

# Clinical Consequences of Inadequate Pain Relief: Barriers to Optimal Pain Management

Jaime L. Baratta, MD  
Eric S. Schwenk, MD  
Eugene R. Viscusi, MD

*Philadelphia, Pa.*

**Summary:** Uncontrolled postoperative pain may result in significant clinical, psychological, and socioeconomic consequences. Not only does inadequate pain management following surgery result in increased morbidity and mortality but it also may delay recovery, result in unanticipated readmissions, decrease patient satisfaction, and lead to chronic persistent postsurgical pain. Pain is multifactorial in nature, and understanding both the complexity of pain and its side effects is imperative to achieving a successful surgical outcome. In this section, we review the consequences of pain as they pertain to plastic surgery with a focus on the impact of pain on the surgical stress response and risk of wound infections and the effect of improved pain control on flap surgery. Uncontrolled acute postoperative pain may lead to chronic persistent postsurgical pain, which has a high incidence in patients undergoing breast cancer surgery. To achieve optimal postoperative analgesia, one must recognize the barriers to effective pain management, including both physician/nursing-related barriers and patient-related barriers, as well as the increasingly common appearance of opioid-tolerant patients. (*Plast. Reconstr. Surg.* 134: 15S, 2014.)

Postoperative pain is one of the greatest concerns of most patients undergoing surgery. Despite an evolving focus on pain management regimens, 80% of patients continue to experience acute pain after surgery, with the majority experiencing moderate-to-severe pain.<sup>1</sup> Inadequate pain management may lead to significant clinical manifestations, including myocardial ischemia, impaired pulmonary function, ileus, thromboembolism, impaired immune function, and anxiety.<sup>2</sup> In addition, chronic persistent postsurgical pain (CPSP) may have an incidence as high as 50% following a variety of procedures, including breast surgery.<sup>3</sup>

Inadequate pain management may result in significant increases in healthcare costs. As patient satisfaction is an increasingly important factor in determining reimbursements, achieving adequate postoperative pain management becomes an imperative aspect of the overall surgical plan. Numerous studies have shown that uncontrolled postoperative pain may lead to prolonged post-anesthesia care unit stays,

delayed hospital discharge, and unanticipated admission following ambulatory surgery or readmissions following.<sup>4-7</sup> As a majority of plastic surgery procedures are done in an ambulatory setting, delays in recovery and unanticipated readmission may affect reimbursements. When patients undergoing ambulatory surgery were surveyed for predictors of pain severity, the type of surgery was the most important determinant, with plastic surgery, hernia, and laparoscopy resulting in more severe pain than knee arthroscopy and uterine surgery.<sup>7</sup> It is also well documented that inadequate pain control may decrease quality of life and delay recovery and return to normal activities.<sup>8</sup>

In this review, we will describe the clinical impact of uncontrolled pain and the barriers to pain management with a focus on how these issues pertain to the plastic surgery population.

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From the Department of Anesthesiology, Jefferson Medical College, Thomas Jefferson University.  
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## UNDERSTANDING THE DEVELOPMENT OF PAIN

Pain is complex in nature and frequently misunderstood, often making it difficult to treat. The perception of pain involves both the peripheral and central nervous system. Within the central nervous system, both spinal and supraspinal sites play a role. There are 5 generally accepted types of pain: nociceptive, neuropathic, psychogenic, mixed, and idiopathic.<sup>9</sup> Nociceptive pain may be aching, sharp, or throbbing, whereas neuropathic pain is often burning, tingling, crushing, or stabbing. Psychogenic pain may explain complaints that do not match the presenting symptoms, and idiopathic pain is of unknown origin. Mixed patterns with characteristics of both nociceptive and neuropathic pain may exist.

Although the majority of pain is often nociceptive in nature secondary to direct tissue injury, neuropathic pain may develop as a result of direct nerve injury. The pain associated with breast surgery is a combination of nociceptive and neuropathic pain and subsequent inflammation. In a study comparing traditional analgesia to a multimodal approach that included gabapentin, eutectic mixture of local anesthetics, and intraoperative injection of ropivacaine to the brachial plexus in the axilla, the multimodal regimen resulted in both decreased incidence of acute and chronic pain and reduced analgesic consumption following breast cancer surgery.<sup>10</sup> Gabapentin reduces the membrane voltage-gated calcium currents in dorsal root ganglia neurons in neuropathic rats and may produce analgesia by decreasing neurotransmitter release by sensory neurons.<sup>10</sup> Local anesthetics suppress afferent nociceptive signals and resulting inflammation. Direct tissue injury secondary to surgical insult causes nociceptive pain and leads to inflammatory reactions. Inflammatory reactions result from direct nerve injury as well and may cause hypersensitivity and hyperactivity in neurons and a subsequent neuronal transformation that can lead to neuropathic pain.<sup>11</sup> This confluence of neuronal changes may occur in any procedure that results in direct nerve injury and, of the commonly performed plastics procedures, is most commonly seen in breast surgery. In addition, a surgical insult may promote neuroplastic changes within the nervous system and subsequent peripheral and central sensitization. This sensitization may lead to hyperalgesia, an exaggerated pain response to a normally painful stimulus, or allodynia, a painful response to nonpainful stimulus.

