicated in patients with a decreased level of consciousness who are unable to follow instructions, patients with a head injury, and those with decompression sickness. Patients with severe chronic obstructive pulmonary disease who retain CO_2 should be given nitrous oxide–oxygen mixtures carefully, given that the mixture contains 50% oxygen, which may predispose to hypercapnia. Because nitrous oxide diffuses into body cavities, it can worsen a pneumothorax or bowel obstruction.[65]

Minor side effects of nitrous analgesic gas mixtures are reported in 5 to 50% of patients. The most common adverse effect is light-headedness, with paresthesias and nausea reported less frequently. No adverse hemodynamic effects have been documented with the self-administered forms of this agent. Because of their safety, these mixtures are useful in the out-of-hospital care setting.[173,174]

Side effects attributed to nitrous oxide usually resolve within minutes of discontinuation. Chronic use or abuse of nitrous oxide is associated with vitamin B_{12} antagonism and secondary hematologic effects as well as development of myelopathy.[175,176]

Nitrous oxide requires an effective scavenging and ventilation system for prevention of accumulation and toxicity in health care workers, especially pregnant health care workers. Advanced scavenger systems are necessary for the safe use of nitrous oxide in the ED.

Local Anesthesia

Mechanism of Action

Peripheral nerves are responsible for transmitting pain information from pain receptors to the spinal cord. Each fiber consists of an axon surrounded by a covering called the *Schwann cell.* A *myelinated* axon is one that is covered by the projection of a Schwann cell that wraps itself many times around the axon, hence the term *myelin sheath.*

Local anesthetics are much more effective at penetrating unmyelinated or lightly myelinated fibers than heavily myelinated ones. This difference explains the finding that local anesthetic agents provide sensory block without motor neuron effects (see Table 3-1).

Local anesthetic agents reversibly block sodium channels of the lipid membrane and prevent the influx of sodium ions into the axon, blocking depolarization and the nerve action potential. After injection of a local anesthetic, tissue buffers increase the pH of the solution surrounding the agent, driving much of the water-soluble acidic form of the agent to its lipid-soluble nonionic form. The lipid-soluble phase of the drug is able to penetrate the lipid membrane of the axon, where it then ionizes and enters the sodium channel, blocking the channel's ability to allow sodium to enter the cell.

Classes of Local Anesthetic Agents

Local anesthetic agents are chemical compounds that consist of an aromatic and an amine group separated by an intermediate chain. Agents in the class that has an ester link between the intermediate chain and aromatic portion are called *amino esters* and include procaine, chloroprocaine, and tetracaine. Esters are unstable in solution and are metabolized in the body by the plasma enzyme cholinesterase. Amides have an amide link and include lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine. The amides, after absorption into the body, are destroyed by enzymes in the liver.[177]

Specific Agents

Each local anesthetic has a predictable effect when used in appropriate doses and by the appropriate route. The main considerations in the clinical use of these agents are potency, duration of anesthesia, and the speed of onset (Table 3-6).

Potency. The ability of a local anesthetic drug to penetrate the lipid membrane of the axon determines its potency. Agents that have high lipid solubility (e.g., tetracaine, etidocaine) are more potent than those with low lipid solubility (e.g., procaine, mepivacaine). Less potent local anesthetics should be given in more concentrated forms and in larger doses to achieve an equivalent effect.

Table 3-6 Characteristics of Common Local Anesthetic Agents

AGENT	POTENCY (LIPID SOLUBILITY)	DURATION (min)	ONSET	COMMENTS
Procaine	1	60-90	Slow	Solutions of 0.5-2% used in infiltration and blocks
Tetracaine	8	180-600	Slow	Topical for ophthalmic use
Lidocaine	3	90-200	Rapid	Most commonly used agent; 1.5 times as toxic as procaine
Mepivacaine	2.4	120-240	Very rapid	Less potent and less toxic than lidocaine
Bupivacaine	8	180-600	Intermediate	Long-acting agent used in infiltration and blocks
Etidocaine	6	180-600	Rapid	Twice as toxic as lidocaine; used mostly in epidurals

Adapted from Paris PM, Weiss LD: Narcotic analgesics: The pure agonists. In: Paris PM, Stewart RD, eds. Pain Management in Emergency Medicine. Norwalk, Conn: Appleton & Lange; 1988.

