Analgesic Adjuvants Used in Surgical Pain Management

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Introduction

Analgesic adjuvants and anesthetics provide therapeutic alternatives for:
• Patients experiencing opioid intolerance
• Pain symptoms that cannot be optimally controlled with opioids alone.

They are often prescribed to control specific surgical- or trauma-related complaints, including:
• Skeletal muscle spasm
• Visceral muscle spasm
• Inflammation
• Neuropathic pain
• Opioid hyperalgesia.

Nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase (COX) inhibitors, the use of local anesthetics and acetaminophen should always be considered and, unless contraindicated, used to enhance opioid-mediated analgesia. The following chapter will introduce other multimodal adjuvants that may also be considered for patients with difficult-to-manage postsurgical pain, including:
• Local anesthetics (LA)
• α2-agonists
• Muscle relaxants
• Anticonvulsant analgesics
• NMDA receptor antagonists (ketamine)
• Corticosteroids
• Tricyclic antidepressants (TCAs).

Local Anesthetics

Local anesthetics (LAs) represent a class of analgesic compounds that block conduction of noxious impulses in peripheral and spinal nerves. They are broadly classified as either “amides” or “esters” based on the nature of the linkage between the aromatic ring and the tertiary amine. Ester-based LAs, including procaine (Novocaine), were commercially developed in the early 1900s and were widely utilized in surgical and dental practice. Amide LAs, including lidocaine (Xylocaine), were developed later in the 1960s and have since displaced esters in most clinical settings. Bupivacaine (Marcaine), an amide LA with a longer duration of action was introduced in 1972 and, finally, EXPAREL (Bupivacaine Liposome Injectable Suspension) in 2011 that has a 72 hour duration of action.

In contrast to most drugs used in pain medicine, LAs are only effective when injected in the vicinity of pain fibers innervating the surgical wound site. LAs act by reversibly interfering with both the initiation and propagation of neuronal action potentials. They do this by blocking Na⁺ influx through voltage-gated sodium channels in the axonal membrane. Noxious c and A-δ fibers tend to localize at the periphery of a nerve bundle and are more vulnerable to LA blockade than the motor fibers located in the core. Some LAs, such as bupivacaine (Marcaine) and ropivacaine (Naropin), can also differentially block the sodium channel by a process termed “frequency dependent blockade.” By using dilute bupivacaine solutions, the surgeon can effectively block pain fibers firing most frequently, while sparing larger motor and sensory fibers. Differential blockade of various fiber types with low to increasing concentrations of LA occurs in the following order: noxious > cold/warm > light touch > deep touch > proprioception > motor fibers.

The ability of LAs to anesthetize specific regions of the body reduces or eliminates the need for general anesthesia and provides both painless surgery and effective postoperative analgesia. Applications include:
• Infiltration or localized injection into the wound
• Single dose or continuous peripheral nerve blocks
• Central neural blockade.

Pre-incisional neural blockade decreases the incidence and severity of surgical site hyperalgesia and may reduce the risk of developing persistent pain. Patients experience minimal to no discomfort for several hours to days. Reductions in pain intensity are usually associated with significant opioid-sparing and decreased adverse events. LAs such as lidocaine, bupivacaine, and ropivacaine are available at low cost and, in ambulatory surgical settings, offer benefits of reduced PACU stay and less time needed to control postoperative pain. Inpatients can be discharged sooner with fewer complications, such as deep venous thrombosis, ileus, and
pulmonary atelectasis. LAs are generally well tolerated and safe when administered properly. They reliably unbind from their sites of action, leaving no lasting effects.\(^3,4\)

The duration and degree of neural blockade can be customized to specific surgical or patient needs, by varying the concentration of drug, the volume administered, and addition of epinephrine and other adjuvants like clonidine and dexamethasone. Bolus doses of up to 20 to 40 mL of 0.25% to 0.5% bupivacaine or 0.2% to 0.5% ropivacaine may be employed for infiltration or single-dose peripheral nerve block.\(^5,4\) Solutions of 0.25% bupivacaine or ropivacaine 0.2% may be continuously infused perineurally via infusion pumps at 8 to 12 mL/hour for up to 72 hours.\(^3\) Sites of perineural infusion include femoral, sciatic, and common tibial nerves for lower extremity procedures, supraclavicular and interscalene blocks for upper extremity surgery, and paravertebral block for thoracic and abdominal procedures.

