Chapter 11

PAIN MANAGEMENT AMONG SOLDIERS WITH AMPUTATIONS

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INTRODUCTION

Pain management is increasingly recognized as a critical aspect of the care of the polytrauma patient. Aggressive analgesia not only decreases pain but also produces myriad benefits such as improving sleep–wake cycles; decreasing anxiety, stress, and depression; improving pulmonary mechanics; decreasing ileus; reducing hospital stay; decreasing cost; and improving overall outcome. Additionally, aggressive acute pain control leads to a reduction in chronic pain, which remains a persistent challenge: chronic pain rates are over 50% following many surgeries and trauma conditions.[1–6]

HISTORY

Various methods to reduce pain were tried before the development of specific analgesics. In the 17th century, the Italian surgeon Marco Aurelio Severino applied ice to injured areas to reduce pain, but the technique was limited by resultant frostbite, slow onset of relief, painful administration, and limited depth of analgesia. In the 18th century, various compression devices used to reduce pain in extremities were somewhat effective yet limited by their associated ischemic pain and the direct discomfort of the device. The mid-19th century brought several pivotal developments in acute pain management.[7–11] First, Friedrich Serturner extracted morphine from the opium plant in 1803, naming it "morphia" after the Greek god of dreams. Local anesthesia for analgesia became possible through the inventions of the syringe by Charles Gabriel Pravaz of France, the hollow needle by Alexander Wood of Scotland, and the extraction of cocaine from the coca leaf by Albert Niemann of Germany. Carl Koller demonstrated the effectiveness of topical cocaine at the Congress of Ophthalmology in Germany.

Regional anesthesia quickly followed when American William Stewart Halsted performed various peripheral nerve blocks (PNBs), usually via cut-down techniques, in the late 1880s. James Leonard Corning injected cocaine in the lower thoracic "dorsal vertebrae," with numbness occurring 20 minutes later, probably due to epidural blockade. In 1897 George Washington Crile, surgeon and founder of the Cleveland Clinic, performed one of the first leg blocks for a traumatic amputation and introduced the term "block" to describe the effect of blocking afferent input from the periphery to the brain. The desire for safer local anesthetics led Heinrich Braun of Germany to develop procaine (Novocain; Hospira, Inc, Lake Forest, Ill) at the turn of the century as well as the addition of epinephrine to prolong the duration of blockade. Harvey Williams Cushing furthered the use of "cocainization of nerve trunks" prior to amputation as a means to block neural fibers, which were felt to cause shock and hemorrhage in the early 1900s.

Brachial plexus blockade techniques expanded at the outbreak of the First World War when three German physicians, G Hirshel, D Kulenkampff, and M Kappis, demonstrated the first axillary block, supraclavicular block, and interscalene block, respectively. In 1939 meperidine became the first synthetic opioid available, and fentanyl followed 20 years later. Building on the continuous spinal anesthesia techniques of William Lemmon and EB Touhys, F Paul Ansbro introduced continuous supraclavicular techniques in 1946, followed by Manuel Martinez Curbelo's 1949 continuous epidural technique.[12–14] Early nerve localization techniques relied on paresthesias; later anesthesiologists pursued nerve stimulation in the 1960s and 1970s and most recently began using portable high-resolution ultrasound machines.[15–21] Finally, Susan Steele and Ottmar Kick introduced continuous peripheral nerve blocks (CPNBs) in 1998 and 1999.[22,23]

Phantom limb pain (PLP) has been recognized as a significant problem in the amputee patient for centuries; as 16th century French surgeon Ambroise Paré noted, "Truly, it is a thing wondrous, strange, and prodigious which will scarce be credited, unless by such as have seen with their own eyes and heard with their own ears, the patients who many months after cutting away the leg, grievously complained that they yet felt exceeding great pain of that leg so cut off." Silar Weir Mitchell, a surgeon during the US Civil War, is credited with the term "phantom limb pain" to describe this phenomenon.[24]

NEUROPHYSIOLOGY AND MECHANISMS OF PAIN

Neurophysiology

Understanding the normal nociceptive pathway, including the four processes in the sensory pathway of pain perception (transduction, transmission, perception, and modulation), is critical to understanding the specific types of neuropathic pain that many amputees experience. In addition, knowledge of the nociceptive pathway lays the foundation for an understanding of how regional analgesia at various points in the path-

way may be beneficial, and demonstrates that regional analgesia is pathophysiologically a crucial part of the multimodal regimen, which is most effective in the treatment of pain.[25,26]

Transduction

Peripheral nociceptors such as free nerve endings and mechanoceptors convert noxious stimuli into neural impulses that travel along A-δ (fast, myelinated) fibers and C (slow, unmyelinated) fibers, which transmit first (sharp, injurious) pain and second (dull, visceral) pain, respectively. Peripheral sensitization, or lowering of the pain transduction threshold, occurs in severe tissue injury and is maintained by a cycle of mediators, including prostaglandins, leukotrienes, kinins, histamines, substance P, and serotonin, causing more tissue damage. These products of the arachidonic acid pathway are major mediators of hyperalgesia, so inhibitors of this pathway are likely key to any analgesic regimen for pain secondary to severe limb injury.[25]

Transmission

Nociceptive impulses including first (sharp, injurious) pain and second (dull, visceral) pain are transmitted via A-δ (fast, myelinated) fibers and C (slow, unmyelinated) fibers, respectively, which synapse with second order neurons within laminas I, II, and IV of the dorsal horn of the spinal cord using substance P and excitatory aminoacids (aspartate, glutamate). The contralateral spinothalamic tract comprises the majority of second order neurons and ascends to the thalamus; third order neurons transmit pain from the thalamus to the sensory cerebral cortex, the cingulate cortex, the amygdala, and the insulate gyrus.

Perception

The third order neurons, including lateral thalamic projections to the cerebral cortex and medial thalamic projections to the reticular formation (emotional aspect), contribute to the perception of pain. Many medications including opioids, anticonvulsants, antidepressants, and α_2-agonists affect the perception of pain in these areas.

Modulation

The efferent descending inhibitory fibers from the corticospinal tract, hypothalamus, and periaqueductal gray areas modulate afferent input at laminas I and V (primarily) of the dorsal horn by decreasing neurotransmitter release. Serotonin, norepinephrine, and opioid-like encephalins (especially within lamina II at the substantia gelatinosa) are known neurotransmitters in the descending pathways. Modulation is augmented by intrathecal spinal opioids and intrathecal α-agonists.

Mechanism of Phantom Sensations and Phantom Limb Pain

A phantom limb experience is defined as the continued perception of a missing limb, the simple tactile awareness of the missing limb, and the perceived ability to move the missing limb, most likely due to a persisting central nervous system representation of the limb.[26] Between 90% and 98% of all patients who have undergone limb amputation experience a vivid phantom, with even higher incidences following traumatic limb loss or following a preexisting painful condition in the limb. Phantom limb sensations, including tingling, itching, burning, movement, temperature changes, pressure, and pain occur as soon as an anesthetic wears off in 75% of cases, but development of these sensations may be delayed up to several weeks.[27–30] PLP and phantom sensations tend to be brief and last from days to weeks for most amputees, but can become chronic. Sherman et al[31] found in a study of several thousand amputees that over 70% continue to experience PLP as long as 25 years following a limb amputation. A recent epidemiologic study by Richardson and Turo[32] was performed to investigate all postamputation phenomena in a homogenous group of amputees (all with peripheral vascular disease). Sixty amputees were recruited, but only 52 survived until a 6-month postoperative interview. Phantom sensations (kinetic, kinesthetic, exteroceptive) were universal (100%). "Telescoping," the sensation of the distal end of the phantom limb becoming progressively closer to the residual limb, was the most common kinesthetic aspect reported in 67.3% of cases, PLP occurred in 78.8% of cases, and residual limb pain occurred in 51.2% of cases.[32]

The phantom limb tends to occupy a fixed or "habitual" posture. For example, following upper limb amputation, many patients report experiencing the limb as partially flexed at the elbow, with the forearm pronated. However, the phantom limb sometimes occupies a painful or awkward posture (ie, a tightly clenched fist).[28] A soldier who was holding a grenade that exploded in his hand reportedly experienced a phantom hand clenched in a painful posture,[33] and the authors have heard similar experiences from Operation Enduring Freedom and Operation Iraqi Freedom patients treated at Walter Reed Army Medical Center. Thus, the phantom limb may sometimes be experienced as a reactivation of preamputation memories of the limb. Telescoping occurs in two-thirds of limb

amputees.

Many theories have been proposed for the etiology of PLP.[34] The development of neuromas was once thought to cause phantom sensations and pain. Neuromas are bundles of severed nerve fibers that can send ectopic pain impulses through the spinal cord and the thalamus to the somatosensory cortex. However, removal of neuromas does not relieve phantom limb sensation or phantom pain.[35] Modifications of spinal neurons that were dependent on the neurons that subserved the formerly innervated limb may be another explanation for phantom limb sensations. Excessive spontaneous firing of spinal neurons that have lost their proper sensory input from the deafferented limb may be interpreted as PLP or phantom sensations when these abnormal impulses reach the brain.[36–38] However, studies of individuals who were born without limbs but still exhibit phantom limb sensations show no excessive firing of spinal neurons because peripheral nerves connected to these neurons have never developed, suggesting that this theory is probably incorrect.[27]

Most likely, a central representation of the limb persists and is responsible for meaningful experiences of the limb, as proposed by Melzack's "neuromatrix theory."[39] According to this theory, a central representation of the limb is formed and modified within a neuromatrix, a neural network that subserves body sensation; contains the somatic, visual, and limbic systems; and produces characteristic nerve-impulse patterns.[39] This network of neurons is present throughout the brain and has synaptic links that are genetically determined but later sculpted by sensory inputs. The repeated cyclical processing and synthesis of nerve impulses creates a characteristic pattern called the neurosignature. The phantom limb experience is produced by the same neuromatrix that underlies the intact bodily experience. Phantom pain may thus result from the deprivation of modulating inputs from the limbs to the neuromatrix, which can then cause an abnormal neurosignature to be produced.[39]

Therefore, PLP is most likely the result of cortical reorganization within the somatosensory and motor cortices. The brain contains several complete somatotopic maps (homunculi) of the body surface.[40] The primary motor area, lateral premotor area, supplementary motor area, parietal cortex, and basal ganglia all contain complete somatotopic representations of the body.[41,42] It was once believed that these maps were fixed following critical periods during infancy.[43] However, many studies suggest that sensory maps can undergo remodeling in the adult brain.

Experimental evidence demonstrates that the amount of cortical reorganization is associated with the severity of PLP and likely plays a prominent role in its emergence.[44] Studies using noninvasive imaging techniques, such as functional magnetic resonance imaging, have demonstrated changes within the somatosensory and motor cortices in amputees.[45,46] Ramachandran and Hirstein[28] found that sensory maps reorganize in such a way that specific points along the neighboring sensory area evoke modality-specific referred sensations such as warmth and pain. However, if there is a slight error in cortical reorganization such that some of the touch input is accidentally connected to pain areas, it is theorized that amputees may experience pain when these regions are touched.[28] Finally, a sympathetic mechanism that increases sympathetic activity may maintain pain by noradrenergic stimulation of the neuromas or nerve endings in a residual limb.[37]

Residual Limb Pain

Residual limb pain, previously referred to as stump pain, can be a painful and frustrating postamputation phenomena. Residual limb pain is common in early postoperative and rehabilitation phases but regresses to a greater extent than any other of the postamputation phenomena. After 2 years postamputation, prevalence may be as low as 20%.[37] Typically, residual limb pain should subside with healing, but if it persists more than a few months, poor prosthetic fit or overuse and overtraining is often the cause. Residual limb pain is more likely if chronic pain was a problem before surgery and will likely persist longer if postoperative analgesia is inadequate. A survey of veteran amputees in the early 1980s revealed that the severity and duration of residual limb pain correlated well with presence and persistence of phantom pain.[31,47] Multiple other reasons may explain why residual limb pain can persist beyond the normal healing period.