Duration of Anesthesia. Agents that bind well to protein in the sodium channel are longer acting. Tetracaine and bupivacaine have a high affinity for protein and provide long-lasting anesthesia, whereas procaine, a poorly bound agent, does not.

Onset of Action. In most cases it is helpful to have an anesthetic agent that acts quickly. The speed of onset of any local anesthetic agent is directly related to how quickly that agent, after injection, can diffuse through tissues to the nerve and through the nerve membrane.

After injection the anesthetic agent is in two forms, ionized and nonionized. The amount of drug in the nonionized form is determined by its pK_a (the pH at which 50% of the solution is nonionized and 50% is ionized). Because only the nonionized form of the drug diffuses into the nerve, solutions with a low pK_a have a more rapid onset of anesthesia. Local anesthetic agents with higher pK_as take effect more slowly. At a tissue pH of 7.4, 5% of tetracaine (pK_a 8.5) is in the nonionized form compared with 35% of lidocaine (pK_a 7.9) solution.

Low tissue pH (5 or 6) in surrounding infected tissue delays the onset of local anesthesia in situations such as abscess incision and drainage. In this case the anesthetic primarily remains in an ionized state. The onset of action of a local anesthetic can be hastened by the alkalinization of the solution carrying the drug, which also decreases its irritant effect (pain) on injection. This can be done by adding sodium bicarbonate solution to the anesthetic at a ratio determined by the pK_a of the agent (see later).[178,179]

Several other factors influence the clinical effects of local anesthetic agents. These agents (except cocaine) are vasodilators, which tend to shorten the duration of anesthesia. Injection of the solutions into vascular tissues not only shortens the duration of anesthesia but also increases systemic absorption and the chance of systemic toxicity when larger doses are used. For these reasons, epinephrine is often added to local anesthetic solutions.

Allergy. When an allergy to local anesthetics is reported, the offending substance is often one of the preservatives used. True allergies to local anesthetics are exceedingly rare. Because the amide agents and amino ester agents do not cross-react and because different preservatives are used with them, a patient may be given a medication from another class if the allergy history is consistent with a specific anesthetic group. In one study, 236 patients with reported adverse reactions to local anesthetics underwent testing with commercial preparations of unrelated local anesthetics. No patient in the study exhibited systemic reactions.[180]

In patients reportedly allergic to all "-caine" anesthetic agents and in whom the allergy is believed to be legitimate, diphenhydramine can be used as an alternate agent. Diphenhydramine may be used with 1 mL of a 50-mg/mL ampule diluted to 5 or 10 mL (1-0.5% solution) to be used for local infiltration or nerve block. Diphenhydramine may cause direct tissue toxicity and should be avoided in areas with poor collateral circulation.[181,182]

Local and Systemic Toxicity

Local Toxicity. Local anesthetic agents, depending on the concentration, can be directly toxic to tissue. In addition, it is possible that the use of a vasoconstrictor in an anesthetic solution may produce a reduction in blood flow that could increase wound healing time and the vulnerability of the wound to infection. This concept has never been formally demonstrated. Many argue that this reasoning suggests that nerve blocks are preferable to local infiltration for wounds that are extensive, contaminated, or in areas without collateral circulation.

Epinephrine-containing solutions have traditionally been avoided on digits, the penis, the ears, or the nose. It is suggested, however, that dilute epinephrine can be used safely on digits and possibly these other areas as well.[183] A comprehensive review of the use of epinephrine in digits concludes that it is safe when diluted to 1:200,000 or less but should not be used in patients with vascular disease.

Systemic Toxicity. Systemic toxicity of local anesthetics occurs when a sufficient quantity of the drug accumulates in the body so that sodium channel blockade occurs in the heart or the brain. There is a dose-related clinical progression of local anesthetic toxicity from subtle neurologic symptoms to seizures to cardiovascular collapse.