LA-based analgesia has several disadvantages:
- Infiltration techniques, while generally straightforward, may lead to patchy or incomplete blockade if the surgeon uses too limited a dose or does not infiltrate all surgical planes of the wound site.
- When performing peripheral nerve block, LAs must be precisely injected into the desired nerve or plexus sheath. Injection may be complicated or contraindicated due to technical difficulties, patient noncooperation, infection, or anticoagulation concerns.
- LAs are associated with dose-dependent neuro- or cardiotoxicity. Toxicity is a primary concern following unintentional IV administration. However, LAs can also precipitate neuro- and cardiotoxicity when large doses are infiltrated into highly vascular tissues.\(^2,3\)
- Some LAs, including lidocaine and chloroprocaine, are reasonably benign, but potent amides, such as bupivacaine and ropivacaine, are associated with seizures and fatal ventricular arrhythmias. Doses should not exceed 1.7 to 2 mg/kg with bupivacaine, 3 mg/kg with ropivacaine, and 5 mg/kg with lidocaine.
- The addition of epinephrine 1:200,000 decreases the rate of absorption and risk of toxicity.
- Treatment of LA toxicity depends on the agent and dose administered, and the site of injection. For example, symptoms such as dizziness or numb lips caused by lidocaine may resolve quickly with supportive care and oxygen. Cardiotoxicity observed with bupivacaine and ropivacaine usually requires airway and ventilatory support, blood pressure support, and control of arrhythmias. In cases of severe bupivacaine toxicity, advanced life support is essential, and IV administration of lipid emulsion may provide an effective antidote.

Recommended doses of commonly administered LAs are presented in Table 9.1.

**α₂-Agonists**

Alpha-2 (α₂) receptor agonists (eg, clonidine and dexmedetomidine) provide sedation, anxiolysis, and analgesia through central actions in the dorsal horn of the spinal cord and brainstem.\(^8,10\) This combination of anxiolysis and potentiation of analgesia may be desirable for many patients recovering from major surgery. Co-administration of clonidine plus an opioid agonist produces more effective analgesia with a reduction in adverse effects than higher doses of either drug administered by itself. Premedication with oral or transdermal clonidine decreased morphine requirements when administered as part of a multimodal analgesic regimen.\(^11,12\) IV clonidine reduced pain, nausea, and vomiting, and improved patient satisfaction with their pain relief.\(^8,9\) This ability to potentiate opioid-mediated analgesia is particularly useful for patients with opioid tolerance or those highly sensitive to opioids.

Clonidine is available in oral, epidural, and transdermal formulations. Parenteral preparations are available for pain management in the European Union. Clonidine has excellent oral bioavailability, and dosing is equivalent to parenteral administration. Oral tablets are supplied in 0.1 mg, 0.2 mg, and 0.3 mg forms. Starting doses of 2 mcg/kg/qd with titration up to 5 mcg/kg/qd are recommended. Transdermal patches release 0.2 mg clonidine per hour and are convenient for patients who cannot tolerate an oral diet. The patch is usually applied preoperatively or intraoperatively, since the onset of analgesic effect may be delayed 3 to 4 hours.

Perioperative administration of clonidine may be associated with alterations in hemodynamics, including an initial hypertensive phase followed by hypotension and bradycardia. Orthostatic hypotension can limit its safety in elderly and volume-depleted patients. Significant sedation can also occur with higher doses of clonidine. The initial hypertension phase is generally transient and should be treated cautiously with short-acting medications. Volume resuscitation and administration of ephedrine and atropine can be used to treat hypotension and bradycardia.