The treatment of residual limb pain is typically the domain of the physiatrist or physical therapist; however, anesthesiologists and surgeons can also be helpful in the early postoperative period by screening for anatomic residual limb pathology that may be causative. Anatomic causes include ulcers or inflammation secondary to improper prosthesis fit; bony abnormalities (ischemia, spurs, heterotopic ossification, and osteomyelitis); neuroma formation; and, rarely, malignancies or tumors, many of which may be amenable to surgical correction such as neuroma excision and repositioning of the nerve within bone or muscle.[37] Nonsurgical treatments include botulinum toxin injection; nerve blocks; transcutaneous electrical nerve stimulation (TENS); acupuncture; Farabloc (Farabloc, Coquitlam, British Columbia, Canada) steel fiber sheet sheaths or socks; and oral medications, such as nonsteroidal antiinflammatory drugs (NSAIDs),

cyclooxygenase (COX)-2 inhibitors, and acetaminophen for somatic pain, and tricyclic antidepressants and anticonvulsants (eg, gabapentin, pregabalin) for neuropathic pain.[48] Mexiletine and clonidine have also been used successfully for PLP, and are likely effective for residual limb pain as well.[49] A recent case report by Nikolajsen et al[50] proposes that low-dose ketamine is effective in treating residual limb pain when conventional tricyclic antidepressants and opioid therapy have failed. Ketamine decreases the hyperactivity of *N*-methyl-D-aspartate (NMDA) receptors and thus decreases neuronal excitability. Ketamine reduced allodynia and wind-up response, and increased the pressure-pain threshold. Amputee soldiers and veterans may benefit from ketamine therapy to allow reductions in residual limb pain caused by neuromas, which may allow more function with prostheses.[50] Other medications such as mirtazapine, a serotonin-norepinephrine reuptake inhibitor antidepressant, may be more cost-effective than newer generation anticonvulsants and are probably more efficacious than older tricyclic antidepressants.[35] Each component of this multimodal approach is described more extensively below.

MULTIMODAL PAIN MANAGEMENT IN AMPUTEE CARE

Rationale

Capitalizing on synergy among various medications and modalities, multimodal therapy affects the nociceptive pathway at multiple points (Figure 11-1). Synergy among medications should allow the provider to use less of each medication, thereby reducing side effects and the potential risks of each medication. Treating pain at various points of the nociceptive pathway allows multimodal therapy to be more effective than simply increasing the treatment at one point in the pathway. "Practice Guidelines for Acute Management in the Perioperative Setting"[51] recommends that all patients receive an around-the-clock regimen of NSAIDs, selective COX-2 inhibitory blockers, and/or acetaminophen unless contraindicated,[51] because all of these medications reduce inflammatory mediators (which increase after tissue injury), thereby decreasing the transduction aspect of the pain pathway. Regional anesthesia, however, blocks the transmission process in the pain pathway. PNBs and epidurals use local anesthetics to decrease or halt transmission at large peripheral nerves and the dorsal root, respectively. Epidural local anesthetics also diffuse into the intrathecal space and spinal cord to a lesser degree and thus have an effect at the dorsal horn. Intuitively, if pain cannot be transmitted, it will not be perceived or modulated. Adjunctive medications, such as anticonvulsants, antidepressants, and α_2-agonists affect primarily spinal and supraspinal sites. Finally, intrathecal opioids, ketamine, and α-agonists modulate the pain pathway at the dorsal horn.[52]

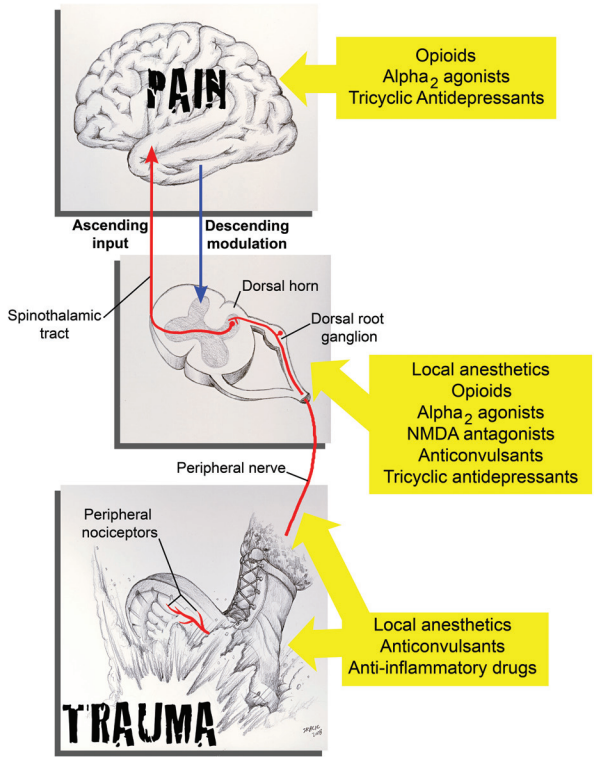

Figure 11-1. Multiple sites of action with multimodal therapy.
NMDA: *N*-methyl-D-aspartate
Reproduced with permission from: Buckenmaier C, Bleckner L. *Military Advanced Regional Anesthesia and Analgesia Handbook*. Washington, DC: Borden Institute; 2009: Figure 27-1.

The basis for multimodal therapy is achieving optimal acute and subacute pain management to optimize the polytrauma patient's overall recovery and rehabilitation. Excellent postoperative analgesia aids postoperative healing by increasing oxygenation and mobility and also reduces anxiety, stress, and depression. Multimodal therapy reduces the potential for opioid-related physical dependence, addiction, and the recently recognized phenomenon of opioid-induced hyperalgesia (OIH)[53,54] resulting from opioid-centered analgesia. Of course, postoperative respiratory depression is a continual threat with opioid-centered postoperative pain plans such as intermittent dosing and patient-controlled analgesia (PCA).[55] The prac-

tice guidelines[51] state that acute perioperative pain management helps maintain the patient's functional abilities and psychological well-being, enhances the quality of life, and prevents the results of undertreatment of perioperative pain. The adverse outcomes of undertreatment include thromboembolic and pulmonary complications, increased intensive care or hospital time, needless suffering, and possibly the development of chronic pain. The guidelines continue by stating that interdisciplinary perioperative analgesia programs with dedicated acute pain service and 24-hour anesthesiologist availability enhance patient comfort and prevent analgesic gaps. Multimodal techniques are specifically recommended.[51]

Treatment Modalities

Regional Anesthesia and Analgesia

Although perioperative regional anesthesia and analgesia (PRAA) has strong support,[51,56,57] the literature on its success in reducing chronic postamputation pain has been inconclusive.[58] However, the weight of evidence suggests a long-term benefit. Studies have demonstrated an association between acute and chronic pain as well as between preamputation pain and chronic pain[4,59]; therefore, postamputation phantom pain may be reduced by inducing local anaesthesia in the limb prior to a planned surgical amputation.[60]

Benefits. Significant benefits to the use of PRAA, including epidural analgesia or PNBs, in the polytrauma patient have been established. Intraoperatively, PRAA provides a stable hemodynamic profile, minimal pulmonary concerns, avoidance of side effects from general anesthesia if used as a sole technique, improved operating room efficiency, and decreased blood loss. Postoperatively, recovery in the postanesthesia care unit improves, postoperative analgesia improves, overall hospital costs diminish, overall outcome improves, and both patient and surgeon satisfaction scores are high.

Intraoperative Hemodynamic Stability. Following the Vietnam War, San Diego Naval Medical Center (California) treated a large number of patients, but the patient demand exceeded the supply of operating room time. Therefore, a system was designed whereby patients underwent surgical procedures in the orthopaedic clinic after a regional anesthetic was placed by the anesthesia department. Over 15,000 patients were safely given regional anesthesia over a 30-year period. In 1997 Waters et al[61] reported findings in a 1-year prospective study of 677 patients. Upper and lower extremity blocks were placed without sedation, after which patients were transported to the clinic for their procedures accompanied only by a corpsman, with minimal monitors. The incidence of complications was low (0.3%) with no postoperative sequelae, attesting to the overall hemodynamic and respiratory safety of peripheral blocks.

In centroneuroaxis blockade, PRAA generally has fewer hemodynamic perturbations than single-shot spinal anesthesia. Auroy and colleagues[62] reported provocative findings in a 1997 French prospective study of over 103,000 regional anesthetics, including over 40,000 spinal blocks, over 30,000 epidural blocks, over 20,000 PNBs, and over 11,000 intravenous (IV) regional anesthetics. The study surveyed 736 anesthesiologists, half in private practice and half in academic settings, with an average of 12 years of experience. The risk of cardiac arrest was 1 per 1,500 for spinal anesthesia, 1 per 10,000 for epidural anesthesia, and 1 per 7,000 for PNB, suggesting a higher cardiac arrest rate for spinal anesthesia compared to other regional anesthetics. Although the authors acknowledged the possibility of selection bias because sicker patients received spinal anesthesia, other studies also report a relatively high rate of cardiac arrest during spinal anesthesia, ranging from 1 per 500 to 1 per 4,000.[63–66] Caplan et al[67] reviewed 14 cases of cardiac arrest in a closed claims analysis, all of which involved healthy patients for minor surgery who suffered cardiac arrest after decreasing blood pressure and pulse. All but one patient had a poor outcome. de Visme and colleagues[68] reported in 2000 "more prolonged hemodynamic effect" in isobaric spinal anesthesia compared to PNBs for hip fractures in 29 elderly patients. Finally, spinal anesthesia often results in significant hypotension and severe bradycardia (33% and 13% incidence, respectively).[69]

Likewise, PNBs may have a greater safety profile than centroneuroaxis blockade. In a 1996 French prospective study by Giaufre et al,[70] over 24,000 regional anesthetics were studied in a pediatric population. The group included 89% receiving a combined anesthetic and general anesthesia, 61% with a centroneuroaxis block, 17% with a PNB, and 22% with local infiltration. Only the centroneuroaxis group reported complications, including dural puncture, cardiac arrhythmias, IV injections, and paresthesias.

Avoiding General Anesthesia Side Effects. If used as a sole anesthetic, regional anesthesia minimizes the risk of central nervous system complications such as postoperative delirium and excessive drowsiness. The likelihood of airway complications including sore throat, traumatized airway, aspiration, and potential for loss of airway in a difficult airway are minimized. Both elevated rate-pressure products during laryngoscopy and intubation as well as potentially low perfusion states during patient positioning and preparation are avoided. Finally, PRAA minimizes the risk of postoperative nausea and vomiting.[71]

Improving Operating Room Efficiency. Surgeons are often concerned about the additional time required for the placement of regional anesthesia; however, use of central and peripheral blocks can actually decrease "anesthesia-controlled time" if managed by a separate "block team" prior to surgery. In 2000 Williams and colleagues[72] studied 369 patients for anterior cruciate ligament repair in a retrospective review using the same surgeon for all the operations. Total time, including intraoperative anesthesia-controlled time plus turnover time, was 31 minutes for PNBs, 36 minutes for PNB combined with general anesthesia, and 41 minutes for general anesthesia.[72] Additionally, regional anesthesia can significantly reduce or eliminate phase I recovery and expedite phase II recovery.[73,74]

Decreasing Blood Loss. Central neuroaxis blockade can decrease perioperative blood loss by 37% to 46%, as demonstrated in many studies,[75,76] but PNBs may also accomplish this benefit. Lumbar plexus blocks have been demonstrated to decrease total blood loss by 49% in total hip arthroplasty.[77,78] Mechanisms by which regional anesthesia decreases blood loss include shunting of blood from the operative site, decreased venous pressure by blockade of sympathetic tone, and the lack of positive-pressure ventilation.

Improving Early Recovery Period. Regional anesthesia potentially improves the recovery period. Ford and colleagues[71] reported a retrospective review of 801 patients comparing general anesthesia to PNBs and a combined general and regional anesthetic. Regional anesthesia patients had less nausea and vomiting (6% vs 20%), less supplemental oxygen requirement (12% vs 81%), and quicker discharge times (51 min vs 104 min). Along with less nausea and vomiting, regional anesthesia patients have less postoperative ileus due to decreased opioid use and decreased sympathetic tone with epidural analgesia.

