Chapter 21

PAIN MANAGEMENT

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INTRODUCTION

How should acute or chronic pain from combat and noncombat wounds and injuries be managed? What are the psychiatric implications of the control or elimination of the pain of injuries?[1] Which wounds cause the worst pain? Do the manifestations of pain in (or treatment strategies for) civilians differ from those for soldiers? Which emerging treatments can help? Are analgesic requirements met, or are they underestimated as in the past?[2,3] Is drug-seeking behavior a contraindication to use of analgesics, or not? It is important to differentiate, with the patient's help, pain resulting from injury, surgery, dressings, amputation, and physical therapy, as well as other types of pain associated with injury, illness, and emotional suffering. Pain caused by combat wounds and noncombat injuries in military personnel and in affected civilians are significant in the current context and may cause subsequent psychopathology.[4–7] Consistent with the medical team approach, collaboration of surgeons, psychiatrists, anesthesiologists, and allied personnel is key to optimal management of pain due to wounds and injuries.

A primary task of medical personnel caring for the wounded, second only to assuring the safety of the patient and staff, is to relieve pain. Prompt, accurate diagnosis of mental disorders is key to the effective and safe relief of pain. Diagnosis of delirium,[8] preexisting brain injury, substance abuse, psychosis, posttraumatic stress disorder (PTSD), Axis II disorder, or depression will affect measurement of pain, diagnostic procedures, precautions, and choice of analgesia. Failure to observe the lack of a pain response in a patient with a history of serious past trauma, or in a chemically paralyzed patient with the inability to communicate a pain response, or not diagnosing delirium, risk of violence, or high alcohol or drug levels, may cause preventable suffering or even death.

Finding solutions to managing pain leads to central clinical and research questions in the care of injuries to patients of all ages. The answers have been modified or discovered in the last 25 years. Previous publications by the authors of this chapter have addressed posttraumatic psychological and neurobiological aspects of injury pain at different stages in the life cycle, and different stages postinjury.[9–12] Pain is an essential focus of the requirements of the Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations), practice guidelines, treatment protocols, and continuing education. Prevention and relief of acute or chronic pain is more achievable as a result of treatment initiated at the scene of injury and continued throughout care. Pain relief for adults and children has a primary place in life-saving surgical care. Furthermore, it is important from a metabolic point of view because it decreases the stress response that activates the release of the catabolic hormones, catecholamines, and cortisol. Treatment to control metabolic and stress responses in burns, for example, has been tested to confirm a reduction in subsequent stress as outlined below.

Which wounds cause the worst pain? The patient is the judge of this, and will answer with self-report if asked, but may not volunteer this information, especially if stoical in temperament. Orthopaedic injuries including amputation may cause patients to rate pain "25" on a 0-to-10 scale, and the pain may rapidly recur with a delay in administering a dose of morphine. Burn patients frequently report their most severe pain being caused by dressing changes or from the donor sites for skin grafts. Although any bodily location—including internal organs—can be the site of severe pain, areas that are highly innervated, and thus most likely to be painful after wounds, are common locations of the most severe pain. These include parts of the face, scalp and neck, arms and hands, genitals and perianal area, and legs. Unexplained behavioral symptoms including confusion, combativeness, anger, emotional withdrawal, or anxiety may be secondary to an unrecognized wound, or a wound causing unrecognized pain.

There is growing evidence to indicate that successful pain relief appears to lessen posttraumatic stress, anxiety, and depression, although in one study, the *N*-methyl-D-aspartic acid (NMDA) antagonist ketamine, which is widely used in burn care, was shown to increase PTSD symptoms while protecting against posttraumatic reduction of hippocampal volume.[13] That study is of 30 burned adults, 15 with and 15 without PTSD, and provides "evidence that smaller hippocampal size in trauma-exposed individuals is a result of traumatic stress."[13(p2194)] Pain continues to be the subject of extensive research, and in hospital settings ongoing pain monitoring and team consultations for complex cases is the standard of care. Such teams include nurses, surgeons, anesthesiologists, psychiatrists, neurologists, pharmacists, physical therapists, ethicists, and others. Pain in those with injuries is the subject of great clinical attention, systematic evaluation, focused research, and a broad and growing range of pharmacological and psychological treatment options. Converging research in both genomics and neurobiology promises to offer new options to improve pain management for the injured patient in the future.

There is a well-established knowledge base with

which to design plans to manage and eliminate pain in injured children and adults.[14,15] Making appropriate use of this knowledge is important for everyone caring for those in pain. The evaluation of children's pain requires understanding their ways of communicating, stage of development, their mental impairments, and the emotional, as well as physical, effects of pain in selecting the appropriate treatments. Similarly, evaluation of adults' pain requires listening to their complaints of pain and recognizing the unique needs of special populations, such as intensive care patients, those with mental or physical disability, substance abusers, and the elderly.

Although psychological elements of treatment, such as preparation for painful procedures and hypnosis, are less likely to be covered by protocols than pharmacological approaches, they enable patients to lessen their own pain and are effective components of care.[1,16–18] Psychological methods of pain relief do not have the risks of drug side effects, toxicity, or dependence but may be less effective than drugs. Systematic pharmacological research with severely injured patients has established the benefits of acute management with high-dose morphine and possibly benzodiazepines (although some literature indicates lorazepam may worsen outcomes),[19] other analgesics, and adjuvants, utilizing intravenous and other routes of administration, mainly in ventilated patients. Further advances in management of injury pain are continuing.

