Patients undergoing total hip and knee arthroplasty experience substantial and sustained postoperative pain. Inadequate analgesia may impede recovery and delay hospital discharge. Traditionally, postoperative analgesia following arthroplasty was provided by intravenous patient-controlled analgesia or epidural analgesia, but each technique has distinct advantages and disadvantages. Recently, peripheral nerve blockade of the lumbosacral plexus has emerged as an alternative analgesic approach. An increasing number of studies have reported multimodal analgesia featuring unilateral peripheral block provide pain relief and functional outcomes similar to that of continuous epidural and superior to systemic analgesia but with fewer side effects. This review discusses the indications, benefits, and side effects associated with conventional and innovative analgesic approaches to facilitate rehabilitation and improve outcome following total joint arthroplasty.

Pain after hip and knee arthroplasty surgery is severe. Failure to provide adequate analgesia impedes aggressive physical therapy and rehabilitation, which is critical to maintaining joint range of motion, and potentially delays hospital dismissal as well as increase the risk of thromboembolism.

Traditionally, postoperative analgesia following total joint replacement was provided by either intravenous patient-controlled analgesia (PCA) or epidural analgesia. However, each technique has distinct advantages and disadvantages. For example, opioids do not consistently provide adequate pain relief and often cause sedation, confusion and delirium, constipation, nausea and vomiting, and pruritus. Epidural infusions containing local anesthetics (with or without an opioid) provide superior analgesia but are associated with hypotension, urinary retention, motor block limiting ambulation, and spinal hematoma secondary to anticoagulation.1

Recently, single-dose and continuous peripheral nerve techniques that block the lumbar plexus (fascia iliaca, femoral, and psoas compartment blocks) with or without sciatic nerve blockade have been used with success for total joint replacement patients.1,4 Appreciation of the indications, benefits, and side effects associated with both conventional and novel analgesic approaches is paramount to maximizing rehabilitative efforts and improving patient satisfaction.

Multimodal Analgesia

Multimodal analgesia is a multidisciplinary approach to pain management, with the aim of maximizing the positive aspects of the treatment while limiting the associated side effects.2,5,6 Because many of the negative side effects of analgesic therapy are opioid-related (and dose dependent), limiting perioperative opioid use is a major principle of multimodal analgesia. Anti-inflammatory medications and acetaminophen are valuable adjuvants to systemic opioids. The addition of nonopioid analgesics reduces opioid use, improves analgesia, and decreases opioid-related side effects. The use of peripheral or neuraxial regional anesthetic techniques and a combination of opioid and nonopioid analgesic agents for breakthrough pain results in superior pain control and attenuation of the stress response, and decreases opioid requirements.7,9

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The optimal bolus dose is determined by the relative potency of the opioid; insufficient dosing results in inadequate analgesia, whereas excessive dosing increases the potential for side effects including respiratory depression. Likewise, the lockout interval is based on the onset of analgesic effects; too short of a lockout interval allows patients to self-administer additional medication prior to achieving the full analgesic effect (and may result in accumulation or overdose of the opioid). A prolonged lockout interval will not allow adequate analgesia. Although the optimal bolus dose and lockout interval are not known, ranges have been determined. Varying the settings within these ranges appears to have little effect on analgesia or side effects.

Although most PCA devices allow the addition of a background infusion, routine use in adult opioid-naive patients is not recommended. However, there may be a role for a background opioid infusion in opioid-tolerant patients. Due to the variation in patient pain tolerance, PCA dosing regimens may need to be adjusted to maximize the benefits and minimize the incidence of side effects.

The adverse effects of opioid administration can cause serious complications in patients undergoing major orthopedic procedures. In a systematic review, Wheeler et al reported gastrointestinal side effects (nausea, vomiting, and ileus) in 37%, cognitive effects (somnolence and dizziness) in 34%, pruritus in 15%, urinary retention in 16%, and respiratory depression in 2% of patients receiving PCA opioid analgesia.