Decreasing Deep Vein Thrombosis. Regional anesthesia, especially when extended into the postoperative period, has been shown to decrease the rate of deep vein thrombosis in many studies[79–81]; this finding is particularly evident when no further pharmacologic prophylaxis is prescribed. Modig et al[79] examined 60 patients undergoing total hip arthroplasty who received either epidural analgesia or systemic narcotics. Only 13% experienced a deep vein thrombosis, and 10% had a pulmonary embolism in the epidural group compared to 67% and 30%, respectively, in the systemic narcotic group.[79] In 1991 Tuman and colleagues[82] showed a decrease in the alpha angle and maximum amplitude value on postoperative thromboelastogram in 80 major vascular patients, as well as fewer arterial occlusions in the epidural group compared to the systemic narcotic group. Finally, in 1993 Christopherson et al[83] examined the effect of epidural analgesia with lower extremity vascular surgery and found a decreased need for revascularization in the epidural group.

Decreasing Hospital Costs. In addition, regional anesthesia can save hospitals significant costs. In 2004 Williams and colleagues[84] reviewed 948 anterior cruciate ligament repairs, comparing the overall hospital costs between patients with and without PNBs. Of those who received blocks, 82% were able to bypass phase I recovery and only 4% required unplanned admissions, compared with an admission rate of 17% for those who did not receive blocks. Based on an average of 3,000 outpatient orthopaedic cases annually, hospital savings could reach $1.8 million annually through the use of regional anesthesia. Other studies also support fewer costs associated with regional anesthesia.[85–87]

Improved Postoperative Analgesia. Many studies report improved postoperative analgesia utilizing regional analgesia with fewer side effects.[76,87–89] Regional analgesia minimizes the risk of central nervous system side effects such as delirium and drowsiness compared to systemic opioids. Grass[76] reported less sedation with sufentanil patient-controlled epidural analgesia compared to IV morphine PCA and intramuscular (IM) opioids, while Guinard et al[87]demonstrated greater sedation with IV fentanyl compared to epidural fentanyl. Salomaki and colleagues[90] showed decreased nausea and vomiting with epidural fentanyl (20%) compared to IV fentanyl (65%). Regional analgesia patients have less nausea and vomiting, less supplemental oxygen requirement, and less postoperative ileus resulting from fewer opioids and the resultant sympathectomy with epidural analgesia.[71] Horlocker et al[91] eliminated the need for any opioids through the use of multimodal analgesia with a continuous lumbar plexus catheter in addition to acetaminophen and ketoroloc for a total knee replacement, and Mulroy et al[92] demonstrated extended relief with up to 24 hours of analgesia using single shot femoral nerve blocks following anterior cruciate ligament reconstruction. PNBs may also decrease pruritis, urinary retention, hypotension, difficulty with ambulation, and respiratory depression.[76] Because of improved analgesia with fewer side effects and fewer opioids used, nursing requirements are significantly diminished.

Improving Patient Outcome. Several studies have shown improved patient outcome with PRAA,[93,94] including decreased intensive care unit stay,[82,86] decreased hospital stay,[86,89] decreased cardiac morbidity,[82,86,95,96] decreased pulmonary dysfunction,[82,87–89,90] earlier return of bowel function,[89,93] decreased neuroendocrine stress,[86,97] fewer infections,[86] decreased mortality,[86,98] and improved rehabilitation. Yeager et al[86] examined 53 patients after abdominal, thoracic, and vascular surgery in 1987, and Tuman et al[82] ex-

amined 80 major vascular patients in 1991. Both studies reported decreased intensive care unit stays with epidural analgesia versus systemic narcotics. In addition, Yeager's epidural group had a 14% incidence of cardiac morbidity (myocardial infarction, congestive heart failure, angina, or arrhythmia) compared to 52% in the systemic narcotic group; Tuman also demonstrated a significant difference (10% vs 27%) in cardiac events. Blomberg and others[95,96] in a series of studies demonstrated a favorable myocardial oxygen supply versus demand balance with a decrease in heart rate, contractility, preload, and afterload, yet an increased coronary blood flow to the endocardium during thoracic epidural blockade. Furthermore, coronary perfusion pressure was maintained, and stenotic but not nonstenotic coronary vessels became dilated.[96,99–104] Studies[88,89] demonstrated fewer pulmonary complications including atelectasis, infiltrates, and cough in an epidural group compared to a systemic narcotic group, and Boylan and colleagues[88] demonstrated earlier tracheal extubation in the epidural group.

Liu et al[105] examined various analgesic techniques on recovery of bowel function and found a local anesthetic plus opioid combination to provide the optimal result, especially compared to systemic opioids. Epidural opioids have been shown to decrease the stress response, specifically free cortisol levels, compared to systemic opioids.[97] Yeager[86] showed a 7% incidence of major infections (pneumonia, sepsis) in the epidural analgesia group, compared to 40% in the systemic narcotic group. In addition, Yeager's epidural group had no deaths while the systemic narcotic group had a 16% mortality rate.[86] Wu and colleagues[98] reported an analysis of the Medicare claims database in 2004 over a 4-year period and showed significantly lower odds of death at 7 and 30 days postoperatively for those patients who had postoperative epidural analgesia. Finally, PRAA has been shown to decrease pain scores, increase range of motion, decrease hospital stay, and decrease rehabilitation time compared to IV PCA, although CPNBs had fewer side effects compared to epidural analgesia.[106,107]

Improving Patient Satisfaction. In 2001 Wu and colleagues[108] reviewed 18 trials that examined patient satisfaction with PRAA and reported that over 70% of these studies demonstrated greater patient satisfaction with regional anesthesia and analgesia compared to general anesthesia with IV PCA. Specifically, Vloka et al[109] demonstrated greater patient satisfaction with PNBs compared to spinal anesthesia for varicose vein surgery, and Borgeat et al[110] demonstrated greater patient satisfaction with postoperative interscalene analgesia compared to IV PCA for shoulder anesthesia. Although patient satisfaction is a complex issue, critical determinants are judicious sedation during the regional procedure as well as optimal postoperative analgesia.[108,111–113]

Risks of Perioperative Regional Anesthesia and Analgesia. Although PRAA has many significant benefits, its use also introduces potential risks, which must be considered for each individual patient. This section will focus first on the "big three" risks, as termed by Finucane,[114,115] namely, local anesthetic toxicity, pneumothorax, and nerve injury. Additionally, the provider should consider other miscellaneous risks before employing PRAA.

Local Anesthesia Toxicity. Local anesthetic toxicity resulting in seizures, cardiac arrest, or both can be a devastating complication that all anesthesia providers must consider. With PNBs, the incidence of seizures is roughly 1 per 1,000, whereas the incidence with epidural anesthesia is roughly 1 per 8,000.[62,116] Brown et al[116] completed a retrospective review of over 25,000 patients with caudal, epidural, and brachial plexus blocks and found the highest rate of local anesthetic toxicity with caudal anesthesia, followed by PNBs, followed by epidural anesthesia. Most cases of seizures occurred after bolusing local anesthesia through needles or catheters, as opposed to perioperative infusions, and did not necessarily result in cardiac arrest even with bupivacaine in this series of patients. The incidence of cardiac arrest, resulting from several different mechanisms, appeared to be similar between epidural anesthesia and PNBs, approximately 1 per 10,000 and 1 per 7,000, respectively.[116] Both epidurals and PNBs may elicit the vasovagal reaction, which is usually self-limiting, as well as cardiac arrest due to local anesthetic toxicity.[117] In addition, accidental intrathecal (spinal) injection and the Bezold-Jarisch reflex may cause cardiac arrest during epidural anesthesia.

Because local anesthetic toxicity can be life-threatening, efforts to decrease this event have largely focused on prevention, including using the lowest effective dose, frequent aspiration with intermittent boluses, the use of a vascular marker such as epinephrine, and avoiding agents with a low therapeutic index (eg, bupivacaine) in highly vascular areas. However, determining meaningful maximum dosages for local anesthetics has been elusive, since the maximum dose depends primarily on where the local anesthetic is given; a standard maximum dose of a particular local anesthetic is not helpful unless location is specified. For example, a greater dose is allowed moving within a continuum from IV, to intercostals, to caudal, to epidural, to PNBs, and finally to subcutaneous administration.[118–120] On the one hand, although 5 to 7 mg/kg of lidocaine is frequently quoted as a maximum dose, twice that dose could be used for PNBs and subcutaneous administration.[114,121–130] On the other hand, even 5 mg/kg lidocaine intravenously could have disastrous

consequences. Therefore, rather than relying on set maximum dosages, the provider must be sure not to inject within a vessel, to use the lowest effective local anesthetic dose possible, and to have Intralipid (KabiVitrum Inc, Alameda, Calif) readily available.

Unfortunately, detection of an intravascular injection can be difficult; merely aspirating for heme prior to injection does not preclude the possibility of an intravascular injection. Therefore, a test dose is critical, which most commonly is epinephrine 15 μg (6 mL of 1:400,000 solution). If the heart rate increases more than 10 points, the practitioner should withdraw the needle and either abandon the procedure or reattempt it if the patient is stable. Additionally, extreme vigilance is required during the bolus injection, especially when using an immobile needle with fractionated 5-mL doses; mobile or multiple injection techniques may decrease the rate of local anesthestic toxicity by spreading local anesthesia in multiple locations.

Choice of the local anesthetic is a critical aspect of decreasing patient risk, because local anesthetics can have varying effects on different organ systems. Lidocaine, for example, can cause seizures and eventually cardiac shock at high concentrations.[131] In addition, according to numerous studies, lidocaine is less cardiotoxic than ropivacaine, which is less cardiotoxic than bupivacaine.[132–136] Providers must be aware of the potential for cardiac complications with the use of local anesthetics, and early treatment of cardiac complications is essential (decreasing mortality from 83% to 33% for bupivacaine and 17% to 0% for ropivacaine in one study).[137,138] The cardiotoxicity of these anesthetics results from both depressed left ventricular function as well as arrhythmogenicity. Animal studies have shown significantly less cardiovascular depression and arrhythmias, greater rate of successful resuscitations, and less mortality after cardiac arrest with ropivacaine compared to bupivacaine. For constant infusions, maximum epidural bupivacaine rates should not exceed 0.5 mg/kg/hr (0.25 mg/kg/hr in infants),[139–143] and this rate should be decreased in the elderly, pregnant women, and those with uremia or liver failure.

Finally, treatment of local anesthesia toxicity should focus on airway management, possible administration of induction agents and/or benzodiazepines to control seizure activity, and control of arrhythmias with amiodarone, vasopressin, epinephrine, Intralipid therapy, and/or defibrillation. Perhaps the most remarkable recent discovery about local anesthesia toxicity is the ability for Intralipid to act as an antidote: the free plasma local anesthetic binds to Intralipid, thereby dramatically decreasing circulating local anesthesia levels.[144–147] In 2003 Weinberg et al[145] reported a study in which 12 dogs were given lethal doses of IV bupivacaine, and the group treated with Intralipid all survived while the control group all died. The currently recommended dosing is 1 mL/kg over 1 minute, followed by 3 mL/kg over 10 minutes, followed by an infusion of 0.25 mL/kg/min after establishment of normal sinus rhythm until hemodynamics have been stabilized. Maintaining an immediately available supply of Intralipid, which is inexpensive and stable at room temperature for long periods, while blocks are performed has become the standard of care.