Dexmedetomidine is a more selective α₂-agonist than clonidine and has a shorter duration of action. Although not specifically approved for the treatment of postoperative pain, IV administration of dexmedetomidine was also associated with a 66% reduction in morphine use in the early postoperative period after major inpatient surgery.\(^13\) However, its use was associated with increased postoperative sedation and bradycardia.\(^14\) As a result, patients receiving dexmedetomidine require monitoring in a PACU or telemetry setting.

**Muscle Relaxants**

The hyperalgesic response to acute surgical injury includes skeletal muscle spasm in dermatomes adjacent to site of incision and dissection.\(^12\) Large muscle groups, including the rectus abdominus following abdominal surgery, the latissimus following flank incisions, and trapezius following cervical vertebral surgery, commonly undergo intense spasm that can be palpated by the surgeon and is a major source of patient discomfort. Accumulation of lactic acid in these muscle groups is very irritating to peripheral nociceptors and can elicit pain as intense as the incision itself. Hyperalgesic muscle spasm can also lead to splinting behavior that impedes pulmonary function, ambulation, and rehabilitation.\(^12\) In general, opioids are ineffective in reversing muscle spasm or pain
related to the spasm. Muscle relaxants are not primary analgesics but can be used to reduce skeletal muscle spasm and indirectly reduce splinting behavior and pain.\textsuperscript{15,16}

Muscle relaxants have virtually no shared structure and no shared mechanism of action. Central-acting muscles relaxants are primarily CNS depressants, while others have activity at skeletal muscles or muscle spindles and are termed “direct muscle relaxants.”\textsuperscript{15,16} Methocarbamol (Robaxin) and carisoprodol (Soma) are examples of central sedatives that have secondary muscle relaxation effects. While effective, they have no direct action on the contractile mechanism of striated muscle or the motor end plate. These and other central-acting muscle relaxants are associated with dependency and abuse and should not be prescribed for prolonged periods of time. Carisoprodol has been ranked number 14 of the 20 most abused mood-altering drugs in the United States.\textsuperscript{16}

Tricyclic analogs, including cyclobenzaprine (Flexeril), block $5HT_2$ receptors in the ventral spinal cord, thereby inhibiting the tonic $\alpha$-motorneuron excitation produced by descending serotonergic nerve fibers.\textsuperscript{17} A more recently developed muscle relaxant tizanidine (Zanaflex) is an $\alpha_2$-agonist that attenuates monosynaptic and polysynaptic motor reflexes in the spinal cord. Tizanidine decreases excitatory neurotransmitter release from small sensory afferents, and decreases activity of both $\alpha$ and $\gamma$ motor neurons reducing peripheral spasm. Tizanidine and cyclobenzaprine are commonly prescribed to patients discharged to home following laminectomy and spinal fusion.

Benzodiazepines such as diazepam (Valium) and lorazepam (Ativan) are muscle relaxants that are most commonly used for surgical inpatients.\textsuperscript{18-20} These agents enhance the actions of gamma aminobutyric acid (GABA) on its receptor, and open inhibitory chloride ion channels.\textsuperscript{19,20} The ability of benzodiazepines to block various neurophysiologic responses follows a specific dose-dependent order: antianpanic $>$ anticonvulsion $>$ sedation $>$ muscle relaxation.\textsuperscript{19} This order explains why effective muscle relaxation is generally associated with antianxiety effects, as well as excessive sedation.

Oral and parenteral doses of diazepam have been approved for relief of muscle spasm. Oral doses range from 2 mg to 10 mg, three to four times daily (up to 30 mg/day). Parenteral doses range from 2 mg to 10 mg IV/IM every 4 to 6 hours. The half-life of diazepam ranges from approximately 24 hours to $>$48 hours.\textsuperscript{20,21} The half-life is prolonged in the elderly and in patients with cirrhosis or hepatitis.\textsuperscript{20}

While not approved for relief of muscle spasms, lorazepam is commonly prescribed for this condition, as well as for anxiety and insomnia. Oral doses range from 2 mg/day to 6 mg/day, given in two or three divided doses. Parenteral doses range from 2 mg/day to 6 mg/day, given in divided doses. Lorazepam is readily and completely absorbed from the GI tract after oral absorption. Peak plasma levels are reached at approximately 2 hours. Lorazepam has a longer therapeutic half-life than diazepam despite the fact that its elimination half-life is shorter (10 to 20 hours).

