81 Acute Postoperative Pain

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KEY POINTS

- The process of nociception is a dynamic process (i.e., neuroplasticity) with multiple points of modulation. Persistent noxious input may result in relatively rapid neuronal sensitization and possibly persistent pain.
- Postoperative pain, especially when poorly controlled, results in harmful acute effects (i.e., adverse physiologic responses) and chronic effects (i.e., delayed long-term recovery and chronic pain).
- By preventing central sensitization, preventative analgesia may reduce acute and chronic pain. Although studies overwhelmingly support the concept of preemptive analgesia, the evidence from clinical trials is equivocal, mostly because of methodological issues.
- Multimodal analgesia entails use of multiple classes of analgesic drugs (acetaminophen, gabapentinoids, nonsteroidal antiinflammatory drugs [NSAIDs], ketamine, and others) to act on different receptors along the pain pathway. Different drugs act synergistically to enhance analgesia and reduce side effects resulting from use of an individual class of drugs. Use of multimodal analgesia is recommended whenever feasible.
- By allowing individual titration of analgesic drugs, use of patient-controlled analgesia (oral, subcutaneous, iontophoretic, intravenous, paravertebral, or epidural) may provide several advantages over traditional provider-administered analgesia (e.g., intramuscular or intermittent intravenous injections) in the management of postoperative pain.
- The incidence of respiratory depression from opioids is not significantly different among the various routes of administration (i.e., oral, intravenous vs. intramuscular vs. subcutaneous vs. neuraxial). Appropriate monitoring of patients receiving opioid analgesics is essential to detect those with opioid-related side effects, such as respiratory depression. When compared with systemic opioids, perioperative epidural analgesia may confer several advantages, including a facilitated return of gastrointestinal function and decrease in the incidence of pulmonary complications, coagulation-related adverse events and cardiovascular events, especially in higher-risk patients or procedures. However, the risks and benefits of epidural analgesia should be evaluated for each patient, and appropriate monitoring protocols should be used during postoperative epidural analgesia.
- Epidural analgesia is not a generic entity because different catheter locations (catheter-incision congruent vs. catheter-incision incongruent), durations of postoperative analgesia, and analgesic regimens (local anesthetics vs. opioids) may differentially affect perioperative morbidity.
- Postoperative pain management should be tailored to the needs of special populations (e.g., opioid-tolerant, pediatric, and obese patients, as well as those with obstructive sleep apnea) who may have different anatomic, physiologic, pharmacologic, or psychosocial issues.

Fundamental Considerations

A revolution in the management of acute postoperative pain has occurred during the past four decades. Widespread recognition of the undertreatment of acute pain by clinicians, economists, and health policy experts has led to the development of a national clinical practice guideline for management of acute pain by the Agency for Healthcare Quality and Research (formerly the Agency for Health Care Policy and Research) of the U.S. Department of Health and Human Services.[1] This landmark document includes acknowledgment of the historical inadequacies in perioperative pain management, importance of good pain control, need for accountability for adequate provision of perioperative analgesia by health care institutions, and a statement on the need for involvement of specialists in appropriate cases. In addition, several professional societies including American Society of Anesthesiologists (ASA),[2] The Joint Commission,[3] American Society of Regional Anesthesia and Pain Medicine, and American Pain Society[4] have developed clinical practice guidelines for acute pain management or provided new pain management standards. With their knowledge of and familiarity with pharmacology, various regional anesthetic techniques, and the neurobiology of nociception, anesthesiologists are prominently associated with the clinical and research advances in acute postoperative pain management. Anesthesiologists developed the concepts of acute pain services (APS) (inpatient pain services), application of evidence-based practice to acute postoperative pain, and

creation of innovative approaches to acute pain medicine (APM), all of which are a natural extension of the anesthesiologist's role as a "perioperative physician," consultant, and therapist throughout the institution, in addition to being a highly skilled expert in the operating room. Provision of effective analgesia for surgical and other medical patients is an important component of this multidimensional role. An area that is often challenging in the acute perioperative pain services (PPS) is the management of patients with acute surgical pain in addition to a baseline chronic pain. These patients are often not well served by the arbitrary distinction of "acute" versus "chronic" pain services in hospitals. Anesthesiologists are well trained to manage acute pain in the patient with concomitant chronic pain as a result of the strength of chronic pain curricula in current anesthesiology training programs. Although this chapter focuses on the patient who has acute perioperative pain, acute management of chronic pain in the hospitalized setting is discussed in Chapter 51, "Management of the Patient with Chronic Pain."

PAIN PATHWAYS AND THE NEUROBIOLOGY OF NOCICEPTION

Surgery produces tissue injury with consequent release of histamine and inflammatory mediators such as peptides (e.g., bradykinin), lipids (e.g., prostaglandins), neurotransmitters (e.g., serotonin), and neurotrophins (e.g., nerve growth factor).[5] Release of inflammatory mediators activates peripheral nociceptors, which initiate transduction and transmission of nociceptive information to the central nervous system (CNS) and the process of neurogenic inflammation in which release of neurotransmitters (e.g., substance P and calcitonin gene-related peptide) in the periphery induces vasodilatation and plasma extravasation.[5] Noxious stimuli are transduced by peripheral nociceptors and transmitted by A-delta and C nerve fibers from peripheral visceral and somatic sites to the dorsal horn of the spinal cord, where integration of peripheral nociceptive and descending modulatory input (i.e., serotonin, norepinephrine, γ-aminobutyric acid, enkephalin) occurs. Further transmission of nociceptive information is determined by complex modulating influences in the spinal cord. Some impulses pass to the ventral and ventrolateral horns to initiate segmental (spinal) reflex responses, which may be associated with increased skeletal muscle tone, inhibition of phrenic nerve function, or even decreased gastrointestinal motility. Others are transmitted to higher centers through the spinothalamic and spinoreticular tracts, where they induce supra-segmental and cortical responses to ultimately produce the perception of and affective component of pain.

Continuous release of inflammatory mediators in the periphery sensitizes functional nociceptors and activates dormant ones. Sensitization of peripheral nociceptors may occur and is marked by a decreased threshold for activation, increased rate of discharge with activation, and increased rate of basal (spontaneous) discharge. Intense noxious input from the periphery may also result in central sensitization ("persistent postinjury changes in the CNS that result in pain hypersensitivity")[6] and hyperexcitability ("exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage").[6] Such noxious input may lead to functional changes in the dorsal horn of the spinal cord and other consequences that may later cause postoperative pain to be perceived as more painful than it would otherwise have been. The neural circuitry in the dorsal horn is extremely complex, and we are just beginning to elucidate the specific role of the various neurotransmitters and receptors in the process of nociception.[5] However, it seems that certain receptors (e.g., *N*-methyl-D-aspartate [NMDA]) may be especially important for the development of chronic pain after an acute injury, although other neurotransmitters or second messenger effectors (e.g., substance P, protein kinase C) may also play important roles in spinal cord sensitization and chronic pain. Our understanding of the neurobiology of nociception has progressed from the hard-wired system proposed by Descartes in the 17th century to the current view of neuroplasticity in which dynamic integration and modulation of nociceptive transmission take place at several levels. There still are many gaps in our knowledge of the specific roles of various receptors, neurotransmitters, and molecular structures in the process of nociception.

An understanding of the neurobiology of nociception is important for appreciating the transition from acute to chronic pain. The traditional dichotomy between acute and chronic pain is arbitrary because acute pain may quickly transition into chronic pain.[7] Noxious stimuli can produce expression of new genes (which are the basis for neuronal sensitization) in the dorsal horn of the spinal cord within 1 hour and these changes are sufficient to alter behavior within the same timeframe.[8] Also, the intensity of acute postoperative pain is a significant predictor of chronic postoperative pain.[9] Control of perioperative pain (e.g., preventive analgesia) and the manner in which it is implemented (e.g., multimodal perioperative pain management) may be important in facilitating short- and long-term patient convalescence after surgery.

ACUTE AND CHRONIC EFFECTS OF POSTOPERATIVE PAIN

Uncontrolled postoperative pain may produce a range of detrimental acute and chronic effects. The attenuation of perioperative pathophysiology that occurs during surgery through reduction of nociceptive input to the CNS and optimization of perioperative analgesia may decrease complications and facilitate recovery during the immediate postoperative period[10] and after discharge from the hospital.

Acute Effects

The perioperative period has a variety of pathophysiologic responses that may be initiated or maintained by nociceptive input. At one time, these responses may have had a beneficial teleological purpose; however, the same response to the iatrogenic nature of modern-day surgery may be harmful. Uncontrolled perioperative pain may enhance some of these perioperative pathophysiologies and increase patient morbidity and mortality. Attenuation of postoperative pain, especially with certain types of analgesic regimens, may decrease perioperative morbidity and mortality.

Transmission of nociceptive stimuli from the periphery to the CNS results in the neuroendocrine stress response,

a combination of local inflammatory substances (e.g., cytokines, prostaglandins, leukotrienes, tumor necrosis factor-α) and systemic mediators of the neuroendocrine response. The dominant neuroendocrine responses to pain involve hypothalamic-pituitary-adrenocortical and sympathoadrenal interactions. Suprasegmental reflex responses to pain result in increased sympathetic tone, increased catecholamine and catabolic hormone secretion (e.g., cortisol, adrenocorticotropic hormone, antidiuretic hormone, glucagon, aldosterone, renin, angiotensin II), and decreased secretion of anabolic hormones.[11] The effects include sodium and water retention and increased levels of blood glucose, free fatty acids, ketone bodies, and lactate. A hypermetabolic, catabolic state occurs as metabolism and oxygen consumption are increased and metabolic substrates are mobilized from storage depots.[11] The extent of the stress response is influenced by many factors, including the type of anesthesia and intensity of the surgical injury, with the extent of the stress response being proportional to the degree of surgical trauma.[12] The negative nitrogen balance and protein catabolism may impede convalescence; however, attenuation of the stress response and postoperative pain may facilitate and accelerate the patient's recovery postoperatively.

The neuroendocrine stress response may enhance detrimental physiologic effects in other areas of the body. The stress response is likely a factor in the postoperative development of hypercoagulability. Enhancement of coagulation (i.e., decreased levels of natural anticoagulants and increased levels of procoagulants), inhibition of fibrinolysis, and increased platelet reactivity and plasma viscosity may enhance the incidence of postoperative hypercoagulable-related events such as deep venous thrombosis, vascular graft failure, and myocardial ischemia.[13] The stress response may also enhance postoperative immunosuppression, the extent of which correlates with the severity of surgical injury.[7] Hyperglycemia from the stress response may contribute to poor wound healing and depression of immune function.

Uncontrolled postoperative pain may activate the sympathetic nervous system and thereby contribute to morbidity or mortality. Sympathetic activation may increase myocardial oxygen consumption, which may be important in the development of myocardial ischemia and infarction,[13] and may decrease myocardial oxygen supply through coronary vasoconstriction and attenuation of local metabolic coronary vasodilation.[14] Activation of the sympathetic nervous system may also delay return of postoperative gastrointestinal motility, which may develop into paralytic ileus. Although postoperative ileus is the result of a combination of inhibitory input from central and local factors,[13,14] an increase in sympathetic efferent activity, such as from uncontrolled pain, may decrease gastrointestinal activity and delay return of gastrointestinal function.

Nociceptors are activated after surgical trauma and may initiate several detrimental spinal reflex arcs. Postoperative respiratory function is markedly decreased, especially after upper abdominal and thoracic surgery. Spinal reflex inhibition of phrenic nerve activity is an important component of this decreased postoperative pulmonary function.[13] However, patients with poor postoperative pain control may breathe less deeply, have an inadequate cough, and be more susceptible to the development of postoperative pulmonary complications.[14] Activation of nociceptors may also initiate spinal reflex inhibition of gastrointestinal tract function and delay return of gastrointestinal motility.[13]

Many detrimental postoperative pathophysiologic effects can occur in the perioperative period and can activate nociceptors and the stress response. Uncontrolled pain may activate the sympathetic nervous system, which can cause a variety of potentially harmful physiologic responses that may adversely increase morbidity and mortality. Nociceptor activation may also result in several detrimental inhibitory spinal reflexes. Control of the pathophysiologic processes associated with acute postoperative pain may attenuate the stress response, sympathetic outflow, and inhibitory spinal reflexes and contribute to improvements in morbidity, mortality, and patient-reported outcomes (e.g., health-related quality of life [HRQL], patient satisfaction).[13]

Chronic Effects

Chronic persistent postsurgical pain (CPSP) is a largely unrecognized problem that may occur in 10% to 65% of postoperative patients (depending on the type of surgery), with 2% to 10% of these patients experiencing severe CPSP.[15] Poorly controlled acute postoperative pain is an important predictive factor in the development of CPSP.[9,16] The transition from acute to chronic pain occurs very quickly, and long-term behavioral and neurobiologic changes occur much sooner than was previously thought.[7] CPSP is relatively common after procedures such as limb amputation (30%-83%), thoracotomy (22%-67%), sternotomy (27%), breast surgery (11%-57%), and gallbladder surgery (up to 56%).[9] Although the severity of acute postoperative pain may be an important predictor in the development of CPSP,[9] a causal relationship has not been definitively established, and other factors (e.g., area of postoperative hyperalgesia) may be more important in predicting the development of CPSP.[17] One such factor may be the severity of the patient's preoperative pain. Patients with more intense levels of preoperative pain may also develop a degree of CNS sensitization predisposing them to the increased likelihood of higher postoperative pain and the subsequent development of chronic pain.[17] Thus, it is important that APS clinicians understand chronic pain conditions and involve themselves in the patient's preoperative care. The increased involvement of the APM team in preoperative anesthesia clinics or services can positively attenuate the incidence and severity of postoperative pain.

Control of acute postoperative pain may improve long-term recovery or patient-reported outcomes (e.g., quality of life). Patients whose pain is controlled in the early postoperative period (especially with the use of continuous epidural or peripheral catheter techniques) may be able to actively participate in postoperative rehabilitation, which may improve short- and long-term recovery after surgery.[18] Optimizing treatment of acute postoperative pain can improve HRQL.[19] Postoperative chronic pain that develops as a result of poor postoperative pain control may interfere with patients' activities of daily living.