All local anesthetics produce systemic toxicity at sufficiently high blood or CNS concentrations. Each local anesthetic has a range of therapeutic safety, beyond which systemic toxicity is more likely to occur (Table 3-7). Overdosage of local anesthetics may occur more commonly in patients with large wounds and in very small patients.

The more lipophilic anesthetic agents (e.g., etidocaine, bupivacaine) are more cardiotoxic. Cardiac toxicity may also be increased for epinephrine-containing anesthetics when inadvertent intravenous injection occurs. Special care should be exercised in children and when performing certain blocks known to produce high blood levels of the anesthetic agent (e.g., intercostal). In pediatric patients, total dose guidelines are important, and the maximum dose should be calculated before administration.

A wide variety of symptoms may be experienced from local anesthetic toxicity. These include light-headedness, headache, paresthesias, tinnitus, decreases in level of awareness, and muscle spasm.[184] The degree to which CNS symptoms are experienced is directly related to the blood level of the local anesthetic.

At the extreme, CNS toxicity may result in seizures. A typical clinical progression usually begins with circumoral paresthesias, dysarthria, and a report of tinnitus or a similar auditory phenomenon. These events may be followed by a decreased level of consciousness progressing to confusion, seizures, and coma. Longer-acting, more potent agents (e.g., bupivacaine and etidocaine) are more likely than lidocaine to cause CNS symptoms at lower blood levels.[184]

Table 3-7 Guidelines for Maximum Doses of Commonly Used Local Anesthesia Agents*

AGENT	WITHOUT EPINEPHRINE	WITH EPINEPHRINE
Lidocaine HCl†	3-5 mg/kg	7 mg/kg
Mepivacaine HCl	8 mg/kg	7 mg/kg‡
Bupivacaine HCl§	1.5 mg/kg	3 mg/kg

Adapted from Stewart RD: Local anesthesia. In: Paris PM, Stewart RD, eds. Pain Management in Emergency Medicine. Norwalk, Conn: Appleton & Lange; 1988.
*All maximum doses should be reduced 20-25% in very young, old, and very sick patients.
†A lidocaine level of 0.5-2.0 g/mL may be reached for every 100 mg of lidocaine infiltrated for blocks.
‡Epinephrine adds to the potential cardiac toxicity of this drug.
§Not to be used for pudendal blocks or intravenous regional anesthesia. Not recommended for children younger than 12 years.
HCl, hydrochloride.

Box 3-5 Techniques That Can Be Used to Reduce the Pain of Injection

Buffering of local anesthetic agents
Counter-irritation
Slower rate of injection
Use of topical anesthetics
Warming of solution
Distraction techniques

Local anesthetic–induced seizures should be treated with intravenous benzodiazepines. Local anesthetic agents also have direct effects on cardiac automaticity, conductivity, contractility, and vascular tone. Management of cardiovascular collapse caused by toxic levels of local anesthetic agents should follow standard advanced cardiac life-support guidelines. Unless the overdose is massive, the toxicity should be relatively short-lived because of the redistribution of the lipophilic agents.

Reducing the Pain of Local Anesthetic Injection

Distraction by manual methods such as scratching, jiggling, or repetitively pinching the skin during needle puncture or injection reduces the discomfort experienced during local anesthetic injection (Box 3-5).[185] The addition of sodium bicarbonate to lidocaine immediately before injection significantly reduces patient discomfort.[179] A standard solution of sodium bicarbonate (8.4% in 50 mL) can be added to a syringe containing lidocaine in a ratio of 1:10 (e.g., 1 mL bicarbonate to 10 mL lidocaine, or 0.5 mL to 5 mL). Buffered lidocaine can be stocked in the ED and is effective for up to 1 week.[186] Bupivacaine also can be buffered, but the ratio should be 1:50 (i.e., 0.1 mL bicarbonate to 5 mL bupivacaine).