A large contribution to pain control for military wounded has been in the field of regional pain control. It is now possible for casualties of bullet or blast injuries to have at least one extremity rendered pain free by the ultrasound-guided placement of a nerve-block catheter and administration of appropriate anesthetic. These catheters may be maintained in place and connected to infusion pumps. This may allow the casualty to remain pain free during the first surgical interventions in theater, through the evacuation to Europe, and through washout and further debridement at Landstuhl Army Regional Hospital in Germany and across the Atlantic to military hospitals in the United States. It is anticipated that this will prove to be another contribution to a lower incidence of narcotic addiction and complex regional pain syndromes in casualties of the global war on terror.

The two temporal components of pain due to acute injuries include acute and chronic pain, which are further classified. Acute pain, the principal subject of this chapter, includes both background pain and procedural pain. Acute pain may be worsened by anxiety, depression, sleep deprivation, and "regeneration of nerve endings (possible neuroma formation, known as postburn neuralgia)."[20(p319)] Chronic pain is usually present for months to years and may not be easily relieved. It may result from scarring, contractures, and injury to a bone or joint; from bone formation in soft tissues (heterotopic ossification)[21,22]; or injury to the peripheral nerves (neuropathic pain). Although this chapter is not comprehensive, it provides scientific background, case illustrations, clinical approaches, and pertinent references to assist in developing an optimal multidisciplinary plan for pain management of patients suffering from combat and noncombat injuries.

ANATOMY OF INJURY-RELATED PAIN

The anatomic location of pain is a sign of tissue injury, underlying infection, or systemic illness. The sensory detection of pain (nociception) and pain are not the same. Nociception is, according to Sherrington,[23] the sensory detection of a noxious event of potentially harmful environmental stimulus. Pain, in contrast, involves sensory and cognitive components, and is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage."[24] The anatomy of pain involves both central and peripheral nervous systems.[25] Patients with larger injuries generally suffer more pain. Due to the involvement of both central and peripheral nervous systems, and afferent and efferent pathways, approaches to pain management are needed to address both central brain and spinal cord receptors and peripheral nerve receptors.

Injury-Related Pain Cases

Case Study 21-1: A 26-year-old Afghani civilian male was injured by enemy rocket fire, sustaining a gaping penetrating injury to his left knee. The patient was dragged by his comrades to an austere casualty collection point inside a secure bunker. He presented screaming and clutching his left knee. Primary survey revealed normal mentation and respiratory status. A rapid secondary survey revealed no other injuries.

The patient was clearly stirred by the visual appearance of his knee. He was given an 800-μg fentanyl transmucosal lozenge to suck on while his knee was rapidly immobilized and dressed and he was comforted by one of his battle buddies. By the time intravenous access was obtained (less than 5 min), his pain response had significantly improved. The simple act of immobilizing and dressing (and thereby concealing) his injury was the essential treatment for his pain. Thirty minutes after his initial assessment, he was titrated with small boluses of intravenous ketamine (0.25 mg/

kg) to a comfortably dissociated state, whereupon a gross decontamination of his wound with copious irrigation could be performed.

The patient's pain was subsequently controlled with immobilization and intermittent use of self-administered transmucosal fentanyl during the next 8 hours until transport could be arranged. The profound effect of covering and immobilizing his wound significantly decreased his pain response.

Case Study 21-2: A 55-year-old Iraqi male sustained direct-fire injury to his left foot, ankle, and tibia. He was treated with a tourniquet for hemorrhage control in the field and was rapidly transported to a surgical element. He was otherwise uninjured and remained alert through his transport. The associated direct-fire injury to several key nerves limited his immediate pain response; pain control was achieved initially through immobilization and intermittent small doses of intravenous morphine.

The surgeon's assessment was that the patient's best option for a functional recovery in the current environment was through a below-the-knee amputation allowing for maximum stump length. As the patient was counseled (through an interpreter) as to the surgical options of either attempts at limb salvage (with tremendous potential for follow-up infection, difficult rehabilitation, and fusion with limited range of motion) or amputation, the patient's "pain" became acutely worse.

After confirming that there had been no change in the status of his injured extremity to account for the surprising increase in pain, the interpreter was asked to inquire from the patient what would alleviate his new increase in "pain." Upon questioning, he made clear the overwhelming angst he felt at the recommendation to amputate his leg. His answer routinely was "Insha'Allah" (English translation "God willing" or "If it is God's will"). The surgeon required a decision from the patient, but the patient was unable to make the decision.

It became apparent that to treat the patient's pain and to continue with any treatment regimen, the patient's psychological pain needed to be addressed. Through the continued verbal analgesic work and religious discourse of the Muslim interpreter, the patient eventually became much less distraught and his pain improved markedly. The patient was subsequently able to make a decision.

This case demonstrates the multifactorial components of pain generation, even in relatively acute traumatic denervation, and how these factors can precipitate a clinically severe pain syndrome, which may be relieved by a culturally appropriate intervention in the patient's own language.

Case Study 21-3: A 4-year-old girl was caught in a burning house, sustaining a 55% full-thickness flame burn and an inhalation injury. Immediately after rescue, she was intubated at the scene by responding medics because of respiratory distress. To facilitate intubation and ventilation during transport, she was chemically paralyzed with cisatracurium and sedated with approximately 0.05 mg/kg of midazolam and 0.05 mg/kg of morphine sulfate as single bolus doses. As a result of witnessing her injuries, her parents were severely traumatized, but reassured that she was receiving optimal care.