As pain is multifactorial, it is important to recognize that successful treatment of pain depends

on a multimodal approach. An analgesic regimen that acts directly on the peripheral nociceptors at the site of tissue injury, at the peripheral nerves supplying the surgical area, and at both spinal and supraspinal sites will yield the most effective pain management strategy.

## CLINICAL IMPACT OF UNCONTROLLED PERIOPERATIVE PAIN

### The Surgical Stress Response and Infections

Inadequate pain control in the perioperative period has been linked to many adverse events, including myocardial ischemia, impaired pulmonary function, ileus, thromboembolism, impaired immune function, and anxiety.<sup>2</sup> The clinical impact of poorly controlled pain in the perioperative period extends to multiple organ systems and can have long-lasting effects (Table 1). Of particular concern in plastic surgery is the potential for postoperative wound infections. Surgical stress induces an inflammatory reaction that involves the release of humoral mediators, such as prostaglandins, kinins, and tumor necrosis factor.<sup>12</sup> These substances, along with the increased levels of cortisol observed during surgery, can exert detrimental systemic effects, including hyperglycemia,<sup>13,14</sup> catabolism,<sup>13,14</sup> and, perhaps most importantly in the setting of plastic surgery and wound healing, impaired immune function.<sup>14</sup> Although unplanned readmissions seem to be uncommon after outpatient plastic surgery procedures, a review of the National Surgical Quality Improvement Program database revealed that one of the most frequent reasons is wound infection,<sup>15</sup> emphasizing the importance of prevention. Although a detailed discussion of postoperative wound infections is out of the scope of this review, the focus will be on pain management and its role in modifying the stress response to surgery.

### Analgesia and Immune Function

Adequate analgesia can suppress the body's stress response, including the release of potentially detrimental stress hormones. The release of glucocorticoids suppresses cellular immunity,<sup>14</sup> creating the potential for infection.  $\beta$ -endorphin is another substance that has been shown to suppress the immune system.<sup>14</sup> Surgical stress increases levels of these and many other compounds. Analgesia that interrupts this response involves using a multimodal approach that takes advantage of several drugs and techniques with different mechanisms

**Table 1. Suggested Dosing of Nonopioid Multimodal Medications**

Drug	Preoperative Dose	Route of Administration	Time Before Surgery	Postoperative Dose
NSAIDs				
Ketorolac	15–30 mg	PO/IV	30 min to 2 h	15–30 mg every 6 h
Ibuprofen	600–800 mg	PO		800 mg every 6 h
Cyclooxygenase-2 inhibitors				
Celecoxib (Celebrex)	200 or 400 mg	PO	30 min to 2 h	200 mg × 1
Antineuropathic				
Gabapentin (Neurontin)	600–1200 mg	PO	30 min to 2 h	600 mg BID (up to 48 h)
Pregabalin (Lyrica)	75–300 mg	PO	30 min to 2 h	75–150 mg BID
Acetaminophen				
PO, Tylenol	1 g	PO/IV	30 min to 2 h	1 g every 6 h
IV, Ofirmev				(weight >50 kg)

BID, twice daily; IV, intravenous; PO, oral.

of action. For example, thoracic epidural analgesia has been shown to attenuate the body's stress response during major abdominal surgery, leading to lower levels of epinephrine and cortisol and higher levels of lymphocytes and T-helper cells.<sup>16</sup> Preservation of lymphocyte function by epidural analgesia has also been demonstrated after spine surgery.<sup>17</sup> This topic is discussed more extensively elsewhere, but for major abdominal surgery, such as a ventral hernia repair with a complex closure, it certainly deserves consideration as one part of an analgesia regimen.

### Role of Multimodal Analgesia to Improve Analgesia

Minimizing the use of opioids in a multimodal analgesia regimen can help decrease their many unwanted side effects, such as nausea and vomiting, pruritus, sedation, and respiratory depression, while blunting the body's stress response. Regional anesthesia techniques, ketamine, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and gabapentinoids should be considered whenever possible, using opioids only as rescue analgesics. The American Society of Anesthesiologists (ASA) Task Force on Acute Pain Management in their 2012 update recommended the use of multimodal analgesia “whenever possible”<sup>18</sup> (Table 1).