### Oral Opioids

Oral opioids are available in immediate-release and controlled-release formulations. Although immediate-release oral opioids are effective in relieving moderate to severe pain, they must be administered as often as every 4 hours. When these medications are prescribed “as needed,” there may be a delay in the administration and a subsequent increase in pain. Furthermore, interruption of the dosing schedule, particularly during the night, may lead to an increase in pain. The adverse effects of oral opioid administration are considerably less compared to intravenous administration and are mainly gastrointestinal in nature. Tramadol (Ultram) is a centrally acting analgesic that is structurally related to morphine and codeine (but is not truly an opioid). Its analgesic effect is through binding to the opioid receptors as well as blocking the reuptake of both norepinephrine and serotonin. Tramadol has gained popularity due to its low incidence of adverse effects, specifically respiratory depression, constipation, and abuse potential. Thus, tramadol may be used as an alternative to opioids in a multimodal approach to postoperative pain, specifically in patients who are intolerant to opioid analgesics.

### Nonopioid Analgesics

The addition of nonopioid analgesics (acetaminophen and nonsteroidal anti-inflammatory drugs [NSAIDs]) reduces opioid use, improves analgesia, and decreases opioid-related side effects. The multimodal effect is maximized through selection of analgesics that have complementary sites of action. For example, acetaminophen acts predominantly centrally, whereas other NSAIDs exert their effects peripherally. The NSAIDs have a mechanism of action through the cyclo-oxygenase (COX) enzymatic pathway and ultimately block 2 individual prostaglandin pathways. The COX-1 pathway is involved in prostaglandin-E2-mediated gastric mucosal protection and thromboxane effects on coagulation. The inducible COX-2 pathway is involved primarily in the generation of prostaglandins included in the modulation of pain and fever but has no effect on...
platelet function or the coagulation system. In general, NSAIDs block both the COX-1 and COX-2 pathways.

The introduction of specific COX-2 inhibitors represented a breakthrough in the treatment of pain and inflammation. However, despite their efficacy, 2 (rofecoxib [Vioxx] and valdecoxib [Bextra]) of 3 COX-2 inhibitors were voluntarily removed from general use due to an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, after 18 months of treatment. Celecoxib (Celebrex) is currently the only COX-2 inhibitor available in the United States, although the Food and Drug Administration has requested that safety information be included regarding potential cardiovascular and gastrointestinal risks of all selective and nonselective NSAIDs except aspirin.9

The major side effects limiting the use of NSAIDs for postoperative pain control (renal failure, platelet dysfunction, and gastric ulcers or bleeding) are related to the nonspecific inhibition of the COX-1 enzyme.12 Advantages of the COX-2 inhibitors are the lack of platelet inhibition and a decreased incidence of gastrointestinal effects.

All NSAIDs have the potential to cause serious renal impairment. Inhibition of the COX enzyme may have only minor effects in the healthy kidney but unfortunately can lead to serious side effects in elderly patients or those with a low-volume condition (blood loss, dehydration, cirrhosis, or heart failure). Therefore, NSAIDs should be used cautiously in patients with underlying renal dysfunction, specifically in the setting of volume depletion due to blood loss.13 Similar to the COX-2 inhibitors, NSAIDs also interfere with the inhibitory COX-1 effect of aspirin on platelet activity and may counter the cardioprotective effects.13

The effect of NSAIDs on bone formation and healing also is of concern to the orthopedic population. Although the data are conflicting, there is evidence from animal studies that COX-2 inhibitors may inhibit bone healing.14 Thus, the adverse effects of COX-2 inhibitors must be weighed against the benefits.

The recent retraction of numerous peer-reviewed articles by Dr Scott S. Reuben, a leading investigator in the perioperative (and multimodal) effects of NSAIDs and COX-2 inhibitors, has necessitated a reanalysis of the impact of these analgesics.15 Overall, the analgesic and opioid-sparing effects of these analgesics in the immediate postoperative period remains well documented. However, a preemptive effect is no longer unequivocal, and long-term benefits (including attenuation of chronic pain) remain unproven.15

**Neuraxial Analgesia**

A variety of single-dose and continuous infusion neuraxial techniques may be performed to provide analgesia following major lower-extremity surgery. Administration of a single dose of neuraxial opioid may be efficacious as a sole analgesic agent for moderate pain of limited duration, such as that associated with primary arthroplasty.16 However, the prolonged moderate-severe pain associated with revision arthroplasty typically necessitates either supplemental oral or intravenous analgesic agents, or a continuous neuraxial infusion.