On arrival to the burn unit she was placed on continuous infusions of these same drugs, at 0.05 mg/kg/h each, and muscle relaxation was stopped to allow a more accurate assessment of comfort. Assessment after spontaneous reversal of neuromuscular blockade revealed a grimacing, writhing child in need of further analgesia and sedation. The morphine sulfate and midazolam infusions were increased, titrating to a Richmond Agitation-Sedation Score of -2.[3] Over the following 2 weeks, until she was extubated, background infusions of these agents were gradually increased, as tolerance developed, in response to continuous monitoring of the status of her comfort. During this time she needed several skin grafting operations, which are associated with substantial postoperative pain. At maximum, doses required to maintain appropriate comfort were 0.50 mg/kg/h of morphine sulfate and 0.40 mg/kg/h of midazolam.

Procedural pain and anticipatory anxiety were important issues for her because she required at least daily bedside procedures during this period of intubation. Sedation for these interventions (dressing changes, intravenous line placement, wound debridement) was provided by the addition of ketamine intravenous boluses at 1 mg/kg, repeated every 20 minutes as needed. When she was awake, the continuous presence of her parents, their verbal explanations and reassurance, and their touching her also facilitated her coping with pain, fear, and hospitalization.

Donor site and skin graft healing were complete by 2 weeks, coincident in improvement of the child's inhalation injury. After extubation, the need for sedation was lessened by removal of the endotracheal tube and for analgesia by healing of wounds. Intravenous background infusions were reduced by 10% per day, alternating drug reductions every 12 hours (eg, 0600 hours reduction in morphine and 1800 hours reduction in midazolam). During this period, as her pain and anxiety lessened, her parents became less stressed and more effective in supporting her and participating in dressing changes.[26]

Case Study 21-4: An 18-year-old man was involved in a high-speed truck accident and trapped in the wreck, which then caught fire. He suffered fractures and deep burns to both legs, a 65% mixed second- and third-degree surface area burn, and a comminuted closed fracture of the right humerus. After extrication and transport, he was intubated and mechanically ventilated for 4 weeks. His comfort management plan included escalating infusions of morphine sulfate and midazolam, supplemented by intravenous boluses of propofol (2–3 mg/kg) for procedures. At day 10 he underwent tracheotomy, which reduced his requirement for intravenous sedation. He underwent excision and grafting of his wounds, but required bilateral below-the-knee amputations. On weaning his sedation he was transiently delirious, and then manifested intrusive recall of the accident contributing to flashbacks and insomnia, which were relieved by lorazepam. He was initially depressed in response to his massive injuries, but this lessened with supportive psychotherapy, acceptance by his friends, and messages of family support. In his recovery phase, he developed severe neuropathic phantom leg pain that interfered with his rehabilitation. This improved with gabapentin, allowing him to be successfully fitted with prosthetics. After 6 months he was able to discontinue the gabapentin.[27]

BIOLOGY OF PAIN

There are several important concepts relevant to pain mechanisms to consider: (*a*) pain receptors in the skin (nociceptors), (*b*) the opioid system, (*c*) increased pain sensitivity (hyperalgesia), and (*d*) the emerging role of the nonopiate pain adjuncts including inhibitors of the enzyme cyclooxygenase-2 (COX-2) and gabapentin.

Pain associated with trauma including burn or other tissue injury is transmitted by peripheral nociceptors—the peripheral endings of primary sensory neurons whose cell bodies are in the dorsal root of the spinal cord and trigeminal ganglia. Unlike other sensory receptors in the skin, nociceptors are without specialized transducing structures and essentially exist as free nerve endings. Different classes of nociceptive fibers can be involved in the experience of pain. Thermal or mechanical nociceptors convey stimuli rapidly (up to 30 m/sec) via thinly myelinated, small-diameter fibers classified as "A" or "A delta." Polymodal nociceptors are also activated by hot stimuli, but transmit impulses more slowly (up to 2 m/sec) along small-diameter unmyelinated "C" fibers. Both A delta and C fibers are widely distributed in skin and in deep tissues.[12] Nociceptive fibers, both A and C, enter the dorsal horn of the spinal cord and split into ascending and descending branches. The fibers terminate primarily in lamina I and in lamina II, although some A-fiber afferents may terminate more deeply in lamina V. Within lamina I, different projection neurons process the incoming stimuli. "Nociceptive-specific" neurons are only excited by nociceptors, but "wide-dynamic-range" neurons receive their input from both nociceptors and other mechanoreceptors.

Several ascending pathways convey afferent stimuli to the brain. The spinothalamic tract originates in lamina I and laminae V–VII and is the major ascending pathway for nociceptive input. The nociceptive-specific and wide-dynamic-range projection neurons in this tract terminate in the contralateral thalamus, particularly ventrobasal and posterior thalamic nuclei. The spinoreticular tract originates in laminae VII and VIII and sends both ipsilateral and contralateral projections to the reticular formation and thalamus. The spinomesencephalic tract originates in laminae I and V, where it projects to the contralateral mesencephalic reticular formation, the periaqueductal gray, and other sites within the midbrain. The spinocervical tract, and even the dorsal column of the spinal cord, also can convey nociceptive stimuli. In addition, in the dorsal horn, A-B fibers conveying sensations such as vibration and light touch are involved in the modification of pain transmission via inhibitory interneurons.

