UpToDate® Official reprint from UpToDate®
www.uptodate.com © 2022 UpToDate, Inc. and/or its affiliates. All Rights Reserved.

Wolters Kluwer

Management of acute perioperative pain

Author: Edward R Mariano, MD, MAS
Section Editor: Scott Fishman, MD
Deputy Editor: Marianna Crowley, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Dec 2021. | **This topic last updated:** Oct 25, 2021.

INTRODUCTION

The goals of perioperative pain management are to relieve suffering, achieve early mobilization after surgery, reduce length of hospital stay, and achieve patient satisfaction. Pain control regimens must take into account medical, psychological, and physical condition; age; level of fear or anxiety; surgical procedure; personal preference; and response to agents given. The optimal strategy for perioperative pain control consists of multimodal therapy to minimize the need for opioids. The overprescribing of opioids has reached a critical level worldwide [1], and surgery may be the trigger for long-term opioid use in many patients [2,3].

This topic will discuss the rationale and therapeutic options for a multimodal approach to control and prevent acute perioperative pain.

MECHANISM OF PERIOPERATIVE PAIN AND ANALGESIA

Perioperative pain results from inflammation caused by tissue trauma (ie, surgical incision, dissection, burns) or direct nerve injury (ie, nerve transection, stretching, or compression) (figure 1) [4]. The patient senses pain through the afferent pain pathway (figure 2), which is the target of various pharmacologic agents.

Tissue trauma releases local inflammatory mediators that can produce augmented sensitivity to stimuli in the area surrounding an injury (hyperalgesia) or misperception of pain due to non-noxious stimuli (allodynia) (figure 3). Other

mechanisms contributing to hyperalgesia and allodynia include sensitization of the peripheral pain receptors (primary hyperalgesia) and increased excitability of central nervous system neurons (secondary hyperalgesia) [4-6].

Traditionally, acute perioperative pain management has relied solely on opioid medications to target central mechanisms involved in the perception of pain (figure 4). A better approach uses several agents or techniques, each acting at different sites of the pain pathway, and is known as multimodal analgesia. This approach reduces the dependence on a single medication and mechanism, and importantly, may reduce or eliminate the need for opioids. Synergy between opioid and nonopioid medications reduces both the overall opioid dose and unwanted opioid-related side effects.

Pain receptor activity can be directly blocked (eg, lidocaine), or antiinflammatory agents (eg, aspirin, nonsteroidal antiinflammatory drugs) can be used to diminish the local hormonal response to injury, thus indirectly decreasing pain receptor activation.

Some analgesic agents target the activity of neurotransmitters by inhibiting or augmenting their activity (eg, ketamine, clonidine, acetaminophen, gabapentin, pregabalin) (figure 5). Neurotransmitters are responsible for carrying electrical signals across the gap junctions between neurons. To produce analgesia, the activity of several neurotransmitters can be targeted, including substance P, calcitonin gene-related peptide, aspartate, glutamate, and gamma-aminobutyric acid (GABA).

PREVENTIVE ANALGESIA

Management of postoperative pain has evolved from the sole administration of opioid medication in response to pain to, instead, the administration of a variety of medications and use of techniques to prevent acute and chronic pain. The concept of "preemptive" analgesia, ie, that analgesic strategies administered prior to surgical incision or stimulus can modify peripheral and central nervous system processing of noxious stimuli, thereby reducing central sensitization, hyperalgesia, and allodynia [4-6], remains controversial. A number of studies have concluded that the preoperative timing is not necessary to achieve a reduction in postoperative pain and opioid use [7].

A more encompassing approach to the reduction of acute and chronic postoperative pain is the concept of "preventive" analgesia. The aim of preventive analgesia is to reduce sensitization by preoperative, intraoperative, and postoperative noxious stimuli, by treatments administered at any time in the perioperative period. A preventive analgesic is effective when postoperative pain or analgesic consumption is reduced beyond the duration of action of the treatment drug or technique [8,9].

There are many effective preventive analgesic techniques using various pharmacological agents and interventions. They reduce nociceptor (pain receptor) activation by blocking or decreasing receptor activation and inhibiting the production or activity of pain neurotransmitters. The end result is a reduction in postoperative opioid use and opioid-related side effects.

Local anesthesia — Local anesthetic can be injected in proximity to the surgical incision and will provide preventive analgesia. A meta-analysis of randomized trials found statistically significant decreases in analgesic consumption and increased time to first rescue analgesic request but no difference in postoperative pain scores in patients who had preincisional local anesthetic wound infiltration [10]. Some randomized trials have shown that local anesthetic injection around small incision sites reduces postoperative somatic pain but is inadequate for visceral pain [10-14].

Systemic analgesics — For preventive analgesia, nonopioid systemic analgesics such as nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, antidepressants, anticonvulsants, and alpha$_2$ agonists can in some cases replace opioids, or can be effectively combined with opioids as part of a perioperative multimodal analgesic regimen, especially for opioid-tolerant patients [15,16].

NSAIDs and acetaminophen are commonly included in multimodal analgesic protocols, and the benefits of these medications in pain management have been well described [17-20]. In our practice, we administer acetaminophen with nonselective NSAIDs or celecoxib for postoperative pain in most patients without contraindications to the drugs. Acetaminophen and NSAIDs have different mechanisms of action, and most studies have found that the combination is more effective than either drug alone [21], though the benefits may be procedure specific, and may not apply to all surgeries [22]. A systematic review of randomized trials found that the combination of acetaminophen (paracetamol) with NSAID was more effective for postoperative pain after a variety of surgical procedures than

acetaminophen or NSAID alone in 85 percent and 64 percent of studies, respectively [21].

STRATEGY FOR PERIOPERATIVE PAIN CONTROL

General approach — We agree with the guiding principles established by a multidisciplinary perioperative pain summit, published in 2021 [23]. The summit consensus report makes recommendations for perioperative pain management including preoperative evaluation; multimodal/multidisciplinary pain management; assessment of pain and modification of pain management as necessary; patient and caregiver education on the treatment plan, goals of therapy, postoperative tapering of analgesics, storage and disposal of opioids; and consultation with pain specialists for patients with problematic pain control. These principles are shown in a table (table 1).

Effective postoperative pain control starts well before the day of surgery, and should be individualized. Having a multimodal approach does not necessarily mean doing the same thing for every patient, every time. Rather, a multimodal approach acts as a checklist to ensure that all applicable categories of pain medications are considered, selected, and dosed according to the individual patient's needs. A primary goal of perioperative pain management is to have the patient comfortable when he or she awakens from anesthesia, with a smooth transition from postanesthesia care to the surgical ward. The following questions should be considered when formulating a plan for perioperative pain control:

- **How much pain is associated with the surgical procedure, and how long is it expected to last?** – For example, some minor outpatient surgical procedures, such as excision of a small mass or limb surgery not involving bones or joints, are associated with lower levels of postoperative pain. For these cases, general anesthesia may be avoided by the use of regional blocks or surgeon-administered local anesthesia, along with monitored anesthesia care. When general anesthesia is indicated, a short-acting agent (eg, fentanyl) at the time of induction and airway management may be the only opioid administered during the anesthetic. Local anesthetic injected into the wound by the surgeon and nonopioid analgesics should suffice for immediate postoperative pain control. In contrast, more invasive procedures can result in moderate to severe pain that will last for days or weeks, such as total joint replacement, open major abdominal surgery, or instrumented spinal fusion.

These patients often require a more complex multimodal approach to perioperative pain control, with higher doses of intravenous (IV) opioids and longer-acting opioids. For surgeries amenable to epidural analgesia, the goal is to establish the appropriate analgesic level prior to emergence, at least 30 minutes before the end of surgery. (See 'Parenteral opioids' below and 'Epidural analgesia with local anesthetics and opioids' below.)

- **Is the procedure amenable to the use of regional or local analgesic techniques?** – Whenever possible, local anesthesia, neuraxial analgesia, or peripheral nerve blocks should be used as part of the multimodal regimen for postoperative pain control. In some cases, a regional analgesic or anesthetic technique will provide adequate pain control without additional systemic medication (eg, brachial plexus block for upper extremity surgery). In other cases, opioids or nonopioid analgesics will be required in addition to one of these modalities. As an example, transversus abdominis plane blocks or infiltration of the incision with local anesthetic may alleviate incisional pain for intraabdominal and abdominal wall surgery (eg, hernia repair) but will not help with visceral pain that results from these procedures. (See 'Peripheral nerve blocks' below and 'Regional analgesia' below.)

  The location of the surgery and anticipated sites of pain determine which nerve blocks should be performed, at which level(s) they should be performed, and whether they are even indicated. As an example, in a patient having upper abdominal surgery for whom epidural analgesia cannot be provided, other regional block techniques (eg, paravertebral or interfascial plane blocks) may provide some pain relief, although additional systemic analgesia using opioids and nonopioid medications will likely be required.

- **Are there particular patient factors that affect the choice of analgesic options?** – Specific regional analgesic techniques (eg, neuraxial blocks) are contraindicated in the setting of abnormal coagulation or platelet dysfunction and may be difficult to perform in patients with anatomic abnormalities such as obesity, ankylosing spondylitis, or prior spine surgery. Patients who chronically use opioids may require complex multimodal plans for perioperative pain control. Older patients and patients with obstructive sleep apnea (OSA) may be more prone to the side effects of sedatives and opioids, requiring either dose modification or avoidance of these medications.

Clinical scenarios — While individual patient characteristics, surgical procedures, and clinical scenarios vary widely, the following are examples of protocols for multimodal perioperative pain management followed at the author's institution. Remember that any multimodal analgesic protocol should serve as a checklist only, and should be modified to meet the needs of the individual patient, with careful consideration of existing staffing and institutional resources, medication formulary, and clinical environment.

- For the patient having minor outpatient surgery, when applicable, we use regional or local anesthesia designed to provide several hours or more of postoperative analgesia, combined with intraoperative monitored anesthesia care or general anesthesia. For patients who receive general anesthesia, we start with nonopioid systemic analgesics in the recovery room and restrict breakthrough, as-needed pain medications to short-acting opioid (eg, fentanyl) boluses only when necessary, or we administer prescribed oral opioids or acetaminophen/opioid combinations prior to discharge. (See 'Fentanyl' below and 'Oral opioids' below and 'Oral NSAIDs' below.)

- For patients having extremity surgery expected to produce moderate to severe postoperative pain, we regularly perform peripheral nerve blocks to provide several hours of postoperative pain relief (eg, brachial plexus block for upper extremity surgery) or insert a perineural catheter to provide two to three days of pain relief with a continuous local anesthetic infusion. (See "Overview of peripheral nerve blocks", section on 'Continuous catheter techniques'.)

- For a patient having minimally invasive abdominal (eg, laparoscopic) surgery or abdominal wall surgery (eg, inguinal herniorrhaphy) under general anesthesia, we employ interfascial plane blocks such as transversus abdominis plane blocks either preoperatively or prior to emergence, in addition to administering systemic opioid and nonopioid analgesics. (See "Abdominal nerve block techniques", section on 'Transversus abdominis plane (TAP) blocks'.)

  Our protocol consists of the following:

  - Transversus abdominis plane blocks with 0.2% ropivacaine 20 mL per side preoperatively or prior to emergence

  -

Fentanyl 100 to 250 mcg IV during induction of anesthesia and throughout the intraoperative period

- Acetaminophen 1000 mg IV postinduction (omit if liver dysfunction)
- Ketorolac 30 mg IV prior to emergence once hemostasis is achieved (omit if kidney dysfunction, enteric anastomosis, or history of gastric bleeding)
- For patients who are admitted postoperatively, we prescribe the following:
  - Scheduled acetaminophen 1000 mg orally every six hours (or IV if strictly nothing by mouth [NPO])
  - If no contraindications to nonsteroidal antiinflammatory drugs (NSAIDs), scheduled enteric-coated diclofenac 50 mg or celecoxib 200 mg orally twice a day with meals (or ketorolac 15 mg IV every six hours if strictly NPO) for two days, then change to as-needed
  - Oxycodone 5 to 10 mg orally every four hours as needed for breakthrough pain
  - Hydromorphone 0.2 to 0.5 mg IV every four hours as needed for severe breakthrough pain not responsive to oral medications

- For the patient having total knee replacement, we insert a catheter for continuous peripheral nerve block and administer a perineural local anesthetic infusion, in addition to systemic opioid and nonopioid pain medications in the perioperative period. We prefer to perform spinal anesthesia for the surgery, or general anesthesia in cases when spinal anesthesia is contraindicated or refused by the patient. Our protocol consists of the following:
  - Continuous adductor canal block with perineural catheter insertion performed preoperatively and initially dosed with 1.5% mepivacaine 10 to 20 mL for rapid onset (see "Adductor canal block procedure guide", section on 'Continuous adductor canal block')
  - Gabapentin 300 to 600 mg orally one time preoperatively for patients already on it, on chronic opioids, or with a comorbid chronic pain condition (see 'Gabapentinoids' below)
  - Acetaminophen 1000 mg and celecoxib 400 mg orally preoperatively [24]

- Spinal anesthesia with 0.75% bupivacaine with or without 10 to 20 mcg intrathecal fentanyl (see 'Intrathecal opioid' below)
- Surgeon-administered local anesthesia infiltration with a mixture of 150 mL 0.2% ropivacaine with epinephrine 2.5 mcg/mL, and ketorolac 30 mg IV just prior to skin closure (see 'Nonsteroidal antiinflammatory drugs' below)
- Postoperatively, we prescribe the following:
  - Perineural infusion of 0.2% ropivacaine 6 mL/hour basal rate with 5-mL patient-controlled bolus (30 min lockout interval)
  - Scheduled oxycodone 5 to 10 mg and acetaminophen 1000 mg orally every six hours
  - Scheduled celecoxib 200 mg orally twice a day for two days, then change to as-needed
  - Oxycodone 5 to 10 mg orally every four hours as needed for breakthrough pain
  - Hydromorphone 0.2 to 0.5 mg IV every four hours as needed for severe breakthrough pain not responsive to oral medications

  For patients who undergo joint replacement, we do not routinely prescribe IV opioid patient-controlled analgesia (PCA). (See 'Patient-controlled analgesia' below.)