**Single-Dose Spinal and Epidural Opioids**

Neuraxial opioids provide superior analgesia compared to systemic opioids. The onset and duration of neuraxial opioids are determined by the lipophilicity of the drug. For example, lipophilic opioids such as fentanyl provide a rapid onset of analgesia, limited spread within the cerebrospinal fluid (and less respiratory depression), and rapid clearance and resolution. Conversely, hydrophilic opioids including morphine and hydromorphone have a longer duration of action but are associated with a higher frequency of side effects such as pruritus, nausea and vomiting, and delayed respiratory depression10,17 (Table 2).

A sustained released formulation of epidural morphine (DepoDur) recently has been released. Limited information exists regarding its efficacy following orthopedic surgery; only 3 investigations have compared DepoDur with conventional intravenous morphine following total hip or knee replacement for a combined series of 285 patients. Importantly, a multimodal analgesic approach, including administration of NSAIDs, peripheral blocks, or both, has not been compared to DepoDur.18,20 The analgesic effect is present for approximately 48 hours. Unfortunately, DepoDur is not to be administered in the presence of local anesthetics (ie, an epidural anesthetic may not be converted to provide epidural analgesia).

It is important to note that the central side effects of opioid administration are much more common (and more prolonged) following neuraxial administration compared to all other routes. For example, in a large series, the frequency of pruritus, nausea and vomiting, and respiratory depression were 37%, 25%, and 3% with an intrathecal morphine injection.21 Therefore, patients who exhibit sensitivity to an opioid when administered systemically should not receive that opioid neuraxially.

**Epidural Analgesia**

Epidural analgesia may consist of an opioid, local anesthetic, or combination local anesthetic-opioid infusion (Table 2). The combination of a local anesthetic-opi-
oid creates a synergistic analgesic effect and allows lower concentrations of each component of the solution. For example, without an opioid adjuvant, the concentration of a local anesthetic solution may be sufficiently high to result in a dense sensory and motor block; patients may be unable to ambulate or void.23 Likewise, a pure opioid epidural infusion may not provide adequate analgesia.23

Therefore, most epidural solutions consist of dilute concentrations of both local anesthetic and opioid. This results in superior analgesia, minimal sensory and motor block (allowing ambulation and mobilization), and decreased incidence of opioid-related side effects (nausea, vomiting, and pruritus).24 Although epidural analgesia provides excellent analgesia, the associated risk of spinal hematoma in (anticoagulated) patients with indwelling epidural catheters has led to a search for alternative methods of providing postoperative analgesia following major orthopedic surgery.25

**PERIPHERAL REGIONAL ANESTHETIC TECHNIQUES**

Lower-extremity peripheral techniques, which allow complete unilateral blockade, traditionally have been underused.26 In part, this is due to the widespread acceptance and safety of spinal and epidural anesthesia. Furthermore, unlike the brachial plexus, the nerves supplying the lower extremity are not anatomically clustered where they can be easily blocked with a relatively superficial injection of local anesthetic.