Pneumothorax. Pneumothorax, the second of the "big three" risks of PRAA, is primarily a risk with supraclavicular brachial plexus block and thoracic paravertebral block, but has been seen with other blocks as well.[148] The risk of pneumothorax during supraclavicular blockade has been reported as high as 5%,[107] but other studies indicate this risk is much less in experienced hands; Franco and Vieira[149] reported no pneumothorax in 1,001 supraclavicular blocks. Incidence of pneumothorax with thoracic paravertebral block is roughly 1 per 300, but it is highly dependent on patient factors such as the presence of scoliosis, as well as provider experience.[150] During block placement, cough, chest pain, or aspiration of air are signs of possible pleural puncture. To reduce the risk of pneumothorax after block placement, nitrous oxide and positive pressure ventilation should be avoided, and a chest film should be considered, particularly if the patient is symptomatic. Outpatients undergoing supraclavicular or thoracic paravertebral blocks should be instructed to report immediately to the emergency room for dyspnea or chest pain. Treatment includes a chest tube if pneumothorax is greater than 25% or symptomatology is severe. Again, prevention is critical and requires adequate training, education, and experience as well as the use of ultrasound imaging techniques.

Nerve Injury. Nerve injury is the third major risk associated with PRAA. Due to an inconsistent definition (various etiologies, sensory versus motor deficits, duration of persistent block, severity, etc), the incidence of nerve injury varies widely among studies, ranging from 0.2% to 2%.[151] Auroy et al[62] reported an incidence of 1 in 5,000 for both epidural and PNBs, compared to 1 in 1,670 for spinal anesthesia. Although the number of patients with persistent neural deficits was small, all patients in the epidural and PNB groups had either paresthesias during block placement or pain on injection.[62] Nerve injury may be more common after general anesthesia than regional anesthesia: the American Society of Anesthesiologists closed-claims analysis found that 61% of the total number of nerve injuries occurred during general anesthesia, and 39% during regional anesthesia, although 90% of lower extremity claims involved regional anesthesia, especially spinal anesthesia.[152] The incidence of nerve injury appears to

decrease with time, as Borgeat et al[148] demonstrated in a prospective study examining interscalene blockade and shoulder surgery, finding that 14% of the patients had persistent sensory deficits on the 10th postoperative day, but the number had decreased to 4% at 3 months and 0.2% at 9 months. Bergman and colleagues[153] showed that using continuous techniques in over 400 axillary catheter placements did not increase the risk of neural injury compared to using single injections. Still, many surgeons perceive that PNBs are associated with a relatively high rate of neural deficits; 21% of hand surgeons reported having seen a "major nerve injury" following axillary blockade.[154]

Sources of nerve injury include trauma, toxicity, ischemia, or more frequently a combination of these mechanisms.[114] Neural trauma could result from the needle, intraneural injection, compression, or stretch. Whether the choice of technique (paresthesia or nerve stimulation) or the use of short bevel needles affects neural trauma is controversial.[155,156] Toxicity from local anesthetic correlates with potency (2-chloroprocaine < lidocaine < etidocaine), although 4% lidocaine or greater causes the greatest injury. High concentrations of local anesthetics can be neurotoxic, but concentrations used at clinical concentrations are considered safe. Clearly, any substance injected within the epineurium can result in neural injury as a result of all three mechanisms. Intraneural or extraneural compression, edema, and vasoconstriction could result in neural ischemia. Partridge[157] examined the use of epinephrine and found that lidocaine with 1:200,000 epinephrine decreased neural blood flow, but so did plain lidocaine, also probably as a result of the coupling of neural activity with oxygen requirements and blood flow. No evidence exists that 1:400,000 epinephrine significantly decreases neural blood flow, and this concentration appears to be an acceptable balance between maintaining a reliable intravascular marker and avoiding neural ischemia.[157]

Prevention of neural injury involves adequate informed consent and effective communication with the patient preoperatively, minimizing sedation to obtain feedback during a 1-mL test dose to help rule out pain on injection that could be associated with intraneural injection, avoiding high concentrations of local anesthesia, avoiding 1:200,000 epinephrine, and possibly implementing the use of ultrasound, which allows visualization of neural tissue, the needle, and local anesthesia spread. Treatment of a possible neural injury begins with a comprehensive yet focused history and physical examination of the complaint with consideration of a wide range of possible etiologies, including preexisting nerve injury, prolonged use or high pressure of the tourniquet, surgical trauma, local edema and swelling, patient position, tight splints or casts, and regional anesthesia. Workup may include imaging studies to evaluate for hematoma, which could be evacuated with return of function, and possibly electromyogram/nerve conduction velocity studies to record baseline function, because changes in these studies lag weeks behind neural injury.[158] Treatment should focus on reversible causes (hematoma, casts), multimodal therapy to treat possible neuropathic pain, and reassurance that most neural injuries improve with time.

Other Risks. Other risks associated with PRAA include epinephrine toxicity, phrenic blockade, bronchospasm, failure of the technique, inadvertent epidural or spinal spread, hematoma, and infection. Epinephrine toxicity may occur with a small, inadvertent IV dose in a susceptible patient or from slow systemic uptake if epinephrine is mixed in the local anesthesia solution, especially if total epinephrine dose exceeds 250 μg, including the surgeon's possible use of epinephrine-containing solutions. Phrenic blockade occurs with virtually all interscalene blocks and deep cervical plexus blocks, although it is well tolerated in patients who don't have significant pulmonary disease. Roughly 40% of supraclavicular blocks result in phrenic blockade. Bronchospasm has also been reported after interscalene block[159] but is not typically seen after other regional anesthetics. Failure of the technique comprises 5% to 15% of regional anesthetics that required a backup plan for all patients; higher failure rates occur with poor patient selection, insufficient time allowed for local anesthesia onset, surgery outside the area of blockade, surgery outlasting the duration of the regional block, and minimal experience or training in regional techniques.

Inadvertent epidural spread occurs frequently with paravertebral blockade,[160] occasionally with lumbar plexus blockade (up to 10% of the time), and rarely with interscalene and deep cervical plexus block. Inadvertent spinal anesthesia possibly resulting in total spinal anesthesia can occur during lumbar plexus block, paravertebral block, interscalene block, and epidural anesthesia via inadvertent dural puncture. Hematoma formation is a well-known complication of epidural/spinal anesthesia, with an incidence between 1 per 5,000 and 1 per 150,000, depending the presence of anticoagulation and needle size.[161,162] The American Society of Regional Anesthesia has specific guidelines on its Web site (www.asra.com) that pertain to central neuroaxis blockade in the presence of anticoagulants. Particularly concerning is the recent relatively high rate of epidural hematoma formation especially with high-risk dosing of low-molecular-weight heparin. Hematoma has also been associated with PNBs, namely lumbar plexus block with Lovenox[163] (Sanofi Aventis, Bridgewater, NJ) as well as axillary catheters.[153]

Finally, infection can result particularly from catheter techniques, varying from 1 case in 10,000 with epidural catheters to up to 1% of cases with CPNB catheters.[153] As many as 30% of catheters become colonized with skin flora, and a small percentage of patients develop either superficial or deep infections. Risk factors associated with catheter infections include diabetes, traumatic placement, longer duration of catheter, frequent unnecessary dressing changes, and lack of systemic antibiotics. Additionally, type and concentration of local anesthesia may affect the risk of infection. In a series of deep CPNB catheter infections treated at Brooke Army Medical Center, patients noted primarily pain deep to the catheter site in the absence of erythema, induration, or drainage.[164]

Evidence-Based Medicine for Regional Analgesia in the Prevention of Phantom Limb Pain. This section reviews both positive and negative epidural and PNB studies that focus on the potential benefits of preemptively administering regional anesthesia to decrease the incidence of PLP. PRAA plays a pivotal role as part of a multimodal plan. Therapies for chronic PLP should address the above hypothesized mechanisms of pain. Regional analgesia addresses two of the putative sites of PLP: the peripheral nerves and the dorsal horn of the spinal cord. Additionally, preemptive analgesia may affect all four components of the nociceptive pathway. As Birbaumer et al[165] revealed, regional anesthesia may prevent cortical reorganization, which may decrease pain perception. Ong and colleagues[58] reported that intraoperative spinal anesthesia alone benefited the amputee with less postoperative pain during the first week, compared to those who did not receive neuraxial anesthesia. Presumably, a mechanism related to spinal modulation and preemptive analgesia accounts for the analgesia lasting long after the sensory blockade has subsided. Preemptive analgesia is also supported by better postoperative analgesia in patients who received regional anesthesia interventions prior to surgical stimulus.[25,34] Regional analgesia with continuous epidural infusion or CPNBs is beneficial because of the ability to provide preoperative, intraoperative, and postoperative analgesia during much of the inflammatory period.[107] First, studies demonstrating a reduction of PLP with PRAA will be discussed, followed by studies that fail to demonstrate a specific benefit.

Epidural studies demonstrating benefit:

1. In 1988 Bach et al[166] published an often referenced article, "Phantom Limb Pain in Amputees During the First 12 Months Following Limb Amputation, After Preoperative Lumbar Epidural Blockade," a prospective, randomized, controlled trial of 25 geriatric vascular patients. The epidural group of 11 patients received analgesia for 3 days preoperatively to alleviate preoperative limb pain, and the control group of 14 patients received perioperative opioids. Both groups had either epidural or spinal anesthesia for their amputation surgery and postoperative meperidine and acetaminophen for analgesia. At 6 and 12 months postamputation, none of the epidural patients reported PLP, while the control group reported incidences of 38% and 27%, respectively. However, the study was small and six patients died before follow-up was complete (see Table 11-1). The relatively low incidence of PLP even in the control group could possibly be attributed to the intraoperative use of preemptive regional anesthesia.[166]
2. Jahangiri and colleagues[167] reported in 1994 that perioperative epidural infusion of diamorphine, clonidine, and bupivicaine 0.125% is safe and effective in reducing the incidence of phantom pain after amputation. Thirteen epidural study patients were compared to 11 control patients who received on-demand opioids. The epidural solution was infused at 1 to 4 mL/hr for 1 to 2 days preoperatively and at least 3 days postoperatively, and both groups received general anesthesia intraoperatively. The study group reported significantly less PLP at 7 days, 6 months, and 1 year, with 8% incidence in the epidural group compared to 73% in the control group at 1 year.[167]
3. In 1996 Katsuly-Liapis[168] reported that preemptive epidural analgesia reduces the incidence of phantom pain in lower limb amputees. This prospective study divided 45 patients for lower-limb amputation into three

TABLE 11-1

INCIDENCE OF PHANTOM LIMB PAIN IN BACH'S STUDY

	Time Since Operation		
Study Group	**7 day**	**6 mo**	**12 mo**
Epidural	27%	0%	0%
Control	64%	38%	27%

Data source: Bach S, Noreng MF, Tjellden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. *Pain*. 1988;33:297–301.

groups. Group A received 3 days of preoperative and 3 days of postoperative epidural analgesia with 0.25% bupivacaine and morphine. Group B received opioids and NSAIDs for preoperative pain followed by epidural analgesia for postoperative pain. Group C received no epidural analgesia. At 6 months and 1 year, the patients in group A reported no phantom pain, while a significant portion of groups B and C did experience phantom pain. The authors concluded that preemptive epidural analgesia reduced the incidence of phantom pain in lower limb amputees during the first year following amputation.[168]

Epidural studies demonstrating no benefit:

1. Nikolajsen et al published a relatively large study in 1997 titled "Randomised Trial of Epidural Bupivicaine and Morphine in Prevention of Stump and Phantom Pain in Lower-Limb Amputation."[169] The 29 patients in the epidural group received bupivacaine 0.25% at 4 to 7 mL/hr with epidural morphine at 0.16 to 28 mg/hr preoperatively, bupivacaine 0.5% intraoperatively (with general anesthesia), and 0.25% bupivacaine at 4 to 7 mL/hr with epidural morphine in 2- to 8-mg boluses as needed postoperatively for an average of 6.9 days. The control group's 31 patients received epidural saline intraoperatively and postoperatively. All patients received postoperative parental opioids as needed as well. Although Nikolajsen found no reduction in PLP at 1 week, 3 months, 6 months, or 12 months postamputation (Table 11-2), the results are questionable because half the patients were lost to follow-up due to death, reamputation, or inability to contact them. In addition, the infusion rate was somewhat low for lumbar epidural, which may have resulted in inadequate spread.[169]
2. In 2001 Lambert[170] reported on a study designed to compare the effect of two different regional techniques, perioperative epidural analgesia and postoperative sciatic catheter analgesia, on PLP. The 14 patients in the epidural analgesia group received bupivacaine 0.166% with morphine at 0.2 to 0.8 mg/h for 24 hours preoperatively, intraoperatively, and continued for 3 days postoperatively. In the sciatic analgesia group, 16 patients had a perineural sciatic catheter placed intraoperatively, which was infused postoperatively with bupivacaine 0.25% at 10 mL/hr for 3 days. Epidural analgesia was shown to provide greater relief of residual limb pain during the first 3 days, yet there was no significant difference in the incidence and severity of PLP at 6 and 12 months. Like Nikolajsen's study, this unblinded study lost 40% of patients to follow-up due to death, and had low epidural infusion rates. Additionally, it was hampered by the lack of a control group (without regional analgesia).[170]

TABLE 11-2

INCIDENCE OF PHANTOM LIMB PAIN IN NIKOLAJSEN'S STUDY

Study Group	Time Since Operation			
	1 wk	3 mo	6 mo	12 mo
Epidural	52%	82%	81%	75%
Control	56%	50%	55%	69%

Data source: Nikolajsen L, Ilkjaer S, Christensen JK, Kroner K, Jensen TS. Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. *Lancet*. 1997;350:1353-1357.