- For the patient having major open abdominal or thoracic surgery, we use continuous epidural analgesia unless contraindicated or refused by the patient. There are a variety of effective multimodal regimens for managing analgesia in this situation. Our protocol consists of the following:
  - A thoracic epidural catheter is placed preoperatively at the vertebral level expected to be the central dermatome of the planned surgical site. A test dose is given through the catheter using 3 mL of lidocaine 1.5% with epinephrine 5 mcg/mL to confirm bilateral decreased cold temperature sensation and lack of intravascular or intrathecal spread.
  - Acetaminophen 1000 mg IV is administered after induction of general anesthesia and prior to incision.

- Fentanyl 100 to 150 mcg IV is administered with induction of general anesthesia and bolused intermittently as needed during surgery.
- If the epidural catheter is dosed during surgery (depending on the likelihood of bleeding, hypotension, and other hemodynamic shifts), the following regimen may be used: bolus lidocaine 2% or bupivacaine 0.25% in 2 mL increments up to 10 mL via the epidural catheter followed by a continuous infusion of lidocaine 2% or bupivacaine 0.25% at 4 to 10 mL per hour. (See 'Epidural analgesia with local anesthetics and opioids' below.)
- If the epidural catheter is not dosed during surgery, we activate it at least 30 minutes before the end of surgery with a continuous infusion of bupivacaine 0.125% at 4 to 10 mL/hour.
- Postoperatively, we continue the epidural infusion of bupivacaine 0.125% at 4 to 10 mL/hour and add a separate epidural infusion of hydromorphone 0.1 to 0.2 mg/hour. At many institutions, the local anesthetic and opioid are compounded into one solution; however, the separate infusion of local anesthetic allows for individual titration in case of hypotension without compromising the analgesia provided separately by the epidural opioid.

If epidural analgesia is not possible, we initiate the minimally-invasive abdominal surgery protocol described above, incorporating interfascial plane blocks such as transversus abdominis plane blocks combined with systemic opioid and nonopioid analgesics on a set schedule and as needed. For patients who will be strictly NPO for a longer period of time, we have a low threshold to start an opioid IV PCA with morphine or hydromorphone. (See 'Epidural analgesia with local anesthetics and opioids' below and 'Peripheral nerve blocks' below and 'Patient-controlled analgesia' below.)

When programming the PCA infusion device, we recommend no basal rate, with a starting bolus dose of morphine 1 mg (or hydromorphone 0.2 mg) and lockout interval of 10 minutes (table 2).

- For the patient having very painful surgery not amenable to regional analgesia (eg, spine fusion), we use a multimodal perioperative protocol that consists of the following:
  -

Gabapentin 300 to 600 mg orally one time preoperatively for patients already on it, on chronic opioids, or with a comorbid chronic pain condition

- Usual outpatient dose of oral long-acting opioid the morning of surgery, if applicable, or administer the dose orally preoperatively
- Fentanyl 100 to 250 mcg IV with induction of anesthesia to provide analgesia for airway management and bolused intermittently as needed during surgery
- Acetaminophen 1000 mg orally preoperatively and dexamethasone 8 mg IV postinduction
- Ketamine 0.5 mg/kg IV with induction of anesthesia, followed by infusion at 0.25 mg/kg/hour IV, as part of a preventive analgesic regimen, discontinued 60 minutes prior to the end of surgery to avoid prolonged emergence from anesthesia (see 'Ketamine' below)
- Hydromorphone or morphine IV throughout surgery as intermittent boluses in response to physiological stimuli, or continuous fentanyl or sufentanil IV infusion as an alternative, aiming for adequate analgesia at the time of emergence
- Surgeon-administered local anesthesia wound infiltration with 0.25% bupivacaine
- Postoperatively, we prescribe the following:
  - Continue usual outpatient dose and schedule for long-acting opioid PO, if applicable
  - Continue usual dose outpatient dose and schedule for gabapentin, if applicable, or start gabapentin 300 mg orally at bedtime, titrate up the daily dose by 300 mg every three days to a goal of at least 1800 mg/day
  - Scheduled oxycodone 5 to 10 mg and acetaminophen 1000 mg orally every six hours
  - Cyclobenzaprine 5 mg orally every eight hours as needed for muscle spasms, or continue the usual outpatient medication for this indication, if applicable

- Oxycodone 5 to 10 mg orally every four hours as needed for breakthrough pain
- Hydromorphone 0.2 to 0.5 mg IV every three hours as needed for severe breakthrough pain not responsive to oral medications

- If a patient continues to report moderate to severe pain despite the protocol, consider replacing the as-needed opioids with IV opioid PCA as described above, with bolus-only with no basal rate (table 2).

THERAPEUTIC OPTIONS

Parenteral analgesics — Opioids are the most widely used treatment of postoperative pain but should be used with caution. Morphine is the prototype opioid and the drug with which other analgesics are compared. An optimal strategy for multimodal analgesia entails maximizing the use of nonopioid analgesics to reduce the patient's exposure to opioids.

Parenteral opioids — Opioids provide swift and potent analgesia when administered parenterally. These medications can be given by intravenous (IV), intramuscular (IM), subcutaneous, transdermal, and transmucosal routes. Doses, routes of administration, and duration of action of commonly used opioids are shown in the table (table 3).

Bolus IV injections are often used for moderate pain, with doses titrated to analgesic requirements and the avoidance of respiratory depression and hemodynamic instability. Opioids given by intermittent injection generally do not maintain steady analgesic plasma levels.

Continuous IV infusions of opioids may be used for moderate to severe pain that is poorly controlled with repeated bolus injections, or for analgesia in mechanically-ventilated patients. Opioids should **only** be administered by continuous infusion in a monitored setting (eg, intensive care unit [ICU]) with pulse oximetry and end-tidal carbon dioxide monitoring capabilities (table 4). (See "Pain control in the critically ill adult patient", section on 'Opioid analgesics'.)

Patient-controlled analgesia (PCA) is useful in conscious patients who can cooperate with and understand instructions for use of the PCA pump. This

technique allows self-dosing with opioids up to a predetermined limit ("lockout" interval) set by the clinician. (See 'Patient-controlled analgesia' below.)

The most commonly used IV opioids for treatment of postoperative pain are morphine, hydromorphone, and fentanyl [25-28].

Morphine — Morphine is the prototypical opioid and remains widely used. The onset of analgesia is rapid, with the peak effect occurring within 20 minutes (when administered IV) [29] and an elimination half-life of two to three hours, though its analgesic duration of action is four to five hours. Dosing for acute pain is as follows:

- IV – 1 to 3 mg every five minutes until pain relief or if associated sedation, oxygen saturation <95 percent, or serious event occurs, such as hypotension.

  After initial pain control, 1 to 3 mg IV every 3 to 4 hours as needed

- IM – 5 to 10 mg every three to four hours as needed, though use of IM injections is no longer recommended, especially for repeat administration because of painful administration, variable absorption, and lag time to peak effect

- Subcutaneous – Infrequently used (eg, palliative care) but not recommended, as repeated subcutaneous administration causes local tissue irritation, pain, and induration

Hydromorphone — Hydromorphone (Dilaudid) is a semisynthetic opioid agonist that has a slightly more rapid onset of analgesia compared with morphine, with peak effect in as little as 10 minutes when given IV [30] and a shorter half-life (2.4 hours) than morphine. Potency of hydromorphone is approximately four to six times that of morphine. Dosing for acute pain is as follows:

- IV – 0.2 to 0.5 mg every five minutes until pain relief or if associated sedation, oxygen saturation <95 percent, or serious event occurs, such as hypotension.

  After initial pain control, 0.2 to 0.5 mg IV every three to four hours as needed

- IM – not recommended for use; variable absorption and lag time to peak effect

Fentanyl — Fentanyl is a synthetic derivative of morphine that is approximately 100 times more potent. It is also more lipid-soluble than morphine.

This results in a more rapid onset of action (two minutes), due to improved penetration of the blood–brain barrier, and a shorter time to peak effect (four minutes) [30,31]. Time to peak effect for IV fentanyl is three to five minutes, and elimination half-life is two to four hours. Fentanyl does not release histamine and may therefore be preferred in the presence of hemodynamic instability or bronchospasm. Dosing for acute postoperative pain in the recovery room is as follows:

- IV – 25 to 50 mcg every five minutes up to a maximum dose prescribed by the clinician for moderate pain after outpatient surgery; 50 to 100 mcg every two to five minutes until pain relief for moderate to severe pain, after which clinician should consider the overall pain control regimen

In the ICU, fentanyl is commonly administered as a continuous IV infusion to provide analgesia in mechanically-ventilated patients. Administration of fentanyl for more than five days may be associated with deposition of the drug in adipose tissue and prolonged sedation.

The use of high-dose fentanyl infusions (10 mcg/kg/hour) has been linked to the development of opioid-induced hyperalgesia in volunteers [32]. In addition, the intraoperative administration of high-dose fentanyl has been associated with the development of acute tolerance [33].

Sufentanil, alfentanil, remifentanil — Sufentanil and alfentanil are derivatives of fentanyl. Sufentanil is 10 times more potent than fentanyl, whereas alfentanil has about one-tenth to one-fifth the potency of fentanyl. Due to their rapid onset of action (within two to three minutes) and short elimination half-lives (approximately 90 minutes), these agents are nearly always used as adjuncts to anesthesia and for immediate analgesia in the operating room. Sufentanil appears to cause less hemodynamic instability, respiratory depression, and chest-wall rigidity than fentanyl or alfentanil.

Remifentanil, another derivative of fentanyl, is an ultrashort-acting agent with a context-sensitive half-life of four minutes, even after many hours of infusion. It is hydrolyzed by nonspecific tissue and plasma esterases so rapidly that it is rarely used outside the operating room. Remifentanil is associated with the development of opioid-induced hyperalgesia.

Meperidine — Meperidine is used only for the short-term management of acute pain. It is contraindicated for patients receiving monoamine oxidase

inhibitors. Meperidine lowers seizure threshold and may have a dysphoric effect, and therefore is not recommended for repeated dosing when compared with other available drugs [34]. Meperidine has a slower rate of metabolism in the elderly and in patients with hepatic and renal impairment. This can lead to accumulation of meperidine and its active metabolite normeperidine, which can cause seizures. Meperidine is not used for PCA because of the risk of accumulation of normeperidine with prolonged administration.

Oliceridine — Oliceridine is an intravenous opioid indicated for short term inpatient use that was FDA approved and available in the United States in 2020. Oliceridine is a G protein-selective mu opioid receptor agonist, with reduced signaling of the beta-arrestin pathway [35]. The maximum recommended daily dose is 27 mg, and the safety profile is reportedly similar to other opioids. It has a black boxed warning about addiction, abuse and misuse; life-threatening respiratory depression; neonatal opioid withdrawal syndrome; and risks when combined with benzodiazepines or other central nervous system depressants. Published evidence on oliceridine is limited [36,37], and its role in postoperative pain management has not been established.

Side effects of opioids — All opioids share common side effects. These include somnolence, depression of brainstem control of respiratory drive, urinary retention, and nausea and vomiting due to direct stimulation of the chemoreceptor trigger zone. Histamine release often follows morphine administration and may produce flushing, tachycardia, hypotension, pruritus, and bronchospasm. Gastrointestinal transit slows with prolonged administration, resulting in constipation and ileus in many patients; this effect is thought to reflect binding to local opioid receptors in the gut. Methylnaltrexone, an opioid antagonist that does not cross the blood–brain barrier, may diminish the peripherally mediated side effects of opioids while maintaining central analgesic effects. (See "Pain control in the critically ill adult patient", section on 'Opioid analgesics'.)

Patient-controlled analgesia — Opioid (IV) PCA is one method for administering IV opioids for moderate to severe postoperative pain, especially among patients who cannot take oral medications. The benefits include decreased delay in patient access to pain medication, decreased likelihood of overdose by programming small bolus doses with a fixed lockout interval and proper monitoring, and titratability (table 2). The use of a continuous background infusion for PCA is **not**

recommended, and should be limited to carefully selected patients who are opioid tolerant and/or receiving care in a critical care unit.

Any opioid can be administered via PCA; the opioids most commonly administered via PCA are morphine, hydromorphone, and fentanyl. Meperidine is not administered by infusion or PCA. (See 'Meperidine' above.)