Side effects associated with diazepam and lorazepam include sedation, dizziness, weakness, unsteadiness, habituation, and memory impairment.\textsuperscript{19,21} Diazepam, lorazepam, cyclobenzaprine, and tizanidine can be combined in multimodal fashion with oral steroids, opioids, and NSAIDs, based on the severity of symptoms. All muscle relaxants should be used cautiously in patients treated with opioids as they can enhance opioid-related respiratory depression and somnolence. Consider reducing opioid dose by 20% to 25% in patients co-administered muscle relaxants and benefiting from reductions in muscle spasm–related pain.

### Anticonvulsant Analgesics

Anticonvulsant analgesics, such as gabapentin (Neurontin) and pregabalin (Lyrica), can effectively control neuropathic pain and are approved for use in patients with:

- Postherpetic neuralgia
- Fibromyalgia
- Diabetic neuropathy.

While not indicated for surgical pain management they are increasingly prescribed in this setting.\textsuperscript{12}

Gabapentin was initially approved for control of partial seizures in adults.\textsuperscript{22} Soon after its release, a number of uncontrolled trials were published attesting to its safety and effectiveness in patients with postherpetic neuralgia, trigeminal neuralgia, and reflex sympathetic dystrophy.\textsuperscript{23} A more recently approved gabapentinoid, pregabalin, was conceived and developed as an antineuropathic analgesic.\textsuperscript{24} Pregabalin has neurochemical and therapeutic similarities to gabapentin but is more selective, has greater tolerability, and is simpler to dose.

Gabapentin and pregabalin exhibit high binding affinity at the $\alpha_2-\delta$ subunit of presynaptic voltage-gated calcium channels.\textsuperscript{25} Their analgesic effects may be related to inhibition of calcium influx and diminished release of excitatory neurotransmitters in spinal and supraspinal pain pathways. Gabapentin and pregabalin also reduce the excitability of irritated and injured peripheral nociceptive fibers. Common side effects observed with a therapeutic dose are dizziness and sedation, which are often tolerable if the dose is started low.

In addition to their use in chronic pain, both gabapentin and pregabalin offer therapeutic options for acute pain and have been advocated for use as perioperative analgesic adjuvants.\textsuperscript{26-28} Pre- and postoperative doses of gabapentin (900 mg) and pregabalin (150 mg) have been shown to reduce opioid consumption in several postsurgical models. Gabapentin and pregabalin appear to be more effective in surgical procedures associated with acute nerve injury rather than inflammatory pain. They do not improve acute pain intensity scores, but both have been shown to reduce wound site hyperalgesia.

Zhang and coworkers recently performed a meta-analysis of pregabalin as an adjuvant for postsurgical pain.\textsuperscript{29} Doses of 300 mg/day did not reduce pain intensity during the first 24 hours following surgery, but significantly decreased opioid consumption during this interval (Figure 9.3). Patients treated with pregabalin benefited from less nausea and vomiting but reported a higher incidence of visual disturbances. Perioperative administration of anticonvulsant analgesics may also reduce central sensitization and the development of persistent pain. Fassoulaki and colleagues\textsuperscript{30} evaluated the benefits of gabapentin (400 mg tid) in women undergoing
mastectomy. Patients treated with gabapentin required less postoperative acetaminophen and opioids than the controls. Of greater importance was the finding that at 3 and 6 months following surgery, 10 of 22 patients treated with gabapentin (45%) reported chronic pain as compared with 18 of 22 untreated controls (82%) \( (P<0.02) \). None of the 22 patients treated with gabapentin required opioids at 6 months vs five of 22 controls \( (P<0.107) \).