Continuous peripheral nerve block studies demonstrating benefits:

1. In 1991 Fisher and Meller[171] reported on a small, prospective study of 11 vascular patients in whom sciatic catheters were placed intraoperatively and infused postoperatively with bupivacaine 0.125% at 10 mL/h for 72 hours, concluding that perineural catheters may have a role in diminishing PLP. These patients demonstrated a 50% decrease in morphine administration within the first 3 days and, more importantly, no PLP at 12 months after above-knee or below-knee amputation; however, the study used retrospective controls and studied a limited number of patients.[171]
2. In 1997 Birbaumer et al published a study titled "Effects of Regional Anesthesia on Phantom Limb Pain Are Mirrored in Changes in Cortical Reorganization"[165] that supports a benefit of PRAA in treating established PLP and possibly in preventing PLP in amputees. As noted above, studies have revealed that substantial reorganization of the primary somatosensory cortex occurs subsequent to amputation and that such cortical reorgani-

zation is positively correlated with PLP. The Birbaumer study hypothesized that pain reduction induced by regional anesthesia leads to less cortical reorganization and thus less phantom pain. Six males with trauma-induced unilateral arm amputations with established PLP were investigated and controlled against four arm amputees without PLP. After the patients were given brachial plexus anesthesia to influence their PLP, researchers performed neuroelectric source imaging while stimulating the fingers and the mouth of each subject, as cortical reorganization was assessed as a dependent variable. The blockade abolished all aspects of cortical reorganization seen by neuroelectric source imaging and simultaneously eliminated the current experience of PLP. Birbaumer concluded that cortical reorganization likely contributes to PLP but probably does not maintain PLP by itself.[165]

3. In 1998 Lierz and colleagues[172] published a case report that demonstrated successful elimination of PLP with regional analgesia after unsuccessful extensive pharmacologic therapy. A 39-year-old male with 39% total-body surface area burns requiring bilateral upper extremity amputations developed severe phantom pain by postoperation day 18, which was treated with NSAIDs, calcitonin, amitriptyline, and carbamazepine, as well as TENS therapy. Due to unrelenting PLP, the patient had bilateral brachial plexus catheters placed on postoperation day 39 (left interscalene and right axillary perineural catheters), which were infused with ropivicaine 0.2% at 4 to 6 mL/hr for 6 days. The regional analgesia resulted in complete pain relief through the 7 months of follow-up.[172]

Continuous peripheral nerve block studies demonstrating no benefit:

1. Elizaga et al[173] reported a retrospective, unblinded study of 19 lower extremity amputees in which study patients received a sciatic catheter placed intraoperatively and maintained postoperatively for an average of 4 days. Patients in the treatment group received 10 mL of bupivacaine 0.5% bolused intraoperatively, then 2 to 6 mL/hr of bupivacaine 0.5% infused intraoperatively and postoperatively; patients in both the treatment and control group received an IV PCA. No differences were found in opioid use or PLP between the two groups, although 70% of patients were lost to follow-up and the intraoperative anesthetic technique was not controlled.[173]
2. Pinzur and colleagues[174] published a prospective, randomized study for the prevention of PLP in 1996. Twenty-one vascular patients scheduled for lower extremity amputations for peripheral vascular disease were given spinal anesthesia intraoperatively as well as perineural sciatic nerve catheters, which were infused with either bupivacaine 0.5% at 1 mL/hr or saline for 72 hours. Residual limb and PLP were assessed for the first 72 hours as well as at 3 and 6 months. While patients who received bupivacaine via the sciatic catheters reported lower pain scores and decreased opioid use for the first 48 hours, there was no difference in the incidence of PLP. Weaknesses of the study included lack of any attempt at preemptive analgesia, and very low infusion rate, resulting in probable inadequate blockade.[174]

Considering the quality of the studies that examined the benefit of epidural and CPNB analgesia in reducing chronic postamputation pain, a greater weight of evidence favors PRAA having some degree of prevention of the development and successful treatment of established PLP. Therefore, regional analgesia may be central to a successful multimodal approach to preventing and treating chronic postamputation pain.

Techniques of Regional Analgesia. This section reviews the placement of epidural and continuous peripheral nerve catheters, localization of nerves, and administration of solutions used during continuous infusions. Because many seriously injured patients present with multiple injuries, ongoing, adequate analgesia naturally remains a paramount patient concern as well as a significant provider challenge. Examining the timing and duration of regional analgesia, Kissin[175] reviewed the need for continuous regional anesthesia techniques when attempting to provide preemptive analgesia by preventing central hypersensitivity. Ideally, regional anesthesia techniques should cover the entire "initiation phase"—the initial inflammatory response, which lasts days or sometimes weeks in the case of polytrauma—which may require sequential catheters to provide optimal long-lasting analgesia.[25,34,175,176] In the current military conflict, these continuous regional analgesia techniques have been successfully placed in the combat theater or at the earliest opportunity in Europe with pumps that accompany the service member back to the United States.

Epidural Catheters. Epidural analgesia has been the mainstay of perioperative regional analgesia for several decades. Using a dilute solution of local anesthesia often combined with an opioid, the anesthesia provider can effectively block transmission of afferent nociception and achieve profound analgesia. Epidural catheters should be placed at the "epicenter" of the incision to optimize segmental analgesia, thereby targeting only those nerve roots requiring blockade. For example, a standard thoracotomy incision at T6 should have a T6 epidural catheter, whereas a standard exploratory laparotomy should have a low thoracic epidural placed for optimal analgesia. Standard technique incorporates a sterile preparation and drape, skin localization, advancement of an epidural needle either with a midline or paramedian approach, confirmation of epidural needle placement by a "loss of resistance" technique, and threading a 20-gauge multiorifice catheter 3 to 5 cm within the epidural space. Typical local anesthetic and opioid concentrations, boluses, and rates are listed in Table 11-3. In addition to the above risks and benefits, epidural analgesia can result in hypotension in up to 30% of cases, particularly with larger boluses of high-concentration local anesthesia in hypovolemic patients. However, establishment of blockade after volume resuscitation in a stable patient with dilute solutions can provide excellent analgesia while maintaining stable hemodynamics.

Peripheral Nerve Blocks. PNBs, which may reduce the risk of hypotension, respiratory depression, urinary retention, and difficulty with ambulation, offer an attractive alternative to epidural analgesia. PNBs include upper and lower extremity blocks, head and neck blocks, and paravertebral blocks. Upper extremity blocks include interscalene, supraclavicular, infraclavicular, and axillary approaches to the brachial plexus; lower extremity approaches include lumbar plexus, sciatic, femoral, popliteal, and ankle blocks. The approach to the brachial plexus (Figure 11-2) is based primarily on the location of the injury or surgery: the interscalene approach is used for shoulder analgesia and the axillary approach for forearm and hand surgery. Similarly, proximal lower extremity blocks can provide analgesia to a neural plexus; for example, the lumbar plexus block results in femoral, obturator, and lateral femoral cutaneous nerve blockade with a single injection. Paravertebral blockade can be performed in the thoracic or lumbar region, resulting in excellent unilateral blockade of nerve roots with minimal risk for hypotension, bradycardia, or respiratory depression.

TABLE 11-3

ROUTINE VOLUMES AND RATES FOR REGIONAL ANESTHESIA TECHNIQUES IN ADULTS

Approach	Single Injection (using 0.5% ropivacaine)*	Continuous Infusion (using 0.2% ropivacaine)*	Patient-Controlled Bolus (total rate should be < 20 mL/hr)
Interscalene	30–50 mL	6–10 mL/hr	2–5 mL bolus q 20–60 min
Supraclavicular	30–40 mL	6–10 mL/hr	2–5 mL bolus q 20–60 min
Infraclavicular	30–40 mL	6–10 mL/hr	2–5 mL bolus q 20–60 min
Axillary	30–50 mL	6–10 mL/hr	2–5 mL bolus q 20–60 min
Paravertebral	3–5 mL each level	6–10 mL/hr	2–4 mL bolus q 20–30 min
Lumbar plexus	30 mL	6–10 mL/hr	2–4 mL bolus q 20–30 min
Femoral	30 mL	6–10 mL/hr	2–5 mL bolus q 20–60 min
Sciatic	20–30 mL	6–10 mL/hr	2–5 mL bolus q 20–60 min
Popliteal	30–40 mL	6–10 mL/hr	2–5 mL bolus q 20–60 min
Epidural-thoracic	6–10 mL	6–10 mL/hr w/ opioid	2–3 mL bolus q 20–30 min
Epidural-lumbar	10–20 mL	10–20 mL/hr w/ opioid	3–4 mL bolus q 20–30 min
Epidural-morphine	3–5 mg	40 μg/mL at 0.4–0.8 mg/hr	NA
Epidural-fentanyl	50–100 μg	2–5 μg/mL at 0.3–1.0 μg/kg/hr	NA

*Ropivacaine percentages not applicable to morphine or fentanyl epidural.
NA: not applicable

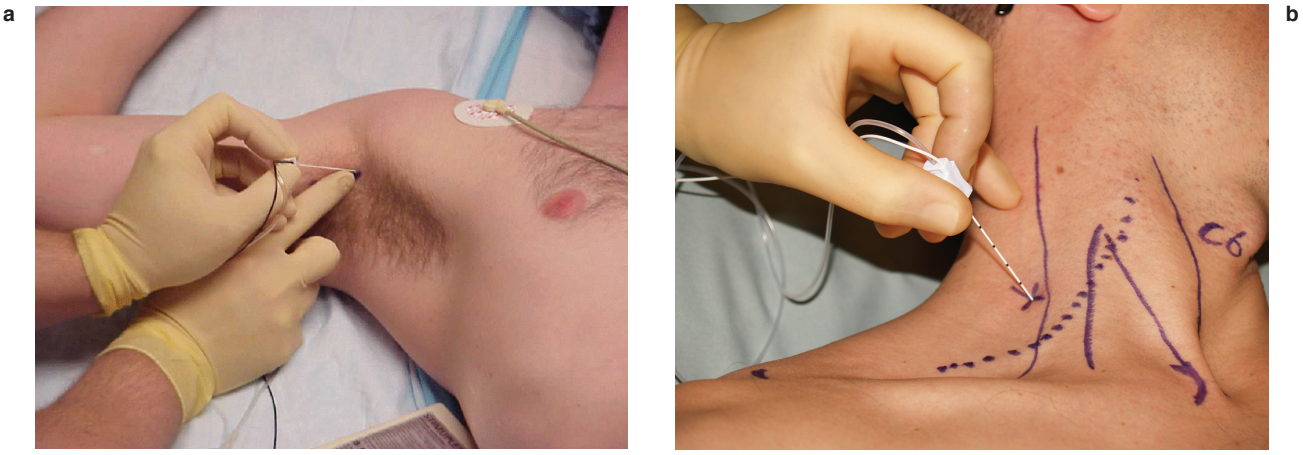

Figure 11-2. Peripheral nerve block of the brachial plexus. **(a)** Axillary approach. **(b)** Interscalene approach.
Reproduced with permission from: Buckenmaier C, Bleckner L. *Military Advanced Regional Anesthesia and Analgesia Handbook*. Washington, DC: Borden Institute; 2009: Figures 10-5 (a) and 7-5 (b).