A systematic review of randomized trials comparing PCA versus conventional administration of opioids evaluated 55 trials [38]. Compared with conventional parenteral analgesia, PCA use was associated with higher opioid consumption and more pruritus but provided better pain control and resulted in greater patient satisfaction. There is insufficient evidence to draw definitive conclusions about the other advantages and disadvantages of these two methods of pain relief. The incidence of other side effects was similar between the groups, with no differences observed in the length of hospital stay. The choice depends on the individual patient, type of surgery and anticipated postoperative pain experience, use of a multimodal analgesic regimen, and expected period of postoperative fasting.

A fentanyl PCA may be used for patients with allergy or intolerance to morphine and hydromorphone, but is less desirable in most patients because of its short duration of action. Fentanyl is preferred in patients with renal and hepatic insufficiency. Alternatively, hydromorphone may be used in patients with renal insufficiency [39,40].

The pump can be discontinued when the patient is able to tolerate oral analgesics or sooner if a nurse-administered bolus will suffice as pain levels diminish.

Nonopioid adjunctive medication — Several classes of medications are used as part of a multimodal approach to analgesia. The aim is to achieve superior pain control while reducing the dose and side effects of each particular class of drug (table 5).

Nonsteroidal antiinflammatory drugs — Administration of nonsteroidal antiinflammatory drugs (NSAIDs) can reduce the dose of opioid required and occurrence of opioid-related side effects [41]. In a meta-analysis of 52 randomized trials of multimodal analgesia with nonopioid analgesics, treatment with NSAIDs reduced opioid consumption, pain intensity, nausea and vomiting, and sedation compared with morphine alone [19]. NSAIDs may be part of a multimodal analgesic regimen as adjuncts to other modalities, such as regional analgesia.

- **Nonselective NSAIDs** – Ketorolac, ibuprofen, and diclofenac (outside the US) are the nonselective NSAIDs available for IV use. This class of medications may be used for preventive analgesia. (See 'Preventive analgesia' above and 'Oral NSAIDs' below.)

  Administration of ketorolac reduces opioid consumption by 25 to 45 percent and thereby lowers opioid-related side effects such as ileus, nausea, and vomiting [42-48]. The usual dose of ketorolac is 15 to 30 mg IV over 15 seconds. The usual dose of ibuprofen is 400 to 800 mg IV in 100 mL IV fluid over 30 minutes. NSAID administration in the operating room should be delayed until hemostasis has been achieved, if applicable.

  The effects of NSAIDs on bone healing and anastomotic leak after colorectal surgery are controversial. These issues, and other effects of NSAIDs, are discussed in more detail separately. (See "NSAIDs: Therapeutic use and variability of response in adults" and "Nonselective NSAIDs: Overview of adverse effects" and "Management of anastomotic complications of colorectal surgery", section on 'Controversial, inconclusive, or negative'.)

- **COX-2 inhibitors** – COX-2 inhibitors are NSAIDs that act on the second of two isoforms of the cyclooxygenase enzyme. Single doses of COX-2 inhibitors may be used to decrease postoperative opioid dose requirements. There are no approved IV preparations of pure COX-2 inhibitors in the United States, while parecoxib is used elsewhere. In 2020 the US Food and Drug Administration (FDA) approved an IV formulation of meloxicam, which preferentially inhibits COX-2 at low doses. However, at the doses recommended for acute pain, there is greater effect on COX-1, and when used clinically, meloxicam has effects and toxicities similar to other nonselective NSAIDs. (See "Overview of COX-2 selective NSAIDs", section on 'Meloxicam and etodolac'.)

Ketamine — Ketamine is a noncompetitive, reversible inhibitor of the N-methyl-D-aspartate (NMDA) receptor, and also acts at mu opioid receptors, monoaminergic receptors, gamma aminobutyric acid receptors, and others [49]. It may be used in subanesthetic doses in the perioperative period, generally for patients whose pain may be difficult to manage with opioids alone, either due to a very painful surgical procedure, or due to opioid tolerance or dependence. As an example, low dose perioperative ketamine has been shown to decrease opioid requirements in opioid tolerant patients who undergo spine surgery [50,51] (see "Anesthesia for elective spine surgery in adults", section on 'Analgesia for major

spine surgery'). Ketamine may also be useful for patients who are at increased risk of opioid-related respiratory depression (eg, patients with obstructive sleep apnea [OSA]) (see "Postoperative management of adults with obstructive sleep apnea", section on 'Pain control'). The clinical use of ketamine is limited by its potential to cause hallucinations and a dissociative mental state.

Ketamine is increasingly used as part of multimodal postoperative analgesia regimens, particularly because of its potential to reduce opioid consumption. Although the science that supports the potential benefits of ketamine is compelling, the evidence for the best use of ketamine, alone or in combination, is evolving but inconclusive. In 2018, consensus guidelines on the use of intravenous ketamine for acute pain were published from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists [52]. These guidelines are based on consensus of experts and offer reasonable guidance, with the proviso that this is an area of great interest and emerging experience. We administer intraoperative ketamine for patients who undergo very painful surgery not amenable to regional anesthesia techniques, as part of a multimodal pain control strategy. (See 'Clinical scenarios' above.)

- **Intraoperative** ketamine – Ketamine therapy for perioperative pain management is commonly initiated intraoperatively with a bolus dose of 0.3 to 0.5 mg/kg IV followed by an infusion of 0.1 to 0.5 mg/kg/hour [52,53]. The infusion should be discontinued 60 minutes prior to the end of surgery to prevent prolonged emergence from anesthesia.

  In a 2011 systematic review and meta-analysis of trials of perioperative IV ketamine, there was a reduction in total opioid consumption and an increase in the time to first analgesic [54]. Patients having the most painful surgical procedures, including thoracic, upper abdominal, and major orthopedic operations, had improvement in pain scores despite a decrease in opioid consumption. Ketamine was not effective for patients having surgery associated with mild pain, such as tonsillectomy, dental, or head and neck surgery.

  In another meta-analysis of randomized trials including patients who underwent spine surgery, supplemental ketamine reduced morphine consumption and pain scores during the first 24 postoperative hours, without an increase in adverse events [55].

- **Postoperative** ketamine – The benefit of adding ketamine to PCA with opioids is less established. A meta-analysis of randomized trials comparing ketamine plus morphine or hydromorphone PCA versus morphine or hydromorphone PCA included 37 trials with 2500 patients who underwent a variety of surgical procedures [56]. Addition of ketamine to PCA (by either a separate infusion or added to the opioid PCA solution) resulted in a small decrease in postoperative pain at rest at 6 to 72 hours (<1 cm pain reduction on a 10-cm visual analog scale), lower cumulative postoperative opioid consumption (5 mg at 24 hours, 20 mg at 72 hours), and less postoperative nausea and vomiting (PONV; RR 0.71). There were no differences in adverse events, including hallucinations, dysphoria, or vivid dreams, though adverse events may have been underreported.

  The optimal dose range for postoperative ketamine infusion has not been determined.

Limited evidence suggests that intranasal and oral ketamine may be effective for treatment of acute pain in selected patients (eg, children, patients with difficult IV access) [57].

There may also be a role for ketamine in the prevention and treatment of postoperative chronic pain syndromes, but the effective timing and dosing regimen has not been established [58,59]. (See 'Persistent postsurgical pain' below.)

Lidocaine — IV lidocaine can be administered by infusion intraoperatively and/or postoperatively for the management of pain. We use IV lidocaine for some patients as part of a multimodal pain strategy when regional anesthesia techniques are not possible. Whenever IV lidocaine is administered, the possibility of local anesthetic systemic toxicity should be considered. (See "Local anesthetic systemic toxicity".)

An international consensus statement on the intraoperative use of IV lidocaine made several recommendations, including the following, while recognizing that the optimal doses for lidocaine have not been established [60]:

- Dosing for IV lidocaine should be based on ideal body weight.
- Initial bolus should be ≤1.5 mg/kg IV, followed by continuous infusion at ≤1.5 mg/kg/hour IV.
-

The infusion may be initiated intraoperatively and may be continued postoperatively in a monitored setting for up to 24 hours, depending on local protocol.

- Administration of IV lidocaine should be delayed for at least four hours after the patient has received a regional anesthetic or local anesthetic infiltration.
- A regional anesthesia procedure should be delayed at least four hours after discontinuing an IV lidocaine infusion.

Although there has be a long history of using IV lidocaine in acute and chronic pain settings, the literature on the beneficial effects of perioperative IV lidocaine is inconclusive, both overall and for specific types of surgery.

- A 2018 meta-analysis of 68 randomized trials that compared IV lidocaine with either placebo or epidural analgesia after various surgical procedures found unclear evidence of beneficial effects of lidocaine on gastrointestinal recovery, postoperative nausea, opioid consumption, or postoperative pain [61]. The overall quality of the evidence for most outcomes was very low. In contrast with a previous meta-analysis by the same group of authors [62], there were no differences in outcomes for particular types of surgery.

- Some small single institution randomized trials have reported opioid-sparing benefits and improved pain scores after IV lidocaine for specific types of surgery (eg, laparoscopic inguinal hernia repair) [63].

- A 2020 meta-analysis of 10 randomized trials (508 patients) of patients who underwent colorectal surgery, IV lidocaine resulted in statistically significant but clinically irrelevant reductions in pain scores, time to defecation, and length of stay [64]. Postoperative morphine consumption was similar between groups.

The side effects of IV lidocaine are discussed in detail elsewhere. (See "Major side effects of class I antiarrhythmic drugs".)

Magnesium — Magnesium is an antagonist of the NMDA receptor. IV magnesium has been found to be an effective adjuvant for reduction of opioid requirement. It may be useful in opioid-tolerant patients or when there are medical concerns related to opioid dose.

Two meta-analyses of trials evaluated intraoperative IV magnesium sulfate compared with placebo or no treatment in over 1200 patients. Perioperative IV

magnesium reduced opioid consumption and pain scores in the first 24 hours postoperatively, without serious adverse effects [65,66]. In one of the analyses, 24-hour morphine consumption decreased by 24.4 percent (7.6 mg [95% CI 5.8-9.5 mg]); pain scores at 24 hours after surgery were reduced on a 100-point scale by 4.2 (95% CI 2.1-6.3) at rest and 9.2 (95% CI 2.3-16.1) on movement [65]. Both bolus and continuous infusion regimens were effective. Total perioperative doses ranged from 1.03 to 23.5 g, without correlation between dose and reduction in morphine consumption. The optimal regimen has not been determined.

Magnesium may provide benefit when used in patients who are also receiving ketamine. In a trial of 50 patients having scoliosis surgery, the addition of IV magnesium to an intraoperative ketamine regimen decreased postoperative morphine consumption by 30 percent, with improved sleep and satisfaction scores, but no change in pain scores [67].

We do not routinely use magnesium as part of a perioperative pain control regimen.

Dexamethasone — Dexamethasone is effective for prevention of PONV, and may also reduce postoperative pain. Lower doses of dexamethasone may be required for PONV prophylaxis (ie, 4 to 5 mg IV) than for postoperative pain (>0.1 mg/kg IV). (See "Postoperative nausea and vomiting", section on 'Glucocorticoids'.)

The beneficial effects of dexamethasone for postoperative pain are unclear and likely apply to specific types of procedures. In a 2011 meta-analysis of 24 randomized trials including approximately 2750 patients and multiple surgical procedures, dexamethasone >0.1 mg/kg IV, but not lower doses, resulted in a small reduction in postoperative pain and opioid consumption [68]. Similarly, in a 2019 meta-analysis of six studies of patients who underwent various types of surgery (eg, abdominal, pelvic, lower extremity) under spinal anesthesia, perioperative dexamethasone reduced 24 hour morphine consumption by a significant but possibly clinically irrelevant amount (4 mg, 95% CI 3-5 mg) [69].

Data on the safety of prophylactic dexamethasone are inconclusive, and the use of dexamethasone should be individualized. There may be benefits in specific surgical populations such as in spine surgery [70,71]. However, risks of perioperative corticosteroids may include impaired healing, hyperglycemia, and immunocompromise which prevent their routine incorporation into perioperative analgesic care. These issues are discussed separately. (See "Postoperative nausea

and vomiting", section on 'Glucocorticoids' and "Anesthesia for tonsillectomy with or without adenoidectomy in children", section on 'Dexamethasone'.)

Intravenous acetaminophen — IV acetaminophen may be used in patients in whom oral or rectal administration is not an option. IV acetaminophen has a more rapid and predictable onset of effect (5 to 10 minutes) and time to peak concentration (15 minutes) in most patients compared with rectal or oral administration (onset 10 to 60 minutes or more) and may have short-term advantages over the oral formulation for preventive analgesia during total joint arthroplasty [72], although this benefit may be mitigated by the use of spinal anesthesia [73].

When oral administration is an option and multimodal analgesia employed, IV and oral routes of administration of acetaminophen are similarly effective for treatment of postoperative pain [74-82]. A meta-analysis of randomized trials found that the addition of acetaminophen (IV or oral) to morphine following major surgery resulted in a small, but statistically-significant, decrease in morphine use postoperatively [41].

The addition of acetaminophen to nonsteroidal antiinflammatory drugs (NSAIDs) within a multimodal regimen can improve pain control and reduce postoperative morphine consumption [83]. A systematic review comparing the use of NSAIDs alone or in combination with acetaminophen for postoperative pain showed that the combination was more effective than NSAIDs alone in 64 percent of the studies [21]. The benefits of combining acetaminophen and NSAIDs, versus NSAID alone, may be procedure specific [22].