Preventive Analgesia

The older terminology of "preemptive" analgesia referred to an analgesic intervention that preceded a surgical injury

and was more effective in relieving acute postoperative pain than the same treatment following surgery. The precise definition of preemptive analgesia is one of the major controversies in this area of medicine and contributes to the question of whether preemptive analgesia is clinically relevant. Definitions of preemptive analgesia include what is administered before the surgical incision, what prevents the establishment of central sensitization resulting from incisional injury only (i.e., intraoperative period), what prevents central sensitization resulting from incisional and inflammatory injury (i.e., intraoperative and postoperative periods), or the entire perioperative period encompassing preoperative interventions, intraoperative analgesia, and postoperative pain management (i.e., preventive analgesia).[6] The first two definitions are relatively narrow and may contribute to the lack of a detectable effect of preemptive analgesia in clinical trials. The rationale for preemptive analgesia was based on the inhibition of the development of central sensitization. Effectively, noxious input initiated by surgical procedures induced a state of CNS hyperactivity that accentuates pain. Although a very popular and discussed theory, a single analgesic treatment (either peripheral or neuraxial) before the incision does not reduce postoperative pain behaviors beyond the expected duration of the analgesic effect.[20] When the block of nociceptive afferents diminishes, the surgical injury is able to reinitiate central sensitization. Clinical trials have been negative.[21] For these reasons, this terminology has fallen out of favor.

As stated previously, intense noxious input (e.g., postoperative pain from the periphery) can change the CNS (i.e., central sensitization) to induce "pain hypersensitivity" and hyperexcitability (i.e., exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage). Preventive analgesia is aimed at inhibiting the development of this type of chronic pain. This definition broadly includes any regimen given at any time during the perioperative period that controls pain-induced sensitization. Central sensitization and hyperexcitability can develop after the surgical incision in a patient who has no history of preoperative pain.

In contrast, some patients may already have existing acute or chronic pain and developed central sensitization prior to the surgical incision. These patients with preexisting pain may have even more intense pain in the postoperative period. This augmentation of preexisting pain can occur in the acutely hospitalized and even in those patients in subacute or chronic outpatient settings. Preventing the establishment of altered central processing by analgesic treatment may result in short-term (e.g., reduction in postoperative pain and accelerated recovery) and long-term (e.g., reduction in chronic pain and improvement in HRQL[19] benefits during a patient's convalescence). Unfortunately, many clinical studies (e.g., trials) lack clarity of study design and clear terminology of preemptive versus preventative analgesia.[21,22]

Timing of the intervention may not be as clinically important as other aspects of preventive analgesia (i.e., intensity and duration of the intervention). An intervention administered before the surgical incision is not preventative if it is incomplete or insufficient such that central sensitization is not prevented. Incisional and inflammatory injuries are important in initiating and maintaining central sensitization. Confining the definition of preventative analgesia to only the intraoperative (incisional) period is not relevant or appropriate because the inflammatory response lasts well into the postoperative period and continues to maintain central sensitization.

Maximal clinical benefit is observed when there is complete multi-segmental blockade of noxious stimuli with extension of this into the postoperative period. Preventing central sensitization with intensive multimodal analgesic interventions[21] could theoretically reduce the intensity or even eliminate acute postoperative pain/hyperalgesia and chronic pain after surgery.[9]

Multimodal Approach to Perioperative Recovery/ Enhanced Recovery after Surgery

The analgesic benefits of controlling postoperative pain are generally maximized when a multimodal strategy to facilitate the patient's convalescence is implemented. Yet, postoperative pain treatment may not provide major improvements in some outcomes because it is unlikely that a unimodal intervention can be effective in addressing a complex problem such as perioperative outcomes.[10,23] The complex nature of nociception and mixed mechanisms of generating surgical pain are also responsible for failure of unimodal analgesia to adequately address postoperative pain.[10,23] Principles of a multimodal analgesia include using multiple strategies and drug classes to manage patient expectation and control postoperative pain to allow early mobilization, enteral nutrition, and to attenuate the perioperative stress response.[10] These strategies include: patient education, local anesthetic-based techniques (local infiltration, peripheral nerve blocks, and neuraxial analgesia),[10] and a combination of analgesic drugs that act via different mechanisms on different receptors within the pain transmission pathway to provide synergistic effect, superior analgesia, and physiologic benefits.

A multimodal approach to perioperative recovery to control postoperative pathophysiology and facilitate rehabilitation is an integral part of almost all enhanced recovery after surgery (ERAS) pathways and will result in accelerated recovery and decreased length of hospitalization.[24] One of the key components of a multimodal analgesic regimen within any ERAS pathway is the minimization of opioid use and side effects from opioids by utilizing nonopioid analgesics and techniques.[25] Patients undergoing major abdominal or thoracic procedures and who participate in a multimodal strategy have a reduction in hormonal and metabolic stress, preservation of total-body protein, shorter times to tracheal extubation, lower pain scores, earlier return of bowel function, and earlier fulfillment of intensive care unit discharge criteria when compared to patients receiving traditional pain management.[24] ERAS pathways integrate the most recent evidence from surgery, anesthesiology, nociceptive neurobiology, and pain treatment, and transforms traditional care programs into effective postoperative rehabilitation pathways.[24] This approach will decrease perioperative morbidity, costs of care, decrease the length of hospital stay, and improve patient satisfaction without compromising safety.[26,27] ERAS pathways are more common in adult surgical patients, although there is increasing interest in utilizing ERAS in pediatric patients.[26] Widespread implementation of these programs requires

multidisciplinary collaboration, change in the traditional principles of postoperative care, additional resources, and expansion of the traditional APS, which may be limited in the current economic climate.[28]

Treatment Methods

Many options are available for the treatment of postoperative pain, including systemic (i.e., opioid and non-opioid) analgesics and regional (i.e., neuraxial and peripheral) analgesic techniques. By considering patients' preferences and making an individualized assessment of the risks and benefits of each treatment modality, the clinician can optimize the postoperative analgesic regimen for each patient. Essential aspects of postoperative monitoring of patients receiving various postoperative analgesic treatment methods are listed in Box 81.1.[29]

BOX 81.1 Monitoring and Documentation of Postoperative Analgesia

Analgesic Medication*

Medication, concentration, and dose of drug
Settings of PCA device: demand dose, lockout interval, continuous basal infusion
Amount of drug administered (including number of unsuccessful and successful doses)
Limits set (e.g., 1- and 4-h limits on dose administered)
Supplemental or breakthrough analgesics

Routine Monitoring

Vital signs: temperature, heart rate, blood pressure, respiratory rate, average pain score
Pain score at rest and with activity, pain relief

Side Effects

Cardiovascular: hypotension, bradycardia, or tachycardia
Respiratory status: respiratory rate, level of sedation
Nausea and vomiting, pruritus, urinary retention

Neurologic Examination

Assessment of motor block or function and sensory level
Evidence of epidural hematoma

Instructions Provided

Treatment of side effects
Concurrent use of other CNS depressants
Parameters for triggering notification of the covering physician
Provision of contact information (24 hr/7 day per week) if problems occur
Emergency analgesic treatment if the PCA device fails

*Postoperative analgesia includes systemic opioids and regional analgesic techniques. This list incorporates some of the important elements of preprinted orders, documentation, and intravenous PCA and epidural analgesia daily care described in the ASA Practice Guidelines for Acute Pain Management.[29]

CNS, Central nervous system; *PCA*, patient-controlled analgesia.

Systemic Analgesic Techniques

OPIOIDS

Advantages and Characteristics

Opioid analgesics are one of the cornerstone options for the treatment of postoperative pain. They generally exert their analgesic effects through μ-receptors in the CNS, although opioids may also act at peripheral opioid receptors. A theoretical advantage of opioid analgesics is that there is no analgesic ceiling. Realistically, the analgesic efficacy of opioids is typically limited by the development of tolerance or opioid-related side effects such as nausea, vomiting, sedation, or respiratory depression. Opioids may be administered by the subcutaneous, transcutaneous, transmucosal, or intramuscular route, but the most common routes of postoperative systemic opioid analgesic administration are oral and intravenous (IV). Opioids may also be administered at specific anatomic sites such as the intrathecal or epidural space (see later sections, "Single-Dose Neuraxial Opioids" and "Continuous Epidural Analgesia").

There is wide intersubject and intrasubject variability in the relationship of opioid dose, serum concentration, and analgesic response in the treatment of postoperative pain. Serum drug concentrations may exhibit wider variability with certain routes of administration (e.g., intramuscular) than with others (e.g., IV). In general, opioids are administered parenterally (intravenously or intramuscularly) for the treatment of moderate to severe postoperative pain, in part because these routes provide a more rapid and reliable onset of analgesic action than the oral route does. Parenteral opioid administration may be necessary in patients who are unable to tolerate oral intake postoperatively. The transition from parenteral to oral administration of opioids usually occurs after the patient resumes oral intake and postoperative pain has been stabilized with parenteral opioids.

Intravenous Patient-Controlled Analgesia

Various factors, including the aforementioned broad interpatient and intrapatient variability in analgesic needs, variability in serum drug levels (especially with intramuscular injection), and administrative delays, may contribute to inadequate postoperative analgesia. A traditional prescribed as-needed (PRN) analgesic regimen probably cannot compensate for these limitations. By circumventing some of these issues, IV patient-controlled analgesia (PCA) optimizes delivery of analgesic opioids and minimizes the effects of pharmacokinetic and pharmacodynamic variability in individual patients. IV PCA is based on the premise that a negative-feedback loop exists; when pain is experienced, analgesic medication is self-administered, and when pain is reduced, there are no further demands. When the negative-feedback loop is violated, excessive sedation or respiratory depression may occur. Although some equipment-related malfunctions can occur, the PCA device itself is relatively free of problems, and most problems related to PCA use result from user or operator error.[30]

A PCA device can be programmed for several variables, including the demand (bolus) dose, lockout interval, and background infusion (Table 81.1). An optimal demand or bolus dose is integral to the efficacy of IV PCA because an insufficient demand dose may result in inadequate analgesia, whereas an excessive demand dose may result in a higher incidence of undesirable side effects such as respiratory depression.[31] Although the optimal demand dose is uncertain, the data available suggest that the optimal

TABLE 81.1 Intravenous Patient-Controlled Analgesia Regimens

Drug Concentration	Size of Bolus*	Lockout Interval (min)	Continuous Infusion
AGONISTS			
Morphine (1 mg/mL)			
Adult	0.5-2.5 mg	5-10	—
Pediatric	0.01-0.03 mg/kg (max, 0.15 mg/kg/h)	5-10	0.01-0.03 mg/kg/h
Fentanyl (0.01 mg/mL)			
Adult	10-20 μg	4-10	—
Pediatric	0.5-1 μg/kg (max, 4 μg/kg/h)	5-10	0.5-1 μχg/kg/h
Hydromorphone (0.2 mg/mL)			
Adult	0.05-0.25 mg	5-10	—
Pediatric	0.003-0.005 mg/kg (max, 0.02 mg/kg/h)	5-10	0.003-0.005 mg/kg/h
Alfentanil (0.1 mg/mL)	0.1-0.2 mg	5-8	—
Methadone (1 mg/mL)	0.5-2.5 mg	8-20	—
Oxymorphone (0.25 mg/mL)	0.2-0.4 mg	8-10	—
Sufentanil (0.002 mg/mL)	2-5 μg	4-10	—
AGONIST-ANTAGONISTS			
Buprenorphine (0.03 mg/mL)	0.03-0.1 mg	8-20	—
Nalbuphine (1 mg/mL)	1-5 mg	5-15	—
Pentazocine (10 mg/mL)	5-30 mg	5-15	—

*All doses are for adult patients unless noted otherwise. Units vary across agents for size of the bolus (mg vs. mg/kg vs. mcg vs. μg/kg) and continuous infusion (mg/kg/h vs. μχg/kg/h). The anesthesiologist should proceed with titrated intravenous loading doses if necessary to establish initial analgesia. Individual patient requirements vary widely, with smaller doses typically given to elderly or compromised patients. Continuous infusions are not initially recommended for opioid-naïve adult patients.

demand dose is 1 mg for morphine and 40 μg for fentanyl in opioid-naïve patients; however, the actual dose for fentanyl (10-20 μg) is often less in clinical practice.[30] The lockout interval may also affect the analgesic efficacy of IV PCA. A lockout interval that is too long may result in inadequate analgesia and decrease the effectiveness of IV PCA. A lockout interval that is too short allows the patient to self-administer another demand dose before feeling the full analgesic effect of the previous dose and thus may contribute to an increase in medication-related side effects. In essence, the lockout interval is a safety feature of IV PCA, and although the optimal lockout interval is unknown, most intervals range from 5 to 10 minutes, depending on the medication in the PCA pump; varying the interval within this range appears to have no effect on analgesia or side effects.[30]

Most PCA devices allow administration of a continuous or background infusion in addition to the demand dose. Initially, routine use of a background infusion predicted certain advantages, including improved analgesia, especially during sleep; however, analgesic benefits of a background infusion have not been successful in opioid-naïve patients. A background infusion only increases the analgesic dosage used and the incidence of adverse respiratory events in the postoperative period, especially in adult subjects. Furthermore, use of a nighttime background infusion does not improve postoperative sleep patterns, analgesia, or recovery profiles.[32] Although routine use of continuous or background infusion as part of IV PCA in adult opioid-naïve patients is not recommended, a background infusion in opioid-tolerant or pediatric patients may be effective (see later sections, "Opioid-Tolerant Patients" and "Pediatric Patients") (also see Chapter 24).

When compared with traditional PRN analgesic regimens, IV PCA provides superior postoperative analgesia and improves patient satisfaction, but the presence of economic benefits is not clear.[33] A metaanalysis revealed that IV PCA (vs. as-needed opioids) provides significantly better analgesia and patient satisfaction; however, these patients used more opioids and had a more frequent incidence of pruritus than those treated with PRN opioids, but there was no difference in the incidence of adverse events.[33] With regard to economic outcomes, whether IV PCA is less expensive than traditional PRN intramuscular opioid administration is not clear because the calculations of cost are complex.