When employed as analgesic adjuvants for postsurgical pain, the following doses are recommended:
- Gabapentin 600 mg to 900 mg preoperatively, followed by 600 mg to 900 mg tid for 24-72 hours
- Pregabalin 75 mg to 150 mg preoperatively, followed by 75mg to 150 mg bid for 24 to 72 hours.

Both drugs are cleared by the kidneys, hence, dosage should be reduced significantly in patients with renal impairment.

**NMDA Receptor Antagonists**

**(Ketamine)**

Ketamine (2-(O-chlorophenyl)-2-methylamino cyclohexanone) is a nonopioid, central-acting dissociative anesthetic. At subanesthetic doses, ketamine provides rapid and highly potent analgesia without many of the serious adverse effects observed with opioids.\(^{12}\) Although ketamine’s exact mechanism of action remains unclear, several hypotheses have been proposed to explain its clinical effect. Ketamine binds and antagonizes N-methyl-D-aspartate (NMDA) receptors in the CNS. It also provides analgesia by interacting with sigma opiate receptors at the spinal and central level, and by activation of phencyclidine receptors.\(^{31,32}\)

Ketamine potentiates opioid-mediated analgesia and provides a significant opioid-sparing effect.\(^{12,31,32}\) Measurable reductions in the opioid dose requirement can reduce the incidence of annoying side effects such as nausea, vomiting, and oversedation, as well as life-threatening adverse effects such as respiratory depression. A commonly used approach is to provide a ketamine infusion as an adjunct for IV-PCA with morphine or hydromorphone. A continuous ketamine infusion of 0.1 to 0.2 mg/kg/hour and up to 2 mg/kg/day provides useful augmentation of opioid PCA with minimal to no adverse effects (Table 9.2). Ketamine can also be administered directly via a PCA device. PCA solutions may be formulated with ketamine and morphine in a 1:1 ratio. Patient boluses of 0.5 mg morphine plus 0.5 mg ketamine every 6 to 8 minutes are as effective as boluses with higher concentration morphine (1 mg) every 6 to 8 minutes.

Ketamine has particular utility in opioid-tolerant patients. Urban and colleagues\(^{33}\) performed a prospective randomized study to assess the use of ketamine (0.2 mg/kg on induction of general anesthesia, then 2 mcg/kg/hour for the next 24 hours) vs placebo as an adjunct to IV-PCA hydromorphone in 26 opioid-tolerant patients undergoing spinal fusions. Co-administration of ketamine resulted in significantly less pain in the PACU, during the first postoperative day, and during physical therapy. Patients in the ketamine group required significantly less hydromorphone than the control group.

Elia and colleagues\(^{34}\) performed a meta-analysis that evaluated ketamine for postoperative pain. They reported that low-dose IV ketamine decreased postoperative pain intensity up to 48 hours, decreased cumulative 24-hour morphine consumption, and delayed the time to first request of rescue analgesic. Similar results were obtained regarding the use of ketamine in a 2006 Cochrane analysis.\(^{31}\)

Major complications associated with ketamine include hyperdynamic cardiovascular responses and psychomimetic reactions. Relative contraindications to bolus dosing include patients with uncontrolled hypertension, congestive heart failure, tachyarrhythmias, myocardial ischemia, head and globe injuries, and increased intracranial pressure.\(^{33}\) It is unclear whether low-dose infusions are absolutely contraindicated in all of these settings. Low-dose infusions (0.1 mg/kg/hour) are associated with an improved CNS tolerability profile, although a small number of patients may experience diplopia, mild hallucinations, and confusion.

**Corticosteroids**

Oral corticosteroids offer potent anti-inflammatory effects that may reduce the intensity of postsurgical pain. Glucocorticoids bind to specific cytoplasmic and nuclear receptors in injured cells, thereby stabilizing lysosomal membranes and preventing the release of destructive acid hydrolases.\(^{35}\) The anti-inflammatory actions of glucocorticoids involve suppression of phospholipase A\(_2\) and arachidonic acid release, as well as reductions in the synthesis of prostaglandins and leukotrienes. Reductions in inflammation and edema are especially beneficial in controlling bone pain, compressive neuropathic pain, and pain from bowel obstruction and organ capsule distention.\(^{35}\) In addition to these anti-inflammatory effects, oral corticosteroids promote gluconeogenesis, reduce nausea and vomiting, stimulate the appetite, and lead to a sense of well-being.