The available IV preparation is significantly more expensive than oral acetaminophen. However, the use of IV acetaminophen may provide benefits that offset the additional cost. In one large database study of 61,017 patients who underwent cholecystectomy, administration of IV acetaminophen was associated with shorter length of hospital stay and lower hospital costs, compared with oral acetaminophen [84].

The usual dose of IV acetaminophen for patients over 50 kg is 650 mg every four hours or 1000 mg every six hours, not to exceed 4 g per day. A reduced dose of acetaminophen should be used for low-weight adults and adolescents (body weight ≤50 kg) and in patients with mild or moderate hepatic insufficiency, chronic alcoholism, malnutrition, or dehydration. Patients with severe renal insufficiency

(creatinine clearance ≤30 mL/min) may receive the usual dose, but not more often than once every six hours. Acetaminophen is contraindicated in patients with severe hepatic insufficiency or severe progressive liver disease.

Regional analgesia — Neuraxial and other regional techniques may be effective treatments for postoperative pain and may provide superior pain control when compared with systemic opioids, while avoiding some of the side effects of systemic opioid administration [43]. For example, as part of an enhanced recovery protocol, epidural analgesia may facilitate early return of bowel function [85] and improve pain control [86], but its effect on length of stay and other outcomes is less consistent [85,86]. A meta-analysis of analgesia after intraabdominal surgery found that continuous epidural opioid analgesia significantly improved control of postoperative pain compared with opioid PCA, though it was associated with a higher incidence of pruritus [87].

Neuraxial opioid — Intraoperative administration of epidural or intrathecal opioid reduces the need for systemic opioid postoperatively [88-100]. For major abdominal surgeries with extensive incisions, epidural infusions with local anesthetic provide superior pain relief when compared with parenteral opioids. With less extensive surgery, however, intrathecal opioids alone can be used for postoperative analgesia. A single dose of intrathecal (spinal) opioid can provide substantial pain relief up to 18 to 24 hours postoperatively. Neuraxial analgesia is also suitable for those patients who are chronically dependent on opioids.

Intrathecal opioid — Small intrathecal doses of preservative-free morphine (0.1 to 0.2 mg) or fentanyl (10 to 20 mcg) are commonly coadministered with local anesthetic as part of a spinal anesthetic. Preservative-free hydromorphone (75 to 150 mcg) may be used as an alternative to morphine [101]. The onset of analgesia and its duration depend on the drug's relative lipophilicity or hydrophilicity and how it is transported within the cerebrospinal fluid (CSF). (See "Spinal anesthesia: Technique", section on 'Adjuvants'.)

Opioids administered intrathecally act principally on mu receptors in the substantia gelatinosa of the dorsal horn of the spinal cord by suppressing excitatory neuropeptide release from nerve fibers (type C). The degree of uptake from the CSF by the dorsal horn is determined primarily by the physicochemical properties of the drug and, in particular, lipid solubility. Lipid-soluble compounds enjoy greater direct diffusion into neural tissue as well as greater delivery to the dorsal horn by spinal segmental arteries.

Morphine is highly ionized and hydrophilic and does not penetrate lipid-rich tissues as well as fentanyl. Intrathecal morphine reaches maximum effect in about 45 minutes and lasts for 18 to 24 hours. By comparison, fentanyl, which is more lipophilic (lipid-soluble), penetrates into the lipid-rich dorsal horn to act more quickly, but its duration of action is shorter [102]. The lipophilicity of hydromorphone is midway between that of morphine and fentanyl. When used for labor analgesia, intrathecal fentanyl reaches maximal effect in 5 to 10 minutes and provides effective pain relief for one to two hours [103].

If a patient has severe breakthrough pain despite intrathecal morphine or hydromorphone administration, supplemental IV opioid may be administered as needed, with appropriate respiratory monitoring (oxygen saturation and end-tidal carbon dioxide preferred). Typically, fentanyl (50 to 100 mcg IV) or morphine (1 to 3 mg IV) will produce almost immediate pain relief. Once breakthrough pain is controlled, the intrathecal morphine that was administered often provides adequate analgesia. Rarely, IV PCA with fentanyl, morphine, or hydromorphone will be required for inadequate pain relief after intrathecal morphine. (See 'Patient-controlled analgesia' above.)

Epidural opioid — The dose of epidural morphine is about 5 to 10 times the dose used for intrathecal administration. A dose of 2 to 3 mg of epidural morphine is commonly used for lumbar and low thoracic epidurals; however, for less painful surgery or high-risk patients, lower doses can provide adequate analgesia with fewer side effects. For example, epidural morphine 1.5 mg was as effective as 3 mg for postcesarean delivery pain and was associated with a 60 percent reduction in pruritus [104].

Epidural analgesia with local anesthetics and opioids — A combination of a local anesthetic and opioid is commonly administered by infusion via an epidural catheter for postoperative pain, especially for abdominal and thoracic surgical procedures. This combination reduces the dose required and the frequency of side effects [105-107]. Commonly used combinations for postoperative analgesia include bupivacaine (0.125%) or ropivacaine (0.2%) plus fentanyl (2 mcg/mL) or hydromorphone (20 mcg/mL) [108-113]. Sufentanil or morphine may also be used. A meta-analysis of five randomized trials compared the efficacy of epidural infusion with local anesthetic alone versus combined local anesthetic and opioid for patients undergoing laparotomy. The study concluded that combination therapy was

associated with a significant reduction in visual analog scale pain scores on the first postoperative day [114].

Epidural analgesia must be individualized to each patient's requirements. For abdominal surgery, the epidural catheter should be placed at a low thoracic or high lumbar level. For thoracic surgical procedures, the catheter should be placed at a midthoracic level. Epidural medications can be given by continuous infusion or may be given by patient-controlled epidural analgesia (PCEA). With PCEA, the patient has the ability to self-administer a bolus of epidural medication. The PCEA pump may be programmed with or without a basal infusion, a bolus dose, a lockout period before another bolus is possible, and a total allowable dose over a specific time period. For obstetric patients and surgical patients, bolus-only PCEA with local anesthetic and opioid may provide similar analgesia to continuous infusion while requiring significantly less volume of the compounded solution [115,116].

Protocols for epidural infusion depend on the drugs chosen and are institution-specific. An example is as follows:

- Epidural PCEA using bupivacaine 0.1% with hydromorphone 20 mcg/mL
- Initial rate for epidural infusion: 6 mL/hour, titrate within 4 to 12 mL/hour
- PCEA settings:
  - PCEA demand dose: 2 mL, range 2 to 4 mL
  - Lockout interval: 20 minutes
  - One hour maximum limit: 16 mL

Epidural infusions (basal with or without PCEA) are usually started in the operating room prior to completion of surgery to achieve targeted pain control at the conclusion of surgery. Postoperatively, additional incremental boluses of local anesthetic (eg, 2 to 10 mL of bupivacaine 0.125% or lidocaine 1 to 2%) may be administered by the anesthesiologist if the patient is experiencing breakthrough pain upon emergence from anesthesia. When a bolus is given, the patient must be monitored closely for hypotension. Once analgesia is achieved, the epidural infusion regimen is resumed. If the patient continues to experience breakthrough pain, the regimen should be adjusted to increase the basal rate, PCEA bolus volume, or both, with careful consideration of the maximum allowable hourly volume. Since epidural regimens vary by institution, every provider should refer to

his or her institutional policies and procedures governing epidural infusion management.

Occasionally, postoperative analgesia is not satisfactory due to extensive surgery or patchy coverage by the epidural block. If PCEA or continuous infusion of low-dose combined local anesthetic and opioid solution is inadequate, an alternative approach is to split the epidural infusion. With this technique, a continuous epidural infusion of local anesthetic is used, while the opioid is administered by IV PCA. The split approach may provide more effective pain control if an epidural block does not cover the entire surgical site or if the patient has other, nonsurgical pain.

Rarely, other adjuvants may be administered via epidural infusion in combination with local anesthetics: alpha$_2$ agonists (eg, clonidine), NMDA receptor antagonists (eg, ketamine), and cholinesterase inhibitors (eg, neostigmine). The use of adjuvants may be opioid-sparing and may improve postoperative analgesia for surgical patients while decreasing the incidence of opioid-related adverse effects [117-122].

Side effects and complications of neuraxial analgesia — Patients receiving neuraxial analgesia must be monitored carefully for side effects and potential complications, which can rarely be life-threatening. Systemic toxicity, hypotension, inadequate or failed block, pruritus, nausea and vomiting, and respiratory depression are all possible after administration of epidural or spinal local anesthetic and opioid. Some patient populations are at greater risk for respiratory depression, including the elderly, patients with obesity or OSA, and those receiving opioid or sedative medication by another route. These issues are discussed in more detail separately. (See "Adverse effects of neuraxial analgesia and anesthesia for obstetrics".)

Delayed respiratory depression — Delayed respiratory depression due to rostral spread of opioids to the respiratory center in the medulla is possible with epidural or intrathecal administration of opioids. Respiratory depression may occur up to 18 hours after a hydrophilic agent, such as morphine, is injected. The incidence of delayed respiratory depression is approximately 0.1 percent at a dose of 0.2 mg morphine and occurs predominantly in obese patients [102].

Observational studies report that the overall incidence of respiratory depression in patients given single-injection neuraxial opioids is in the range of 0.01 to 3 percent.

A meta-analysis of randomized and observational trials comparing single-injection or continuous neuraxial opioids with parenteral (ie, IV, IM, or IV patient-controlled) opioids found no difference in the incidence of respiratory depression [123].

The combination of bolus-only IV PCA and intrathecal opioids does not necessarily increase the risk of respiratory depression over that with either modality alone [124-126]. However, a basal rate on the IV PCA is not recommended for the patient who has received neuraxial opioid.

Monitoring the patient who has received neuraxial analgesia — Patients who have received neuraxial analgesia must be monitored carefully for analgesic efficacy and for side effects and complications, which can rarely be life-threatening. The patient receiving an epidural opioid infusion should not have standing orders for systemic opioids because of the risk of respiratory depression. In addition to nursing protocols, all patients with postoperative epidural catheters in place should be examined by a clinician at least daily to assess the following:

- Vital signs
- Adequacy of pain relief and level of activity tolerated
- Degree of motor blockade
- Nausea and pruritus
- Signs suggestive of localized infection (ie, erythema, tenderness, swelling, discharge) at the site of epidural catheter placement
- Neurological changes suggestive of spinal hematoma [127] (see "Neuraxial anesthesia/analgesia techniques in the patient receiving anticoagulant or antiplatelet medication", section on 'Neurologic monitoring')

Hypotension is common after major abdominal surgery. A careful assessment of fluid balance and other potential causes of hypotension are warranted before implicating the epidural infusion as the source. Nausea, severe pruritus, or an unacceptable degree of motor block may warrant a change in the epidural infusion rate or medication. Management of neuraxial opioid-induced pruritus and complications of neuraxial anesthesia are discussed separately. (See "Adverse effects of neuraxial analgesia and anesthesia for obstetrics", section on 'Pruritus'.)

Nursing protocols for patients who have received intrathecal opioids and epidural infusions vary by institution but should include:

-

Scheduled monitoring of vital signs, level of sedation, motor function, and pain, with guidelines for notification of pain service clinician

- Maintenance of patent IV access
- Immediate availability of naloxone and ephedrine
- Avoidance of parenteral or oral opioids or sedatives without pain service clinician approval

We suggest the following protocol for respiratory monitoring for patients who have received neuraxial opioids:

- All patients receiving neuraxial opioid infusions should be monitored for adequacy of ventilation, including rate and depth of respiration, oxygenation (pulse oximetry if indicated), and level of sedation [128].
  - Monitor once per hour for the first 12 hours
  - Monitor once every two hours from 12 to 24 hours
  - Monitor at least every four hours after 24 hours if stable for the entire time the infusion is used
- For single neuraxial injection of hydrophilic opioid (eg, morphine), monitor as above for a minimum of 24 hours, longer as dictated by patient's medical condition and other medications. After epidural injection of sustained release morphine, monitor every four hours for a minimum of 48 hours.

Patients with conditions which place them at increased risk for respiratory depression (eg, obesity, OSA, extremes of age, concomitant administration of systemic sedatives or opioids) may require more intensive monitoring (eg, pulse oximetry, capnography). Obstetric patients seem to be at lower risk of respiratory depression than nonpregnant patients after neuraxial administration of hydrophilic opioids (ie, morphine or hydromorphone) [129]. Monitoring for respiratory depression after neuraxial opioids for cesarean delivery analgesia is discussed separately. (See "Anesthesia for cesarean delivery", section on 'Spinal drugs for CD'.)

Peripheral nerve blocks — Peripheral nerve blocks may be used to provide surgical anesthesia. They can also be used for postoperative pain relief by injecting a long-acting local anesthetic when performing the block or by inserting a catheter to allow continuous infusion of medication. Peripheral nerve blocks are typically

performed using ultrasound guidance to locate the nerve or by using a nerve stimulator, or both. For perineural infusions used for postoperative pain relief, low doses of a long-acting local anesthetic (eg, 0.2% ropivacaine) at rates of 4 to 10 mL/hour are commonly used [130-135].

Peripheral nerve blocks commonly used for postoperative pain include brachial plexus blocks for upper extremity pain and blocks of the sciatic or femoral nerves, or other branches of the lumbar plexus, including saphenous nerve block at the level of the adductor canal or below the knee, for lower extremity pain. (See "Upper extremity nerve blocks: Techniques" and "Lower extremity nerve blocks: Techniques".)