There are multiple projections from thalamic nuclei to the cortex, primarily somatic sensory and association cortex. Although at least two classes of somatosensory cortical neurons can be identified with respect to their receptive fields and source of thalamic input, nociceptive inputs do not map to the cortex as do tactile inputs. Further, lesions to the somatosensory cortex do not result in loss of pain, suggesting that parallel or distributed processing of nociception in the cortex is likely.[28,29] Studies examining cortical activation following painful stimuli highlight the multiplicity of regions involved, including the contralateral prefrontal cortex, as well as the middle and inferior frontal gyrus (Brodmann areas 6, 8, 9, 44, and 45).[30,31]

The intense barrage of incoming pain stimuli associated with a trauma results in a decrease in thresholds for subsequent excitation of spinal neurons, as well as a greater response to subsequent stimuli and an expansion of receptive fields.[32]All of these adaptive changes likely underlie the increased pain sensitivity, or hyperalgesia, that typically follows a significant burn or multiple traumas. Hyperalgesia has long been characterized as "primary" if limited to the area of injury or "secondary" if it extends to areas adjacent to the site of damage.[33] Primary hyperalgesia appears to require sensitization of both peripheral nociceptors and spinal neurons, whereas secondary hyperalgesia seems to depend on sensitization of spinal neurons alone.[34,35] Both types of increased pain sensitivity can occur immediately following injury, but secondary hyperalgesia may take hours before reaching its peak and is likely to resolve before primary hyperalgesia.[30] Interestingly, experimental data suggest that chemosensitive nociceptors can be recruited to become mechanosensitive receptors following injury.[31] This ability to recruit otherwise "silent" nociceptors may play a role in primary hyperalgesia following injury or inflammation.

Any form of major trauma, including burn injury, results in a local and systemic response that includes fever, anorexia, and pain in the injured (primary hyperalgesia) and uninjured areas. Until recently, as indicated in the previous paragraph, this sensation was thought to occur by transmission of nerve impulses from the injured region to the spinal cord and the brain.[36] Other mechanisms, in addition to nerves, may play a role.[37] Drugs that silence sensory nerves work well to relieve acute pain. When inflammation occurs, drugs for acute pain are less effective. Local inflamma-

tion at the site of injury (eg, burn) causes a rapid and long-lasting increase in the proinflammatory-signaling molecule in the brain, especially interleukin-1β in the cerebral spinal fluid. Blockers of interleukin 1β (eg, COX-2 inhibitors) strongly inhibit the hypersensitivity to pain.[36,37] Increased levels of interleukin-1β cause increased expression of COX-2 and prostaglandin E synthase, with a resultant increase in prostaglandin E_2. Thus the use of COX-2 inhibitors currently available will not only have antiinflammatory and antipyretic effects but also have antihyperalgesic effects by acting at local and central sites. Among those available are celecoxib (Celebrex [Pfizer Inc, New York, NY), nimesulide (Mesulid [various manufacturers], and meloxicam (Mobic [Abbott Laboratories, Abbott Park, Ill]). Additionally, trauma/inflammation-induced upregulation of protein kinase Cδ (PKCδ) and NMDA in the spinal neurons may also play a role in the hyperalgesia and mechanical allodynic.[38] A growing body of evidence supports the notion that the upregulation of protein kinase Cα (PKCα) and NMDA are implicated in the mechanisms of chronic nociception.[38] Hence the rationale for use of drugs such as ketamine, an NMDA antagonist.

PRINCIPLES OF PAIN THERAPY

Laboratory research is clarifying the synthetic and degradative pathways by which the levels of endogenous opioids are maintained in the body.[39,40] In addition to the clarification of the dynorphin gene, the neural systems involved in pain and anxiety have been located. The three classes of endogenous opioid peptides are: (1) endorphin, (2) met-leu-enkephalin, and (3) dynorphin. Additional transmitters modulating pain include the monoamine (dopamine, norepinephrine, and serotonin) systems, substance P, and the γ-aminobutyric acid system—each with its own specific brain receptor sites. Clinically, opioids are the first-line drug used to treat pain associated with injury. Selection of analgesics such as nonsteroidal antiinflammatory drugs (NSAIDs), COX-2 inhibitors, benzodiazepines, anticonvulsants, and adjuvants (eg, stimulants, tricyclic or serotonergic antidepressants, neuroleptics) may be made to modulate and potentiate the effects of narcotics. However, the analgesic effects of opioids are unpredictable, particularly under chronic pain conditions. This is partly due to downregulation of opioid receptors,[37] and to the development of a condition called opioid-induced hyperalgesia (OIH).

Recent observations suggest that chronic administration of opioids leads to OIH. Thus, treatment with opioids is a double-edged sword; the treatment of pain may lead to a hyperalgesic state. OIH can occur during maintenance therapy, withdrawal, or both. OIH has been studied in three different clinical settings: (1) in former opioid addicts on methadone therapy, (2) in patients treated with opioids, and (3) in human volunteers. OIH can occur following both low-dose and high-dose opiate therapy.[41–43] Mechanisms involved in OIH include sensitization of peripheral nerve endings, enhanced facilitation of the nociceptive signal transduction, altered kinetics of nociceptive transmitters, and increased sensitization of the second-order neurons to neurotransmitters.[41,43] Excitatory amino acids (glutamate), NMDA receptors, and PKC seem to play a role in the development of OIH. The greater the opioid therapy, the greater the OIH will be.