The analgesic effect of glucocorticoids has been well documented, especially in the postoperative setting. Peak analgesic potency appears comparable to that provided by optimal doses of NSAIDs and acetaminophen, however, the onset of clinical effect is delayed. In patients treated with 16 mg IV dexamethasone following recovery from breast surgery, analgesic effects were not observed until 4 hours postdose.\(^{36}\) On the other hand, the duration of analgesia provided by single IV doses of glucocorticoid may be prolonged for up to 3 days. In ambulatory surgical settings, patients treated with a single dose of IV ketorolac experienced a rapid onset of analgesia, while those treated with methylprednisolone generally report more pain in the PACU, but require less rescue analgesics during postoperative day 2 and 3.\(^{35}\) Prednisone and dexamethasone are rapidly absorbed across the GI mucosa following oral administration but may be given parenterally to patients not tolerating oral diets. The optimal glucocorticoid analgesic dose is not established, as controlled dose-finding studies have not been performed. Dexamethasone doses of 3 mg to 4 mg provide useful antiemetic effects, although doses as high as 8 mg to 12 mg may be required to gain effective analgesia.\(^{36}\) The combination of a glucocorticoid plus an NSAID provides additive anti-inflammatory effects and analgesia.\(^{37}\)

For patients with known contraindications to NSAIDs, glucocorticoids may offer a safe and useful substitute. In a meta-analyses focused on risk and benefits, no significant side effects were found in 17 studies (941 patients) utilizing single doses of...
Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) have also been advocated as analgesic adjuvants for postsurgical pain. While this drug class was originally developed to manage depression, TCAs were found to effectively control neuropathic pain, fibromyalgia, and neck and low back pain. Mechanisms underlying the analgesic activity of TCAs remain unclear but appear to be distinct from their antidepressant properties. TCAs inhibit presynaptic reuptake proteins, decrease serotonin and norepinephrine reuptake, and increase norepinephrine concentrations in spinal cord and brainstem. Norepinephrine binds to and activates postsynaptic α-α-adrenergic receptors, thereby suppressing pain transmission. Analgesic effects are achieved more rapidly and with lower doses than for antidepressant effects. Traditionally, the tertiary amine amitriptyline (Elavil) has been favored for acute pain management over nortriptyline.

It should be appreciated that TCAs are not approved for any pain indications, however, amitriptyline has been advocated for postsurgical pain control as well as nighttime sedation. TCAs are most effective for surgical procedures associated with neural trauma and postoperative neuropathic symptoms. These include amputation and traumatic or surgical injuries to the intercostal nerves, branches of the brachial plexus, and inguinal and genitofemoral nerves. The surgeon should consider starting doses of 12.5 mg to 25 mg and increase to 50 mg as tolerated.

TCAs offer several advantages for selected patient populations when used for multimodal analgesia. They are not narcotics and are nonhabituating, are inexpensive, easily prescribed, and widely available in pharmacies and hospital formularies. Use caution when using TCAs in patients treated with MAOIs, SSRIs, cimetidine, haloperidol, or phenothiazines. Also use caution when drugs that lower the seizure threshold, prolong the QT interval, or have anticholinergic properties are co-administered. Monitor for blurred vision, orthostatic hypotension, urinary retention, and constipation. Less caution may be needed with low-dose administration (12.5 mg to 25 mg), however, sedation and dry mouth are commonly observed. For this reason, it is best to administer TCAs at bedtime where they may help to improve sleep. Common adverse events observed with TCAs are presented in Table 9.3.