IV PCA may provide advantages when assessing other patient-related outcomes such as patient satisfaction; these outcomes have become more important as healthcare organizations use them as a measure of quality and a tool for marketing purposes. Patients usually prefer IV PCA over intravenously, intramuscularly, or subcutaneously administered PRN opioids. Greater patient satisfaction with IV PCA may be the result of superior analgesia and perceived control over the administration of analgesic medications and avoidance of disclosing pain or securing analgesic medication from nurses; however, the reasons for patient satisfaction are complex and many factors may contribute to or predict satisfaction with IV PCA. Although IV PCA use

overall creates better satisfaction, the proper assessment of patient satisfaction can be complex.[34]

The incidence of opioid-related adverse events from IV PCA is not different from that of PRN opioids administered intravenously, intramuscularly, or subcutaneously. The rate of respiratory depression associated with IV PCA is infrequent (approximately 1.5%) and is not more frequent than that with PRN systemic or neuraxial opioids.[35] Factors that may influence the frequency and intensity of respiratory depression with IV PCA include use of a background infusion, advanced age, concomitant administration of sedative or hypnotic drugs, and coexisting pulmonary disease such as obstructive sleep apnea (OSA).[36] IV PCA-related respiratory depression may also be caused by errors in programming or administration (i.e., operator error).[37]

NON-OPIOIDS

Nonsteroidal Antiinflammatory Agents

Nonsteroidal antiinflammatory drugs (NSAIDs) consist of a diverse group of analgesic compounds with different pharmacokinetic properties. The primary mechanism by which NSAIDs exert their analgesic effect is through inhibition of cyclooxygenase (COX) and synthesis of prostaglandins, which are important mediators of peripheral sensitization and hyperalgesia. In addition to being peripherally acting analgesics, NSAIDs can also exert their analgesic effects through inhibition of spinal COX.[38] The discovery of at least two COX isoforms (i.e., COX-1 is constitutive and COX-2 is inducible) with different functions (i.e., COX-1 participates in platelet aggregation, hemostasis, and gastric mucosal protection, whereas COX-2 participates in pain, inflammation, and fever) has led to the development of selective COX-2 inhibitors that differ from traditional NSAIDs, which block both COX-1 and COX-2.[39] The discovery of a COX-3 variant may represent a primary central mechanism by which acetaminophen and other antipyretics decrease pain and fever; however, the precise relationship between COX-3 and acetaminophen is still uncertain.[40]

NSAIDs given alone generally provide effective analgesia for mild to moderate pain. NSAIDs are also traditionally considered a useful adjunct to opioids for the treatment of moderate to severe pain. Yet, some quantitative, systematic reviews suggest that NSAIDs, alone or in combination with opioids, may be more beneficial than previously thought (Table 81.2 and Fig. 81.1). NSAIDs may be administered orally or parenterally and are particularly useful as components of a multimodal analgesic regimen by producing analgesia through a different mechanism from that of opioids or local anesthetics. Several meta-analyses have examined the analgesic efficacy of NSAIDs (including COX-2 inhibitors) and acetaminophen when added to IV PCA with opioids. Surprisingly and importantly, NSAIDs[41,42] resulted in a statistically significant (but probably not clinically meaningful) reduction in pain scores.[43,44] Although all regimens significantly decreased morphine consumption, only NSAIDs reduced risk for the opioid-related side effects of nausea, vomiting, and sedation.

Perioperative use of NSAIDs has several side effects, including decreased hemostasis, renal dysfunction, and gastrointestinal hemorrhage. Inhibition of COX and the formation of prostaglandins cause many of the side effects, which mediate many diverse processes throughout the body. Decreased hemostasis from NSAID use is from platelet dysfunction and inhibition of thromboxane A2 (generated by COX-1), an important mediator of platelet aggregation and vasoconstriction. Evidence of the effect of NSAIDs on perioperative bleeding is equivocal; a surveillance study of perioperative ketorolac administration did not demonstrate a significant increase in operative site bleeding. Whether NSAIDs may also have a deleterious effect on bone healing and osteogenesis is controversial. Although NSAIDs have been used following acetabular/hip fractures and hip replacement surgery to reduce heterotopic ossification, the short-term effect of NSAIDs on other skeletal tissues is less clear.[45] Two recent systematic reviews indicated that when examining the highest-quality studies, there was no increased risk of nonunion with NSAID exposure. Certainly, a short-term NSAID regimen can be used for treatment of post-fracture pain without significantly increasing the risk of disrupted healing.[46] A brief (<14 days) exposure to normal-dose NSAIDs (e.g., ketorolac <120 mg/day) was safe after spinal fusion; however, use of large-dose ketorolac

TABLE 81.2 Relative Efficacy of Single-Dose Analgesics in Providing Greater than 50% Relief of Moderate to Severe Postoperative Pain

Drug*	Mean NNT†	95% CI
Acetaminophen (1000 mg PO)	3.8	3.4-4.4
Aspirin (600-650 mg PO)	4.4	4.0-4.9
Aspirin (1000 mg PO)	4.0	3.2-5.4
Diclofenac (50 mg PO)	2.3	2.0-2.7
Diclofenac (100 mg PO)	1.9	1.6-2.2
Ibuprofen (600 mg PO)	2.4	1.9-3.3
Ketorolac (10 mg PO)	2.6	2.3-3.1
Ketorolac (30 mg IM)	3.4	2.5-4.9
Naproxen (550 mg PO)	2.7	2.3-3.3
Celebrex (200 mg PO)	3.5	2.9-4.4
Celebrex (400mg PO)	2.1	1.8-2.5
Tramadol (100 mg PO)	4.8	3.8-6.1
Gabapentin (600 mg PO)	11	6.0-35
Codeine (60 mg) + acetaminophen (600-650 mg PO)	4.2	3.4-5.3
Oxycodone (5 mg) + acetaminophen (325 mg PO)	2.5	2.0-3.2
Codeine (60 mg PO)	16.7	11.0-48.0
Morphine (10 mg IM)	2.9	2.6-3.6
Oxycodone (15 mg PO)	2.4	1.5-4.9

*Data obtained in part and modified from Bandolier with permission. http://www.bandolier.org.uk/booth/painpag/Acutrev/Analgesics/lftab.html.
†NNT in this case refers to the number of patients who must be treated to obtain greater than 50% relief of moderate to severe postoperative pain. NNT conveys statistical and clinical significance, is useful in comparing the efficacy of different interventions, and summarizes treatment effects in a clinically relevant manner. A lower mean NNT implies greater analgesic efficacy in this example. *CI*, confidence interval; *IM*, intramuscular; *NNT*, number needed to treat; *PO*, oral route.

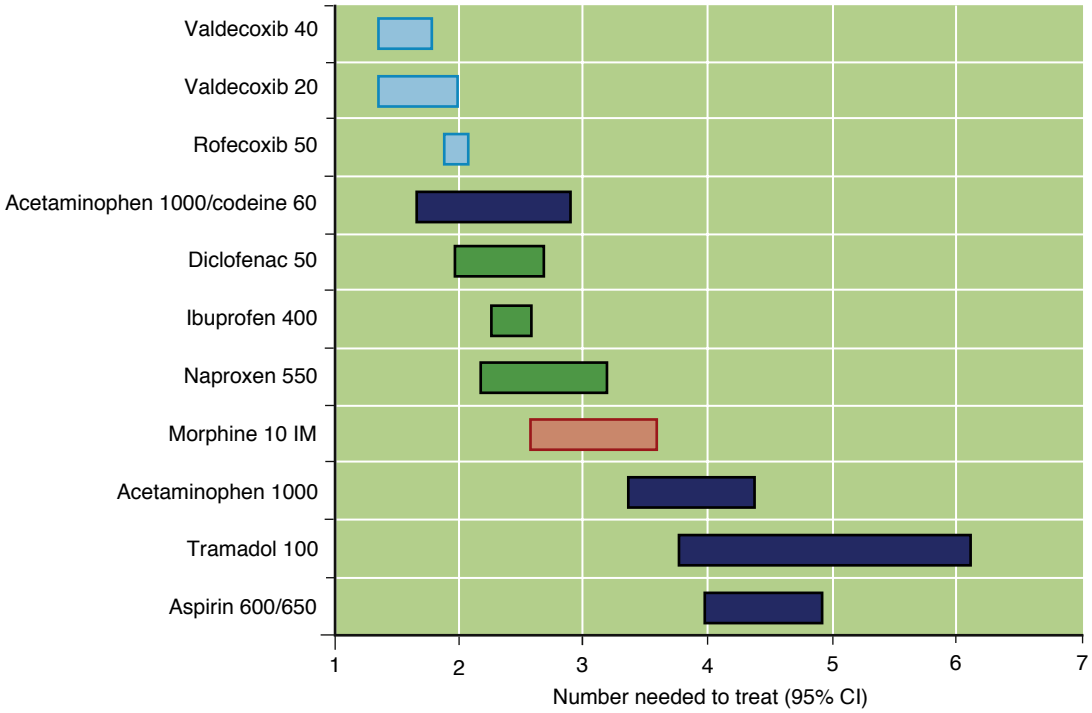

Fig. 81.1 Number needed to treat (NNT) for at least 50% pain relief in patients with moderate to severe pain. The mean and 95% confidence interval *(CI)* for the NNTs are shown for several opioid and nonopioid analgesics from Table 81.2. The NNTs are derived from trials investigating the efficacy of a single dose of nonopioid analgesic versus placebo in providing more than 50% pain relief for moderate to severe postoperative pain. Numbers with drug names are doses in mg. (From Bandolier. http://www.medicine.ox.ac.uk/bandolier/.)

(>120 mg/day) increased the risk of nonunion, suggesting a dose-dependent effect of perioperative NSAIDs on spinal fusion healing.[47] Spine surgeons will more commonly err on the conservative side and refuse to have postoperative spine fusion patients receive NSAIDs.

Perioperative NSAID-induced renal dysfunction may occur in high-risk patients, such as those with hypovolemia, abnormal renal function, or abnormal serum electrolytes, because prostaglandins dilate the renal vascular beds and mediate diuretic and natriuretic renal effects. NSAIDs should not be withheld in patients with normal preoperative renal function, as euvolemic patients with normal renal function are unlikely to be affected, although NSAIDs may cause a clinically unimportant transient reduction in renal function in the early postoperative period in patients with normal preoperative renal function.[48] Gastrointestinal bleeding may be more likely with NSAID intake because of inhibition of COX-1, which is required for the synthesis of cytoprotective gastric mucosal prostaglandins. Bronchospasm may be induced by NSAIDs (including aspirin).[49] Because expression of peripheral COX-2 is increased during inflammation, selective inhibition of COX-2 could theoretically provide analgesia without the side effects associated with COX-1 inhibition. COX-2 inhibitors have a less frequent incidence of gastrointestinal complications[50] and exhibit minimal platelet inhibition, even when administered in supratherapeutic doses.[51] However, long-term use of COX-2 inhibitors has an excess cardiovascular risk such that rofecoxib was withdrawn from the market.[52] The cardiovascular risks of COX-2 inhibitors are heterogeneous and influenced by many factors such as the specific medication, dosage, and patient characteristics.[52] Issues surrounding the perioperative use of COX-2 inhibitors are slightly different from those of longer-term use of COX-2 inhibitors. The perioperative use of potent COX-2 inhibitors resulted in a higher rate of cardiovascular events in high-risk (coronary artery bypass grafting)[53] but not lower-risk (major noncardiac surgery) patients. Celecoxib, a COX-2 inhibitor, has less COX-2 selectivity than other more potent COX-2 inhibitors (rofecoxib) and is still clinically available.[54] Nissen and associates conducted a randomized controlled trial (RCT) of 24,081 patients randomly assigned to celecoxib, naproxen, or ibuprofen and found that celecoxib was noninferior to ibuprofen or naproxen with regard to cardiovascular safety.[55] Liu and associates studied 10,873 patients admitted for total joint arthroplasty and concluded that perioperative use of NSAIDs was not associated with increased risk of postoperative myocardial ischemia and may reduce the hospital length of stay.[55,56]

Another controversial topic regarding NSAIDs is the association with postoperative bleeding. It is not surprising that several metaanalyses indicate that COX-2 inhibitors, which exhibit minimal platelet inhibition even when administered in supratherapeutic doses, are not associated with an increase in perioperative bleeding.[57-59] More recent metaanalyses also indicate that traditional NSAIDs (ibuprofen, ketorolac) are not associated with an increase in perioperative bleeding. Finally, some studies have been published suggesting a link between NSAIDs and anastomotic leak, but most studies are flawed or have preexisting selection bias and a metaanalysis did not demonstrate a statistically significant increase in incidence of anastomotic dehiscence with NSAIDs. Newer formulations of NSAIDs are approved for treatment of acute postoperative pain (IV ibuprofen,[60]

and intranasal ketorolac[3]). Cost of the new drugs remains to be an issue, especially in today's cost-conscious healthcare environment.[61,62]

Acetaminophen

Acetaminophen has been used for several decades and is believed to have a central role of action in analgesia. It has antipyretic and antiinflammatory properties. Its mechanism of action is through activation of descending serotonergic pathways in the CNS and via the inhibition of prostaglandin synthesis.[63] It is used most often in conjunction with other medications as part of a multimodal analgesia protocol. Maximum recommended dose is 4 gm/day in adult patients. The US Food and Drug Administration (FDA) approved IV acetaminophen formulation for use in the United States in 2011.[64] Sinatra and colleagues studied the efficacy of IV acetaminophen after joint arthroplasty in a placebo-controlled study.[65] The study group had decreased pain scores, used fewer opioids, had a longer median time to morphine rescue compared to placebo, and were more satisfied with pain management. A metaanalysis of 865 patients enrolled in four clinical trials addressing the impact of addition of IV acetaminophen to multimodal analgesia after total hip and knee arthroplasty concluded that there was a significant decrease in pain score and opioid consumption on POD 1 to 3. Nausea and vomiting were decreased in the groups who received acetaminophen.[66] However, the quality of the studies included in the analysis was questioned. Peak plasma concentration is achieved faster after IV versus oral administration of acetaminophen.[67] Evidence to support the premise that increased bioavailability would enhance clinical efficacy is lacking. Cost effectiveness of the IV formulation and patient ability to tolerate oral intake, based on the targeted surgery, should be accounted for when considering integrating IV acetaminophen into a multimodal analgesia protocol. Data from 2013 show that the average increase in cost to hospitals adopting IV acetaminophen can be significant, based on its use.[68]

Gabapentinoids

Gabapentin and pregabalin, antiepileptic drugs also used in the treatment of neuropathic pain, interact with calcium channel α_2-delta ligands to inhibit calcium influx and subsequent release of excitatory neurotransmitters. However, oral pregabalin is absorbed more rapidly and has more absolute bioavailability (≥90% vs. <60%) than gabapentin.[69] Despite these differences, oral gabapentin improves the analgesic efficacy of opioids both at rest and with movement, and reduces opioid consumption and opioid-related side effects, but with a possibly increased incidence of side effects such as sedation and dizziness.[70-72] A metaanalysis investigating the analgesic efficacy of pregabalin for acute postoperative pain demonstrated use of pregabalin was associated with a decrease in opioid consumption and opioid-related side effects, but no difference in pain intensity.[73] Another meta-analysis suggested that perioperative administration of pregabalin may provide additional analgesia in the short term but also results in an increase in side effects such as dizziness/light-headedness or visual disturbances.[74]

Although gabapentinoids are commonly used as part of a multimodal analgesic regimen, it should be noted that there have been recent publications questioning the analgesic benefits of gabapentinoids.[75] Several studies have noted that the quality of evidence for a clinically relevant benefit of gabapentinoids is low and the serious adverse events in available trials were poorly reported.[76-78] When examining trials with low risk of bias, gabapentinoids may actually have a minimal opioid-sparing effect but the risk of serious adverse events seems increased, as the use of gabapentin is associated with increased rates of respiratory depression among patients undergoing laparoscopic surgery.[79] Finally, gabapentinoids may not provide any additional analgesia for some surgical procedures including total hip arthroplasty.[80] The use of gabapentinoids should be considered on an individual basis after surgery.