Intercostal nerve blocks can be used for postoperative analgesia after breast surgery, thoracotomy, video-assisted thoracoscopy, chest tube placement, and upper abdominal procedures [136,137]. (See "Thoracic nerve block techniques", section on 'Intercostal nerve block'.)

Paravertebral block can be used to provide analgesia at any spinal level, most commonly at the thoracic and upper lumbar spinal levels. Paravertebral nerve block can provide postoperative pain relief after breast, thoracic, or flank surgery [138-140]. (See "Thoracic nerve block techniques", section on 'Thoracic paravertebral block'.)

Interfascial plane blocks such as the transversus abdominis plane (TAP) block is used for postoperative analgesia for various abdominal procedures, including inguinal hernia repair, laparoscopic and open bowel resection, abdominal hysterectomy, cesarean delivery, and radical retropubic prostatectomy. Local anesthetic is injected under ultrasound guidance in the plane between the transversus abdominis and internal oblique muscles [141-144]. TAP blocks are used as part of enhanced recovery protocols for colorectal surgery, as part of multimodal pain control regimens designed to reduce the need for opioids [145-147]. (See "Abdominal nerve block techniques", section on 'Transversus abdominis plane (TAP) blocks'.)

Oral analgesics — A wide variety of oral pain medications are available for the treatment of acute pain both before and after surgery. Choices include acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), opioids, combination medications, alpha$_2$ agonists, and anticonvulsants (table 6). A goal

for perioperative administration of nonopioid analgesics is to reduce the overall dose of opioids.

Acetaminophen — Acetaminophen (325 to 1000 mg by mouth [PO] [or by rectum] every four to six hours, to a maximum dose of 4 g/day) can be used for mild pain or in combination with other medications for moderate to severe pain. When oral administration is possible and multimodal analgesia employed, this route is not inferior to intravenous administration of acetaminophen for postoperative pain treatment in most cases. (See 'Intravenous acetaminophen' above.)

Oral NSAIDs — Both nonselective nonsteroidal antiinflammatory drugs (NSAIDs) and those that act selectively on the COX-2 isoform of cyclooxygenase may be administered for perioperative pain control.

Nonselective NSAIDs — Oral nonsteroidal antiinflammatory drugs (NSAIDs) commonly used for postoperative pain include ibuprofen (400 mg every four to six hours), diclofenac (50 mg three times daily), and ketoprofen (50 mg twice daily). In one systematic review, the postoperative administration of oral NSAIDs was found to reduce morphine requirement by 10 mg in the first 24 hours [148]. If oral medication is not tolerated, rectal administration may be considered as an alternative route. Gastrointestinal side effects of NSAIDs are discussed separately. (See "NSAIDs (including aspirin): Pathogenesis of gastroduodenal toxicity" and "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity".)

Preoperative administration of oral NSAIDs prior to elective minor surgery has been shown to reduce postoperative pain [43,44,149-152]. (See 'Preventive analgesia' above.)

COX-2 inhibitors — In Cochrane reviews of placebo-controlled randomized trials of postoperative pain control, use of celecoxib (200 or 400 mg orally), etoricoxib (120 mg orally), or parecoxib (20 or 40 mg IV or IM) delays and decreases the need for rescue opioid analgesics, without significant side effects [153-155]. COX-2 inhibitors may be administered as a single preoperative dose or regularly scheduled doses postoperatively [156]. (See 'Preventive analgesia' above.)

In several trials, single-dose COX-2 inhibitors showed greater analgesic efficacy and tolerability than opioids but were similar to nonselective NSAIDs for postoperative pain management [44,48,157-159]. In the United States, COX-2 inhibitors carry a "black-box" warning related to cardiovascular risk, although this risk appears to be

associated with long-term use. (See "Overview of COX-2 selective NSAIDs" and "NSAIDs: Adverse cardiovascular effects".)

NSAIDs are discussed in more detail separately. (See "NSAIDs: Therapeutic use and variability of response in adults" and "Nonselective NSAIDs: Overview of adverse effects".)

Oral opioids — When the patient can tolerate oral medication, the opioid regimen for patients with moderate to severe pain can be changed from IV to oral opioid, including oxycodone, hydrocodone, hydromorphone, morphine, or combination medication. General opioid dosing guidelines are provided in the table (table 3).

Ideally, the dose should be calculated on the basis of 24-hour opioid consumption and appropriate conversion calculated (table 3). As an example, a patient taking 40 mg of IV morphine over 24 hours may be given 10 to 15 mg of oxycodone every four hours or 4 mg of hydromorphone every four hours. Opioids should be prescribed carefully, starting with the minimum dose needed to alleviate pain, and after maximizing nonopioid analgesic options.

Examples of oral opioid and combination dosing include:

- Codeine 15 to 60 mg orally every four to six hours
- Oxycodone 5 to 10 mg orally every four to six hours
- Hydromorphone 2 to 4 mg orally every four to six hours
- Combination therapies such as oxycodone-acetaminophen (combinations of 300 to 325 mg acetaminophen/2.5 to 10 mg oxycodone, one or two tablets orally every four to six hours), oxycodone-aspirin (325 mg aspirin/4.8 mg oxycodone, one or two tablets orally every four to six hours), acetaminophen-codeine (eg, Tylenol No. 3, which is 300 mg acetaminophen/30 mg codeine, one to two tablets orally every four to six hours)

Alpha-2 receptor agonists — The exact mechanism by which alpha$_2$ agonists (clonidine, dexmedetomidine) produce analgesia remains unknown; it is postulated that release of acetylcholine may play a role [160].

Alpha$_2$ agonists also reduce the undesirable physiological and psychological effects of opioid withdrawal [161]. Studies indicate that alpha$_2$ agonists such as clonidine and dexmedetomidine exert a potent analgesic response and that their potency is increased by concomitant opioid therapy [162,163].

Although not routinely used, preoperative oral clonidine 150 to 200 mcg has been shown to provide perioperative hemodynamic stability and reduce the requirement of postoperative opioid analgesics [164-166].

Gabapentinoids — We do not suggest routinely administering gabapentinoids (ie, gabapentin or pregabalin) for postoperative pain control, due to lack of consistent clinical efficacy and potential for harm (eg, sedation, dizziness, respiratory depression).

We consider gabapentin selectively, as part of multimodal pain control as follows:

- We continue gabapentinoids for patients who are already taking one of them.
- We administer gabapentin for patients chronically taking opioids before surgery; gabapentin may facilitate discontinuation of opioids after surgery. In a single institution randomized trial of approximately 400 patients who underwent various types of surgery, three days of perioperative gabapentin resulted in a modest increase in the rate of opioid cessation after surgery (hazard ratio 1.24, 95% CI 1.00-1.54) with similar pain scores between groups [167].
- We administer perioperative gabapentin for patients with chronic neuropathic pain conditions. (See "Pharmacologic management of chronic non-cancer pain in adults", section on 'Pharmacologic therapy for neuropathic pain'.)

In these situations, we typically administer 300 to 600 mg orally (lower dose in older adults) as a single preoperative dose. The optimal dose and number of doses of gabapentin have not been determined. Higher doses (up to 1200 mg orally as a single dose) or more prolonged therapy may be used and may be more effective, but may result in greater sedation [168]. Pregabalin can be used as an alternative to gabapentin, given as a single preoperative dose of 75 to 150 mg orally (lower dose in older patients).

- **Efficacy** — Gabapentin and pregabalin are effective in the management of chronic neuropathic pain, and have also been used in the acute setting. However, a 2020 meta-analysis of 281 randomized trials of 24,682 patients who underwent various types of surgery found that the use of gabapentin or pregabalin resulted in statistically significant but clinically unimportant differences in acute, subacute, or chronic postoperative pain and opioid use, compared with placebo [169]. The incidence of dizziness and visual

disturbance was increased with use of gabapentinoids; respiratory depression was not reported in most studies. The overall quality of the data was judged to be low.

- **Side Effects —** Gabapentinoids are associated with sedation, dizziness, postoperative cognitive dysfunction and delirium [170,171]. Respiratory depression has been reported in older patients and in those who receive gabapentin along with other analgesics [172-175]. Thus, gabapentinoids should be used cautiously when coadministered with opioids. In a database study of approximately 5.5 million surgical patients who received opioids on the day of surgery, 890,000 of whom received gabapentinoids as well, concomitant administration of gabapentinoid and opioid increased the risk of overdose and other respiratory complications, compared with administration of opioids alone, though the absolute risk of these complications was very low (eg, for overdose, 1.4 per 10,000 patients who received both gabapentinoid and opioid, compared with 0.7 per 10,000 who received opioid alone) [174]. The adjusted hazard ratio for a composite outcome of overdose, respiratory complications and unspecified adverse effects of opioids was 1.7 (95% CI 1.62 to 1.79).

In addition, there is potential for abuse of gabapentinoids [176,177].

SPECIAL POPULATIONS

Postoperative pain control may be particularly challenging in some categories of patients.

Morbid obesity — For morbidly obese surgical patients, we use postoperative regional analgesic techniques when possible and appropriate to minimize the use of opioids and sedatives, particularly in those with a history of obstructive sleep apnea (OSA). Patients with OSA are at increased risk of respiratory depression when opioids and sedatives are administered. For morbidly obese patients with OSA, it may be prudent to use local anesthetic (eg, bupivacaine 0.125%) without opioid for continuous epidural analgesia, although this decision depends on the individual patient, surgery, and epidural coverage.

Multimodal analgesia with nonopioid analgesics (eg, nonsteroidal antiinflammatory drugs [NSAIDs], acetaminophen) should be used for these patients even in the absence of epidural catheter placement [178-181]. In exceptional cases when a

morbidly obese patient has severe postoperative pain despite multimodal analgesia and cannot have epidural analgesia (eg, patients who are anticoagulated), bolus-only intravenous (IV) opioid patient-controlled analgesia (PCA) may be used. However, these patients must be closely monitored for analgesic effect and respiratory depression throughout the postoperative period. (See 'Patient-controlled analgesia' above and "Anesthesia for the patient with obesity", section on 'Sedative premedication'.)

Opioid-dependent patients — The opioid-dependent patient will require an individualized plan for postoperative pain control. Opioid requirement for these patients may be high and unpredictable because of opioid tolerance. When possible, a plan for postoperative pain management should be made in advance of surgery, including possible consultation with a pain management specialist.

A multimodal analgesic strategy should be employed with an emphasis on regional analgesic modalities whenever possible. Systemic nonopioid medications (eg, nonsteroidal antiinflammatory drugs [NSAIDs], acetaminophen, gabapentin or pregabalin, ketamine, lidocaine) should be used in combination with opioids. (See "Management of acute pain in the patient chronically using opioids for non-cancer pain", section on 'Nonopioid strategies for pain control'.)

Management of perioperative pain in patients who chronically take opioids for pain and for patients with opioid use disorder is discussed in detail separately. (See "Management of acute pain in the patient chronically using opioids for non-cancer pain" and "Management of acute pain in adults with opioid use disorder".)

Breastfeeding women — Most analgesics are safe for breastfeeding women. Codeine and tramadol should be avoided, and oxycodone and aspirin should be used with caution. Management of pain in breastfeeding women is discussed separately. (See "Overview of the postpartum period: Normal physiology and routine maternal care", section on 'Safety of common analgesics in breastfeeding women'.)

PERSISTENT POSTSURGICAL PAIN

Normally, incisional pain gradually resolves over a period of days to weeks. Increasing pain or pain that persists for months may be due to surgical factors (eg, local scar formation, infection, dehiscence/hernia, foreign body reaction, incisional neuroma) or to patient factors and conditions unrelated to the surgery (eg,

endometriosis, pelvic mass, malignancy, spinal radiculopathy). These patients should have a thorough history and physical examination with attention to the surgical site. (See "Complications of abdominal surgical incisions".)

Persistent pain may develop after surgery in 10 to 50 percent of patients, depending on the type of surgery. Severe chronic pain develops in 2 to 10 percent of these patients [182] and is most often neuropathic. Data suggest that most pharmacologic interventions at the time of surgery are not effective at prevention of chronic postoperative pain. A 2013 meta-analysis of 40 randomized controlled trials including various drugs used specifically for perioperative analgesia showed a small but statistically significant reduction in the development of chronic pain following treatment with ketamine only [58]. A 2017 meta-analysis of randomized trials that evaluated the effects of gabapentinoids on postoperative pain after breast cancer surgery found that gabapentin and pregabalin did not reduce the incidence of chronic postsurgical pain [183]. In contrast, a randomized trial in 130 cardiac surgery patients found that administration of pregabalin for 2 weeks postoperatively reduced the prevalence of persistent pain at 6 months, with or without intraoperative ketamine [184].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Acute pain management".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Managing pain after surgery (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Pain control regimens should be tailored to the needs of the individual patient, taking into account the patient's age, medical and physical condition, level of fear/anxiety, personal preferences, type of surgical procedure, and response. An optimal strategy for perioperative pain control consists of multimodal therapy to minimize the need for opioids. (See 'Introduction' above.)

- We suggest a multimodal approach to preventive analgesia with regional analgesic techniques and drugs such as nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, and gabapentinoids when indicated, before induction of general anesthesia (**Grade 2B**). (See 'Preventive analgesia' above.)