Tolerance to opioids can also occur acutely[44]; this emphasizes the importance of alternative or adjunct therapy with opioids for treatment of pain. Strategies to treat tolerance and OIH can include rotation from phenanthrene (morphine) to a piperidine (fentanyl) opioid derivative. The administration of NMDA antagonists (ketamine) prevents opioid-induced hyperalgesia and also overcomes tolerance.[45] Dexmedetomidine, an α_2 agonist more potent than clonidine, has analgesic/sedative effects, particularly in combination with other drugs, and may reduce the incidence of delirium and other complications of withdrawal from opiates.[46–49]

Experience gained from treating other pain-associated conditions such as cancer, herpes, diabetic neuropathy, and degenerative diseases can also be applied to posttraumatic pain syndromes.[50] The available therapies shown to be effective include anticonvulsant drugs, tricyclic and other antidepressants (duloxetine, venlafaxine), topical lidocaine, and tramadol. Of great recent interest is gabapentin. The mechanism of its action is unclear, but its effects on the $\alpha_2\delta$ calcium-channel subunit may result in decreased release of the neurotransmitter and suppression of central sensitization.[51] The combination therapy of gabapentin with morphine resulted in greater reduction of pain than did either drug alone or placebo. The combination also had beneficial effects on pain-related interference with daily activities, mood, and quality of life.[51] Combination therapies have the potential to simultaneously alleviate pain, insomnia, and mood instability or depression. Tolerance will most likely develop to this combination based on previous reports on receptor behavior and neuroplasticity.

ADVERSE EFFECTS OF PAIN

Many factors contribute adverse physiological, behavioral, and psychological effects to the experience of pain and injuries.[52] It is often difficult to differentiate the specific contribution of pain to the range of psychological problems that develop following injury. The injury itself may or may not be unexpected and normally initiates an ongoing experience of severe pain. Shortly after the injury, these patients often find themselves in an emergency setting where they may undergo application of wound dressings and possibly extensive surgery. Hospitalization involves separation from the military component and friends, who themselves may have been injured or killed. Treatment usually includes painful dressing changes and support for adjustment to permanent and emotionally traumatic changes in their bodies' appearance and function. The traumatic nature of severe injuries is compounded by the fact that some are inflicted in battle, while others are due to mistakes, accidents, or intoxication, or are intentionally inflicted or self-inflicted. Injured patients frequently manifest severe psychological reactions such as nightmares, flashbacks, acute sadness and grief, irritability or anger, and behavioral regression.[11,53] For example, the psychological intensity of burn trauma, and particularly the relentless stress of extended hospital treatment for a burn, has been compared to "inescapable shock" or "learned helplessness,"[54] both of which are models for PTSD.[55,56]

About one third to one half of injured people eventually develop PTSD, and over half display significant posttraumatic stress symptoms.[57] PTSD and posttraumatic stress symptoms are reactions to diverse traumatic events related to combat and civilian injuries, assaults, witnessing violence, disasters, medical illness, physical and sexual abuse, and other psychological traumas not involving injury.[58,59] Symptoms of this disorder include increased intrusive recollections, numbing and avoidance, and hyperarousal.[60] The manifestation of these symptoms is triggered by environmental factors, such as exposure to objects, people, or situations reminiscent of the trauma. PTSD occurs when symptoms are experienced for most days and interfere in either a social or occupational setting. PTSD causes significant difficulties for a person's social, educational, occupational, biological, and life-cycle development. Children with PTSD are often so preoccupied with intrusive recollections or are so hyperaroused that they have difficulty processing social information.[61,62]

The intrusion of trauma-related memories and extreme levels of arousal that traumatized individuals experience interfere with job performance and learning at school. Traumatized people often avoid social situations secondary to fear and anxiety that memories will reoccur. Patients with injuries also develop mood (especially depressive), anxiety, sleep, sexual, behavioral, elimination, and attentional problems. PTSD symptoms cause tremendous morbidity and may persist for many years. Evidence indicates that once posttraumatic symptoms become persistent, they are refractory to treatment.[63] Accordingly, it is important in each case of a person sustaining an injury to seek interventions that may prevent or ameliorate the development of PTSD. Evidence is slowly accumulating suggesting that the early postinjury preventive or therapeutic administration of cognitive behavior therapy, or of drugs (eg, morphine, propranolol, serotonin reuptake inhibitors, or tricyclic antidepressants) can block the emergence of PTSD symptoms in some cases, including combat injuries.[64–68]

GENETICS

This section briefly outlines the genetics of pain, the genetics of opiate drug responses, and the important genetic determinants of racial differences in response to pain or its treatment. The human genome project has revealed data on genomic variations that may influence pathologic states, and are certain to influence treatment advances in the future. Nevertheless, the molecular biology and genetics of pain has lagged behind the research in diseases such as hereditary, cardiovascular, and oncologic disorders. Reports continue to emanate, however, on the genetic factors influencing nociceptive sensitivity and responses to drugs. Genes involved in pain perception, pain processing, and pain management include opioid receptors, transporters, NMDA receptors, α_{2A} adrenoceptors, and more recently discovered, guanine triphosphate cyclohydrolase—the rate-limiting enzyme for tetrahydrobiopterin synthesis, a key modulator of peripheral neuropathic and inflammatory pain.[69,70]

Pain is a complex trait with interaction of multiple genes, each with varying effect, that together with environmental and cultural factors, play a role in sensation of pain. Altered sensitivity to pain can be due to hereditary disorders; usually these are due to homozygous disorders. For example, a mutation in nerve growth factor has been found and in this instance there was complete absence of pain.[71] Recently, a "pain protective haplotype," the guanine triphosphate gene, has been identified with allelic frequency of 15%.[72] This haplotype was associated with decreased pain sensitiv-

ity in low-back-pain patients following herniated disc surgery and in volunteers undergoing experimental pain.[70] The degree of activity or inactivity of enzymes that metabolize drugs may also influence drug efficacy. It is well established that polymorphisms of the cytochrome P-450 (CYP2D6) enzymes influence analgesic efficacy of codeine, tramadol, and tricyclic antidepressants.[69] Similarly, blood levels of some NSAIDS are dependent on CYP2C9 activity.