KETAMINE

Ketamine is traditionally recognized as an intraoperatively administered anesthetic; however, small subanesthetic dose (analgesic) ketamine can facilitate postoperative analgesia because of its NMDA-antagonistic properties, which may be important in attenuating central sensitization and opioid tolerance.[81] Ketamine can be administered orally, intravenously (PCA or as a continuous infusion), subcutaneously, or intramuscularly. A systematic review of perioperative ketamine use found that perioperative analgesic doses of ketamine reduce rescue analgesic requirements and pain intensity.[82] In addition, perioperative ketamine reduced 24-hour PCA morphine consumption and postoperative nausea or vomiting and had minimal adverse effects.[82] A subsequent systematic review found that IV ketamine for postoperative analgesia was an effective adjunct for postoperative analgesia, particularly in patients undergoing painful procedures such as upper abdominal, thoracic, and major orthopedic surgeries.[83] The administration of ketamine in postoperative pediatric patients is also associated with decreased postoperative pain intensity.[84] One potential concern is the possible impact of ketamine's amnestic effects on the neuropharmacologic and cognitive level of patients with use of perioperative ketamine infusions.[85] Although possible, these effects infrequently occur when the medication is given in analgesic doses. Ketamine has also been given epidurally and intrathecally, but racemic mixtures of ketamine are neurotoxic, and therefore the use of neuraxial racemic ketamine is strongly discouraged. Although further studies are needed to elucidate the specific parameters (e.g., dose, duration of use) for ketamine in the perioperative period, this analgesic can be considered on an individual basis as part of a multimodal approach to postoperative analgesia.

Tramadol

Tramadol is a synthetic opioid that exhibits weak μ-agonist activity and inhibits reuptake of serotonin and norepinephrine, although the relative degree of contribution of each modality to postoperative analgesia is not certain.[86] Although tramadol exerts its analgesic effects primarily through central mechanisms, it may have peripheral local

TABLE 81.3 Properties of Neuraxial Opioids

Property	Lipophilic Opioids	Hydrophilic Opioids
Common drugs	Fentanyl, sufentanil	Morphine, hydromorphone
Onset of analgesia	Rapid onset (5-10 min)	Delayed onset (30-60 min)
Duration of analgesia*	Shorter duration (2-4 h)	Longer duration (6-24 h)
CSF spread	Minimal CSF spread	Extensive CSF spread
Site of action	Spinal ± systemic	Primarily spinal ± supraspinal
Side effects		
Nausea and vomiting	Lower incidence with lipophilic than with hydrophilic opioids	
Pruritus	Lower incidence with lipophilic than with hydrophilic opioids	
Respiratory depression	Primarily early; minimal delay	Both early (<6 h) and delayed (>6 h) possible

*The duration of analgesia varies. *CSF*, Cerebrospinal fluid.

anesthetic properties and has been used as an adjunct for brachial plexus block.[87] Tramadol is effective in treating mild to moderate postoperative pain[88] and is comparable in analgesic efficacy to aspirin (650 mg), with codeine (60 mg), or ibuprofen (400 mg) (see Table 81.2 and Fig. 81.1).[88] The addition of acetaminophen to tramadol (vs. tramadol alone) may decrease the incidence of side effects of tramadol without reducing its analgesic efficacy.[89] Use of tramadol in IV PCA results in similar pain scores when compared with that from IV PCA opioids; however, the side effect profile is different between the two groups (i.e., a more frequent incidence of postoperative nausea/vomiting but lower pruritus with tramadol).[90] Advantages of tramadol for postoperative analgesia include a relative lack of respiratory depression, major organ toxicity, depression of gastrointestinal motility, and a theoretically lower potential for abuse.[86] Common side effects (overall incidence of 1.6%-6.1%) include dizziness, drowsiness, sweating, nausea, vomiting, dry mouth, and headache.[88] Tramadol should be used with caution in patients with seizures or increased intracranial pressure and is contraindicated in those taking monoamine oxidase inhibitors.[88]

Regional Analgesic Techniques

A variety of neuraxial (primarily epidural) and peripheral regional analgesic techniques may be used for the effective treatment of postoperative pain. In general, the analgesia provided by epidural and peripheral techniques (particularly when local anesthetics are used) is site-specific and superior to that with systemic opioids, and use of these techniques may even reduce morbidity and mortality.[13] However, as with all approaches, the risks and benefits should be compared, especially regarding the controversies about use of these techniques in the presence of various anticoagulants.

Single-Dose Neuraxial Opioids

Administration of a single dose of opioid may be efficacious as a sole or adjuvant analgesic drug when administered intrathecally or epidurally. One of the most important factors in determining the clinical pharmacology for a specific opioid is its degree of lipophilicity (vs. hydrophilicity) (Table 81.3). Once they have reached the cerebrospinal fluid (CSF) through direct intrathecal injection or gradual migration from the epidural space, hydrophilic opioids (i.e., morphine and hydromorphone) tend to remain within the CSF and produce a delayed but longer duration of analgesia, along with a generally more frequent incidence of side effects because of the cephalic or supraspinal spread of these compounds. Neuraxial administration of lipophilic opioids, such as fentanyl and sufentanil, provides a rapid onset of analgesia, and their rapid clearance from CSF may limit cephalic spread and the development of certain side effects such as delayed respiratory depression. The site of analgesic action for hydrophilic opioids is overwhelmingly spinal, but the primary site of action (spinal vs. systemic) for single-dose neuraxial lipophilic opioids is not as certain.

The differences in pharmacokinetics between lipophilic and hydrophilic opioids may influence the choice of opioid aiming to optimize analgesia and minimize side effects for a particular clinical situation. Single-dose intrathecal administration of a lipophilic opioid may be useful in situations (e.g., ambulatory surgical patients) in which rapid analgesic onset (minutes) is combined with a moderate duration of action (<4 hours). Single-dose hydrophilic opioid administration provides effective postoperative analgesia and may be useful in patients monitored on an inpatient basis, for whom a longer duration of analgesia would be beneficial.

Single-dose epidural administration of lipophilic and hydrophilic opioids is used to provide postoperative analgesia, with considerations generally similar to those discussed for single-dose intrathecal administration of opioids. A single bolus of epidural fentanyl may be administered to provide rapid postoperative analgesia; however, diluting the epidural dose of fentanyl (typically 50-100 μg) in at least 10 mL of preservative-free normal saline will decrease the onset and prolong the duration of analgesia, possibly as a result of an increase in initial spread and diffusion of the lipophilic opioid. Single-dose epidural morphine is effective for postoperative analgesia and use of a single-dose hydrophilic opioid may be especially helpful in providing postoperative epidural analgesia when the epidural catheter's location is not congruent with the surgical incision (e.g., lumbar epidural catheter for thoracic surgery). Smaller doses of epidural morphine may be required for elderly patients and thoracic catheter sites. Commonly used dosages for intrathecal and epidural administration of neuraxial opioids are provided in Table 81.4.

TABLE 81.4 Dosing of Neuraxial Opioids

Drug	Intrathecal or Subarachnoid Single Dose	Epidural Single Dose	Epidural Continuous Infusion
Fentanyl	5-25 μg	50-100 μg	25-100 μg/h
Sufentanil	2-10 μg	10-50 μg	10-20 μg/h
Alfentanil	—	0.5-1 mg	0.2 mg/h
Morphine	0.1-0.3 mg	1-5 mg	0.1-1 mg/h
Hydromorphone	—	0.5-1 mg	0.1-0.2 mg/h
Extended-release morphine*	Not recommended	5-15 mg	Not recommended

*See package insert for details on dosage and administration.
Doses are based on the use of a neuraxial opioid alone. No continuous intrathecal or subarachnoid infusions are provided. Lower doses may be effective when administered to the elderly or when injected in the cervical or thoracic region. Units vary across agents for single dose (mg vs. μg) and continuous infusion (mg/h vs. μg/h).

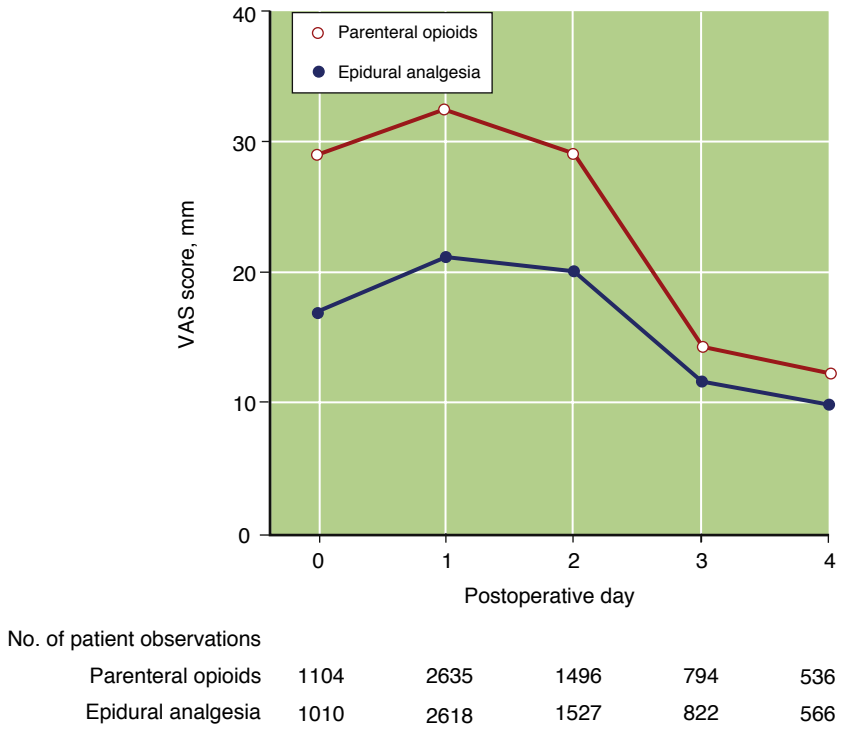

Fig. 81.2 Mean and standard deviation of visual analog pain scores (*y* axis) for both epidural analgesia (represented by *dark blue circles*) and parenteral opioids (represented by *open red circles*) for each postoperative day (*x* axis) up to the fourth day after surgery. (From Block BM, Liu SS, Rowlingson AJ, et al. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA*. 2003;290:2455–2463, with permission.)

Continuous Epidural Analgesia

Analgesia delivered through an indwelling epidural catheter is a safe and effective method for management of acute postoperative pain. Postoperative epidural analgesia can provide analgesia superior to that of systemic opioids (Fig. 81.2).[91,92] Of note, however, epidural analgesia is not a generic term but incorporates a wide range of options, including the choice and dose of analgesic drugs, location of catheter placement, and onset and duration of perioperative use.[93] Although this section focuses on the postoperative management of epidural analgesia, intraoperative use of the epidural catheter as part of a combined epidural-general anesthetic technique results in less pain and faster patient recovery immediately after surgery than general anesthesia followed by systemic opioids does. Each of these options may affect the quality of postoperative analgesia, patient-reported outcomes, and even rates of morbidity and mortality.

Analgesic Drugs

Local Anesthetics. Epidural infusion of local anesthetic alone may be used for postoperative analgesia, but in general it is not as effective in controlling pain as local anesthetic-opioid epidural analgesic combinations are.[91,92] The precise location of action of local anesthetics in the epidural space is not clear, and potential sites include the spinal nerve roots, dorsal root ganglion, or spinal cord itself.[94] Epidural infusion of local anesthetic alone may be warranted for postoperative analgesia in an attempt to avoid opioid-related side effects; however, the sole use of local anesthetics is less

TABLE 81.5 Recommended Catheter Insertion Sites for Surgical Procedures

Location of Incision	Examples of Surgical Procedures	Congruent Epidural Catheter Placement
Thoracic	Lung reduction, radical mastectomy, thoracotomy, thymectomy	T4-8
Upper abdominal	Cholecystectomy, esophagectomy, gastrectomy, hepatic resection, Whipple procedure	T6-8
Middle abdominal	Cystoprostatectomy, nephrectomy	T7-10
Lower abdominal	Abdominal aortic aneurysm repair, colectomy, radical prostatectomy, total abdominal hysterectomy	T8-11
Lower extremity	Femoral-popliteal bypass, total hip or total knee replacement	L1-4

L, Lumbar level; *T*, thoracic level.

common than the use of a local anesthetic-opioid combination because of a significant failure rate (from regression of sensory blockade and inadequate analgesia) and relatively high incidence of motor block and hypotension.[93]

Opioids for Epidural Infusion. Opioids may be used alone for postoperative epidural infusion and do not generally cause motor block or hypotension from sympathetic blockade.[93] There are differences between continuous epidural infusion (CEI) of lipophilic (e.g., fentanyl, sufentanil) and hydrophilic (e.g., morphine, hydromorphone) opioids. The analgesic site of action (spinal vs. systemic) of CEI of lipophilic opioids is not clear. Although some data suggest a benefit from epidural (vs. IV) infusion of lipophilic opioids,[95] the overall advantage of administering CEI of lipophilic opioids alone is marginal.[93]

The analgesic site of action for continuous hydrophilic opioid infusion is primarily spinal. Continuous infusion of a hydrophilic opioid may be especially useful for providing postoperative analgesia when the site of catheter insertion is not congruent with the site of surgery or when side effects (e.g., hypotension, motor block) are attributed to the epidural local anesthetic. Use of a continuous infusion rather than intermittent boluses of epidural morphine may result in superior analgesia with fewer side effects. CEI of hydrophilic opioids may provide analgesia superior to that of traditional PRN administration of systemic opioids.