Localization techniques:

- **Nerve stimulation**, which originated in the 1960s, is now used for most PNBs. This technique provides a quantifiable endpoint for needle placement without causing a potentially uncomfortable paresthesia.[18,19,177] However, little evidence exists that the widespread use of nerve stimulation has increased the safety of neural blockade.[178] Typically, the needle is advanced close to the nerve as the nerve stimulator is dialed to a final stimulation between 0.2 and 0.5 mA.[179] After negative aspiration, a 1-mL test dose ("Raj test") is injected to rule out a possible intraneural injection (marked by pain or high pressure on injection) and to confirm proper needle position, followed by an intravascular test dose using local anesthesia with 15 μg of epinephrine (6 mL with a 1:400,000 solution); an increase of greater than 10 beats/minute or greater than 15 points on the systolic blood pressure over the resting values indicates intravascular position of the needle, requiring its withdrawal. After negative test doses, the total local anesthesia dose (see Table 11-3) is given in 5-mL aliquots with frequent aspiration.
- **Ultrasound technology** specifically for regional anesthesia has revolutionized regional anesthesia within the past 5 years. Nerve blocks using ultrasound may be performed with either ultrasound alone or in combination with nerve stimulation. The potential benefits of ultrasound-guided regional anesthesia are numerous. Higher success rates and decreased onset times have been demonstrated in several studies, because the anesthesiologist can optimize needle placement during injection to ensure appropriate spread.[21,180,181] Because vascular and neural structures, as well as others such as pleura, can be well-visualized, fewer complications from needle penetration or vascular injection occur. In the case of trauma, the sole use of ultrasound technique should also decrease pain compared to nerve stimulation, which causes extremity movement. In the case of amputation, ultrasound allows for block placement when the loss of a limb precludes the ability to observe motor stimulation from a nerve stimulator. The risks of the application of ultrasound are minimal; however, indirect challenges do exist, including potential breaks in sterile technique with extra equipment or inability to see the actual needle tip on ultrasound, resulting in inadvertent needle advancement.

Continuous Peripheral Nerve Blocks. CPNBs offer improved analgesia over single shot nerve blocks by virtue of longer duration with minimal motor block. Many combat-wounded service members present with multiple-extremity injury, and ongoing, adequate analgesia remains a paramount concern. Occasionally, dual catheters may be required in a single patient to achieve adequate analgesia in multiple areas. Ganesh and Cucchiaro[182] reported on a study in which adolescents were discharged 24 hours following extremity surgery

with dual CPNBs with good to excellent analgesia. This practice will likely become more common because it potentially reduces hospital stay, economic impact, opioid use, and opioid side effects. Ropivacaine may be preferred for its greater safety margin in cases when multiple infusions are employed, and until more data is available, total infusion rates should be less than 0.5 mg/kg/hr.[139]

Catheters and Pumps. Peripheral catheters are either stimulating or nonstimulating devices, most commonly a "catheter through needle" technique. The stimulating system (eg, Arrow StimuCath, Teleflex Medical, Research Triangle Park, NC) employs an insulated needle as well as a stimulating, single-orifice catheter that is advanced 3 to 5 cm through the needle; once proper stimulation is achieved, incremental boluses are administered through the catheter. The nonstimulating catheter system utilizes an insulated needle with a side port for aspiration and injection; after proper needle placement, injection of local anesthesia is made through the needle, followed by advancement of the multiorifice catheter an additional 3 to 5 cm through the needle.

Electronic pumps, such as Stryker (Stryker Instruments, Kalamazoo, Mich) and AmbIT (Sorenson Medical Inc, West Jordan, Utah; Figure 11-3), as well as elastomeric pumps, such as Accufuser (McKinley Medical, Wheat Ridge, Colo) and On-Q (I–Flow Corporation, Lake Forest, Calif; Figure 11-4), are commercially available. Electronic pumps are very reliable and programmable for various settings, including patient-control settings. Both the Stryker and the Sorenson pumps are approved for flight within the Department of Defense. Elastomeric pumps are simple devices that allow dependable infusion rates and do not require batteries. Both types are small, portable, and disposable, although the Sorenson pump may be reused by replacing a disposable cassette.

Figure 11-3. AmbIT (Sorenson Medical Inc, West Jordan, Utah) portable electronic pump (used with permission).

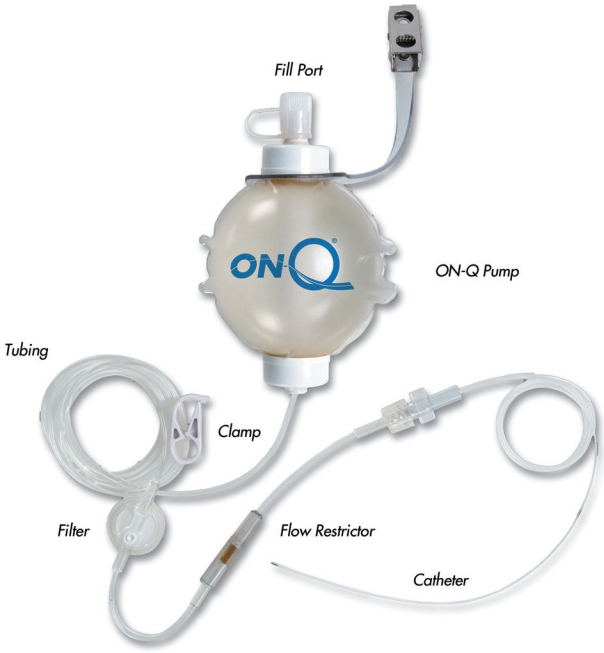

Figure 11-4. On-Q pump (I –Flow Corporation, Lake Forest, Calif; used with permission).

Solutions. When utilizing epidural analgesia, the combination of local anesthesia and opioids appears to afford the greatest advantage, resulting in synergistic analgesia.[105,183–186] Opioid choices include morphine, a hydrophyllic, and fentanyl and sufentanyl, which are lipophyllic. Morphine can be used in lesser amounts: its epidural/IV dose ratio is 0.25, compared to 1.0 for fentanyl and over 1.0 for sufentanyl; however, some studies suggest that fentanyl and sufentanyl have fewer side effects.[187] Epidural hydromorphone has steadily gained in popularity over the past decade, with one study showing that it causes less pruritis.[188] Typically, either 0.0625% to 0.125% bupivacaine or 0.1% to 0.2% ropivacaine is used in conjunction with an opioid at 10 to 20 mL/hr (6–10 mL/hr for thoracic and 2–3 mL every 20–30 min for lumbar epidural analgesia).[183,189,190] As noted above, maximum epidural bupivacaine rates should not exceed 0.5 mg/kg/hr (0.25 mg/kg/hr in infants),[139–143] and the rate should be decreased for pregnant or elderly patients or those with uremia or liver failure. Morphine rates should be infused at 0.4 to 0.8 mg/hr, and fentanyl typically ranges from 0.25 to 1.0 μg/kg/hr. Higher opioid rates should prompt increased monitoring within the intensive care unit.

Medications

The treatment of PLP has been a difficult process, with a variety of treatments attempted but few providing consistent long-term relief. Drug therapies are the most commonly used treatment modalities for PLP. Drug therapies used to treat PLP include opioids, anticonvulsants, lidocaine/mexiletene, clonidine, ketamine, amitriptyline, NSAIDs, and calcitonin. These drugs have been shown to reduce PLP severity and have an analgesic effect on pain in some cases, but few have demonstrated long-term PLP relief.[191]

Opioids

Traditionally, opioids form the cornerstone of acute pain management; however, they are often overused, and recent studies have revealed more problems with an opioid-based regimen. Still, as a component of multimodal therapy, opioids complement both oral analgesics and regional analgesia. Opioids notably bind with opioid receptors peripherally and centrally, providing analgesia without loss of touch, proprioception, or consciousness. Peripherally, they reduce neurotransmitter release and nociceptor sensitization, particularly in inflammatory tissue; centrally, they modulate afferent input in the substantia gelatinosa of the dorsal horn lamina where C fibers terminate, as well as in cortical areas to blunt perception of pain. Acute pain specialists currently are armed with a wide range of opiate choices including (in increasing potency) meperidine, morphine, methadone, hydromorphone, and fentanyl, with various route of administration such as IV (including PCA), intramuscular, oral, transmucosal, transdermal, subcutaneous, epidural, intrathecal, and intraarticular. Providers should remember that morphine-6-glucuronide can accumulate in the presence of renal insufficiency.[191] Methadone is unique in acting through NMDA receptor antagonism and serotonin reuptake inhibition, yet can be challenging to manipulate because of its long half-life.[192] Transdermal fentanyl (Duragesic, Ortho-McNeil-Janssen Pharmaceuticals, Inc, Raritan, NJ) is approved for chronic pain management but not for acute pain management, in which its use has resulted in several negative outcomes.

PCAs offer a significant advantage over opioids administered by nurses, empowering the patient to self-administer analgesia as needed, thereby decreasing analgesia gaps and decreasing excess opioid dosing that could result in excess sedation and respiratory depression. Expanding the PCA arsenal to include various agents (eg, morphine, hydromorphone, fentanyl) at equianalgesic doses allows the opioid to be easily changed if it is ineffective or causes side effects. A novel, transdermal fentanyl PCA, IONSYS (Janssen-Cilag International, Beerse, Belgium) is currently available that could dramatically reduce some of the drawbacks of the PCA modality. IONSYS uses an iontopheretic transdermal system in which a small current is applied to a reservoir of fentanyl, allowing a 40-μg dose to move effectively across the dermis and be readily absorbed via cutaneous capillaries. The system significantly reduces both nursing and pharmacy workload. It has a built-in 10-minute lockout and requires replacement after 80 doses or 24 hours, whichever occurs first.[193,194] Table 11-4 lists various PCA options.

Oral opioid choices include short-acting agents such as Percocet (Endo Pharmaceuticals, Chadds Ford, Pa), a combination of oxycodone and acetaminophen; Vicodin (Abbott Laboratories, Abbott Park, Ill), made of hydrocodone and acetaminophen; and hydromorphone; as well as long-acting agents including methadone, sustained-release morphine, and sustained-release oxycodone (OxyContin, Purdue Frederick Co, Stamford, Conn). When changing either the opiate or the route of administration, the

TABLE 11-4

PATIENT-CONTROLLED ANALGESIA MODALITIES

Drug	Equianalgesic Dose (mg/mL)	Basal (mg/hr)	PCA Dose (mg)	Lockout (min)	Load (mg)
Morphine	1	0, 1	1, 2, 3	6–12	5–10
Meperidine	10	0, 10	10, 20, 30	6–10	50–100
Hydromorphone	0.2	0, 0.2	0.2, 0.4, 0.6	6–10	1–2
Fentanyl (μg)	25	0, 25	20, 25, 30	6–10	100–200

PCA: patient-controlled analgesia

TABLE 11-5

NARCOTIC CONVERSION CHART

Narcotic	IV Dose (mg)	PO Dose (mg)
Morphine	10	30–60
Hydromorphone	2	10
Methadone	10	20
OxyContin (Purdue Frederick Co, Stamford, Conn)	15	30

IV: intravenous
PO: orally

provider must use great care in converting the dose (Table 11-5). Once a new 24-hour dose is calculated based on a different medication or route, half the calculated dose should be given in divided doses in an appropriate frequency to allow for varying pharmacodynamics and pharmacokinetics. In addition, multimodal therapy with adjunctive agents requires reduced dosing as well.