Catechol-o-methyltransferase is a key regulator of pain perception, cognitive function, and affective mood. Polymorphisms in this enzyme and μ-opioid receptors are known modulators of pain sensitivity and opioid efficacy.[73,74] In addition to endogenous factors that alter pain sensitivity, exogenously administered small molecules (peptides) that can alter gene activity have been shown to influence pain response. Progress in molecular biology has enabled gene expression modulation (in animal models) using "knock outs" or antisense ribonucleic acid (RNAi) and small RNA molecules (sRNA). Gene therapy for patients with chronic pain shows encouraging results. Additional studies that have been performed on candidate genes transmitting pain include opioid receptors, transporters, and other targets of pharmacotherapy. Future studies should also elucidate the side-effect profiles of these gene manipulations. The challenge is to deliver this RNAi or sRNAs to target tissues such as the central nervous system. Genes can also affect signaling pathways related to pain sensitivity and clinical response.[7,74] Future studies could characterize the roles of different genes and metabolizing enzymes along with demographic and clinical variables that may influence treatment of pain both in acute and chronic situations.[75]

Few studies of pain in humans have described the ethnic or racial background of their subjects. In spite of this limitation, findings from any given study are then generalized to other ethnic and social groups, although there is no evidence base for such generalization of the results of these studies. Therefore, genetic studies of varying ethnic and social groups are indicated. The importance of genetic factors controlling drug disposition and response has received increased attention.[76] For example, the variability of a single drug, midazolam, was 11-fold.[77] Selective sequencing of CYP3A4 and CYP3A5 genes revealed 18 single-nucleotide polymorphisms (SNPs), including eight novel CYP3A4 SNPs. These differences may or may not account for such variability. Thus, the so-called standard doses of a drug may have toxic effects in some but fail to produce expected effect in others. Racial and ethnic differences have been described for a range of drugs and reflect genetic, environmental (cultural and dietary), and pathogenetic causes. Polymorphism of drug-metabolizing enzymes (eg, CYP2D6 of the cytochrome P-450 system) is well recognized and can affect drug therapy, such that lower or higher drug doses should be used. Thus, differences in response to pain treatment can be due to pharmacokinetic, pharmacodynamic, or pharmacogenetic factors. The identification of such genetic differences will result in better therapeutics. The role of pharmacogenetics can also be confounded by injury-induced alterations in drug metabolism.[78]

METHODS OF PAIN ASSESSMENT

The perception of pain is subjective and poses unique challenges for its objective assessment. The measurement of pain has developed to assess both the self-report of pain experience and behavioral observations. Behavioral measurements can lead to data correlating behaviors to subjective reports of pain. Self-report measures are used for patients over 4 years of age, and require sufficient cognitive and language abilities. Psychiatric disorders may indicate an increased requirement for analgesia. For example, a severely injured woman with borderline personality disorder who complained constantly of pain was later shown to have had negligible levels of endorphins. Alternatively, patients with Axis II psychiatric disorders may exaggerate their needs for analgesia and need psychiatric or substance abuse evaluation, especially in later stages of care when their wounds are largely healed. Other patients, such as those suffering depression or bipolar disorder, once treated with antidepressants or mood stabilizers may have significantly reduced pain. Patients with factitious disorders may use pain or self-inflicted injuries to obtain opiates. Patients with a brain injury, delirium, or limited cognitive and language skills may not be able to accurately complete self-report measures of pain.

Various methods assess pain in children.[79] Surveys of pediatric anesthesiologists have reported that the infant's respiratory rate is commonly used as an indicator of pain.[80] Other useful behavioral indices in young children include facial expression,[81] body movement (particularly limb withdrawal to painful signals[82]), and crying. Psychophysiological indices include blood pressure, pulse, respiratory rate, and neurochemical activity.[82] There are combined behavioral and psychophysiological indices (eg, the COMFORT scale,[83] which is composed of six behavioral dimensions [alertness, calmness, muscle tone, movement, facial tension, and respiratory response] and two physiologi-

cal dimensions [heart rate and mean arterial pressure]) to assess postoperative pain. Using this scale, it was found that the most accurate variables for measuring pain were behavioral activity, mean arterial pressure, and heart rate.[84] Methods in older patients take advantage of the ability to self-report symptoms and experiences. The Poker Chip Tool[85] allows children ages 4 to 8 to describe their pain as "pieces of hurt," using one to four poker chips. The Faces Scale[86] asks children to choose a picture of a face with expressions of various gradations of pain, rated 0 to 5, from "no pain" to "the worst pain."

The most practical and standard pain assessment tools in adolescents and adults are verbal or visual (or both) analogue scales, asking patients to rate their pain on a continuum of intensity along a line using numerical anchors, commonly from 0 to 10, from "no pain" to "the worst pain."[87] Visual analogue scales, the most commonly used instruments, have good psychometric properties and are easily administered. The numerical anchors have been enhanced in the visual analogue instruments by adding colors to the intensity ratings.[75] Pain diaries are also useful, and require the repeated numerical rating of pain over the course of time along with other relevant information such as activities, stressors, or alleviation with medications.