Local Anesthetic-Opioid Combinations. Use of a local anesthetic and an opioid in an epidural infusion may have advantages over infusions consisting of a local anesthetic or opioid alone. When compared with a local anesthetic or opioid alone, a local anesthetic-opioid combination provides superior postoperative analgesia (including improved dynamic pain relief), limits regression of sensory blockade, and possibly decreases the dose of local anesthetic administered, although the effect on the incidence is uncertain.[93] CEI of a local anesthetic-opioid combination also provides analgesia superior to that of IV PCA with opioids.[91] It is unclear whether the analgesic effect of the local anesthetic and opioid in epidural analgesia is additive or synergistic. The choice of local anesthetic for CEI varies. In general, bupivacaine or ropivacaine is chosen because of the differential and preferential clinical sensory blockade with minimal impairment of motor function. Concentrations used for postoperative epidural analgesia are lower than those used for intraoperative anesthesia. The choice of opioid also varies, although many clinicians prefer a lipophilic opioid (e.g., fentanyl, sufentanil) to allow rapid titration of analgesia.[93] Use of a hydrophilic opioid (morphine, hydromorphone) as part of a local anesthetic-opioid epidural analgesic regimen may also provide effective postoperative analgesia. The optimal local anesthetic and opioid dose that provides the lowest pain scores with the fewest medication-related side effects is unknown and further investigation is needed to determine the optimal combinations for other types of surgical procedures with different epidural catheter insertion sites and to compare the efficacy of these optimal continuous infusions with patient-controlled epidural analgesia (PCEA).

Adjuvant Drugs. A variety of adjuvants may be added to epidural infusions to enhance analgesia while minimizing side effects, but none has gained widespread acceptance. Two of the more studied adjuvants are clonidine and epinephrine. Clonidine mediates its analgesic effects primarily through the spinal dorsal horn α_2-receptors on primary afferents and interneurons, as well as the descending noradrenergic pathway, and the epidural dose typically used ranges from 5 to 20 μg/h. Clinical application of clonidine is limited by its side effects: hypotension, bradycardia, and sedation. Hypotension and bradycardia are both dose dependent. Epidural administration of NMDA antagonists, such as ketamine, can theoretically be useful in attenuating central sensitization and potentiating the analgesic effect of epidural opioids, but additional safety and analgesic data are needed.

Location of Catheter Insertion

Insertion of the epidural catheter congruent to the incisional dermatome (i.e., catheter-incision–congruent analgesia) (Table 81.5) results in optimal postoperative epidural analgesia by infusing analgesics to the appropriate incisional dermatomes, providing superior analgesia, minimizing side effects (e.g., lower extremity motor block and urinary retention), and decreasing morbidity.[13,93] When compared with catheter-incision–congruent epidural analgesia, catheter-incision–incongruent epidural analgesia (e.g., low lumbar catheter placement for thoracic procedures) results in increased pain and early removal of the epidural catheter because of ineffective analgesia. By targeting delivery of

analgesic drugs to the appropriate dermatomes, catheter-incision–congruent epidural analgesia may result in smaller drug requirements and decreased medication-related side effects. There is a more frequent incidence of lower extremity motor block with the use of lumbar epidural catheters, and an earlier-than-anticipated termination of epidural analgesia may also result. Use of a high thoracic epidural for abdominal or thoracic surgery does not inhibit sympathetic nerve activity in the lower extremities and may result in a relatively infrequent incidence of urinary retention, thus diminishing the need for routine bladder catheterization. Placement of thoracic epidural catheters is relatively safe, and a more frequent incidence of neurologic complications is not documented with placement of a thoracic (vs. lumbar) epidural catheter. Furthermore, the benefits of epidural analgesia in decreasing morbidity in patients undergoing abdominal and thoracic surgery are seen only with thoracic (congruent), not lumbar (incongruent) epidural catheter placement.

Side Effects of Neuraxial Analgesic Drugs

Many medication-related (opioid and local anesthetic) side effects can occur with the use of postoperative epidural analgesia, but before automatically ascribing the cause to the epidural analgesic regimen, other causes should be considered, such as small intravascular volume, bleeding, and low cardiac output leading to hypotension and cerebrovascular accident, pulmonary edema, and evolving sepsis leading to respiratory depression. Standing orders and nursing protocols for analgesic regimens, neurologic monitoring, treatment of side effects, and physician notification about critical variables should be standard for all patients receiving neuraxial and other types of postoperative analgesia (see Box 81.1).

Hypotension. The local anesthetics used in an epidural analgesic regimen may block sympathetic fibers and contribute to postoperative hypotension. Although the precise incidence of postoperative hypotension with postoperative epidural analgesia is uncertain, a systematic review of studies investigating postoperative analgesia found a mean (95% CI) incidence of hypotension for epidural analgesia as 5.6 (3.0%-10.2%).[35] Strategies to treat noncritical hypotension caused by epidural analgesia include decreasing the overall dose of local anesthetic administered (by decreasing the rate or concentration), infusing an opioid epidural alone because it is unlikely that neuraxial opioid administration would contribute to postoperative hypotension, and treating the underlying cause of the decrease in blood pressure.[93]

Motor Block. Use of local anesthetics for postoperative epidural analgesia may also contribute to lower extremity motor block in approximately 2% to 3% of patients, and this may lead to the development of pressure sores in the heels.[96] A metaanalysis noted a mean incidence of motor block of 3.2% with PCEA.[91] A lower concentration of local anesthetic and catheter-incision–congruent placement of epidural catheters for abdominal or thoracic procedures may decrease the incidence of motor block. Although motor block resolves in most cases after stopping the epidural infusion for approximately 2 hours, persistent or increasing motor block should be evaluated promptly, and spinal hematoma, spinal abscess, and intrathecal catheter migration should be considered as part of the differential diagnosis.

Nausea and Vomiting. Nausea and vomiting associated with neuraxial administration of single-dose opioid occurs in up to 50% of patients, and the cumulative incidence in those receiving continuous infusions of opioid may be as high as 80%. The overall data (neuraxial opioids and/or local anesthetic combined) suggest that the incidence of postoperative vomiting is similar between epidural analgesia and systemic opioids, although female patients will exhibit a more frequent incidence regardless of analgesic modality.[97] The incidence of neuraxial opioid-related nausea and vomiting may be dose dependent, although a recent metaanalysis suggested that a larger dose (≥0.3 mg) of intrathecal morphine did not increase the risk of postoperative nausea or vomiting compared to smaller dose (<0.3 mg) of intrathecal morphine.[98] Nausea and vomiting from neuraxial opioids may be related to the cephalad migration of opioid within the CSF to the area postrema in the medulla. Use of fentanyl alone or in combination with a local anesthetic in an epidural infusion is associated with a less frequent incidence of nausea and vomiting than infusions of morphine are. A variety of drugs have been used successfully to treat neuraxial opioid-induced nausea and vomiting, including naloxone, droperidol, metoclopramide, dexamethasone, ondansetron, and transdermal scopolamine.

Pruritus. Pruritus is one of the most common side effects of epidural or intrathecal administration of opioids, with an incidence of approximately 60% versus about 15% to 18% for epidural local anesthetic administration or systemic opioids.[99] A systematic review of studies investigating postoperative analgesia found a mean (95% CI) incidence of pruritus for epidural analgesia as 16.1 (12.8%-20%) versus 13.8 (10.7%-17.5%) for IV opioid PCA.[97] Although the cause of neuraxial opioid-induced pruritus is uncertain, peripheral histamine release is not the cause but may be related to central activation of an "itch center" in the medulla or activation of opioid receptors in the trigeminal nucleus or nerve roots with cephalad migration of the opioid. It is unclear whether the incidence of neuraxial opioid-related pruritus is dose dependent. Many drugs have been evaluated for the prevention and treatment of opioid-induced pruritus, which can be difficult to manage and quite bothersome for some patients. IV naloxone, naltrexone, nalbuphine, and droperidol appear to be efficacious for the pharmacologic control of opioid-induced pruritus. Serotonin receptor antagonists may also be an effective modality in the prevention of neuraxial opioid-induced pruritus. The use of epidural morphine is associated with postpartum reactivation of herpes simplex labialis.

Respiratory Depression. Neuraxial opioids used in appropriate doses are not associated with a more frequent incidence of respiratory depression than that seen with systemic administration of opioids. The incidence of respiratory depression with neuraxial administration of opioids is dose dependent and typically ranges from 0.1% to 0.9%. The incidence of respiratory depression, as defined by a slow

TABLE 81.6 Patient-controlled Epidural Analgesia Regimens

Analgesic Solution*	Continuous Rate (mL/h)	Demand Dose (mL)	Lockout Interval (min)
GENERAL REGIMENS			
0.05% bupivacaine + 4 μg/mL fentanyl	4	2	10-20
0.0625% bupivacaine + 5 μg/mL fentanyl†	4-6	3-4	10-20
0.1% bupivacaine + 5 μg/mL fentanyl	6	2	10-20
0.2% ropivacaine + 5 μg/mL fentanyl	5	2	20
THORACIC SURGERY			
0.0625%-0.125% bupivacaine + 5 μg/mL fentanyl†	3-4	2-3	10-20
ABDOMINAL SURGERY			
0.0625% bupivacaine + 5 μg/mL fentanyl†	4-6	3-4	10-20
0.125% bupivacaine + 0.5 μg/mL sufentanil	3-5	2-3	10-20
0.1%-0.2% ropivacaine + 2 μg/mL fentanyl	3-5	2-5	10-20
LOWER EXTREMITY SURGERY			
0.0625%-0.125% bupivacaine + 5 μg/mL fentanyl†	4-6	3-4	10-20

*Regimens listed are samples of local anesthetic-lipophilic opioid combinations from the literature.
†Patient-controlled epidural analgesic regimens commonly used at the Johns Hopkins Hospital.

respiratory rate, should be less than 1%.[35] The precise incidence of respiratory depression in actual clinical practice may be difficult to determine, as there are many criteria (e.g., respiratory rate, oxygen saturation, partial pressure of carbon dioxide, and need to administer respiratory stimulants/reversal drugs) that have been used to define respiratory depression.[35] Neuraxial lipophilic opioids cause less delayed respiratory depression than hydrophilic opioids, although administration of lipophilic opioids may cause early significant respiratory depression. Delayed respiratory depression is primarily associated with the cephalad spread of hydrophilic opioids, which typically occurs within 12 hours after injection of morphine. Risk factors for respiratory depression with neuraxial opioids include increasing dose, increasing age, concomitant use of systemic opioids or sedatives, possibility of prolonged or extensive surgery, and the presence of comorbid conditions (e.g., OSA). Clinical assessments, such as the respiratory rate, may not reliably predict a patient's ventilatory status or impending respiratory depression. Treatment with naloxone (and airway management if necessary) is effective in 0.1- to 0.4-mg increments; however, because its clinical duration of action is relatively short in comparison to the respiratory depressant effect of neuraxial opioids, continuous infusion of naloxone (0.5-5 μg/kg/h) may be needed.[100] Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration have been published.[101]

Urinary Retention. Urinary retention associated with the neuraxial administration of opioids is the result of an interaction with opioid receptors in the spinal cord that decreases the detrusor muscle's strength of contraction. The incidence of urinary retention is more frequent with neuraxially administered opioids than when given systemically. Urinary retention does not depend on the opioid dose and may be treated with the use of low-dose naloxone, although at the risk of reversing the analgesic effect. Urinary retention occurred in 23.0% of patients, with the most frequent rate in those receiving epidural analgesia.[97] However, the exact incidence of urinary retention seen clinically may be difficult to determine because patients who undergo major surgical procedures are often routinely catheterized.

Patient-Controlled Epidural Analgesia

Epidural analgesia has traditionally been delivered at a fixed rate or as a CEI; however, the administration of epidural analgesia through a patient-controlled device (PCEA) has become more common. Like IV PCA, PCEA allows individualization of postoperative analgesic requirements and may have several advantages over CEI, including lower drug use and better patient satisfaction. PCEA may also provide analgesia superior to that afforded by IV PCA.[91]

PCEA is a relatively safe and effective technique for postoperative analgesia on routine surgical wards. Observational data from two series of over 1000 patients each reveal that more than 90% of patients with PCEA receive adequate analgesia, with a median pain score of 1 (of a possible 10) at rest and 4 with activity.[102,103] The incidence of side effects is 1.8% to 16.7% for pruritus, 3.8% to 14.8% for nausea, 13.2% for sedation, 4.3% to 6.8% for hypotension, 0.1% to 2% for motor block, and 0.2% to 0.3% for respiratory depression.[102,103] These rates are favorable and comparable to those reported with CEI.

The optimal PCEA analgesic solution and delivery parameters are unclear. Use of a continuous or background infusion in addition to the demand dose is more common with PCEA than with IV PCA and may provide analgesia superior to that of the use of a demand dose alone.[104] In general, most acute pain specialists have gravitated toward a variety of low-concentration local anesthetic-opioid combinations (Table 81.6) in an attempt to improve analgesia while minimizing side effects, such as motor block and respiratory depression. As for CEI, addition of an opioid to the local anesthetic can provide analgesia superior to that

of either analgesic alone. A lipophilic opioid is usually chosen because its rapid analgesic effect and shorter duration of action may be more suitable for use with PCEA.[102] Use of lower concentrations of a local anesthetic (e.g., bupivacaine, ropivacaine) may provide excellent analgesia without significant motor block.[105]

Benefits of Epidural Analgesia

Use of perioperative epidural anesthesia and analgesia, especially with a local anesthetic-based analgesic solution, can attenuate the pathophysiologic response to surgery and may be associated with a reduction in mortality and morbidity when compared with analgesia with systemically administered opioids.[13,14] Metaanalysis of randomized data (141 trials enrolling 9559 subjects) found that perioperative use of neuraxial anesthesia and analgesia (vs. general anesthesia and systemic opioids) reduced overall mortality (primarily in orthopedic patients) by approximately 30%.[106] Use of epidural analgesia can decrease the incidence of postoperative gastrointestinal, pulmonary, and possibly cardiac complications.[13,107]

By inhibiting sympathetic outflow, decreasing the total opioid dose, and attenuating spinal reflex inhibition of the gastrointestinal tract, postoperative thoracic epidural analgesia can facilitate return of gastrointestinal motility without contributing to anastomotic bowel dehiscence.[107,108] Randomized clinical trials demonstrate that use of postoperative thoracic epidural analgesia with a local anesthetic-based analgesic solution allows earlier return of gastrointestinal function and fulfillment of discharge criteria.[109] When compared with those who receive epidural opioids for postoperative analgesia, patients who receive epidural local anesthetics have an earlier return of gastrointestinal motility after abdominal surgery.[109]

Perioperative use of epidural analgesia with a local anesthetic-based regimen in patients undergoing abdominal and thoracic surgery decreases postoperative pulmonary complications,[110,111] presumably by preserving postoperative pulmonary function through providing superior analgesia and thus reducing "splinting" behavior and attenuating the spinal reflex inhibition of diaphragmatic function.[112] A metaanalysis of 48 randomized clinical trials[113] and another large, randomized clinical trial[114] demonstrated that use of thoracic epidural analgesia with a local anesthetic-based regimen decreased the incidence of pulmonary infections and complications. However, patients who received postoperative epidural opioids, intercostal blocks, wound infiltration, or intrapleural analgesia did not have a significant decrease in the incidence of pulmonary complications.[113] A subsequent meta-analysis confirmed the benefits of thoracic epidural analgesia in decreasing perioperative pulmonary complications.[115]

Use of postoperative thoracic, but not lumbar, epidural analgesia may decrease the incidence of postoperative myocardial infarction, possibly by attenuating the stress response and hypercoagulability, improving postoperative analgesia, and providing favorable redistribution of coronary blood flow. The finding that only thoracic epidural analgesia decreases the incidence of postoperative myocardial infarction corroborates experimental data on the physiologic benefits of thoracic epidural analgesia, such as a reduction in the severity of myocardial ischemia or size of infarction, attenuation of sympathetically mediated coronary vasoconstriction, and improvement of coronary flow to areas at risk for ischemia. The use of thoracic epidural analgesia in patients undergoing cardiac surgery decreased the risk of postoperative supraventricular arrhythmias and respiratory complications.[116]

Although postoperative epidural analgesia decreases postoperative gastrointestinal, pulmonary, and possibly cardiac morbidity, the benefits of postoperative epidural analgesia are not as evident in other areas, such as postoperative coagulation, cognitive dysfunction,[117] and immune function. While the use of *intra*operative regional anesthesia decreases the incidence of hypercoagulable-related events (e.g., deep venous thrombosis, pulmonary embolism, vascular graft failure),[106] *post*operative epidural analgesia does not obviously decrease the incidence of hypercoagulable-related events.