- Following ambulatory surgery, we suggest treatment of acute pain in the recovery room with nonopioid systemic analgesics, followed by short-acting intravenous (IV) opioids if needed, then NSAIDs, acetaminophen, and a short course of oral opioid if needed upon discharge (**Grade 2C**). (See 'Oral analgesics' above and 'Parenteral opioids' above.)

- Following minimally-invasive intraabdominal surgical procedures, when appropriate, we suggest regional analgesic techniques, such as local anesthetic wound infiltration, transversus abdominis plane blocks, or other interfascial plane blocks. For further analgesia when postoperative fasting is required, we suggest patient-controlled analgesia (PCA) or nurse-administered opioid boluses using IV opioids (**Grade 2C**) (see 'Patient-controlled analgesia' above). We suggest the addition of an NSAID and acetaminophen if not contraindicated (**Grade 2C**) (see 'Nonopioid adjunctive medication' above). Oral medication can be prescribed as tolerated. (See 'Oral analgesics' above.)

- For major open abdominal or thoracic surgery, and for the patient who is dependent on opioids, we suggest neuraxial analgesic techniques in addition to general anesthesia, using either continuous epidural analgesia or single-injection epidural or spinal opioid (**Grade 2C**). In addition to preventive analgesia, the neuraxial approach provides effective, targeted postoperative analgesia. (See 'Preventive analgesia' above and 'Neuraxial opioid' above.)

- For neuraxial analgesia, we administer morphine via the epidural (up to 3 mg morphine) or intrathecal (up to 0.2 mg morphine) route to provide postoperative pain relief for up to 18 to 24 hours; this can be supplemented with NSAIDs without increasing the risk of postoperative respiratory depression (see 'Preventive analgesia' above and 'Neuraxial opioid' above and 'Patient-controlled analgesia' above and 'Nonopioid adjunctive medication' above). If further analgesia is required, additional IV opioids by nurse-administered bolus or PCA can be used with appropriate monitoring. (See 'Monitoring the patient who has received neuraxial analgesia' above.)

- For those patients for whom pain relief is required for more than 24 hours, we suggest postoperative patient-controlled epidural analgesia (PCEA) with a lumbar or low thoracic epidural catheter placed preoperatively (**Grade 2B**) (see 'Epidural analgesia with local anesthetics and opioids' above). Patients who have received neuraxial opioid or continuous epidural infusions should be monitored for efficacy and side effects. (See 'Monitoring the patient who has received neuraxial analgesia' above.)

- For morbidly obese patients undergoing abdominal or thoracic surgery, we suggest postoperative epidural analgesia or an alternative regional analgesic technique to reduce systemic opioid requirement and the risk of respiratory depression (**Grade 2C**). The medications administered via the epidural catheter should be individualized. (See 'Morbid obesity' above.)

Use of UpToDate is subject to the Subscription and License Agreement.

REFERENCES

1. Alam A, Juurlink DN. The prescription opioid epidemic: an overview for anesthesiologists. Can J Anaesth 2016; 63:61.

2. Mudumbai SC, Oliva EM, Lewis ET, et al. Time-to-Cessation of Postoperative Opioids: A Population-Level Analysis of the Veterans Affairs Health Care System. Pain Med 2016; 17:1732.
3. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. JAMA Intern Med 2016; 176:1286.
4. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. Can J Anaesth 2001; 48:1000.
5. Woolf CJ, Chong MS. Preemptive analgesia--treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993; 77:362.
6. Suzuki H. Recent topics in the management of pain: development of the concept of preemptive analgesia. Cell Transplant 1995; 4 Suppl 1:S3.
7. Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology 2002; 96:725.
8. Rosero EB, Joshi GP. Preemptive, preventive, multimodal analgesia: what do they really mean? Plast Reconstr Surg 2014; 134:85S.
9. Katz J, Clarke H, Seltzer Z. Review article: Preventive analgesia: quo vadimus? Anesth Analg 2011; 113:1242.
10. Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg 2005; 100:757.
11. Ke RW, Portera SG, Bagous W, Lincoln SR. A randomized, double-blinded trial of preemptive analgesia in laparoscopy. Obstet Gynecol 1998; 92:972.
12. Ghezzi F, Cromi A, Bergamini V, et al. Preemptive port site local anesthesia in gynecologic laparoscopy: a randomized, controlled trial. J Minim Invasive Gynecol 2005; 12:210.
13. Updike GM, Manolitsas TP, Cohn DE, et al. Pre-emptive analgesia in gynecologic surgical procedures: preoperative wound infiltration with ropivacaine in patients who undergo laparotomy through a midline vertical incision. Am J Obstet Gynecol 2003; 188:901.

14. Leung CC, Chan YM, Ngai SW, et al. Effect of pre-incision skin infiltration on post-hysterectomy pain--a double-blind randomized controlled trial. Anaesth Intensive Care 2000; 28:510.
15. Hadi I, Morley-Forster PK, Dain S, et al. Brief review: perioperative management of the patient with chronic non-cancer pain. Can J Anaesth 2006; 53:1190.
16. Mitra S, Sinatra RS. Perioperative management of acute pain in the opioid-dependent patient. Anesthesiology 2004; 101:212.
17. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 1993; 77:1048.
18. Hebl JR, Dilger JA, Byer DE, et al. A pre-emptive multimodal pathway featuring peripheral nerve block improves perioperative outcomes after major orthopedic surgery. Reg Anesth Pain Med 2008; 33:510.
19. Elia N, Lysakowski C, Tramèr MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology 2005; 103:1296.
20. Trabulsi EJ, Patel J, Viscusi ER, et al. Preemptive multimodal pain regimen reduces opioid analgesia for patients undergoing robotic-assisted laparoscopic radical prostatectomy. Urology 2010; 76:1122.
21. Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg 2010; 110:1170.
22. Thybo KH, Hägi-Pedersen D, Dahl JB, et al. Effect of Combination of Paracetamol (Acetaminophen) and Ibuprofen vs Either Alone on Patient-Controlled Morphine Consumption in the First 24 Hours After Total Hip Arthroplasty: The PANSAID Randomized Clinical Trial. JAMA 2019; 321:562.
23. Mariano ER, Dickerson DM, Szokol JW, et al. A multisociety organizational consensus process to define guiding principles for acute perioperative pain management. Reg Anesth Pain Med 2021.
24. Kandarian BS, Elkassabany NM, Tamboli M, Mariano ER. Updates on multimodal analgesia and regional anesthesia for total knee arthroplasty patients. Best Pract Res Clin Anaesthesiol 2019; 33:111.

25. Wittels B, Sevarino FB. PCA in the obstetric patient. In: Acute pain: Mechanism and Management, Sinatra, RS, Hord, AH, Ginsberg, B, Preble, LM (Eds), Mosby-Year Book, St. Louis 1992. p.175.
26. Rapp-Zingraff N, Bayoumeu F, Baka N, et al. Analgesia after caesarean section: patient-controlled intravenous morphine vs epidural morphine. Int J Obstet Anesth 1997; 6:87.
27. Cade L, Ashley J. Towards optimal analgesia after caesarean section: comparison of epidural and intravenous patient-controlled opioid analgesia. Anaesth Intensive Care 1993; 21:696.
28. Wittels B, Glosten B, Faure EA, et al. Postcesarean analgesia with both epidural morphine and intravenous patient-controlled analgesia: neurobehavioral outcomes among nursing neonates. Anesth Analg 1997; 85:600.
29. Aubrun F, Mazoit JX, Riou B. Postoperative intravenous morphine titration. Br J Anaesth 2012; 108:193.
30. MacKenzie M, Zed PJ, Ensom MH. Opioid Pharmacokinetics-Pharmacodynamics: Clinical Implications in Acute Pain Management in Trauma. Ann Pharmacother 2016; 50:209.
31. Ing Lorenzini K, Daali Y, Dayer P, Desmeules J. Pharmacokinetic-pharmacodynamic modelling of opioids in healthy human volunteers. a minireview. Basic Clin Pharmacol Toxicol 2012; 110:219.
32. Mauermann E, Filitz J, Dolder P, et al. Does Fentanyl Lead to Opioid-induced Hyperalgesia in Healthy Volunteers?: A Double-blind, Randomized, Crossover Trial. Anesthesiology 2016; 124:453.
33. Chia YY, Liu K, Wang JJ, et al. Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. Can J Anaesth 1999; 46:872.
34. Latta KS, Ginsberg B, Barkin RL. Meperidine: a critical review. Am J Ther 2002; 9:53.
35. DeWire SM, Yamashita DS, Rominger DH, et al. A G protein-biased ligand at the μ-opioid receptor is potently analgesic with reduced gastrointestinal and respiratory dysfunction compared with morphine. J Pharmacol Exp Ther 2013; 344:708.
36. Viscusi ER, Skobieranda F, Soergel DG, et al. APOLLO-1: a randomized placebo and active-controlled phase III study investigating oliceridine (TRV130), a G

protein-biased ligand at the μ-opioid receptor, for management of moderate-to-severe acute pain following bunionectomy. J Pain Res 2019; 12:927.

37. Singla NK, Skobieranda F, Soergel DG, et al. APOLLO-2: A Randomized, Placebo and Active-Controlled Phase III Study Investigating Oliceridine (TRV130), a G Protein-Biased Ligand at the μ-Opioid Receptor, for Management of Moderate to Severe Acute Pain Following Abdominoplasty. Pain Pract 2019; 19:715.
38. Hudcova J, McNicol E, Quah C, et al. Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. Cochrane Database Syst Rev 2006; :CD003348.
39. Davison SN, Mayo PR. Pain management in chronic kidney disease: the pharmacokinetics and pharmacodynamics of hydromorphone and hydromorphone-3-glucuronide in hemodialysis patients. J Opioid Manag 2008; 4:335.
40. Murtagh FE, Chai MO, Donohoe P, et al. The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. J Pain Palliat Care Pharmacother 2007; 21:5.
41. McDaid C, Maund E, Rice S, et al. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review. Health Technol Assess 2010; 14:1.
42. Pavy TJ, Paech MJ, Evans SF. The effect of intravenous ketorolac on opioid requirement and pain after cesarean delivery. Anesth Analg 2001; 92:1010.
43. Mixter CG 3rd, Meeker LD, Gavin TJ. Preemptive pain control in patients having laparoscopic hernia repair: a comparison of ketorolac and ibuprofen. Arch Surg 1998; 133:432.
44. Bikhazi GB, Snabes MC, Bajwa ZH, et al. A clinical trial demonstrates the analgesic activity of intravenous parecoxib sodium compared with ketorolac or morphine after gynecologic surgery with laparotomy. Am J Obstet Gynecol 2004; 191:1183.
45. Varrassi G, Marinangeli F, Agrò F, et al. A double-blinded evaluation of propacetamol versus ketorolac in combination with patient-controlled analgesia morphine: analgesic efficacy and tolerability after gynecologic surgery. Anesth Analg 1999; 88:611.
46. Chui PT, Gin T. A comparison between ketorolac and diclofenac in laparoscopic sterilization. Eur J Anaesthesiol 1995; 12:597.

47. O'Hanlon JJ, Beers H, Huss BK, Milligan KR. A comparison of the effect of intramuscular diclofenac, ketorolac or piroxicam on post-operative pain following laparoscopy. Eur J Anaesthesiol 1996; 13:404.

48. Ng A, Temple A, Smith G, Emembolu J. Early analgesic effects of parecoxib versus ketorolac following laparoscopic sterilization: a randomized controlled trial. Br J Anaesth 2004; 92:846.

49. Maher DP, Chen L, Mao J. Intravenous Ketamine Infusions for Neuropathic Pain Management: A Promising Therapy in Need of Optimization. Anesth Analg 2017; 124:661.

50. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology 2010; 113:639.

51. Boenigk K, Echevarria GC, Nisimov E, et al. Low-dose ketamine infusion reduces postoperative hydromorphone requirements in opioid-tolerant patients following spinal fusion: A randomised controlled trial. Eur J Anaesthesiol 2019; 36:8.

52. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med 2018; 43:456.

53. Quibell R, Prommer EE, Mihalyo M, et al. Ketamine*. J Pain Symptom Manage 2011; 41:640.

54. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth 2011; 58:911.

55. Pendi A, Field R, Farhan SD, et al. Perioperative Ketamine for Analgesia in Spine Surgery: A Meta-analysis of Randomized Controlled Trials. Spine (Phila Pa 1976) 2018; 43:E299.

56. Wang L, Johnston B, Kaushal A, et al. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials. Can J Anaesth 2016; 63:311.

57. Yenigun A, Yilmaz S, Dogan R, et al. Demonstration of analgesic effect of intranasal ketamine and intranasal fentanyl for postoperative pain after pediatric tonsillectomy. Int J Pediatr Otorhinolaryngol 2018; 104:182.

58. Chaparro LE, Smith SA, Moore RA, et al. Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database Syst Rev 2013; :CD008307.

59. McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. Acta Anaesthesiol Scand 2014; 58:1199.

60. Foo I, Macfarlane AJR, Srivastava D, et al. The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety. Anaesthesia 2021; 76:238.

61. Weibel S, Jelting Y, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. Cochrane Database Syst Rev 2018; 6:CD009642.

62. Weibel S, Jokinen J, Pace NL, et al. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis. Br J Anaesth 2016; 116:770.