In spite of their popularity, opioids cause both short- and long-term sequelae that are particularly problematic in the trauma patient.[56] Besides the side effects of sedation and the potential for respiratory depression, as well as their ineffectiveness in dynamic and neuropathic pain, opioids frequently are associated with nausea, vomiting, constipation, ileus, urinary retention, and pruritis. Long-term consequences include possible immunosuppression of B and T cell function, opioid tolerance, OIH, and the potential for opioid addiction in susceptible patients. OIH can occur even after short-term administration and results in a paradoxical decrease in a patient's pain threshold such that they are more sensitive to pain. The mechanism of OIH appears to include enhanced NMDA activity, increased levels of the pronociceptive spinal dynorphin, and increased excitatory pathways from the rostral ventromedial medulla to the dorsal horn. "Rekindling" of OIH may occur with a subsequent administration of a small dose of opioid after the apparent resolution of OIH.[53,56,195]

In the acute treatment of amputation pain in 31 patients, Wu et al[196] compared an IV bolus and infusion of morphine and lidocaine administration with a diphenhydramine control group in a cross-over study. They found that morphine relieved 45% of residual limb pain and 48% of PLP, while IV lidocaine relieved only 33% of residual limb pain and only 25% of PLP.[196] In another cross-over study, Huse et al[197] reported the efficacy of oral morphine for chronic PLP. They administered long-acting, oral morphine (70–300 mg daily) to 12 patients in a cross-over method, half receiving morphine for 12 weeks and the other half receiving placebo, followed by 6- and 12-month follow-ups. Although 42% of patients had greater than 50% reduction in pain, 50% of patients reported no pain relief. In three patients who responded to morphine, somatosensory evoke potential evaluations demonstrated decreased cortical reorganization.[197] Loeser[6] may offer the best advice on opioid use with amputees: as long as the patients' activities of daily living increase, a cautious trial of opioids is reasonable; however, if their activities of daily living decrease while their opioid dose increases, then the provider should wean them off of opioids.

Anticonvulsants

Anticonvulsants have long played a role in the treatment of neuropathic pain conditions, including peripheral diabetic neuropathy, postherpetic neuralgia, causalgia, and reflex sympathetic dystrophy (now called chronic regional pain syndrome). With the advent of newer and safer anticonvulsants, researchers have demonstrated a significant benefit with their use in acute pain management. Gabapentin and pregabalin, which are structural analogs of γ-aminobutyric acid, reduce calcium influx at the calcium channel and activate spinal noradrenergic activity, thereby reducing spinal cord excitatory amino acids, glutamate, and aspartate.[198] Pregabalin is the newest agent and although more expensive, it has a more favorable pharmacokinetic profile, allowing more rapid titration as well as twice daily dosing. Most commonly, gabapentin is dosed at 300 mg three times daily, then increased by 300 mg per dose every 3 days to a maximum daily dose of 3,600 mg. The most frequent side effects of these drugs are dizziness and drowsiness in roughly 10% of patients, yet both drugs seem to be well-tolerated in most patients. In several studies, including a look at the use of gabapentin in the treatment of PLP, their benefits include improved analgesia with an average use of 50% less opioids, decreased opioid-induced hyperalgesia and tolerance, decreased anxiety, possibly decreased chronic pain, and increased patient satisfaction.[199–202]

Carbamazepine reduces intense, brief, lancinating PLP, but has not been demonstrated to be effective for other types of phantom pain.[24,203] Gabapentin had little immediate effect on PLP but was shown to reduce pain intensity and visual analog scale scores after a 5-week treatment period in one study,[201] but this pain reduction was not replicated in subsequent studies,[204,205] although gabapentin was shown to be opioid-sparing.

Lidocaine/Mexiletene

The local anesthetic lidocaine and the oral analog mexiletene, class Ib antiarrhythmics, provide analgesia separate from their direct local anesthetic properties. Administered systemically, local anesthetics can decrease pain and opioid requirements, possibly through decreasing ectopic afferent neural activity at the NMDA receptor within the dorsal horn. IV lidocaine continuous infusion (1–2 mg/min) and topical lidocaine have been shown to decrease pain in the burn patient.[206] Mexiletene (with an initial dose of 150 mg twice daily) can be administered empirically or following a positive IV lidocaine test, after documenting the absence of conduction abnormalities on a 12-lead electrocardiogram. Mexiletene can be increased by 150 mg every 3 days to a maximum of 900 mg daily, although nausea and vomiting may limit dose escalation.

The combination of clonidine and mexiletene appears particularly beneficial in difficult, central-mediated pain syndromes such as PLP, as reported by Davis[49] and in one author's (RJM) personal experience in treating Brooke Army Medical Center patients from 2003 to 2007. As indicated above, Wu et al[196] demonstrated minimal benefit from the acute administration of IV lidocaine in PLP, and Davis[49] reported good to excellent relief from oral mexiletene alone in 58% of patients and good relief with a combination of mexiletene and clonidine in an additional 35% of patients, for a total 83% response rate for mexiletene when used in conjunction with clonidine.

Clonidine

Clonidine is an α_2-agonist acting at the locus caeruleus and in the dorsal horn of the spinal cord at α_2 antinociceptive receptors, causing analgesia, sedation, and anxiolysis from a supraspinal, spinal, and peripheral site of action. Whether given by an oral, IV, intrathecal, epidural, transdermal, or perineural route, it has been shown to decrease pain scores, decrease opioid requirements, decrease opioid-induced hyperalgesia, and prolong nerve blocks in a synergistic manner with other analgesics. In a hemodynamically stable patient, clonidine should be initiated at 0.1 mg by mouth twice daily, increasing to a maximum of 0.3 mg twice daily, observing for hypotension. While Davis[49] reported success with transdermal clonidine for outpatients, especially combined with mexiletene, providers at Brooke Army Medical Center found oral clonidine effective and easier to titrate for inpatients.

Ketamine

Historically, ketamine has played a central role in anesthesia for the trauma patient due to the profound analgesia and hemodynamic stability it provides. However, ketamine has increasingly been used for postoperative analgesia and acute pain management in the trauma patient; in fact, its use throughout the inflammatory period of injury may result in decreased central hypersensitivity resulting from the continual C fiber wind-up phenomenon in the polytrauma patient. Ketamine binds noncompetitively to the phencyclidine site of the NMDA receptor as well as to the σ-opioid receptor, resulting in intense analgesia; other benefits include prevention of opioid-induced hyperalgesia, decreased opioid tolerance, decreased opioid requirements, increased sense of well-being and patient satisfaction, decreased nausea and vomiting, decreased risk of respiratory depression, and decreased chronic pain. Although anesthetic doses may be associated with secretions as well as agitation and hallucinations, subanesthetic doses, with the addition of a benzodiazepine if necessary, are tolerated extremely well. The combination of ketamine and morphine in low PCA doses (1 mg morphine and 1 mg ketamine) has been shown to be particularly beneficial, with few side effects when ketamine doses are below 150 μg/kg/hr (2.5 μg/kg/min).[207–209]

Studies on ketamine have shown that it does not reduce the occurrence of PLP, but may temporarily reduce the severity of pain. A prospective observational study of 14 limb amputees showed that following administration of ketamine, 72% of subjects continued to experience PLP. However, only 9% of subjects given ketamine reported severe PLP, compared to 71% of controls.[210] Nikolajsen et al[211] reported profound acute reduction of both residual limb pain and PLP after a 0.1-mg/kg bolus followed by a 7-μg/kg/min infusion for 45 minutes. Nikolajsen[50] also reported on the efficacy of oral ketamine on chronic residual limb pain over a 3-month period. Another NMDA antagonist, dextromethorphan, was given daily (120–180 mg/day) to three amputation patients with PLP for 3 months, resulting in a significant reduction in PLP without side effects.[212] However, a further follow-up study randomizing 53 subjects to either epidural ketamine plus bupivacaine or epidural saline plus bupivacaine failed to demonstrate increased efficacy of epidural ketamine in treating PLP.[213]

Antidepressants

Tertiary amines, most notably amitriptyline, as well as secondary amines such as nortriptyline and desipramine, are effective in neuropathic and central hypersensitivity conditions primarily by blocking norepinephrine and serotonin reuptake in the dorsal horn. Their limitations result from a broad side-effect

profile including antihistamine, anticholinergic, and antiadrenergic effects that together frequently cause sedation, dry mouth, constipation, and possible tachycardia and orthostasis. Although amitriptyline has been most studied, the secondary amines may be equally effective and have fewer side effects. After ruling out significant cardiac contraindications by history, physical, and electrocardiogram, amitriptyline can be started at 10 to 25 mg every evening, increasing to 50 mg after 1 week of therapy, although its analgesic properties may take 3 to 4 weeks to take effect.

Amitriptyline has not been shown to be a consistently effective treatment for PLP. A randomized, placebo-controlled study of amitriptyline showed that it did not significantly reduce chronic PLP over a 6-week period.[214] Panerai et al,[215] however, demonstrated efficacy of both chlorimipramine and nortriptyline in central pain syndromes such as PLP in a randomized, controlled trial. Finally, mirtazapine, a newer antidepressant that modulates both serotonin and norepinephrine with fewer side effects than the tricyclic antidepressants, demonstrated efficacy in reducing PLP in one case series.[35]

Acetaminophen

Atlhough acetaminophen is a relatively weak analgesic, it is attractive as part of a multimodal pain regimen because it does not cause platelet dysfunction, gastritis, significant renal toxicity, bone-healing concerns, or associated nausea and vomiting. The mechanism of action is reported to function at a central COX-3 receptor, producing analgesia. Numerous studies have demonstrated synergy with other analgesics with at least 20% opioid sparing,[216,217] as well as decreased nausea, vomiting, and sedation using up to 4,000 mg daily in divided doses.

Nonsteroidal Antiinflammatory Drugs

NSAIDs also play a potentially critical role in multimodal therapy although with notable limitations. Traditional NSAIDs inhibit both COX-1 and COX-2 receptors, thereby decreasing the production of prostaglandins and thromboxane, and also decreasing nociception, respectively. Traditional NSAIDs bind receptors only peripherally, whereas the newer COX-2 agents work both peripherally and centrally, decreasing both peripheral and central sensitivity.[3] Their use is associated with many benefits including decreased opioid requirements, decreased pain scores, decreased nausea and vomiting, decreased constipation, decreased sedation, and finally decreased heterotopic ossification, a complication frequently associated with the polytrauma patient. Traditional NSAIDs are limited by potential adverse effects such as platelet dysfunction, gastritis, renal impairment, and impaired bone healing, most of which is dose-dependent. Oral COX-2 agents, currently only celecoxib, may be an attractive alternative because they do not cause platelet dysfunction and have decreased gastritis risk, although their risk of renal impairment and bone-healing problems is similar to traditional NSAIDs. Unfortunately, the COX-2 inhibitors have been associated with increased thromboembolic events including myocardial infarction, as well as higher rates of congestive heart failure and hypertension. Recently, some of the traditional NSAIDs have also been associated with an increased thromboembolic risk.[218,219] However, in some patients, traditional NSAIDs, including ketorolac (for up to 5 days) and COX-2 inhibitors can be helpful in achieving greater analgesia, particularly for dynamic pain and as part of a multimodal regimen.[220–222]

Calcitonin

Salmon calcitonin has been noted to have analgesic properties in the treatment of Paget disease, possibly related to binding with serotonin receptors within the hypothalamus and limbic system. Calcitonin has been shown to provide analgesic effects for PLP.[170,223] Jaeger and Maier[223] reported a prospective, double-blinded, cross-over trial with calcitonin 200 units over 30 minutes. Each of the calcitonin groups showed a significant reduction in pain scores compared to placebo.