Slow injection of local anesthetics also attenuates the pain of infiltration, and to a greater degree than buffering of the solution.[187] Injection of local anesthetic into the edges of the laceration is less painful than injection through intact skin surrounding the wound.[188] When time permits, warming the anesthetic or applying a topical anesthetic agent can also greatly decrease the initial sensation associated with needle injection.[178]

Topical Anesthesia

Topical anesthetics are generally of two types: those that can be applied to intact skin and those used on open skin. The agents are absorbed and exert their anesthetic effect on adjacent superficial nerves. The topical application of local anesthetics should be done with just as much caution as injection of anesthetics to avoid systemic toxicity. The dose of topical anesthetic should be monitored to avoid applying doses associated with toxicity. As with injectable local anesthetic agents, topical solutions are often described in terms of percent of agent; 1% equals 10 mg/mL of anesthetic, and a 5% solution has 50 mg/mL.

Topical agents are particularly useful in children and in patients who are intimidated by needles. Topical agents do not provide anesthesia as effectively as subcutaneous infiltration or nerve blocks. These agents may provide a substantial decrease in the intensity of superficial stimuli. The long application time necessary for effective analgesia can be a principal drawback of these agents. In some patients the ritual of applying the topical anesthetic and delaying the procedure until there will be less pain can be an effective tool in controlling pain and the response to subsequent interventions.

Topical Anesthetics Applied to Intact Skin

Eutectic Mixture of Local Anesthetics. Eutectic mixture of local anesthetics (EMLA) is a mixture of lidocaine and prilocaine in an alkaline oil mixture in which the anesthetics are present primarily in their nonionized form, allowing them to diffuse through the skin. The term *eutectic* refers to mixtures that result in a melting point higher than that of either agent alone.

An EMLA mixture should be applied to the desired area with an occlusive dressing 30 to 60 minutes before the desired procedure is performed. Heating EMLA for 20 minutes improves analgesia, but the heated mixture is less effective than a routine 60-minute application with or without heat.[189] The duration of action after a 60-minute application is 1 to 5 hours.

Indications for the use of EMLA include venipuncture, arterial puncture, lumbar puncture, or arthrocentesis when a 30- to 60-minute delay in performing the procedure is not an impediment. EMLA can be applied in triage, particularly for pediatric patients, whose intravenous injection can then be started later in the ED with little or no pain.

Ethyl Chloride and Fluori-Methane sprays. Ethyl chloride and fluori-methane sprays are occasionally used for superficial analgesia. The agents evaporate quickly and cool the skin, providing brief (<1 minute) local anesthesia owing to the cold. The induced analgesia is brief, and any injection or incision should be made immediately after the application of the agent, which will typically be observed to create a brief "frosting" effect in which the skin blanches white.

Agents Applied to Mucosal Surfaces

Cocaine. Cocaine is unique among local anesthetic agents given that it is a potent vasoconstrictor in addition to being an anesthetic that can be applied to mucosal surfaces. Cocaine is frequently used in the nose, where a 4% (40 mg/mL) solution provides rapid anesthesia for the treatment of epistaxis and other nasal procedures. Although the maximum safe dose is unknown, a total of no more than 200 mg is typically applied in adults. Cocaine should not be used in patients with known coronary artery disease owing to the potential for coronary artery vasoconstriction.

Lidocaine. Both 2% and 4% lidocaine solutions are available in a viscous matrix for use on mucosal surfaces. Gel lidocaine can be used in nasal procedures, including the passing of nasogastric tubes and gastric lavage tubes. It can be used for urethral anesthesia during Foley catheter placement as well, but to be effective it is injected into the urethra with a catheter-tip syringe and be in contact with the area for 5 to 20 minutes. Lidocaine spray (4 or 10%) is useful for upper airway anesthesia, including intranasal use for nasogastric tube insertion.

Tetracaine. Tetracaine is a potent ester used for surface anesthesia of the cornea. Tetracaine stings when placed in the eye, but

only for 10 to 15 seconds, after which there is excellent corneal anesthesia.

Benzocaine. Almost insoluble in water, benzocaine remains on mucous membranes in the mouth and is used commonly to provide superficial analgesia for oral procedures and pain.