63. Ghimire A, Subedi A, Bhattarai B, Sah BP. The effect of intraoperative lidocaine infusion on opioid consumption and pain after totally extraperitoneal laparoscopic inguinal hernioplasty: a randomized controlled trial. BMC Anesthesiol 2020; 20:137.

64. Rollins KE, Javanmard-Emamghissi H, Scott MJ, Lobo DN. The impact of peri-operative intravenous lidocaine on postoperative outcome after elective colorectal surgery: A meta-analysis of randomised controlled trials. Eur J Anaesthesiol 2020; 37:659.

65. Albrecht E, Kirkham KR, Liu SS, Brull R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. Anaesthesia 2013; 68:79.

66. De Oliveira GS Jr, Castro-Alves LJ, Khan JH, McCarthy RJ. Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology 2013; 119:178.

67. Jabbour HJ, Naccache NM, Jawish RJ, et al. Ketamine and magnesium association reduces morphine consumption after scoliosis surgery: prospective randomised double-blind study. Acta Anaesthesiol Scand 2014; 58:572.

68. De Oliveira GS Jr, Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology 2011; 115:575.

69. Heesen M, Rijs K, Hilber N, et al. Effect of intravenous dexamethasone on postoperative pain after spinal anaesthesia - a systematic review with meta-analysis and trial sequential analysis. Anaesthesia 2019; 74:1047.

70. Choi YS, Shim JK, Song JW, et al. Combination of pregabalin and dexamethasone for postoperative pain and functional outcome in patients undergoing lumbar spinal surgery: a randomized placebo-controlled trial. Clin J Pain 2013; 29:9.

71. Sharma M, Gupta S, Purohit S, Goyal AK. The Effect of Intravenous Dexamethasone on Intraoperative and Early Postoperative Pain in Lumbar Spine Surgery: A Randomized Double-Blind Placebo-Controlled Study. Anesth Essays Res 2018; 12:803.

72. Politi JR, Davis RL 2nd, Matrka AK. Randomized Prospective Trial Comparing the Use of Intravenous versus Oral Acetaminophen in Total Joint Arthroplasty. J Arthroplasty 2017; 32:1125.

73. O'Neal JB, Freiberg AA, Yelle MD, et al. Intravenous vs Oral Acetaminophen as an Adjunct to Multimodal Analgesia After Total Knee Arthroplasty: A Prospective, Randomized, Double-Blind Clinical Trial. J Arthroplasty 2017; 32:3029.

74. Fenlon S, Collyer J, Giles J, et al. Oral vs intravenous paracetamol for lower third molar extractions under general anaesthesia: is oral administration inferior? Br J Anaesth 2013; 110:432.

75. Plunkett A, Haley C, McCoart A, et al. A Preliminary Examination of the Comparative Efficacy of Intravenous vs Oral Acetaminophen in the Treatment of Perioperative Pain. Pain Med 2017; 18:2466.

76. Jibril F, Sharaby S, Mohamed A, Wilby KJ. Intravenous versus Oral Acetaminophen for Pain: Systematic Review of Current Evidence to Support Clinical Decision-Making. Can J Hosp Pharm 2015; 68:238.

77. Hickman SR, Mathieson KM, Bradford LM, et al. Randomized trial of oral versus intravenous acetaminophen for postoperative pain control. Am J Health Syst Pharm 2018; 75:367.

78. Wasserman I, Poeran J, Zubizarreta N, et al. Impact of Intravenous Acetaminophen on Perioperative Opioid Utilization and Outcomes in Open Colectomies: A Claims Database Analysis. Anesthesiology 2018; 129:77.

79. Stundner O, Poeran J, Ladenhauf HN, et al. Effectiveness of intravenous acetaminophen for postoperative pain management in hip and knee arthroplasties: a population-based study. Reg Anesth Pain Med 2019; 44:565.

80. Wilson SH, Wolf BJ, Robinson SM, et al. Intravenous vs Oral Acetaminophen for Analgesia After Cesarean Delivery: A Randomized Trial. Pain Med 2019; 20:1584.

81. Westrich GH, Birch GA, Muskat AR, et al. Intravenous vs Oral Acetaminophen as a Component of Multimodal Analgesia After Total Hip Arthroplasty: A Randomized, Blinded Trial. J Arthroplasty 2019; 34:S215.

82. Patel A, Pai B H P, Diskina D, et al. Comparison of clinical outcomes of acetaminophen IV vs PO in the peri-operative setting for laparoscopic inguinal hernia repair surgeries: A triple-blinded, randomized controlled trial. J Clin Anesth 2020; 61:109628.

83. Martinez V, Beloeil H, Marret E, et al. Non-opioid analgesics in adults after major surgery: systematic review with network meta-analysis of randomized trials. Br J Anaesth 2017; 118:22.

84. Hansen RN, Pham AT, Böing EA, et al. Hospitalization costs and resource allocation in cholecystectomy with use of intravenous versus oral acetaminophen. Curr Med Res Opin 2018; 34:1549.

85. Khan SA, Khokhar HA, Nasr AR, et al. Effect of epidural analgesia on bowel function in laparoscopic colorectal surgery: a systematic review and meta-analysis. Surg Endosc 2013; 27:2581.

86. Turunen P, Carpelan-Holmström M, Kairaluoma P, et al. Epidural analgesia diminished pain but did not otherwise improve enhanced recovery after laparoscopic sigmoidectomy: a prospective randomized study. Surg Endosc 2009; 23:31.

87. Werawatganon T, Charuluxanun S. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. Cochrane Database Syst Rev 2005; :CD004088.

88. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984; 61:276.

89. Gwirtz KH, Young JV, Byers RS, et al. The safety and efficacy of intrathecal opioid analgesia for acute postoperative pain: seven years' experience with 5969 surgical patients at Indiana University Hospital. Anesth Analg 1999; 88:599.

90. Palmer CM, Nogami WM, Van Maren G, Alves DM. Postcesarean epidural morphine: a dose-response study. Anesth Analg 2000; 90:887.
91. Abouleish E, Rawal N, Rashad MN. The addition of 0.2 mg subarachnoid morphine to hyperbaric bupivacaine for cesarean delivery: a prospective study of 856 cases. Reg Anesth 1991; 16:137.
92. Chestnut DH. Efficacy and safety of epidural opioids for postoperative analgesia. Anesthesiology 2005; 102:221.
93. Chadwick HS, Ready LB. Intrathecal and epidural morphine sulfate for post-cesarean analgesia--a clinical comparison. Anesthesiology 1988; 68:925.
94. Satoh O, Hatakeyama Y, Miyazawa F, et al. [Intrathecal morphine for postoperative pain relief after transvaginal hysterectomy]. Masui 1992; 41:1517.
95. Dualé C, Frey C, Bolandard F, et al. Epidural versus intrathecal morphine for postoperative analgesia after Caesarean section. Br J Anaesth 2003; 91:690.
96. Terajima K, Onodera H, Kobayashi M, et al. Efficacy of intrathecal morphine for analgesia following elective cesarean section: comparison with previous delivery. J Nippon Med Sch 2003; 70:327.
97. Sarvela J, Halonen P, Soikkeli A, Korttila K. A double-blinded, randomized comparison of intrathecal and epidural morphine for elective cesarean delivery. Anesth Analg 2002; 95:436.
98. Abouleish E, Rawal N, Fallon K, Hernandez D. Combined intrathecal morphine and bupivacaine for cesarean section. Anesth Analg 1988; 67:370.
99. Fassoulaki A, Gatzou V, Petropoulos G, Siafaka I. Spread of subarachnoid block, intraoperative local anaesthetic requirements and postoperative analgesic requirements in Caesarean section and total abdominal hysterectomy. Br J Anaesth 2004; 93:678.
100. Sarma VJ, Boström UV. Intrathecal morphine for the relief of post-hysterectomy pain--a double-blind, dose-response study. Acta Anaesthesiol Scand 1993; 37:223.
101. Sviggum HP, Arendt KW, Jacob AK, et al. Intrathecal Hydromorphone and Morphine for Postcesarean Delivery Analgesia: Determination of the ED90 Using a Sequential Allocation Biased-Coin Method. Anesth Analg 2016; 123:690.

102. Gadsden J, Hart S, Santos AC. Post-cesarean delivery analgesia. Anesth Analg 2005; 101:S62.
103. Palmer CM, Cork RC, Hays R, et al. The dose-response relation of intrathecal fentanyl for labor analgesia. Anesthesiology 1998; 88:355.
104. Singh SI, Rehou S, Marmai KL, Jones PM. The efficacy of 2 doses of epidural morphine for postcesarean delivery analgesia: a randomized noninferiority trial. Anesth Analg 2013; 117:677.
105. Niiyama Y, Kawamata T, Shimizu H, et al. The addition of epidural morphine to ropivacaine improves epidural analgesia after lower abdominal surgery. Can J Anaesth 2005; 52:181.
106. Wu CL, Hurley RW, Anderson GF, et al. Effect of postoperative epidural analgesia on morbidity and mortality following surgery in medicare patients. Reg Anesth Pain Med 2004; 29:525.
107. de Leon-Casasola OA, Karabella D, Lema MJ. Bowel function recovery after radical hysterectomies: thoracic epidural bupivacaine-morphine versus intravenous patient-controlled analgesia with morphine: a pilot study. J Clin Anesth 1996; 8:87.
108. Jørgensen H, Fomsgaard JS, Dirks J, et al. Effect of epidural bupivacaine vs combined epidural bupivacaine and morphine on gastrointestinal function and pain after major gynaecological surgery. Br J Anaesth 2001; 87:727.
109. Jørgensen H, Fomsgaard JS, Dirks J, et al. Effect of continuous epidural 0.2% ropivacaine vs 0.2% bupivacaine on postoperative pain, motor block and gastrointestinal function after abdominal hysterectomy. Br J Anaesth 2000; 84:144.
110. Tanaka M, Watanabe S, Ashimura H, et al. Minimum effective combination dose of epidural morphine and fentanyl for posthysterectomy analgesia: a randomized, prospective, double-blind study. Anesth Analg 1993; 77:942.
111. Senard M, Kaba A, Jacquemin MJ, et al. Epidural levobupivacaine 0.1% or ropivacaine 0.1% combined with morphine provides comparable analgesia after abdominal surgery. Anesth Analg 2004; 98:389.
112. Senard M, Joris JL, Ledoux D, et al. A comparison of 0.1% and 0.2% ropivacaine and bupivacaine combined with morphine for postoperative patient-controlled epidural analgesia after major abdominal surgery. Anesth Analg 2002; 95:444.

113. Scott DA, Blake D, Buckland M, et al. A comparison of epidural ropivacaine infusion alone and in combination with 1, 2, and 4 microg/mL fentanyl for seventy-two hours of postoperative analgesia after major abdominal surgery. Anesth Analg 1999; 88:857.

114. Jørgensen H, Wetterslev J, Møiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database Syst Rev 2000; :CD001893.

115. Gambling DR, Yu P, Cole C, et al. A comparative study of patient controlled epidural analgesia (PCEA) and continuous infusion epidural analgesia (CIEA) during labour. Can J Anaesth 1988; 35:249.

116. Liu SS, Allen HW, Olsson GL. Patient-controlled epidural analgesia with bupivacaine and fentanyl on hospital wards: prospective experience with 1,030 surgical patients. Anesthesiology 1998; 88:688.

117. Chia YY, Chang TH, Liu K, et al. The efficacy of thoracic epidural neostigmine infusion after thoracotomy. Anesth Analg 2006; 102:201.

118. Lauretti GR, de Oliveira R, Reis MP, et al. Study of three different doses of epidural neostigmine coadministered with lidocaine for postoperative analgesia. Anesthesiology 1999; 90:1534.

119. Wilson JA, Nimmo AF, Fleetwood-Walker SM, Colvin LA. A randomised double blind trial of the effect of pre-emptive epidural ketamine on persistent pain after lower limb amputation. Pain 2008; 135:108.

120. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesth Analg 2004; 99:482.

121. Farmery AD, Wilson-MacDonald J. The analgesic effect of epidural clonidine after spinal surgery: a randomized placebo-controlled trial. Anesth Analg 2009; 108:631.

122. De Kock M, Wiederkher P, Laghmiche A, Scholtes JL. Epidural clonidine used as the sole analgesic agent during and after abdominal surgery. A dose-response study. Anesthesiology 1997; 86:285.

123. American Society of Anesthesiologists Task Force on Neuraxial Opioids, Horlocker TT, Burton AW, et al. Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration. Anesthesiology 2009; 110:218.

124. Devys JM, Mora A, Plaud B, et al. Intrathecal + PCA morphine improves analgesia during the first 24 hr after major abdominal surgery compared to PCA alone. Can J Anaesth 2003; 50:355.

125. Kong SK, Onsiong SM, Chiu WK, Li MK. Use of intrathecal morphine for postoperative pain relief after elective laparoscopic colorectal surgery. Anaesthesia 2002; 57:1168.

126. Swart M, Sewell J, Thomas D. Intrathecal morphine for caesarean section: an assessment of pain relief, satisfaction and side-effects. Anaesthesia 1997; 52:373.

127. Horlocker TT, Vandermeuelen E, Kopp SL, et al. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). Reg Anesth Pain Med 2018; 43:263.

128. Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration: An Updated Report by the American Society of Anesthesiologists Task Force on Neuraxial Opioids and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology 2016; 124:535.