Nontraditional Therapies

TENS, acupuncture, and virtual reality mirror treatments have also shown some success in reducing PLP or delaying the onset of chronic phantom pain.[192,224,225]

Transcutaneous Electrical Nerve Stimulation, Spinal Cord Stimulation, and Deep Brain Stimulation

TENS has shown some success in relieving PLP, but again, study results have been varied. Spinal cord stimulation and deep brain stimulation of the ventral caudal thalamic nucleus are techniques that have led to short-term relief of PLP in several studies.[226–230] A series of studies showed that the stimulation of the posterior columns of the spinal cord led to 65% of patients having a 25% reduction in pain levels immediately after surgery, but only 33% showing long-term reduction in pain levels.[231,232] Other reports have shown little or no reduction in PLP following dorsal column stimulation.[233,234]

Sympathetic Blocks for Postamputation Pain

An infrequent intervention for amputation pain is sympathetic blocks, specifically lumbar sympathetic block and stellate ganglion block. A practitioner must first recognize the signs of sympathetically mediated pain, which include allodynia, decreased range of motion, edema, and possible skin changes such as a cold and clammy or sweaty extremity with possible hair changes. Pain may become worse during physical or emotional stress due to catecholamine release, which may activate nerve terminals and neuromas. Classically, local anesthetics are injected near the sympathetic ganglia, which relieves pain and sympathetic symptoms within minutes, making the extremity warm with improved blood flow and color. Pain physicians have documented the effective use of stellate ganglion blocks to prevent reactivation and worsening of pain in patients with a history of chronic regional pain syndrome who are undergoing upper extremity surgery. In addition, there are case reports of stellate ganglion block to treat acute postoperative pain in patients without chronic regional pain syndrome.[235] A stellate ganglion block with fentanyl alone has also been reported to be effective.[236] Temperature increase in the extremity without motor or sensory blockade is indicative of effective stellate ganglion or lumbar sympathetic block; stellate ganglion blocks may be accompanied by a possible Horner syndrome (ptosis, miosis, and anhydrosis). However, pain relief following sympathetic blocks may result from undetected somatic block from local anesthetic spread to the epidural space or lumbar nerve roots.[237]

Acupuncture

Some amputees have gained relief from PLP by rubbing their intact limb and stimulating normal afferent input at the peripheral, spinal, and cortical levels. Based on this concept, acupuncture in the intact limb has been used as a means to stimulate normal afferent input to the nervous system and elicit an analgesic effect that reduces the intensity of PLP and phantom sensations.[238,239] Bradbrook[239] found that acupuncture was an effective treatment in two patients who had had nontraumatic limb amputation (following congenital talipes and myeloma of the pelvis). These two patients reported immediate and significant reduction in severity of PLP as measured with a visual analog scale following several sessions of acupuncture in regions of the intact limb anatomy in relation to the subjects' PLP and phantom sensations.[239] However, in another single case of a patient who had undergone traumatic limb amputation following a motor vehicle accident, acupuncture was not effective in reducing the severity of PLP and phantom sensations. It remains unclear through what specific mechanism acupuncture alleviates PLP, and as with many other therapies, accupuncture has not been shown to consistently relieve PLP in patients who have undergone traumatic limb amputations.

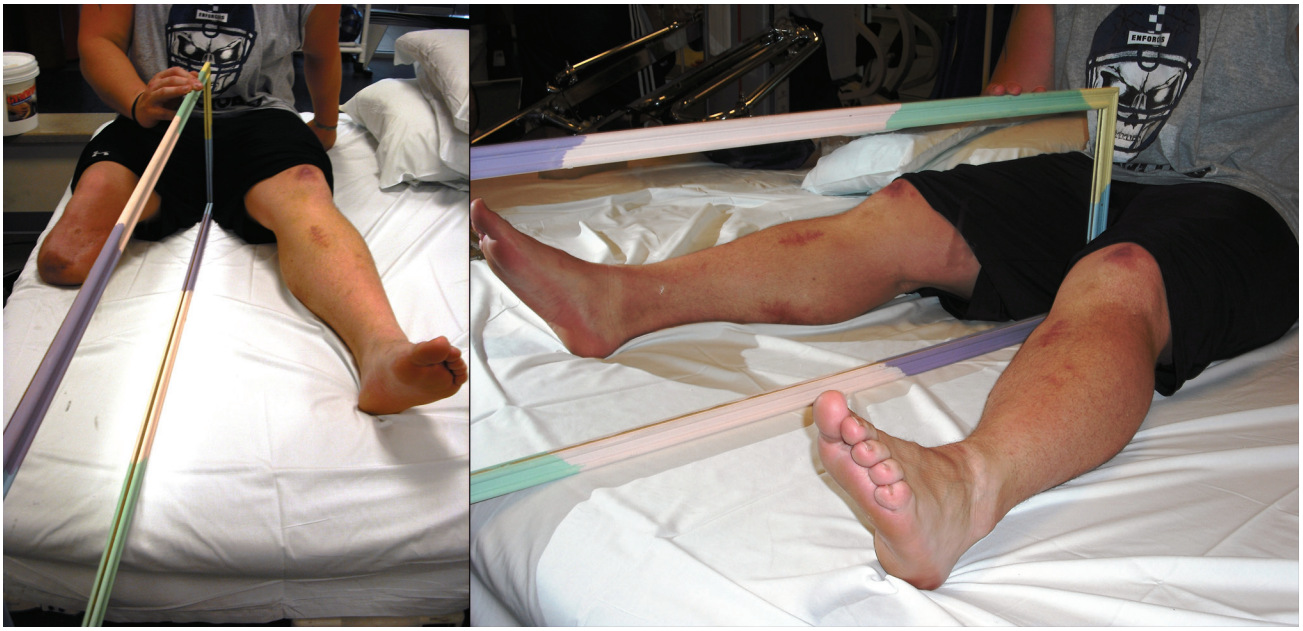

Figure 11-5. Right lower extremity amputee participating in mirror therapy as treatment for phantom limb pain.

Mirror Therapy

Another proposed treatment is based on the concept that the perception and experience of PLP may emerge due to conflicts within the brain between visual and proprioceptive feedback mechanisms.[224] Based on this visual-proprioceptive dissociative feedback postulate, Ramachandran and colleagues[224] proposed that using the reflected image of the intact limb in a mirror to create the visual illusion of the missing limb might reduce the conflict between visual and proprioceptive inputs and, consequently, reduce PLP. They used this technique in upper extremity amputees and found that approximately 60% of subjects in one case series of 15 amputees reported an improvement in their PLP.[224] This technique required the amputee to view the reflected image of the intact hand performing specific movements, while performing the same movements with the amputated, or "phantom," hand. While performing these movements with the intact hand, many subjects reported feeling the phantom hand moving simultaneously, accompanied by pain relief.

Two of the authors (BLC and JWT) were part of a recently concluded randomized, sham-controlled study of unilateral lower extremity amputees using mirror therapy (Figure 11-5) compared to cover mirror and mental visualization therapies, finding a strong benefit of mirror therapy (Figure 11-6).[225] This study showed that all six amputees (100%) who were randomized to mirror therapy had pain relief and eight of nine subjects (89%) who crossed over to mirror therapy after being randomized initially to either covered mirror or mental visualization therapies had benefit from mirror therapy, so that a total of fourteen of fifteen subjects (93%) using mirror therapy had pain relief.

Although the results of these studies appear to provide further support for the postulate that a mismatch between visual and proprioceptive inputs contributes to the generation of PLP, it is not clear why a mismatch would cause pain. Head first posited the existence of two major somatesthetic sensory systems, one he termed epicritic and the other protopathic.[240] The epicritic system is rapid and is transmitted to the brain by lemniscal afferent pathways. In contrast the protopathic system is slow and is carried to the brain by a chain of neurons. Head suggested that the epicritic system gates the protopathic system and that loss of the epicritic system can induce pain because the protopathic system is uninhibited.[240] Melzack and Wall[27] subsequently put forth a similar gating hypothesis.

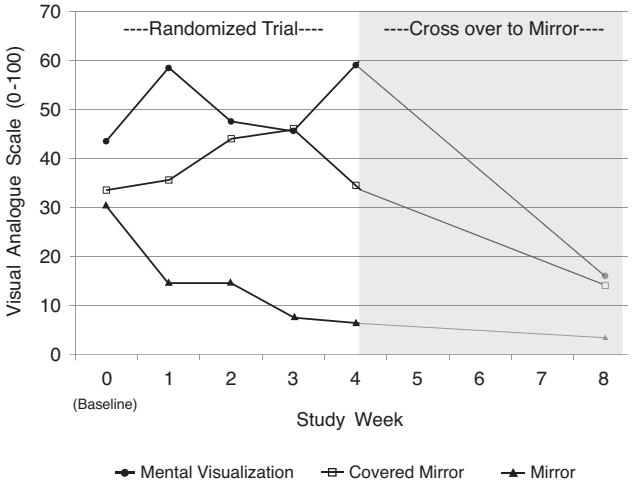

Figure 11-6. Results of controlled trial of mirror therapy. Change in phantom limb pain measured using the VAS. Group medians are depicted for each time point.
Reproduced with permission from: Chan BL, Witt R, Charrow AP, et al. Mirror therapy for phantom limb pain. *N Engl J Med*. 2007;357:2206–2207. Copyright 2007 Massachusetts Medical Society. All rights reserved.

Rossi et al[241] postulated and provided evidence to demonstrate that imagery of movements or actual movements reduces the amplitude of the somatosensory evoked potentials (ie, a gating effect), suggesting that this gating may help reduce phantom pain. The mirror therapy paradigm has been more successful than imagery alone because it led to the activation of mirror neurons, neurons that fire both when a person performs an action and when observing the same action performed, in the cortex contralateral to the amputated limb. Since the activation of these mirror neurons modulates somatosensory inputs, their activation may have blocked protopathic pain perception in the phantom limb.[241] Mirror therapy has now been adopted as part of the routine treatment for PLP offered by several military medical centers, including Walter Reed Army Medical Center.

LOW BACK PAIN

Low back pain (LBP) is reported as a significant impairment in approximately 71% of patients with lower limb amputations.[242] Patients with transfemoral amputations tend to have a greater incidence and severity of LBP than those with transtibial amputations.[243] Leg length discrepancy, excessive lumbar lordosis, and excessive trunk motion may be related to LBP in transfemoral patients. Friel et al[244] found that patients with transfemoral amputations exhibited greater strength but less endurance in their back extensor muscle than

those with transtibial amputation. Friberg[245] found that amputees with LBP tended to have greater leg length discrepancies than those without pain. Back pain tends to decrease following leg length discrepancy correction. In some studies, lumbar lordosis has been correlated with increased LBP, particularly in circumstances with poor prosthetic fit.[245] Leg length discrepancy, lumbar lordosis, and excessive motion of the lumbar spine may lead to abnormal spinal loads, which produce abnormal stress distributions in the tissues. No specific evidence is available to guide treatment of LBP in patients with lower extremity amputations. However, the high prevalence of LBP among patients with lower extremity amputations may have as strong an impact on disability, function, and rehabilitation as residual limb pain and phantom sensations.

FUTURE RESEARCH

Research into methods for preventing and treating postoperative residual limb pain and PLP have demonstrated several therapeutic options. It is likely that a combination of therapies may be needed to effectively treat pain through acute, subacute, and chronic pain conditions following limb amputation. Areas that require additional research are more effective analgesics to be deployed in the battlefield setting, pain immediately following amputation, and treatments for chronic pain (eg, headaches, osteoarthritis, PLP, and LBP). The appropriate timing and duration of regional anesthesia in the acute and subacute period to decrease both acute and chronic pain needs further evaluation. Understanding the mechanism for the development of pain sensation will lead to improved pharmacologic as well as nontraditional methods for controlling and regulating the pain response. Also, further understanding of the cognitive response to pain, especially phantom pain, will help in the development of more effective treatments for PLP and possibly a means for tracking the response to therapies.

SUMMARY

In summary, PLP and pain in the residual limb are significant medical problems after amputation. Many different therapies have been tried with few successes, although multimodal therapy appears to be most effective. Multimodal therapy including appropriate continuous regional analgesia, multiple medications aimed at various locations along the nociceptive pathway, and nontraditional therapies such as mirror therapy, is a promising method of treatment that may bring desperately needed pain relief to service members with limb loss.

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