Comfort management will have different priorities depending on the locale of care: prehospital, inpatient, and outpatient. In the prehospital setting, the priority must be safe and efficient care. The airway must be secured. The patient must cooperate with evaluation and transport. Medication policies should be simple and follow trained protocols. These protocols generally rely on intravenous opiate and benzodiazepine dosing, and may include drugs to facilitate endotracheal intubation, including neuromuscular blocking agents.[88]

In the inpatient setting, the focus is on continuous evaluation and titration of sedatives and analgesics. Inpatient protocols may be more complex, and importantly include regular objective evaluations of pain and anxiety using one or more of several available scales.[89,90] Inpatients may also benefit from patient-controlled analgesia devices, which have been shown to be associated with reduced total opiate requirements.[91] Peripheral nerve blocks[92] or continuous epidural anesthesia are an excellent adjunct in some patients, particularly in the management of short-term or postoperative lower body pain.[93]

In the outpatient setting, where monitoring is less feasible, patient safety is an added important consideration. A differentiation should be made between neuropathic pain (eg, phantom pain) and more standard pain (eg, open wounds). The former is ideally addressed with nonopiate medication or alternative therapies to avoid the specter of opiate dependence.[94]

METHODS OF PAIN MANAGEMENT: OVERVIEW

Until 20 years ago, pain management for acutely injured patients was relatively neglected due to concerns about respiratory depression and its effect on survival. Pain became recognized as critically undertreated, increasing physiological stress and adversely affecting outcomes. Improved pain relief became a priority and was successfully addressed by increased use of opiates, benzodiazepines, other analgesics, and anxiolytics. Today, in managing the pain of severely injured patients with intractable pain and anxiety, combinations of agents are commonly used, with close monitoring of vital signs and symptoms. Among these agents are high-dose opiates and benzodiazepines, NSAIDs, and the judicious use of both atypical and typical antipsychotics, antiepileptic drugs, and antidepressants. Signs of physiological dependence such as increased pulse, blood pressure, or insomnia are common upon tapering sedatives after prolonged administration but do not indicate psychological addiction; these signs are managed by adjusting the weaning regimen.

Pharmacological approaches are the first-line treatment in management of pain due to combat or noncombat injuries. In addition, psychological methods are essential in conjunction with drugs, and their effectiveness is also well established. These include psychoeducation, psychological preparation for procedures, relaxation techniques, hypnosis and self-hypnosis, guided imagery, and therapeutic touch. Psychological approaches enhance trust and communication with the patient, facilitating hope, positive coping, and optimal recovery despite potentially stigmatizing disfigurement and functional losses.

PHARMACOLOGICAL MANAGEMENT OF ACUTE PAIN

Two key principles in acute management of pain include frequent reassessment and dose titration. It is not possible to predict with accuracy the medication requirements of an individual patient. These will vary with pain intensity, anxiety state, personality characteristics, and distractions. Frequent reassessment of the efficacy of pain and anxiety control is essential. Ideally, these findings are documented so that pain and anxiety control can

smoothly transition between shifts of caregivers. There are several acceptable scales that are validated for this purpose.[95] Analgesic and anxiolytic doses will need to be titrated to the findings from these reassessments.

Ideally, every patient care unit will have specific written guidelines describing the preferred methods of pharmacological pain management. These guidelines should have a limited formulary to facilitate development of a working knowledge of drugs used by all staff, and allow for bedside dose-ranging depending on the findings at regular reassessment.

There are a limited number of drug classes used in acute comfort management. The cornerstones are opiates and benzodiazepines. Opiates are potent analgesics with some sedative properties. Although they are very effective, side effects are common and include respiratory depression and ileus. Benzodiazepines are potent anxiolytics. The synergy between these two classes of drugs is strong.[96] Other drugs useful in this setting are propofol (a short-acting intravenous anesthetic), ketamine (an intravenous dissociative agent), haloperidol (an intravenous antipsychotic), and dexmedetomidine (a centrally acting α_2 agonist). A complete program of pain and anxiety management in the intensive care unit is beyond the scope of this chapter, but the reader is referred to many excellent reviews.[97] The important point is that acute pain and anxiety management will have an important effect on subsequent incidence and severity of acute and posttraumatic stress symptoms.[65] Frequent pain and anxiety assessment should be a regular part of care of all acutely injured patients.

PSYCHOLOGICAL MANAGEMENT OF PAIN AND GRIEF

Psychological strategies are quite effective for pain[1] and for associated anxiety and grief. Reassurance, supportive interventions, increasing structure, and a variety of psychosocial interventions geared to the patient's interests can be extraordinarily helpful in relieving pain, anxiety, and the sense of helplessness. Videos, television, hypnosis,[18] guided imagery, relaxation, virtual-reality methods, and therapeutic touch may also effectively relieve pain and discomfort. They should be individualized, because some methods are more acceptable for one individual than for another; they are well established as key interventions for pain relief, with a very low risk of adverse or toxic effects. Psychological management of the patient and interventions also include assessment for safety, empathic listening, modifying cognitive distortions through cognitive behavior therapy, providing hope, and facilitating a positive long-term attitude toward recovery.

Regarding pain-associated sadness and grief, psychotherapeutic approaches should respond to the phase of grief (including grieving their injury) the patients are in, and their phase of recovery from injury. Such grief exacerbates pain, and may be triggered by loss of a close buddy, seeing children die, mass casualties, or terrorist attacks. Some bereaved patients will have prolonged grief disorder, newly proposed for DSM-V.[98] Prolonged grief disorder is distinguished from bereavement by causing impairment for at least 6 months with one of these three symptoms in criterion B, which is called "separation distress":

1. intrusive thoughts related to the deceased,
2. intense pangs of separation distress, and
3. distressingly strong yearnings for that which was lost.

These symptoms must occur daily or to an intense or disruptive degree. In addition, five of the following nine symptoms of criterion C, "cognitive, emotional, and behavioral symptoms," must be present daily or to an intense or disruptive degree:

1. confusion about one's role in life or diminished sense of self;
2. difficulty accepting the loss;
3. avoidance of reminders of the reality of the loss;
4. inability to trust others since the loss;
5. bitterness or anger related to the loss;
6. difficulty moving on with life;
7. numbness (absence of emotion) since the loss;
8. feeling that life is unfulfilling, empty, and meaningless since the loss; and
9. feeling stunned, dazed or shocked by the loss.