129. Bauchat JR, Weiniger CF, Sultan P, et al. Society for Obstetric Anesthesia and Perinatology Consensus Statement: Monitoring Recommendations for Prevention and Detection of Respiratory Depression Associated With Administration of Neuraxial Morphine for Cesarean Delivery Analgesia. Anesth Analg 2019; 129:458.

130. Chin KJ, Singh M, Velayutham V, Chee V. Infraclavicular brachial plexus block for regional anaesthesia of the lower arm. Cochrane Database Syst Rev 2010; :CD005487.

131. Fredrickson MJ, Krishnan S, Chen CY. Postoperative analgesia for shoulder surgery: a critical appraisal and review of current techniques. Anaesthesia 2010; 65:608.

132. Wegener JT, van Ooij B, van Dijk CN, et al. Value of single-injection or continuous sciatic nerve block in addition to a continuous femoral nerve block in patients undergoing total knee arthroplasty: a prospective, randomized, controlled trial. Reg Anesth Pain Med 2011; 36:481.

133. Ilfeld BM, Mariano ER, Girard PJ, et al. A multicenter, randomized, triple-masked, placebo-controlled trial of the effect of ambulatory continuous

femoral nerve blocks on discharge-readiness following total knee arthroplasty in patients on general orthopaedic wards. Pain 2010; 150:477.

134. Paul JE, Arya A, Hurlburt L, et al. Femoral nerve block improves analgesia outcomes after total knee arthroplasty: a meta-analysis of randomized controlled trials. Anesthesiology 2010; 113:1144.
135. Fowler SJ, Symons J, Sabato S, Myles PS. Epidural analgesia compared with peripheral nerve blockade after major knee surgery: a systematic review and meta-analysis of randomized trials. Br J Anaesth 2008; 100:154.
136. Kopacz DJ, Thompson GE. Intercostal blocks for thoracic and abdominal surgery. Tech Reg Anesth Pain Manage 1998; 2:25.
137. Nunn JF, Slavin G. Posterior intercostal nerve block for pain relief after cholecystectomy. Anatomical basis and efficacy. Br J Anaesth 1980; 52:253.
138. Coveney E, Weltz CR, Greengrass R, et al. Use of paravertebral block anesthesia in the surgical management of breast cancer: experience in 156 cases. Ann Surg 1998; 227:496.
139. Kopacz, DJ, Thompson, GE. Neural blockade of the Thorax and abdomen. In: N euronal Blockade in Clinical Anesthesia and Management of Pain, Cousins, MJ, Bridenbaugh, PO (Eds), JB Lippincott-Raven Publishers, Philadelphia 1988. p.45 1.
140. Klein SM, Bergh A, Steele SM, et al. Thoracic paravertebral block for breast surgery. Anesth Analg 2000; 90:1402.
141. McDonnell JG, O'Donnell B, Curley G, et al. The analgesic efficacy of transversus abdominis plane block after abdominal surgery: a prospective randomized controlled trial. Anesth Analg 2007; 104:193.
142. McDonnell JG, Curley G, Carney J, et al. The analgesic efficacy of transversus abdominis plane block after cesarean delivery: a randomized controlled trial. Anesth Analg 2008; 106:186.
143. Carney J, McDonnell JG, Ochana A, et al. The transversus abdominis plane block provides effective postoperative analgesia in patients undergoing total abdominal hysterectomy. Anesth Analg 2008; 107:2056.
144. Aveline C, Le Hetet H, Le Roux A, et al. Comparison between ultrasound-guided transversus abdominis plane and conventional ilioinguinal/iliohypogastric nerve blocks for day-case open inguinal hernia repair. Br J Anaesth 2011; 106:380.

145. Favuzza J, Delaney CP. Outcomes of discharge after elective laparoscopic colorectal surgery with transversus abdominis plane blocks and enhanced recovery pathway. J Am Coll Surg 2013; 217:503.

146. Favuzza J, Brady K, Delaney CP. Transversus abdominis plane blocks and enhanced recovery pathways: making the 23-h hospital stay a realistic goal after laparoscopic colorectal surgery. Surg Endosc 2013; 27:2481.

147. Walter CJ, Maxwell-Armstrong C, Pinkney TD, et al. A randomised controlled trial of the efficacy of ultrasound-guided transversus abdominis plane (TAP) block in laparoscopic colorectal surgery. Surg Endosc 2013; 27:2366.

148. Dahl JB, Nielsen RV, Wetterslev J, et al. Post-operative analgesic effects of paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review. Acta Anaesthesiol Scand 2014; 58:1165.

149. Ng A, Smith G, Davidson AC. Analgesic effects of parecoxib following total abdominal hysterectomy. Br J Anaesth 2003; 90:746.

150. Thompson JP, Sharpe P, Kiani S, Owen-Smith O. Effect of meloxicam on postoperative pain after abdominal hysterectomy. Br J Anaesth 2000; 84:151.

151. Akarsu T, Karaman S, Akercan F, et al. Preemptive meloxicam for postoperative pain relief after abdominal hysterectomy. Clin Exp Obstet Gynecol 2004; 31:133.

152. Chan A, Doré CJ, Ramachandra V. Analgesia for day surgery. Evaluation of the effect of diclofenac given before or after surgery with or without bupivacaine infiltration. Anaesthesia 1996; 51:592.

153. Clarke R, Derry S, Moore RA, McQuay HJ. Single dose oral etoricoxib for acute postoperative pain in adults. Cochrane Database Syst Rev 2009; :CD004309.

154. Lloyd R, Derry S, Moore RA, McQuay HJ. Intravenous or intramuscular parecoxib for acute postoperative pain in adults. Cochrane Database Syst Rev 2009; :CD004771.

155. Derry S, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database Syst Rev 2013; :CD004233.

156. Carpenter PS, Shepherd HM, McCrary H, et al. Association of Celecoxib Use With Decreased Opioid Requirements After Head and Neck Cancer Surgery With Free Tissue Reconstruction. JAMA Otolaryngol Head Neck Surg 2018; 144:988.

157. Barton SF, Langeland FF, Snabes MC, et al. Efficacy and safety of intravenous parecoxib sodium in relieving acute postoperative pain following gynecologic laparotomy surgery. Anesthesiology 2002; 97:306.

158. Malan TP Jr, Gordon S, Hubbard R, Snabes M. The cyclooxygenase-2-specific inhibitor parecoxib sodium is as effective as 12 mg of morphine administered intramuscularly for treating pain after gynecologic laparotomy surgery. Anesth Analg 2005; 100:454.

159. Bikhazi GB, Bajwa ZH, Snabes MC, et al. Parecoxib effectively treats post-laparo tomy pain. Annual Meeting of the American Society for Reproductive Medicine Poster 2003; 481.

160. Gordh T Jr, Jansson I, Hartvig P, et al. Interactions between noradrenergic and cholinergic mechanisms involved in spinal nociceptive processing. Acta Anaesthesiol Scand 1989; 33:39.

161. Gold MS, Redmond DE Jr, Kleber HD. Clonidine blocks acute opiate-withdrawal symptoms. Lancet 1978; 2:599.

162. De Kock M, Crochet B, Morimont C, Scholtes JL. Intravenous or epidural clonidine for intra- and postoperative analgesia. Anesthesiology 1993; 79:525.

163. Omote K, Kitahata LM, Collins JG, et al. Interaction between opiate subtype and alpha-2 adrenergic agonists in suppression of noxiously evoked activity of WDR neurons in the spinal dorsal horn. Anesthesiology 1991; 74:737.

164. Sung CS, Lin SH, Chan KH, et al. Effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Sin 2000; 38:23.

165. Hidalgo MP, Auzani JA, Rumpel LC, et al. The clinical effect of small oral clonidine doses on perioperative outcomes in patients undergoing abdominal hysterectomy. Anesth Analg 2005; 100:795.

166. White PF. The changing role of non-opioid analgesic techniques in the management of postoperative pain. Anesth Analg 2005; 101:S5.

167. Hah J, Mackey SC, Schmidt P, et al. Effect of Perioperative Gabapentin on Postoperative Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort: A Randomized Clinical Trial. JAMA Surg 2018; 153:303.

168. Schmidt PC, Ruchelli G, Mackey SC, Carroll IR. Perioperative gabapentinoids: choice of agent, dose, timing, and effects on chronic postsurgical pain. Anesthesiology 2013; 119:1215.

169. Verret M, Lauzier F, Zarychanski R, et al. Perioperative Use of Gabapentinoids for the Management of Postoperative Acute Pain: A Systematic Review and Meta-analysis. Anesthesiology 2020; 133:265.

170. Myhre M, Jacobsen HB, Andersson S, Stubhaug A. Cognitive Effects of Perioperative Pregabalin: Secondary Exploratory Analysis of a Randomized Placebo-controlled Study. Anesthesiology 2019; 130:63.

171. Memtsoudis S, Cozowicz C, Zubizarreta N, et al. Risk factors for postoperative delirium in patients undergoing lower extremity joint arthroplasty: a retrospective population-based cohort study. Reg Anesth Pain Med 2019.

172. Cavalcante AN, Sprung J, Schroeder DR, Weingarten TN. Multimodal Analgesic Therapy With Gabapentin and Its Association With Postoperative Respiratory Depression. Anesth Analg 2017; 125:141.

173. Weingarten TN, Jacob AK, Njathi CW, et al. Multimodal Analgesic Protocol and Postanesthesia Respiratory Depression During Phase I Recovery After Total Joint Arthroplasty. Reg Anesth Pain Med 2015; 40:330.

174. Bykov K, Bateman BT, Franklin JM, et al. Association of Gabapentinoids With the Risk of Opioid-Related Adverse Events in Surgical Patients in the United States. JAMA Netw Open 2020; 3:e2031647.

175. Deljou A, Hedrick SJ, Portner ER, et al. Pattern of perioperative gabapentinoid use and risk for postoperative naloxone administration. Br J Anaesth 2018; 120:798.

176. Mersfelder TL, Nichols WH. Gabapentin: Abuse, Dependence, and Withdrawal. Ann Pharmacother 2016; 50:229.

177. Evoy KE, Sadrameli S, Contreras J, et al. Abuse and Misuse of Pregabalin and Gabapentin: A Systematic Review Update. Drugs 2021; 81:125.

178. Young A, Buvanendran A. Recent advances in multimodal analgesia. Anesthesiol Clin 2012; 30:91.

179. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol 2009; 22:588.

180. Jin F, Chung F. Multimodal analgesia for postoperative pain control. J Clin Anesth 2001; 13:524.

181. White PF. Multimodal analgesia: its role in preventing postoperative pain. Curr Opin Investig Drugs 2008; 9:76.

182. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006; 367:1618.

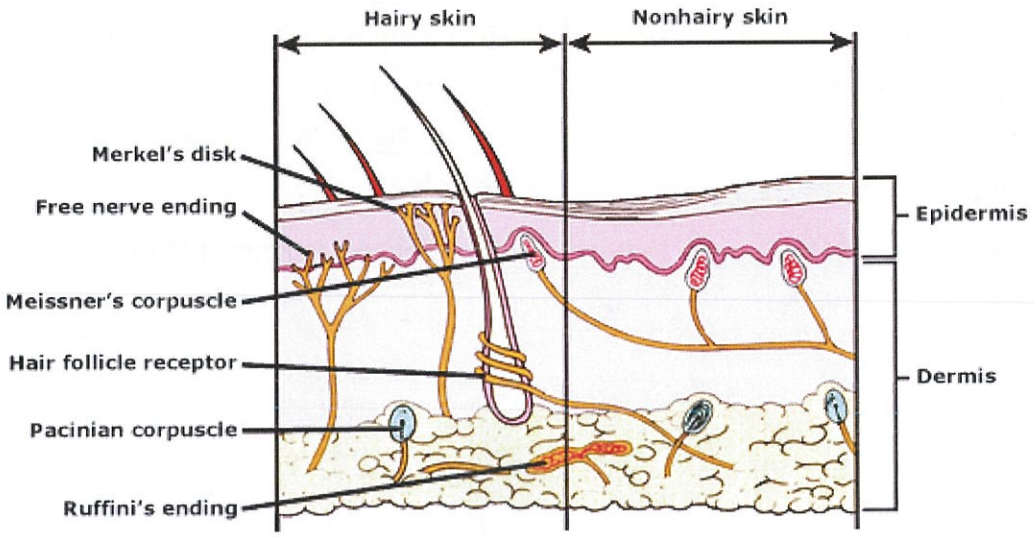
183. Rai AS, Khan JS, Dhaliwal J, et al. Preoperative pregabalin or gabapentin for acute and chronic postoperative pain among patients undergoing breast cancer surgery: A systematic review and meta-analysis of randomized controlled trials. J Plast Reconstr Aesthet Surg 2017; 70:1317.

184. Anwar S, Cooper J, Rahman J, et al. Prolonged Perioperative Use of Pregabalin and Ketamine to Prevent Persistent Pain after Cardiac Surgery. Anesthesiology 2019; 131:119.

Topic 398 Version 81.0

GRAPHICS

Somatic sensory receptors in the skin



Hairy and nonhairy skin have a variety of sensory receptors within the skin.

Adapted with permission from: Bear MF, Connors BW, Paradiso MA. Neuroscience: Exploring the brain, Philadelphia: Williams & Wilkins, 1996. Copyright © 1996 Lippincott Williams & Wilkins.

Graphic 56118 Version 4.0