Agents Applied to Open Skin

Tetracaine, Adrenaline, and Cocaine. The combination of tetracaine, adrenaline (epinephrine), and cocaine (TAC) has been largely replaced with lidocaine, epinephrine, and tetracaine (LET). From 5 to 10 mL of this combination of agents may be applied to an open wound with sterile cotton, which is then covered and held in place for 10 to 20 minutes. Anesthesia has been described in approximately 85% of cases of wounds of the scalp and face and a lower percentage of extremity wounds.[190] Application of the solution to mucous membranes (eye, intranasal) can result in toxic blood levels of tetracaine and should be avoided.[191]

Lidocaine, Epinephrine, and Tetracaine. LET is as effective as and less expensive than TAC.[192,193] To account for the 20-minute onset, the application can be administered at the time of triage in children with a simple laceration.[194]

Intravenous Regional Anesthesia (Bier Block)

The intravenous regional anesthesia procedure known as the *Bier block* is an effective and rapid technique to anesthetize extremities for fracture reduction or repair of extensive wounds. This method involves the intravenous injection of a local anesthetic agent (lidocaine, prilocaine) into a previously exsanguinated limb. This procedure is adapted for use in the ED in the form of a mini-dose of 100 mg of lidocaine and is described in procedure manuals. A safe alternative is to use the relatively nontoxic local anesthetic agent prilocaine.

Nonpharmacologic Interventions

Transcutaneous Electrical Nerve Stimulation

TENS systems use electrical stimulation to induce analgesia, likely through the activation of descending sensory pathways and modulation of nociceptive signals at the level of the spinal cord. TENS units include a pulse generator, an amplifier, and electrodes. Studies show varying degrees of effectiveness, and the devices are rarely indicated for use in the ED.[195,196]

Hypnosis

The induction of hypnosis allows patients to refocus attention away from pain and anxiety-producing stimuli to other images and feelings. Hypnosis can be used as an adjunct to pharmacologic interventions or as a substitute. Hypnosis can be induced with only brief interventions on the part of the clinician.[197,198] Hypnosis is usually not practical in the ED owing to time constraints and distracting ambient noise.

Pain Management in Children

Pain in children is both more difficult to assess and more challenging to treat. When used properly, most of the interventions can be used in children. The major difference in providing analgesia to children is the difficulty of accurately assessing the perception of pain, particularly in the very young.[199]

The general approach to a child can be important in developing a trusting relationship with both child and parent. Both verbal and nonverbal cues from the child and parents should be observed and appreciated, given the unique developmental aspects of each age group. Threatening equipment should be de-emphasized (e.g., syringes, scissors, and suture holders should be kept out of sight of the child). Play therapy and a slow, friendly, nonthreatening manner can be helpful. The decision to separate children from their parents should be individualized, but separation should be avoided when possible.[200]

Most principles relating to pharmacokinetics of drugs, including absorption, distribution, and elimination, are similar for children and adults. In neonates and infants younger than 3 months, opioid clearance is delayed, plasma drug levels are higher because of decreased protein binding, and the blood-brain barrier is immature and more permeable to opioids. Opioids should be given carefully to patients in this age group and at smaller weight-based doses than are used in older children. Neonates also require smaller doses of local anesthetics owing to decreased protein binding and slower metabolism. For mild pain, acetaminophen can be very effective in doses of 15 mg/kg PO or 20 mg/kg rectally (PR) every 4 hours. Sucrose solutions are effective agents in this age group when applied to a pacifier and given PO.

Pain Management in Elder Patients

Approximately 80% of elder patients have at least one chronic ailment commonly associated with pain.[201] Elders are more sensitive to analgesics, especially opioids, and reduced dosages achieve adequate analgesia while avoiding side effects.

Opioids, even in low doses, may produce sedation, confusion, or constipation in the elder patient. The patient and caregivers should be alerted to these possibilities. NSAIDs are used in reduced doses or avoided altogether in the elder patient, given the potential for adverse effects on renal function.

