Pain management is increasingly recognized as a critical aspect of the care of the amputation patient. Aggressive analgesia not only decreases pain and suffering, but produces a myriad of benefits, including improving sleep/wake cycles, decreasing anxiety, stress and depression, improving pulmonary mechanics, decreasing hospital stays and cost and improving overall outcome. Additionally, aggressive acute pain control likely leads to a reduction in chronic amputation pain involving chronic residual limb pain (RLP) and/or phantom limb pain (PLP).

A phantom limb experience is defined as the continued awareness of a missing limb and the perceived ability to move the missing limb, most likely due to a persisting central nervous system representation of the limb or “neuromatrix.” This neuromatrix represents a neural network within the brain, sculpted by sensory inputs. Phantom pain may result from the loss of modulating inputs from the limbs to the neuromatrix, which can then cause an abnormal neurosignature to be produced, resulting in “cortical reorganization.”
Over 90 percent of patients who have undergone limb amputation experience a vivid phantom, with even higher incidences following traumatic limb loss or a preexisting painful condition in the limb. Phantom limb sensations, including tingling, itching, burning, movement, temperature changes, pressure and pain, usually occur immediately following surgery and are nearly universal in amputees. Telescoping, a sensation that the distal portion (farthest from the body) of the limb progressively moves closer to the residual limb, is the most common kinesthetic aspect reported in two-thirds of patients. Over 70 percent of amputees continue to experience some PLP up to 25 years after limb amputation. Typically, RLP subsides with healing, but may persist due to poor prosthetic fit, overuse, heterotopic ossification (excess bone growth), neuroma, infection or inflammation, or other causes. Amputation pain is more prevalent if chronic pain exists prior to surgery or if postoperative analgesia is inadequate. Historically, PLP and RLP have been treated with “unimodal” (single, or specific approach) therapy, focusing on opiate therapy and simply adding other analgesics as necessary over time. However, “multimodal (multiple approach) therapy” capitalizes on the synergy (interaction) between various medications and attacks the pain pathway at multiple points during the acute (abrupt, intense, and relatively short duration) and subacute (gradual, less intense, and longer duration) phases following amputation. Acute perioperative (during surgery) pain management, often led by an “Acute Pain Service,” helps maintain the patient’s functional abilities and psychological well-being, enhances rehabilitation, minimizes analgesia gaps and hospital stays, and avoids the results of undertreatment of perioperative pain. Synergy between medications allows decreased dosing of each medication, reducing the side effects of each medication. Treating pain at various points of the nociceptive pathway (the neural network that conducts pain signals) including transduction, transmission, perception and modulation, allows multimodal therapy to be more effective than simply increasing the treatment at only one point in the pathway. For example, patients should receive an around-the-clock regimen of nonsteroidal anti-inflammatory drugs (NSAIDs), selective cox-2 inhibitory blockers (COXIBs) and/or acetaminophen unless contraindicated since they reduce inflammatory mediators (e.g., redness, heat, edema), which increase after tissue injury, decreasing the transduction aspect of the pain pathway. NSAIDs also reduce heterotopic ossification as a result of their inhibition of osteoblastic activity (bone growth). Regional anesthesia blocks the transmission process in the pain pathway, decreasing the barrage of painful stimuli to the cerebral cortex. Additional medications, such as anticonvulsants, antidepressants, NMDA (N-methyl D-aspartate) antagonists, alpha 2 agonists, and systemic sodium channel blocking agents affect primarily spinal and supraspinal (above the spine) sites, especially descending modulating pathways, as described below. After the primary inflammatory period subsides, analgesics are gradually eliminated over the first few weeks or months after amputation. As a cornerstone of multimodal therapy, opioids notably bind with opioid receptors, reduce neurotransmitter release and
nociceptor sensitization (particularly in inflammatory tissue), modulate afferent (conductive) input in the dorsal horn of the spinal cord, and provide analgesia without loss of touch, proprioception (sense of body position) or consciousness. Unfortunately, excess opiates can increase the potential for physical dependence, addiction, tolerance and the phenomenon of “opioid-induced hyperalgesia” (OIH) resulting from opioid-centered analgesia. OIH actually decreases the patient’s pain threshold, thereby accentuating perceived pain, which can be clinically difficult to distinguish from opiate tolerance; this phenomenon can occur relatively acutely and is probably dependent on dose and duration of opiate therapy. By using opioid-sparing techniques, multimodal therapy reduces the likelihood of the negative aspects of excess opioids.

Preemptive analgesia (preventing subsequent pain by administering analgesia before surgery or traumatic stress) has received significant attention in the past 10-15 years, with conflicting results. Currently, preventive analgesia (applying aggressive analgesia modalities before, during and after surgery or traumatic stress) appears far more promising. The continuous painful sensory input immediately following amputation leads to inflammatory changes both peripherally and centrally, which, if left unchecked, gives way to a wind-up phenomenon causing hypersensitivity and lingering pain syndromes. Therefore, while regional anesthesia interventions prior to surgical stimulus result in improved postoperative analgesia, continuous postoperative epidural infusion or continuous peripheral nerve blocks (CPNBs) are of greater benefit because of the ability to provide preoperative, intraoperative and postoperative analgesia during much of this critical inflammatory period.

In addition to regional anesthesia, other analgesic adjuncts contribute to multimodal therapy. Relatively new anticonvulsants, gabapentin and pregabalin, are structural analogs of GABA (gamma-aminobutyric acid), reduce calcium influx at the calcium channel, and activate spinal noradrenergic activity (increased heart rate, blood pressure and sugar level), thereby reducing spinal cord excitatory amino acids, glutamate and aspartate. While up to 10 percent of patients experience dizziness and drowsiness, both medications seem to be well-tolerated in most patients and offer improved analgesia, decreased anxiety, opiate requirement, OIH and tolerance, possibly decreased chronic pain, and increased patient satisfaction.

Clonidine is an alpha 2 agonist acting at the locus ceruleus (area of the brain that processes sensory signals) and in the dorsal horn of the spinal cord causing analgesia, sedation and anxiolysis (relief of anxiety) from supraspinal, spinal and peripheral sites of action. Whether given by oral, intravenous, intrathecal, epidural, transdermal or perineural methods, it has been shown to decrease pain scores, opiate requirements and OIH, and prolong nerve blocks in a synergistic manner with other analgesics. Combined with mexiletine (an oral analog of lidocaine), it appears to offer significant potential for preventing PLP.

Finally, ketamine has enjoyed a central role in anesthesia for the trauma patient due to the profound analgesia and hemodynamic (blood circulation) stability it provides. Increasingly, however, ketamine has been used for postoperative analgesia and acute pain management in the challenging patient as it binds to the phencyclidine site of the NMDA receptor as well as opiate receptors; in fact, its use throughout the inflammatory period of injury may decrease central hypersensitivity and chronic pain, help prevent OIH, decrease opiate requirements and tolerance, increase sense of well-being and patient satisfaction, decrease nausea and vomiting and decrease risk of respiratory depression.

Other promising adjuncts include tricyclic antidepressants, benzodiazepines in certain patients, calcitonin, mirror therapy, transcutaneous electrical nerve stimulation (TENS), sympathetic nerve blocks, spinal cord stimulation and acupuncture. Together with the other modalities discussed previously, these analgesics appear to be most effective when used in an optimal multimodal approach, thereby limiting the opiate requirement and opiate side effects. Certainly, healthcare providers treating amputation pain today have a wide range of analgesics that together offer the best chance to minimize pain and suffering in the amputee while maximizing function and recovery.