The duration must be at least 6 months from the onset of separation distress; it must cause clinically significant distress or impairment in social, occupational or other important areas of functioning; and lastly, it cannot be due to a substance, general medical condition, or other disorder. When present, family support is key to relieving pain, anxiety, and grief. Family understanding, coping, resilience, and capacity to support need to be assessed and reinforced. Provision of supports, including counseling and psychotropic medications where indicated, facilitates the capacity to care for the patient.

SPECIAL PROBLEMS

Ventilated Patient

Analgesia and sedation in the mechanically ventilated patient has the added factor of maintaining airway security and patient safety. The agitated patient will not only suffer emotionally, but may die if the endotracheal tube or vascular access devices are dislodged.[99] A "lightly asleep but arousable" state, or a Richmond Agitation-Sedation Score of -2, is a common objective when caring for intubated patients in the intensive care unit.

Burns and Multiple Traumas

Patients with burns and multiple traumas will have very large amounts of noxious stimulation associated with wounds and their management. The level of analgesic required can have adverse effects on respiratory and hemodynamic status. At times, these adverse effects must be accepted and managed (via mechanical ventilatory or vasopressor support or both) to ensure adequate patient comfort and safety. It is important that other potential causes of these problems (most commonly sepsis) be excluded.

Amputation Pain

Amputated limbs are a common cause of acute and chronic pain syndromes. It is important to distinguish acute surgical pain (eg, bone and soft-tissue pain) from neuropathic pain (eg, phantom pain), as pharmacological and nonpharmacological management strategies differ.[100]

Weaning

Most pain and anxiety medications stimulate receptor changes that mandate weaning if consequences of abrupt withdrawal are to be avoided.[101] Opiate withdrawal will cause tremulousness, autonomic hyperactivity, diarrhea, and emesis. Benzodiazepine withdrawal can result in seizures. Gradual weaning is well tolerated, with low rates of withdrawal symptoms or drug dependence, even when very high drug doses are used acutely.[102]

Pediatric Pain

Pain in children is treated according to similar principles to those outlined in this chapter, but with specific changes adapted to the pediatric population for body weight, any pediatric illnesses, developmental status, and dependency on parents and family.[10] Dosages are calculated on a milligram per kilogram basis, and treatment is modified if there is concomitant pediatric illness. The developmental status of the child—infant, toddler, school age, and adolescent—requires adaptation to the physical, mental, emotional, and relationship characteristics of those stages.

Psychiatric Risk Factors

The principal risk factors for pain complications include inadequate analgesia, delirium, unrecognized infection or injury, sleep disorders, preexisting psychopathology, self-inflicted injuries, prior addiction, PTSD or other anxiety disorder, emergent depression, somatoform disorders, and factitious disorder. Diagnosis and specific treatment of these conditions or disorders is essential to effectively manage the associated pain. Not all apparently psychological contributions to pain are that, and further diagnostic investigation is often warranted.

Pain Management and the Issue of Addiction

Prior addiction to or abuse of alcohol or other substances is very commonly associated with noncombat injuries, as is withdrawal from the drug of abuse, especially alcohol, during acute treatment of the injuries. As a result, treatment of all injuries should include a careful history of substance abuse, toxicology screening, ongoing evaluation of possible withdrawal, treatment of withdrawal symptoms, and interventions to reduce the risk of continuing addictive behavior posttreatment.[103]

THE ETHICS OF PAIN CONTROL

Pain control may become complicated. As noted above, inadequate relief of pain results in increased risk for adverse psychiatric sequelae and poorer outcomes. There is therefore an ethical obligation to relieve pain to reduce the likelihood of harm. Acutely, treatment of serious pain is occasionally complicated by excess sedation, respiratory depression, or hypotension. Over the longer term with chronic pain management, drug dependency can occur, particularly in patients who have been substance abusers. If, in the management of chronic pain, overuse of pain medication occurs or is perceived, serious medical com-

plications may arise and could result in challenging medicolegal consequences. It is an ethical imperative that such risks, as well as those of undertreatment, are acknowledged, considered, and appropriately managed in formulating a sound treatment plan for the injured patient.[104–106]

SUMMARY

The objective of this chapter is to aid in improving management of acute or chronic pain from combat and noncombat wounds. It addresses the psychiatric implications of the control or elimination of injury pain, the wounds causing the worst pain, and differences in treating soldiers from civilians. Four case examples (of patients aged 4, 18, 26, and 55) that were presented with combat and noncombat injuries provide practical illustrations of the range of approaches to pain problems needing evaluation and treatment. Biological factors are presented that affect pain, including anatomic, genetic, and pharmacological considerations. A range of established and emerging treatments is described, and ways to assess whether or not analgesic requirements are met, underestimated, or exceeded are detailed. The problem of addictive behavior in the military must be considered both acutely, and later in care, but is not a contraindication to providing adequate pain relief. Approaches to pain from injury, surgery, dressings, amputation, and emotional causes are discussed. Pain caused by wounds and other injuries in military personnel and civilians is significant, and may trigger subsequent PTSD, depression, or behaviors associated with disability, especially in vulnerable individuals. Consistent with the medical team approach, as well as the authorship of this chapter, multidisciplinary collaboration of psychiatrists, surgeons, anesthesiologists, and allied personnel is key to optimal pain management.

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