The benefits of postoperative epidural analgesia are optimized when the epidural catheter is inserted in a location corresponding to the dermatomes covered by the surgical incision (i.e., catheter-incision–congruent analgesia), which results in a smaller dose of drug administered and decreased incidence of drug-induced side effects, such as pruritus, nausea, vomiting, urinary retention, motor block, and hypotension.[102] When compared with catheter-incision–incongruent epidural analgesia, catheter-incision–congruent analgesia provides earlier return of gastrointestinal function, a lower incidence of myocardial infarction, and superior analgesia.[112] The ability of postoperative epidural analgesia to attenuate postoperative pathophysiology and improve outcomes also depends on the type of drugs used (opioids vs. local anesthetics). Maximal attenuation of perioperative pathophysiology occurs with the use of a local anesthetic-based epidural analgesic solution. The use of a local anesthetic-based (vs. opioid-based) analgesic solution is associated with earlier recovery of gastrointestinal motility after abdominal surgery[109] and less frequent occurrence of pulmonary complications.[113] Epidural analgesia is not a generic entity because different catheter locations and analgesic regimens may differentially affect perioperative morbidity.

It is unclear whether perioperative epidural analgesia may improve patient-reported outcomes.[112] Use of postoperative epidural analgesia may be associated with an improvement in postoperative analgesia and patient-reported outcomes such as patient satisfaction[34] and HRQL.[19] When compared with systemic opioids, epidural local anesthetics consistently provide superior analgesia.[91,92] Although the concept of satisfaction is complex and difficult to measure accurately, the analgesic benefits of postoperative epidural analgesia may contribute to greater patient satisfaction[34] and improved HRQL.[19]

There may be a possible link between the perioperative use of regional anesthesia/analgesia and a decrease in cancer recurrence.[118] There are several hypothetical reasons why the perioperative use of regional anesthesia and analgesia would be of benefit in patients undergoing cancer surgery, including attenuation of perioperative immunosuppression and decreased use of inhaled anesthetics/opioids. A regional anesthetic-induced sympathectomy should increase blood flow to the extremities with subsequent improvement in tissue oxygenation and a potential favorable local anesthetic

effect on tumor-cell killing. However, there are multiple factors that may potentially affect cancer recurrence and the impact of perioperative regional analgesic techniques on a long-term outcome such as cancer recurrence is uncertain at this time. Use of neuraxial anesthesia/analgesia for total hip or knee replacement may decrease the risk of surgical site infections compared with general anesthesia.[119]

Risks With Epidural Analgesia

The benefits of perioperative epidural anesthesia-analgesia must be weighed against the risks associated with this technique. Some complications are associated with placement of an epidural catheter, and several risks related to the use of indwelling epidural catheters (e.g., epidural hematoma and abscess) should be discussed in the context of postoperative epidural analgesia. A review of neurologic complications after regional anesthesia revealed that the rate of neurologic complications after central neuraxial blockade is less than 4 in 10,000 (0.04%); the rate of neuropathy after a peripheral nerve block is less than 3 in 100 (3%).[120] However, permanent neurologic injury after either central neuraxial or peripheral nerve block is rare in contemporary anesthetic practice.[120] Elements of routine monitoring of patients receiving neuraxial analgesia are presented in Box 81.1.

The concurrent use of anticoagulants and neuraxial anesthesia and analgesia has always been a relatively controversial issue but has been highlighted over the past decade by the increased incidence of spinal hematoma after the introduction of low-molecular-weight heparin in North America in 1993.

Different types and classes of anticoagulants have different pharmacokinetic properties that affect the timing of neuraxial catheter or needle insertion and catheter removal. Despite many observational and retrospective studies investigating the incidence of spinal hematoma in the setting of various anticoagulants and neuraxial techniques, no definitive conclusion regarding the absolute safety of neuraxial anesthesia and anticoagulation has been reached. The American Society of Regional Anesthesia and Pain Medicine (ASRA) lists a series of guidelines based on the available literature for administration (insertion and removal) of neuraxial techniques in the presence of various anticoagulants, including oral anticoagulants (warfarin), antiplatelet agents, fibrinolytics-thrombolytics, standard unfractionated heparin, and low-molecular-weight heparin.[121] The ASRA guidelines include the concept that the timing of neuraxial needle or catheter insertion or removal should reflect the pharmacokinetic properties of the specific anticoagulant. Frequent neurologic monitoring is essential. Concurrent use of multiple anticoagulants may increase the risk of bleeding, and the analgesic regimen should be tailored to facilitate neurologic monitoring, which may be continued in some cases for 24 hours after removal of the epidural catheter. Although the ASRA guidelines were developed with the latest available literature, these guidelines are limited by the relatively rare incidence of epidural hematoma; there are observational studies during which procedures (e.g., epidural catheter removal) are performed outside the boundaries presented in the ASRA guidelines.[122] A version of the ASRA guidelines on neuraxial anesthesia and anticoagulation[121] can be found on their website (www.asra.com), and some of these statements address the newer anticoagulants. Finally, the risk of epidural hematoma may be different for obstetric versus surgical patients.[123]

Infection associated with postoperative epidural analgesia may result from exogenous or endogenous sources.[93] Serious infections (e.g., meningitis, spinal abscess) associated with epidural analgesics are rare (<1 in 10,000),[124] although a more frequent incidence has been observed (approximately 1 in 1000-2000).[124] Closer examination of the studies that reported a more frequent incidence of epidural abscess reveals that the patients had a relatively longer duration of epidural analgesia or coexisting immunocompromising or complicating diseases (e.g., malignancy, trauma).[93] Use of epidural analgesia in the general surgical population with a typical duration of postoperative catheterization (approximately 2-4 days) is not generally associated with epidural abscess formation.[102] Even though serious infectious complications are rare after short-term (<4 days) epidural infusions, there may be a relatively more frequent incidence of superficial inflammation or cellulitis (4%-14%) and an even higher rate of catheter colonization (20%-35%), with the proportion of positive cultures increasing with longer duration of catheterization; however, the catheter colonization rate may not be a good predictor of infection of the epidural space.[125] A practice advisory from the ASA discussing the prevention, diagnosis, and management of infectious complications associated with neuraxial techniques has been published.[126]

Although epidural analgesia may provide superior postoperative analgesia, migration of the epidural catheter out of the epidural space and into the intrathecal, intravascular, or subcutaneous space decreases the effectiveness of this technique. The failure rate (i.e., earlier-than-anticipated discontinuation of the catheter for any reason, placement of a nonfunctioning epidural catheter) ranges from approximately 6% to 25%, with many centers reporting a rate between 10% and 20%, but the incidence of actual premature epidural catheter dislodgement may be less frequent (mean, 5.7%; 95% confidence interval, 4.0%-7.4%).[127,102] Fortunately, the rate of intrathecal and intravascular migration of an epidural catheter is most likely much less frequent than the failure rate. Some authors have gone further to define a successful epidural as the one that provides good pain relief and facilitates postoperative mobilization and rehabilitation for as long as the catheter is in place.[128] In that sense, determining failure rate maybe even more difficult and only local institutional audits are able to define local failure rate.

Despite the less frequent occurrence of intravascular and intrathecal migration of postoperative epidural catheters, use of an epinephrine-containing test dose, administration of local anesthetic in fractionated doses, and aspiration of the catheter before bolus administration of local anesthetics may prevent complications (e.g., high or total spinal, seizures, neurotoxicity).[93] The issue of whether lower extremity compartment syndrome can be consistently masked by the use of a local anesthetic-based epidural analgesic regimen is unresolved because use of systemic opioid analgesia has also been associated with a delayed diagnosis of compartment syndrome.[129]

Peripheral Regional Analgesia

The use of peripheral regional analgesic techniques as a single injection or continuous infusion can provide site-specific analgesia superior to that with systemic opioids[130] and may even result in improvement in various outcomes.[131] A variety of wound infiltration and peripheral regional

techniques (e.g., brachial plexus, lumbar plexus, femoral, sciatic-popliteal, and scalp nerve blocks) can be used to enhance postoperative analgesia. Peripheral regional techniques may have several advantages over systemic opioids (i.e., superior analgesia and decreased opioid-related side effects) and neuraxial techniques (i.e., decreased risk for spinal hematoma and less hemodynamic instability).[132]

A one-time injection of local anesthetic for peripheral regional techniques may be used primarily for intraoperative anesthesia or as an adjunct to postoperative analgesia. When compared with placebo, peripheral nerve blocks with local anesthetics provide superior analgesia and are associated with reduced opioid use, decreased opioid-related side effects, and improvement in patient satisfaction.[132] The duration of postoperative analgesia resulting from the local anesthetic in the peripheral nerve block varies but may last up to 24 hours after injection. Additives to local anesthetics can also increase the duration of action of local anesthetic and improve the quality of nerve blocks. Some of these adjuvants include dexamethasone, clonidine, and dexmedetomidine.[133] An earlier systematic review indicated that local anesthetics may also provide effective wound infiltration analgesia postoperatively for a variety of procedures.[134] A more recent meta-analysis suggested that local anesthetic administered via wound catheters may not reduce pain intensity after surgery.[135]

Continuous infusions of local anesthetics can be administered through peripheral nerve catheters. There are many methods to insert peripheral nerve catheters, including nerve stimulation and ultrasound guidance.[136] RCTs suggest that use of peripheral regional analgesia may facilitate postoperative rehabilitation as evidenced by accelerated resumption of passive joint range-of-motion, decrease in time until discharge readiness, and earlier actual discharge from the hospital or rehabilitation center.[136,137] Continuous peripheral nerve blocks may be used in the outpatient (home) setting typically using a portable ambulatory pump.[136] When compared with systemic opioids, use of continuous infusions or patient-controlled peripheral analgesia results in superior analgesia, decreased opioid-related side effects, and greater patient satisfaction.[130,132] The optimal parameters (i.e., local anesthetic, concentration, opioid, adjuvants, and continuous vs. PCA vs. intermittent boluses) for peripheral analgesia are still being determined. With the evolution of the ultrasound guidance technology and description of new block technique, peripheral nerve blocks are now more integrated into new clinical pathways.

Truncal Blocks

Several nonepidural/truncal regional analgesic techniques can be used for the management of postoperative thoracic and abdominal pain. Some of these techniques are well established and others are relatively new, including; paravertebral and intercostal blocks, transversus abdominis plane (TAP) blocks, quadratus lumborum blocks,[138] erector spinae plane blocks,[139] interpleural (intrapleural) analgesia, and cryoanalgesia. Thoracic paravertebral block has been used for thoracic, breast, and upper abdominal surgery and for the treatment of rib fracture pain.[140] Possible sites of analgesia for a thoracic paravertebral block include direct somatic nerve, sympathetic nerve, and epidural blockade.[140] A thoracic paravertebral block can be administered as a single injection or as continuous infusion through a catheter, may provide analgesia equal or superior to that of thoracic epidural analgesia, and is a valuable alternative to thoracic epidural analgesia.[128,141] Paravertebral blocks may be especially useful in providing postoperative analgesia after breast surgery.[142] When compared to thoracic epidural analgesia, paravertebral analgesia has been shown to provide equivalent analgesia but with a better side effect profile (e.g., lower incidence of hypotension) and also lower the risk of postoperative pulmonary complications.[141,143] Continuous infusions of local anesthetics through a paravertebral catheter are preferable to intermittent boluses, as the former is associated with lower pain scores.[144]

TAP nerve block is an approach for blocking the abdominal wall neural afferents to provide postoperative analgesia. Typically performed under ultrasound guidance, TAP blocks have been mostly described in adult patients (with some in pediatric patients) and used in a variety of surgical patients.[145,146] Several systematic reviews indicate that TAP blocks may reduce postoperative morphine requirements, nausea and vomiting, and possibly the severity of pain after abdominal surgery.[145,147] Although superior early postoperative analgesia appears to occur (within 24 hours of surgery), the surgical procedures, analgesic dosing, techniques, and timing for optimal analgesia following TAP block need further examination. A host of truncal blocks have been described to provide analgesia for the thoracic and abdominal wall. These blocks are yet to be compared head-to-head with well-established analgesic modality.