REFERENCES


### TABLE 9.1 — Onset and Duration of Local Anesthetic Action

<table>
<thead>
<tr>
<th>(hr)</th>
<th>With Epinephrine</th>
<th>Prolongation</th>
<th>Toxic Dose</th>
<th>Onset (min)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single Administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Ester</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procaine</td>
<td>3-5</td>
<td>½-1</td>
<td>++</td>
<td>10-12 mg/kg</td>
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<tr>
<td>Chloroprocaine</td>
<td>10</td>
<td>½-1</td>
<td>++</td>
<td>10-12 mg/kg</td>
<td></td>
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<tr>
<td>Tetracaine</td>
<td>&lt;15</td>
<td>2-3+</td>
<td>++</td>
<td>2 mg total</td>
<td></td>
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<tr>
<td>Benzocaine (topical)</td>
<td>&lt;2</td>
<td>½+</td>
<td>++</td>
<td>200 mg total</td>
<td></td>
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<tr>
<td><strong>Amide</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Lidocaine</td>
<td>&lt;2</td>
<td>½-1</td>
<td>++</td>
<td>4-5 mg/kg (7 with epinephrine)</td>
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<tr>
<td>Bupivacaine</td>
<td>5</td>
<td>2-4</td>
<td>+/-</td>
<td>1.7-2 mg/kg</td>
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<tr>
<td>Mepivacaine</td>
<td>&lt;5</td>
<td>½-1½</td>
<td>++</td>
<td>4-5 mg/kg (7 with epinephrine)</td>
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<td>Prilocaine</td>
<td>&lt;2</td>
<td>1</td>
<td>?</td>
<td>8-10 mg/kg</td>
<td></td>
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<tr>
<td>Ropivacaine</td>
<td>1½-3</td>
<td>+/-</td>
<td>3 mg/kg</td>
<td></td>
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<tr>
<td>Bupivacaine Liposomal Suspension, EXPAREL</td>
<td>15</td>
<td>72</td>
<td>?</td>
<td>Higher than plain bupivacaine</td>
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</tbody>
</table>

++ Significant potentiation, +/- Some potentiation

### TABLE 9.2 — Ketamine for Supplementation of Postsurgical Analgesia

<table>
<thead>
<tr>
<th>Intraoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus 0.2-0.3 mg/kg at anesthetic induction</td>
<td>Initiate infusion 0.1 mg/kg/hr in PACU; maintain for 24-72 hours as required&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>OR Bolus 0.1 mg/kg at anesthetic induction, then initiate infusion 0.1 mg/kg/hr and maintain for 24-72 hours as required&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Maintain infusion 0.1 mg/kg/hr for 24-72 hours as required&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Infusion may be increased to 0.2 mg/kg/hr or more in selected patients. Side effects, including agitation, auditory and visual hallucinations, and tremor, increase in incidence and severity with increasing ketamine dose. Judicious administration of valium and ativan may reduce the severity of side effects. Avoid ketamine in patients with histories of severe rate-related coronary or valvular heart disease, raised intracranial pressure, and seizures.

### TABLE 9.3 — Tricyclic Antidepressants: Side Effect Profile

<table>
<thead>
<tr>
<th>Generic (Trade) Name</th>
<th>Formulations (mg)</th>
<th>Maximum Daily Dose (mg)</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tertiary Amine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline (Elavil) (active metabolite: nortriptyline)</td>
<td>Tablet: 10, 25, 50, 75, 100, 150 Parenteral: 10 mg/mL</td>
<td>300</td>
<td>++++</td>
</tr>
<tr>
<td><strong>Secondary Amine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline (Pamelor)</td>
<td>Capsule: 10, 25, 50, 75 Oral solution: 10 mg/5 mL</td>
<td>150</td>
<td>+++</td>
</tr>
</tbody>
</table>
In mixed sensory nerves, noxious C-fibers and A-delta fibers are generally localized to the outer regions of the nerve, (mantle) while larger motor and sensory fibers are localized in the center of the nerve (core). Because of a concentration gradient from the site of local anesthetic deposition to the center of the nerve, the mantle fibers are first to be blocked and last to recover. As local anesthetic diffuses further into the nerve, core fibers are blocked, however, they are first to recover. This orientation of fibers favors selective conduction blockade in noxious fibers and analgesic effects that outlast the duration of sensory/motor anesthesia.