### Analgesia and Outcomes after Flap Surgery

Flap surgery has become increasingly common in plastic surgery. There is evidence that epidural analgesia improves pain control after transverse rectus abdominis myocutaneous flap surgery and may hasten hospital discharge.<sup>19</sup> Epidural analgesia also may have a role in decreasing blood loss after flap surgery. Epidural analgesia has been shown to improve pain control and decrease intra- and postoperative blood loss in the setting of spine surgery.<sup>20</sup> For larger abdominal,

thoracic, or spine procedures involving plastic surgery, an epidural should be considered. Epidural analgesia blunts the sympathetic response to surgery, potentially improving blood flow to tissues. Although its effects on flap loss are not completely clear, epidural analgesia has been shown to improve the microcirculation in flap venules that were exposed to venous ischemia, while general and spinal anesthesia did not.<sup>21</sup> Sympathetic discharge resulting from uncontrolled pain may contribute to flap loss, but the lack of a benefit of spinal anesthesia suggests that other factors likely also play a role, so it is uncertain whether other analgesic techniques and medications have the same beneficial effects as epidurals.

Although NSAIDs have often been avoided in plastic surgery due to bleeding concerns, the literature does not support such beliefs. A retrospective review of 215 females undergoing breast reconstruction with a transverse rectus abdominis myocutaneous flap found that ketorolac decreased opioid consumption after surgery without increasing bleeding.<sup>22</sup> This topic is discussed in more detail elsewhere in this edition, but bleeding and flap loss concerns seem unwarranted given the existing evidence, and in fact, NSAIDs are a useful adjunct as part of a multimodal analgesia regimen and are recommended by the ASA Task Force on Acute Pain Management.<sup>18</sup>

### Anxiety and Patient Outcomes

An underappreciated problem that can pose a barrier to optimal recovery after plastic surgery is a patient's emotional state and, in particular, anxiety. Many patients worry about their appearance after surgery, especially women undergoing partial or radical mastectomy. The thought of being “disfigured” or losing femininity can cause significant distress. Women who have high preoperative levels of anxiety before breast surgery experience

more postoperative acute pain<sup>23,24</sup> and are more likely to develop chronic postsurgical pain.<sup>25</sup> Recognition and treatment of preoperative anxiety play an important role in preventing the development of chronic pain syndromes and give the provider an opportunity to address the many concerns patients often carry with them into surgery. This cannot be fully completed on the day of surgery but, rather, should be started, if possible, during the initial consultation in the surgeon's office (Table 2).

### CHRONIC PERSISTENT POSTSURGICAL PAIN

CPSP may result from inadequately treated acute postoperative pain. The simplified definition of persistent postoperative pain is pain persisting longer than 3 months after surgery. However other causes of pain must be ruled out before diagnosing CPSP. CPSP has an incidence of 10–50% following a variety of surgical procedures, including inguinal hernia repair, amputation, coronary artery bypass surgery, thoracotomy, and breast surgery.<sup>3</sup> Of these patients, 2–10% can experience severe and debilitating chronic pain.<sup>3</sup> Risk factors for the development of CPSP may include genetic susceptibility,<sup>26</sup> preoperative pain, severe postoperative pain,<sup>27</sup> type of surgery, and psychological variables, such as preoperative anxiety.<sup>23,28</sup> However, predicting which patients are at risk for CPSP remains a challenge.

The incidence of CPSP following breast cancer surgery has been reported as high as 20–50%.<sup>29</sup> Although the mechanism of CPSP is not well understood, chronic pain associated with breast cancer surgery is believed to be secondary

to inflammatory and neuropathic components as well as central sensitization and may result from surgical insult or adjuvant therapy such as chemotherapy or radiation. The exact pathogenesis is unknown but may be due in part to nerve damage secondary to surgical technique or related to phantom breast pain.<sup>30</sup> CPSP has been detected in patients undergoing mastectomy with or without lymph node dissection, breast reconstruction, and breast-conserving surgery, such as lumpectomy with lymph node dissection. Subsequent radiation and chemotherapy may also contribute to CPSP following breast cancer surgery.