The analgesic efficacy and the mechanism of interpleural analgesia are no longer controversial (i.e., sensory or sympathetic block, or both). Interpleural analgesia is inferior to epidural and paravertebral analgesia for control of postoperative pain, preservation of lung function after thoracotomy, and reduction of postoperative pulmonary complications.[113] Intercostal blocks may provide short-term postoperative analgesia and may be repeated postoperatively; however, the incidence of pneumothorax increases with each intercostal nerve blocked (1.4% per nerve, with an overall incidence of 8.7% per patient).[148] Like interpleural analgesia, intercostal blocks do not reduce the incidence of pulmonary complications postoperatively when compared with epidural analgesia.[113]

Intraarticular and Local Infiltration Analgesia

Local peripheral administration of opioids (e.g., intraarticular injection after knee surgery) may theoretically provide analgesia for up to 24 hours after surgery and decrease the incidence of chronic pain, as peripheral opioid receptors are found on the peripheral terminals of primary afferent nerves and are upregulated during inflammation of peripheral tissues. Results of the several randomized clinical trials investigating this topic have been summarized. A subsequent qualitative systematic review found no evidence for analgesic effect of intraarticular morphine after knee arthroscopy.[149] A systemic effect of intraarticularly injected morphine cannot be excluded. A systematic review suggested that intraarticular administration of NSAIDs may provide clinically relevant peripheral analgesia.[150] Intraarticular injection of local anesthetics may provide a limited duration of postoperative analgesia, but the clinical benefit from intraarticular injection of local anesthetics is unclear. High-volume infiltration of local anesthetic (LIA) is especially popular after total knee arthroplasty (TKA). Proponents cite its simplicity and

no requirement for postoperative management as reasons to adopt the technique. A systematic review of 27 RCTs on LIA for TKA and total hip arthroplasty (THA) showed that LIA for TKA was associated with reduced pain scores and opioid requirements up to 72 hours after surgery.[151,152] Clinicians should be aware that there have been cases of glenohumeral chondrolysis reported in association with postarthroscopy infusion of local anesthetic.[153]

OTHER TECHNIQUES

Other nonpharmacologic techniques, such as transcutaneous electrical nerve stimulation (TENS), acupuncture, exercise/activity, and psychological approaches, can be used to alleviate postoperative pain. The mechanism by which TENS produces analgesia is unclear but may be related to modulation of nociceptive impulses in the spinal cord, release of endogenous enkephalins, or a combination of these, and other, mechanisms. Although the analgesic efficacy of these techniques is controversial, TENS and acupuncture may provide postoperative analgesia, decrease postoperative opioid requirements, reduce opioid-related side effects, and attenuate activation of the sympathoadrenal system. In general, all these approaches to postoperative pain are relatively safe, noninvasive, and devoid of the systemic side effects seen with other analgesic treatment options.[154] TENS may be of benefit in providing postoperative analgesia and decreasing analgesic consumption.[155,156] Early mobilization and activity therapy improve functional outcomes following orthopedic surgical procedures[157] and are effective in reducing pain behaviors in animal models of surgical neuropathic pain.[158] Although some methodologic issues have been raised with many of the available trials and the precise role of these treatments in postoperative pain management is not clear, they represent alternative therapies to add to the clinician's armamentarium. In the case of exercise and activity programs, these represent inexpensive and easily available therapies.

While this chapter has focused on the neurobiology of nociception and pharmacologic treatments available for the treatment of postoperative pain, the experience of pain is complex, multifaceted, and "an unpleasant sensory and emotional experience," as defined in part by the International Association for the Study of Pain. The differential behavior response to surgical incision may be related to global (i.e., personality, gender, age, and culture) and specific (i.e., fear, depression, anger, and coping) psychological factors.[159] Cognitive therapy and behavior therapy may be efficacious in reducing pain and alleviating psychological factors associated with pain.[160] Identifying and addressing psychological factors can reduce pain, improve the efficacy of pharmacologic analgesics, and diminish patients' distress, in part through enhancement of the placebo effect.[159] Although the placebo effect may have a psychological origin, the placebo response may exert part of its effects through activation of endogenous opioids and be useful in reducing the intensity of pain.[161]

POSTOPERATIVE ANALGESIA IN SPECIAL POPULATIONS

The foregoing discussion has provided a general approach to the principles and practice of acute postoperative pain management, but this approach may need to be modified for certain populations that have unique anatomic, physiologic, pharmacologic, affective, and cognitive issues. Management of acute pain should be tailored to the specific needs of a particular population. Although each topic by itself could merit a separate chapter in some textbooks, the general principles and essence of the issues associated with each population are outlined, and references are made to other more extensive sources.

OPIOID-TOLERANT PATIENTS: PATIENTS WITH PREEXISTING PAIN

Opioid-tolerant patients can be categorized into three groups: (1) those who have chronic pain for which they receive opioid-based analgesic therapy, (2) those who use opioids recreationally as a result of a substance use disorder, and (3) those who take opioids for a combination of numbers (1) and (2). Regardless of the reason the individual is using opioids, the management of their perioperative pain is considerably more challenging than for those who are opioid-naïve.

Even though there is no specific threshold or timeframe for when a patient becomes opioid tolerant, the FDA has provided guidelines for defining the opioid tolerant patient.[162] In summary, patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine per day; 25 μg transdermal fentanyl per hour; 30 mg oral oxycodone per day; 8 mg oral hydromorphone per day; 25 mg oral oxymorphone per day; or an equianalgesic dose of another opioid for one week or longer.

Postoperative pain may be difficult to manage in opioid-tolerant patients because the standard approaches used for baseline assessment and assessment of response to therapy in opioid-naïve or research patients are often less accurate for opioid-tolerant patients. Although opioid-tolerant patients require larger doses of analgesic medications (in addition to their baseline pain medication requirements) in the immediate postoperative period, many healthcare providers still do not provide adequate postoperative pain relief, in part because of the fear of addiction or medication-related side effects. In dealing with patients with chronic opioid use, healthcare providers often mistakenly interchange several pharmacologic terms (i.e., tolerance, physical dependence, and addiction), a practice that may contribute to misunderstanding and inappropriate treatment decisions.

Tolerance refers to the pharmacologic property of an opioid in which an increasing amount is needed to maintain a given level of analgesia. *Physical dependence* is another pharmacologic property of opioids characterized by the occurrence of a withdrawal syndrome on abrupt discontinuation of the opioid or administration of an antagonist. Tolerance and physical dependence are pharmacologic properties of opioids and are not synonymous with the aberrant psychological state or behavior associated with *addiction*, a chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological, or social harm to the user, and continued use despite that harm.

Several principles of pain assessment and treatment can be applied to the postoperative management of opioid-tolerant patients. The physician should expect high self-reported pain scores; base treatment decisions on objective pain

TABLE 81.7 Guidelines for Equianalgesic Dosing of Opioid Agonists

	RELATIVE STRENGTH COMPARED	EQUIANALGESIC DOSE (MG)	
Drug	**With Morphine**	**Oral**	**Parenteral**
Morphine	–	30	10
Buprenorphine	Much, much stronger	N/A	0.4 (7.5 μg/h TD)
Butorphanol	Much stronger	N/A	2
Codeine	Weaker	200	125
Fentanyl	Much, much stronger	N/A	0.1 (16.5 μg/h TD)
Hydrocodone	Equivalent to mildly weaker	30	N/A
Hydromorphone	Much stronger	7.5	1.5
Levophanol	Much stronger	4	N/A
Methadone	Stronger	10	5
Nalbuphine	Equivalent	N/A	10
Oxycodone	Stronger	20	N/A
Oxymorphone	Stronger	10	1
Pentazocine	Weaker	150	60
Tapentadol	Weaker	100	N/A
Tramadol	Much weaker	300	N/A

Equianalgesic doses are approximate and intended to serve only as an estimate of opioid requirements. Actual doses may vary, in part because of wide interpatient variability in response to opioids. Doses should be individualized and gradually titrated to effect. *TD*, Transdermal.

assessment (e.g., ability to breathe deeply, cough, ambulate) in conjunction with patients' self-reported pain scores; recognize the need to identify and treat two major problems, maintenance of a basal opioid requirement and control of incisional pain; and recognize that detoxification is not usually an appropriate goal in the perioperative period.[163-165]

The treatment of patients with prior opioid use requires the management of the expectations of the patient, the patient's family, and the physician's surgical colleagues. The goal of inpatient management of pain in patients with chronic pain or acute-on-chronic pain is to stabilize and rationalize (if necessary) the patient's outpatient pain medication regimen. The goal is not to treat long-standing persistent pain that has been managed on an outpatient basis, because it is unlikely in the very limited time in which you are a member of the patient's care team that you will be able to make a substantial positive difference. Therefore, several general strategies can be used for the treatment of postoperative pain in an opioid-tolerant patient or in a patient with chronic pain who is receiving opioids. Although patients with chronic pain are not synonymous with opioid-tolerant patients, many of these patients are also opioid tolerant, and the same general principles and strategies discussed earlier may be applied to these patients as well. The physician can create a treatment plan early and discuss it with the patient, surgical team, and nursing staff; replace the patient's baseline or basal opioid requirements postoperatively; anticipate an increase in postoperative analgesic requirements[166]; maximize the use of adjuvant drugs; consider the use of regional analgesic techniques; and plan for the transition to an oral regimen. The physician, patient, and other providers need to be aware that the nonopioid adjuvant medications (not including tramadol, NSAIDs, acetaminophen) may be started while the patient is an inpatient, but they are unlikely to have substantial impact on the patient's chronic pain while hospitalized. Recognizing and addressing non-nociceptive sources of distress may be especially important for patients with chronic pain.

Administration of a PRN analgesic regimen alone for opioid-tolerant patients is discouraged because replacing the basal opioid requirement in the postoperative period can optimize pain relief and possibly prevent opioid withdrawal. Basal opioid requirements can be administered systemically (typically intravenously) until the patient can tolerate an oral analgesic regimen.[30] For example, 50% to 100% of the patient's baseline opioid requirement can be administered by an IV PCA regimen, with a demand dose to cover the additional incisional pain. Conversion tables (Table 81.7) may facilitate equianalgesic conversion of opioids (i.e., different routes of administration of one opioid or conversion between two different opioids); however, these tables provide only estimations to assist healthcare providers in initiating opioid titration.[167]

Opioid-tolerant patients generally require increased postoperative analgesic levels, including a larger demand dose.[30,166] Patients may need frequent adjustment of the IV PCA demand dose or continuous infusion, depending on the analgesic requirements. There is individual variability in response to different opioids, and if a decision is made to switch opioids, the choice of opioid is probably not as important as using an equianalgesic dose. Patients may experience different side effects with different opioids, and rotating to another opioid may be reasonable if the patient is not tolerating the first opioid.[168] Adjuvant drugs such as NSAIDs should be administered on a regularly scheduled basis to optimize analgesic efficacy and possibly provide an

opioid-sparing effect. Use of regional analgesic techniques with neuraxial opioids may provide excellent analgesia in opioid-tolerant patients while theoretically preventing withdrawal symptoms, although the clinician should be prepared to diagnose and treat perioperative opioid withdrawal in these patients.

After the patient is tolerating oral intake, conversion from IV opioids to oral form that would be more suitable for discharge home may be initiated. Opioid-tolerant patients can generally be converted to a combination of a regularly administered, controlled-release formulation of opioid (i.e., sustained-release morphine) and short-acting, immediate-release opioid on a PRN basis. Although conversion of IV opioid to an oral form can be accomplished over a period of 24 hours in opioid-tolerant patients, this process may take longer in extremely difficult cases. In patients with a relatively high basal requirement of IV opioid (e.g., high, continuous background infusion of IV opioid PCA), clinicians should be aware not to abruptly discontinue the IV infusion of opioid during this transition but ideally decrease the high basal requirement of IV opioid in a stepwise fashion to account for the slower onset of the sustained-release. Converting from an IV to an oral form of opioid is not an exact science, and the conversion tables available can serve only as a rough guide because of significant interpatient and intrapatient variability in the sensitivity to opioids, lack of complete cross-tolerance between opioids (which may lead to greater than anticipated potency of a new opioid), and changes in the level of pain, which may rapidly decrease in the immediate postoperative period.[167] Because of these factors, conversion of approximately 50% to 75% of the equianalgesic dose to a sustained-release preparation of opioid or a transdermal fentanyl patch, with the remainder converted to a short-acting opioid delivered on a PRN basis, may be a reasonable starting point in patients whose pain is reasonably controlled, although additional titration may be necessary.

Although opioids are most commonly used in these patients, with consultation of the inpatient pain services (if available), the physicians can consider the use of analgesic (low-dose) ketamine.[169] Ketamine can be given as a basal infusion as a part of the ketamine PCA or a combination ketamine and opioid PCA, subcutaneously or orally. Ketamine may have significant advantages (such as greater analgesic response, less frequent rates of respiratory depression, and minimal impact on the gastrointestinal system) over continued opioid use in the opioid-tolerant or chronic pain patient in the postoperative setting.

Patients taking medications containing buprenorphine have some similar challenges to those of the opioid-tolerant or chronic pain patient in the perioperative setting, but these patients also have the added difficulties associated with the partial *mu* opioid agonist pharmacodynamics of buprenorphine. Although buprenorphine is a partial agonist, when given in conjunction with a full *mu* opioid agonist, it functions as a pharmacologic antagonist. It also possesses variable time to dissociation from the opioid receptor; therefore, when used in combination with a full agonist, it is challenging to time the switch from antagonism of the *mu*-opioid receptor action to the full agonism of morphine, oxycodone, hydromorphone, and other similar opioids. This can create a dangerous situation in which a previously appropriate dosage of one of the full agonists becomes enough to result in respiratory depression or other dose-related adverse events. Although it is ideal to not take buprenorphine 3 days in advance of surgery, it is often not feasible in many of our surgical settings in which patients are first seen by the anesthesiologist directly prior to the operation. Also, a similar situation can occur in patients who are taking buprenorphine as opioid replacement therapy for an opioid use disorder (OUD) (otherwise known as medication-assisted therapy) where discontinuing buprenorphine can precipitate withdrawal symptoms and the substitution of a full opioid agonist may provoke OUD relapse. In situations in which patients have not discontinued their buprenorphine therapy well in advance of their surgery, the patient should receive their baseline buprenorphine via sublingual or transdermal routes. Alternatively, and if necessary, convert the patient buprenorphine requirements to an IV equivalent while the patient is in the immediate perioperative period. Although the patient is maintained on a stable dosage of buprenorphine, additional full agonist opioids may be titrated to pain reduction, or alternatively, nonopioid adjuvants (including clonidine, ketamine, lidocaine, or dexmedetomidine) can be used instead of opioids for the patient's postoperative pain. Some authors suggest stopping buprenorphine preoperatively and switching to a short-acting opioid, or methadone, to prevent withdrawal symptoms if the surgery is major and will generate severe pain. The choice of methadone is a reasonable one, as it is an effective full opioid agonist but also has a long half-life, thereby providing benefit for continuation of medication-assisted treatment (MAT). Regardless of the approach, coordinated communication between the acute pain team, surgical service, and the primary buprenorphine prescriber should take place to make sure that the patient eventually goes back to their prescribed buprenorphine dose.[170] Sometimes, the logistics of this process can be difficult. Therefore, more often than not, anesthesiologists opt to continue buprenorphine perioperatively and optimize all components of multimodal analgesia for postoperative pain management. Regional anesthesia and local infiltration techniques should be used whenever feasible in these patients.[171]

PEDIATRIC PATIENTS

As in adults, undertreatment of acute pain occurs in a substantial percentage of children.[172] Pediatric patients continue to be undertreated.[166] In addition to anatomic, physiologic, pharmacodynamic, and pharmacokinetic differences between children and adults, there are barriers unique to pediatric patients that may interfere with effective postoperative pain control. Control of postoperative pain is important in pediatric patients because poor pain control may result in increased morbidity or mortality.[173]

Some of the most important barriers to pain control in pediatric patients are the myths that children and infants do not feel pain, that pain is not remembered, and that there is no untoward consequence of experiencing pain.[172] These incorrect assumptions about pain in pediatric patients may hinder management of pediatric pain. Because of developmental, cognitive, and emotional differences, assessment of pain in pediatric patients can be difficult. Pediatric patients may have difficulty conceptualizing and quantifying

a subjective experience such as pain. The lack of routine assessment and reassessment of pain may interfere with effective acute pain management.[172] Special scales are available to assist young children in self-reporting of pain; however, interpretation of behavior and physiologic parameters may be used to estimate pain intensity in preverbal children or those who cannot self-report their pain. Furthermore, assessing pain in children with intellectual disabilities presents unique challenges.[174]

A plan for postoperative pain management should be discussed with the family and patient before surgery, as pediatric patients may have many anxieties about pain and analgesic use after surgery. In general, the oral route of analgesic administration is preferred for mild to moderate pain. IV or regional analgesia is appropriate for moderate to severe postoperative pain.[172,175] Use of intramuscular injections is strongly discouraged because of the pain associated with injection and variable absorption of analgesic medications. Fear of needles may inhibit control of postoperative pain because pediatric patients may choose to suffer in silence rather than receive a painful and anxiety-provoking intramuscular injection. Addressing medication-related side effects is important to alleviate patient-related distress and improve compliance with the postoperative analgesic regimen.