The assessment of pain in elder patients can be complicated by depression, dementia, and atypical patterns of pain presentation.[202] As with children, careful attention should be paid to the assessment of pain in the elderly owing to communication barriers.

Out-of-Hospital Analgesia

Out-of-hospital providers frequently encounter patients with painful conditions. Patients obtain pain relief more quickly when pain medications are initiated by out-of-hospital personnel, although pain control in the out-of-hospital setting is challenging to perform adequately.[203-206]

Protocols for the administration of fentanyl and morphine exist in most emergency medical services (EMS) systems and are usually limited to single-dose therapy before orders are obtained from the medical control physician.[207] There is no difference in the relative value of fentanyl or morphine as the initial agent for prehospital pain treatment.[208]

The out-of-hospital environment is less controlled than the ED, and the information regarding a patient's underlying condition is more limited, making the safe administration of pain medications more difficult. As in the ED, establishing rapport with the patient, providing calm reassurance, and using careful movement and handling, including proper splinting, are the first steps to which pharmacologic support can be added. Pain can be assessed in the out-of-hospital setting through use of numerical and verbal rating scales, as would occur in the ED.[209]

Unfortunately, moderate to severe pain is treated infrequently in the out-of-hospital environment.[210,211] One study of lower extremity and hip fractures demonstrated that only 18% of patients received an analgesic.[210-212] Self-administered 50% nitrous oxide offers many advantages for use in the field.[213] In addition, morphine 0.1 mg/kg is safe for out-of-hospital use and should be considered the first-line agent for severe pain as it is in the ED.

BOX 3-6 Common Outpatient Pain Agents by Type

Analgesic Options for Acute Pain
1. Acetaminophen

Opioids to Be Used in Combination with NSAIDs and Acetaminophen
2. NSAIDs
3. Oxycodone
4. Hydrocodone

Analgesic Options for Chronic Pain
1. NSAIDs
2. Tramadol

Opioids to Be Used in Combination with NSAIDs and Acetaminophen*†
3. Oxycodone long-acting preparation or for breakthrough pain
4. Tricyclic antidepressants

Analgesic Options for Neuropathic Pain
1. Gabapentin
2. Tricyclic antidepressants
3. Carbamazepine

NSAIDs, nonsteroidal anti-inflammatory drugs.
*A variety of opioid and acetaminophen combination agents are available.
†Chronic opioid management should be managed by the primary outpatient physician.

The National Association of EMS Physicians encourages the increased use of analgesics in the out-of-hospital environment.

TREATMENT ENDPOINTS

Pain is a subjective experience, and use of pain relief as the endpoint of treatment results in a subjective marker of treatment success or failure. In the ED, management of acute pain should specify the initial dose, the repeat dose and interval, and a specific desired endpoint, such as the patient expressing that pain is at 3 or less on a 10-point pain scale. Pain orders that are wide-ranging or vague should be avoided in the acute setting, given that they frequently lead to underdosing and inadequate pain relief.

KEY CONCEPTS

- Pain should be rapidly assessed, treated, and frequently reassessed in tandem with diagnostic evaluations (see Fig. 3-7).
- Therapy for acute pain is different from therapy for chronic pain (Box 3-6).
- Titrated intravenous opioid analgesics are the principal therapeutic approach to the treatment of moderate and severe acute pain. The intramuscular route has several disadvantages and is not recommended.
- Oral oxycodone, with an onset of action similar to that of intramuscular or subcutaneous opioids, can be used for mild to moderate pain when an intravenous injection is not otherwise needed.
- Acetaminophen and NSAIDs should be added to pain therapy when not contraindicated.
- Morphine, fentanyl, and hydromorphone are the preferred parenteral opioid agents in the ED.
- There is no validity to the belief that morphine causes more smooth muscle spasm than other opioids. Morphine is safe and appropriate for patients with acute biliary or renal colic.
- Topical and local anesthetics can be used to treat pain associated with the majority of ED procedures and should be considered for use in isolated painful conditions.
- Low tissue pH (5 or 6) in infected tissue delays the onset of local anesthesia.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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