In a study of 479 women undergoing a variety of breast surgeries, the incidence of chronic pain 1 year after surgery varied among procedures. The incidence of chronic pain for the mastectomy with reconstruction group was 49%, whereas those undergoing mastectomy alone was 31%.<sup>31</sup> For patients undergoing breast reduction, 22% reported persistent pain, whereas 38% of women undergoing augmentation complained of pain. Reconstruction with breast implants resulted in a higher incidence of pain than in those without (53% versus 30%).<sup>31</sup> For those reporting pain, arm pain and pain with movement were more likely in patients having undergone mastectomy with or without reconstruction.<sup>31</sup> A large study examined 3253 women undergoing breast cancer surgery, including both mastectomy and lumpectomy with sentinel lymph node dissection or axillary dissection and subsequent radiation, and found that 47% reported persistent pain (13% severe, 39% moderate, and 48% light pain) and 58% reported sensory disturbances at the surgical site at 1–3 years after surgery.<sup>30</sup> Predictors of pain included

**Table 2. Consequences of Unrelieved Pain**

Organ Systems	Physiologic Responses
Cardiovascular	Increased heart rate, peripheral vascular resistance, arterial blood pressure, and myocardial contractility, resulting in increased cardiac work, myocardial ischemia, and infarction
Pulmonary	Respiratory and abdominal muscle spasm (splinting), diaphragmatic dysfunction, decreased vital capacity, impaired ventilation and ability to cough, atelectasis, increased ventilation/perfusion mismatch, hypoventilation, hypoxemia, hypercarbia, increased postoperative pulmonary infection
Gastrointestinal	Increased gastrointestinal secretions and smooth muscle sphincter tone, reduced intestinal motility, ileus, nausea, and vomiting
Renal	Oliguria, increased urinary sphincter tone, urinary retention
Coagulation	Increased platelet aggregation, venostasis, increased deep vein thrombosis, thromboembolism
Immunologic	Impaired immune function, increased infection, tumor spread or recurrence
Muscular	Muscle weakness, limitation of movement, muscle atrophy, fatigue
Psychological	Anxiety, fear, anger, depression, reduced patient satisfaction
Overall recovery	Delayed recovery, increased need for hospitalization, delayed return to normal daily living, increased healthcare resource utilization, increased healthcare costs

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young age (18–39 years) and adjuvant radiation therapy, whereas axillary lymph node dissection was associated with increased likelihood of pain compared with sentinel lymph node dissection.<sup>30</sup> When looking at the long-term effects of chronic pain following breast cancer surgery, 52% of the 113 women questioned reported persistent pain at a mean time of 9 years after surgery with quality-of-life scores significantly lower in those reporting persistent pain.<sup>32</sup>

Although the exact mechanism for the development of CPSP is not known, it is well accepted that peripheral and central sensitization of the nervous system are involved.<sup>2</sup> Such sensitization and alteration of the nervous system may result from repetitive or prolonged noxious stimuli. It is therefore imperative to treat acute postoperative pain to minimize the likelihood of subsequent neuroplastic changes. Utilizing a multimodal analgesic regimen is important in the prevention of CPSP.

### **BARRIERS TO OPTIMAL PAIN MANAGEMENT**

There are numerous barriers to developing and achieving effective postoperative pain management. As pain is complex in nature, the barriers to effective pain management are multifactorial. Common barriers may be physician/nursing related or patient related. The increasing incidence of opioid tolerance and opioid abuse is becoming a significant barrier to develop an effective analgesic regimen (Table 3).

#### **Physician/Nursing-Related Barriers**

Physician- and nursing-related barriers include lack of knowledge about analgesic regimens, negative attitudes toward prescribing opioids, and inadequate understanding of the complex nature of pain and subsequent difficulty with pain-assessment techniques. In addition, surgeons may fear specific drugs, particularly NSAIDs, secondary to the concern for their effect on platelet aggregation and subsequent bleeding risk. Despite the ASA recommendations to utilize opioids as adjuncts rather than first-line analgesics, both patients and physicians underestimate the importance of NSAIDs, acetaminophen, gabapentinoids, and local anesthetics as part of a balanced analgesic regimen. It is well known that opioids possess significant side effects that may impair recovery and quality of life; ignoring or minimizing them can inhibit effective pain management. Many physicians do not understand proper

opioid-prescribing techniques. Postoperative pain is acute in nature and will improve as the surgical site heals. Short-acting opioids via either intravenous patient-controlled analgesia or immediate-release oral opioids are most effective in achieving pain relief while still maintaining safety when compared with long-acting opioids. Extended-release/long-acting opioid formulations are specifically contraindicated for the treatment of new acute pain because they increase the risk of fatal opioid-related respiratory death.<sup>33</sup> The Food and Drug Administration strengthened the labels for these products in September 2013, stating that they should only be used for stable chronic pain when all other modalities failed.<sup>33</sup> Furthermore, there is no evidence that extended-release/long-acting formulations provide superior pain relief compared with immediate-release forms.<sup>34</sup>