Use of an IV PCA device allows individualization of analgesic requirements and offers pediatric patients autonomy. Children as young as 4 years have the cognitive and physical capability to appropriately use an IV PCA device.[176] Although morphine is the standard by which other opioids are compared, morphine does not appear to have an analgesic advantage over other opioids (e.g., hydromorphone) when given in equianalgesic doses. Because of toxicity from its metabolite and much better alternatives, meperidine should not be used in the pain management of pediatric (or adult) patients.[172] A metaanalysis examining whether the addition of a background or continuous infusion to an IV PCA opioid regimen would be associated with an increased risk of respiratory depression indicated that the addition of a continuous or background infusion was associated with a higher incidence of respiratory events in adult but not in pediatric patients.[32] Nurse- or parent-controlled analgesia is also effective and may be used in certain circumstances, but close monitoring of the patient may be needed because significant respiratory depression occurs in approximately 1.7% of patients, although some data suggest that children receiving PCA by proxy do not have a higher incidence of adverse events compared to those who do not.[177,178] For pediatric patients unable to use IV PCA, continuous infusions or intermittent IV administration of opioids is effective in providing postoperative analgesia.[179] Although respiratory depression may occur with opioids regardless of the route administered, clinically significant respiratory depression in pediatric patients is relatively uncommon.[176] Unlike adults, pediatric patients do not appear to exhibit multiple episodes of clinically significant oxygen desaturation postoperatively when treated with neuraxial, IV, or intramuscular opioids.[180] Use of nonopioid analgesic agents, such as NSAIDs or acetaminophen, may improve overall analgesia, reduce the amount of opioid used postoperatively, and decrease some opioid-related side effects such as postoperative nausea and vomiting.[181] For rectal administration of acetaminophen postoperatively, a larger dose (40 mg/kg followed by three doses of 20 mg/kg at 6-hour intervals) than that previously recommended may result in appropriate serum analgesic levels.[182] In addition, other analgesics such as ketamine and tramadol may be considered as adjunct analgesic drugs for the treatment of postoperative pediatric pain in specific clinical situations.[84,183]

Peripheral and neuraxial regional analgesic techniques are commonly used and effective for acute pain management in pediatric patients. The use of ultrasound-guided regional analgesic techniques has been described and may further increase the use of efficacious regional analgesic techniques for pediatric postoperative pain management.[184] One of the more frequently used techniques is epidural analgesia, which can be delivered as a single dose or by using a continuous-infusion catheter technique. The catheter may be inserted (typically using general anesthesia) anywhere along the epidural space (e.g., thoracic, lumbar, caudal), but the caudal approach seems to be the most common technique because the catheter can be easily advanced cephalad to the appropriate dermatome. Local anesthetics or opioids, or both, can be administered through the epidural catheter or needle to provide effective postoperative analgesia. Although epidural (caudal) analgesia may be safely administered to neonates, the clinician should recognize that the maximal continuous infusion dose is probably smaller than that in older children because of lower levels of α_1-acid glycoprotein (which binds local anesthetics) and diminished ability of the relatively immature liver to metabolize amide local anesthetics.[185] The addition of adjuvant drugs, such as clonidine, in the epidural infusion may enhance postoperative analgesia.[186]

Continuous epidural (caudal) analgesia may be used in the postoperative setting, and the infection rate associated with continuous epidural analgesia is extremely low despite the relatively high colonization rate.[125] In addition, continuous peripheral catheter techniques can be used effectively in pediatric patients. Regional analgesic techniques may be useful in providing analgesia for wound incision (e.g., herniorrhaphy or orchiopexy), thoracotomy, and orthopedic procedures.[187] Local anesthetics may also be administered topically to provide analgesia. Despite a lack of data comparing outcomes for regional analgesia versus systemic opioids in the pediatric population, some evidence suggests that the use of epidural analgesia is associated with improvement in some outcomes such as earlier tracheal extubation, return of gastrointestinal function, and length of hospital stay.[188] Finally, other modalities such as acupuncture may be a potentially useful adjunct for the treatment of pediatric postoperative pain, although further large scale randomized, controlled clinical trials are needed to define the role of these modalities in the treatment of pediatric postoperative pain.[189]

OBESITY, OBSTRUCTIVE SLEEP APNEA, AND SLEEP

Patients with obesity and OSA may be at a more frequent risk for postoperative complications. Obesity and OSA are separate disease states, but there is some association between the two because OSA occurs in a relatively higher percentage of obese than nonobese patients. Yet, the

optimal postoperative analgesic and monitoring regimen for patients with OSA is not clear. Data suggest that sleep is disrupted in the immediate postoperative period and may influence postoperative morbidity and patient-oriented outcomes.

Obesity is defined as a body mass index (BMI) of greater than 30 kg/m^2, with morbid and supermorbid obesity defined as a BMI of greater than 40 and 60 kg/m^2, respectively. The prevalence of obesity has continued to increase over the past decades to epidemic proportions (including children and adolescents) and is similar across the different ethnic, educational, and income groups.[190-192] Patients with OSA may be at higher risk for pulmonary hypertension, cardiomyopathy, systemic hypertension, and possibly myocardial infarction than their non-OSA counterparts. The pathophysiology of airflow obstruction is related primarily to upper airway pharyngeal collapse, including the retropalatal, retroglossal, and retroepiglottic pharynx, during sleep, especially during rapid eye movement sleep. During these obstructive episodes, OSA patients may exhibit hypoxia, bradyarrhythmias or tachyarrhythmias, myocardial ischemia, abrupt decreases in left ventricular stroke volume and cardiac output, or increases in pulmonary and systemic blood pressure.

Based on our understanding of the pathophysiology of OSA, postoperative pain management can be difficult in this population. Patients with OSA may be at an increased risk for respiratory arrest.[193] Although it is not clear whether OSA will increase the risk of postoperative hypoxemia when compared to other morbidly obese subjects without OSA, morbidly obese subjects (with or without OSA) may experience frequent oxygen desaturation episodes in the postoperative period even with the use of supplemental oxygen. Use of sedative doses of benzodiazepines and opioids may result in frequent hypoxemia and apnea, which may be especially dangerous in OSA patients. Use of nonopioids (e.g., tramadol, dexmedetomidine) or an opioid-sparing technique may limit some of the respiratory-related events postoperatively. Avoiding respiratory depressants by optimizing the use of NSAIDs, nonopioid adjuvants (including clonidine, ketamine, dexmedetomidine), complete avoidance of benzodiazepines, epidural analgesia with a local anesthetic-based regimen, peripheral nerve blocks, and local infiltration techniques may attenuate the risk for respiratory depression and arrest.

The American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Obstructive Sleep Apnea created guidelines that include recommendations for postoperative analgesia in patients with OSA.[191] Although the consultants acknowledged that the conclusions regarding postoperative analgesic options were based on insufficient literature evaluating the effects of various analgesic techniques, the presence of equivocal literature regarding the use of epidural opioids versus intramuscular or IV opioids in reducing respiratory depression, and insufficient literature regarding the addition of a basal infusion to systemic patient-controlled opioids, the consultants nevertheless recommended that regional techniques rather than systemic opioids be used in an attempt to reduce the likelihood of adverse outcomes in patients at increased perioperative risk from OSA.[194] In addition, the consultants recommended the exclusion (vs. inclusion) of opioids from neuraxial postoperative analgesia to reduce perioperative risk and the use of NSAIDs to reduce adverse outcomes through their opioid-sparing effect. The consultants were equivocal regarding whether avoiding a basal infusion of opioids in patients with OSA reduces the likelihood of adverse outcomes.[194] Unfortunately, randomized clinical trial data are lacking to provide definitive high-quality evidence-based recommendations for the provision of postoperative analgesia to OSA patients.

INPATIENT PAIN SERVICES

"Acute pain services" or "acute pain medicine" is not synonymous with regional anesthesiology pain services (RAPS) or PPS; each term describes a different role and the terminology can be confusing to other physicians and surgeons in the healthcare system. An APS/APM is a more comprehensive service than a PPS. APS/APM take care of all inpatient acute pain issues including perioperative pain as well as medical pain and acute-on-chronic pain such as sickle cell disease, pancreatitis, and acute exacerbations of inflammatory bowel disease or other condition requiring medicinal or catheter-based techniques for pain relief. A PPS takes care of only perioperative pain patients with the same techniques, and RAPS addresses only those patients with a catheter placed by an anesthesiologist for postoperative pain. Which type of service each hospital has depends greatly on the local expertise, the local financial resources available, and the patient population. Chronic pain services developed from the needs of patients in hospitals with the less comprehensive or RAPS/PPS-type of pain service because these services have a very restricted treatment group. As academic regional anesthesiologists have expanded their role to include that of the perioperative pain physician or the APM physician, they have developed services that encompass all inpatient pain concerns, and the role or necessity of the primarily outpatient pain medicine physician (commonly referred to as the chronic pain physician) in the hospital has been reduced.

Although there are several models for the development of APS/APM, the key organizational aspects are similar (Box 81.2). Development and maintenance of APS/APM requires commitment and financial support at the national and local (institutional and departmental) levels. In the United States, there is a dichotomy at the national and third-party payer levels between the requests for improved inpatient pain control, along with the introduction of practice guidelines or expanded roles for APS, and decreased reimbursement for the provision of such services. Because there is a substantial financial burden associated with the establishment of an inpatient pain service, large-volume or larger hospitals may be more likely to have these services and access to more high-tech analgesic techniques such as regional analgesia. Formal inpatient pain services using postoperative pain protocols are more likely to be present in academic/teaching hospitals when compared to nonteaching hospitals. Whether inpatient pain services actually improve outcomes is unclear. Two earlier systematic reviews have examined the impact of APS on patient outcomes,[7,195] and although both systematic reviews suggest that the introduction of APS is associated with a decrease in pain scores, the effect of APS on the incidence

BOX 81.2 Organizational Aspects of an Inpatient Pain Medicine Service

Educational Activity

Anesthesiologists
Residency-fellowship teaching (if applicable)
Health insurance carriers
Hospital administrators
Nurses
Patients and families
Pharmacists
Surgeons

Administrative Activity

Economic issues
Evaluation of equipment
Human resources: pain service personnel, administrative-secretarial support
Institutional administrative activity
Quality improvement and assurance
Research (if applicable)

Nursing

Continuing education and in-service training
Defining of roles in patient care
Nursing policies and procedures
Pain service nurse (if applicable)
Quality improvement and assurance

Documentation

Hospital policies and procedures
Bedside pain management assessment flow sheet
Daily consultation notes
Educational packages
Protocol driven order-sets

of analgesic-related side effects (e.g., nausea, vomiting), satisfaction, and overall costs is uncertain. Despite the direct costs (e.g., personnel, equipment, medication) associated with managing an APS, there is no properly conducted pharmacoeconomic study available to examine the cost-effectiveness (or lack) of an APS. Use of postoperative epidural analgesia in the context of APS may decrease the cost of patient care through shorter intensive care unit stays and a decreased rate of complications.[13] Nevertheless, an RCT comparing an anesthesiologist-led, nurse-based APS group with PCA versus a control group with systemic boluses of opioid analgesia noted that an APS was likely to be cost effective when the role of the APS was extended to a specific group of major surgical procedures.[196] A dedicated inpatient pain service allows anesthesiologists to extend their presence in the field of perioperative medicine, although there is no universal agreement on how to provide these services in a financially viable way.[195] This represents one of the numerous challenges that face the development of these services. If that service becomes valuable to the local medical scene, financial support will almost always follow in one way or another. As inpatient APM services continue to evolve into comprehensive inpatient pain medicine services, there is less need for a separation of acute and chronic pain services for inpatient pain care. The elimination of this duplication and the indeterminate roles of service(s) can reduce costs and improve continuity of patient pain care.

Despite the costs associated with implementation of a comprehensive inpatient pain service, these services provide a valuable resource at the individual, institutional, and societal levels. With the development of the APS/APM, we now have different training goals for the traditional regional anesthesiology fellowships, including more formal education in chronic pain conditions and management of these conditions while the patient is hospitalized with acute illness. This would involve education on the medical management of these conditions in the short-term, maintenance of the patient's long-term therapies, and knowledge on how these interact with acute pain management.

With skills in regional anesthetic techniques and knowledge of the neurobiology of nociception and the pharmacology of analgesics and local anesthetics, as well as specialty education in the treatment of acute and chronic pain conditions, anesthesiologists are recognized leaders in perioperative pain relief and the development of APS. Provision of inpatient analgesia, along with other services such as critical care medicine and preoperative evaluation, is highly compatible with the emerging identity of anesthesiologists as perioperative physicians and enhances the role of anesthesiologists as valued consultants outside the operating room.

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