#### **Patient-Related Barriers**

Patient-related barriers include lack of communication and fear of opioids with the possibility of addiction. Patients also do not understand the complex nature of pain and the necessity to utilize a multimodal regimen. Patients may struggle with technical aspects, such as using a patient-controlled analgesia or properly managing a local anesthetic infusion pump, so proper instruction is vital. Local anesthetic infusion techniques via an indwelling catheter may fail secondary to catheter migration or dislodgement. In addition, although rare, indwelling catheters do introduce a risk of infection and medication error if the pump is not filled properly. The emergence of long-acting local anesthetics, such as liposomal bupivacaine (Exparel; Pacira Pharmaceuticals, San Diego, CA), may address some of these concerns, although more studies must be done to establish their efficacy, and such a discussion is beyond the scope of this review. Complicated analgesic regimens may also be difficult for patients to understand and adhere to. Communication between the patient, anesthesiologist, and surgeon is imperative to developing a thorough analgesic regimen and optimizing the management of acute postoperative pain.

#### **Opioid Tolerance**

Patients with opioid tolerance are an ever-increasing population, as sales of prescription opioids in the United States have quadrupled between 1999 and 2010.<sup>35</sup> Tolerance is the reduced analgesic effects of opioids, which can occur in patients exposed to opioids for prolonged periods

**Table 3. Barriers to Effective Pain Management**


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Physician/nursing-related barriers
Inadequate understanding of pain
Difficulty with pain assessment
Negative attitudes toward opioids/difficulty in prescribing opioids
Fear of nonopioids, such as NSAIDs, acetaminophen, gabapentinoids, local anesthetics
Minimizing the importance of multimodal analgesia
Lack of communication/instruction with patients
Patient-related barriers
Fear of opioids/addiction
Fear of analgesic side effects
Difficulty adhering to analgesic regimen
Lack of communication regarding pain severity
History of opioid tolerance/abuse
History of opioid agonist therapy for treatment of addiction

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of time, resulting in subsequent desensitization of antinociceptive pathways, specifically the  $\mu$ -opioid receptor and protein kinase and G-protein second-messenger systems. These patients can present a challenge to perioperative pain management as studies show that patients taking chronic opioids require a 2- to 3-fold increase in perioperative opioids when compared with opioid-naïve patients.<sup>36</sup> Preoperative assessment and planning is imperative to achieve effective pain management and avoid withdrawal. As opioids may be less effective in this population, a multimodal analgesic strategy is extremely important.

An increasing number of patients who have a history of opioid abuse and take opioid agonist therapy present unique challenges to postoperative pain management. Opioid agonist therapy includes pure opioid agonists, such as methadone, and partial agonists-antagonists, such as buprenorphine-naloxone (Suboxone; Reckitt-Benckiser, Richmond, VA) and the opioid antagonist naltrexone (Vivitrol; Alkermes, Waltham, MA). When treating these patients, one must recognize that standard opioids may have limited effect on this population, and the most effective treatment is to maximize the use of nonopioids. These patients are also at risk for withdrawal, thus requiring vigilant monitoring and treatment of symptoms (Table 3).

As reimbursements are increasingly being based on patient satisfaction and clinical outcomes, developing a strategy for quality pain management is becoming increasingly important. The American Pain Society updated their recommendations for improving the quality of acute and cancer pain management in 2005.<sup>37</sup> The recommendations encourage a structured, interdisciplinary, systems-based approach focusing on recognizing and treating pain promptly

with routine screening and documentation using well-validated pain assessment methods not limited to pain intensity alone but also location, quality, aggravating, and ameliorating factors. Patients and families must be involved in the pain management plan and improved treatment patterns to include multimodal regimens should be employed. And as pain is ever-changing, continued reassessment and adjustment based on outcomes is necessary.

## CONCLUSIONS

The consequences of inadequate postoperative analgesia are profound, increasing not only the risk of morbidity and mortality but also impairing surgical outcomes through greater risk of wound infections and possible detrimental effects in flap surgery. CPSP pain is also a common problem that likely results in part from uncontrolled postoperative analgesia. In addition to patient dissatisfaction, increased healthcare costs can result. Overall, pain is complex and can be difficult to treat; understanding pain and recognizing the importance of developing an effective analgesic regimen preoperatively while incorporating a multimodal strategy may decrease the physical, psychological, and socioeconomic risks of uncontrolled postoperative pain.

*Jaime L. Baratta, MD*

111 South 11th St  
Suite 8290, Gibbon Building  
Philadelphia, PA 19107  
jaime.baratta@jefferson.edu

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