Because of the anatomic considerations, lower-extremity blocks are technically more difficult and require more training and practice before expertise is acquired. Many of these blocks were classically performed using paresthesia, loss of resistance, or field block technique, with variable success. Advances in needles, catheters, and nerve stimulator technology have facilitated localization of neural structures and improved success rates. These blocks are safe and have certain advantages such as postoperative pain relief and lack of complete sym

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**Table 2**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intrathecal (Single Injection)</th>
<th>Epidural (Epidural Continuous Infusion)</th>
<th>Duration of Analgesia</th>
<th>Opioid Concentration</th>
<th>Epidural Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>5-25 µg</td>
<td>25-100 µg</td>
<td>2-4 h</td>
<td>5-10 µg/mL</td>
<td>40-80 µg/h</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.04-0.08 mg</td>
<td>0.5-1 mg</td>
<td>12-18 h</td>
<td>5-10 µg/mL</td>
<td>0.04-0.08 mg/h</td>
</tr>
<tr>
<td>Morphine (Duramorph)</td>
<td>0.2-0.3 mg</td>
<td>1-5 mg</td>
<td>18-24 h</td>
<td>100 µg/mL</td>
<td>400-800 µg/h</td>
</tr>
<tr>
<td>Extended release epidural morphine (DepoDur)</td>
<td>5-25 mg</td>
<td></td>
<td>48 h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Units may vary across agents for single dosing (µg, mg).
- Epidural solutions for major orthopedic surgery are typically local anesthetics (ropivacaine 0.2% or bupivacaine 0.0625-0.125%) with an opioid adjuvant. Only preservative-free solutions may be used.
- The concentration of the opioid is selected to achieve an infusion rate of 6-10 mL/h. Lower infusion rates may not deliver adequate analgesia, while higher infusion rates will be associated with motor block and inability to ambulate.


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Selection of regional analgesic technique is dependent on the surgical site.32,33 For example, the psoas compartment approach to the lumbar plexus is preferable for surgery to the hip because it is the most proximal lumbar plexus technique, provides complete block of the lumbar plexus, and the needle or catheter insertion site is distant from the surgical incision (allowing preemptive placement). However, for patients undergoing total knee replacement or for patients in whom a psoas approach may be contraindicated due to infection or existing coagulopathy, a more distal approach to the lumbar plexus (femoral or fascia iliaca blockade) is warranted.
knee is provided by the lumbar plexus, adequate analgesia may be achieved with a continuous lumbar plexus technique alone (a single injection, rather than a continuous sciatic technique, is sufficient).\textsuperscript{34,35}

**PERIOPERATIVE OUTCOMES**

For the past decade, applications have focused on prolonged postoperative analgesia (with an indwelling catheter) to assist rehabilitation and hospital discharge.\textsuperscript{2,3,35,36} Several studies have demonstrated that unilateral peripheral block provides a quality of analgesia and surgical outcomes similar to that of continuous epidural analgesia but with fewer side effects.\textsuperscript{4}

Recent innovations emphasize continuous peripheral nerve blocks with scheduled (acetaminophen and tramadol) and as-needed (oxycodone) analgesics; no intravenous opioids are administered. Using strict criteria, 90% of patients undergoing minimally invasive total hip or knee replacement using a comprehensive, preemptive, multimodal analgesic regimen emphasizing peripheral nerve block achieved readiness for hospital discharge within 48 hours.\textsuperscript{2} When a similar regimen was applied to patients undergoing joint replacement with conventional techniques, there also were significantly improved perioperative outcomes and fewer adverse events compared to patients receiving traditional intravenous opioids during the initial postoperative period. Improved perioperative outcomes include a shortened hospital length of stay, and a significant reduction in postoperative urinary retention and ileus formation.\textsuperscript{5}

Finally, because hospital costs appear to be directly related to the length of hospital stay, analgesic techniques associated with improved recovery and reduced complications may decrease the total direct medical costs among these patients. The reduction in mean cost is primarily associated with lower hospital-based (Medicare Part A) costs, with the greatest overall cost difference appearing in patients with significant comorbidities.\textsuperscript{36} These studies support the movement toward continuous peripheral technique as the optimal analgesic method following total knee and hip arthroplasty.

**CONCLUSION**

Analgesic approaches that minimize opioids, such as the use of peripheral nerve blocks and a combination of analgesic agents, allow early mobilization and facilitate rehabilitation as well as decrease hospital stay and costs. Continued investi-

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**Table 3**

<table>
<thead>
<tr>
<th>Peripheral Technique</th>
<th>Technique of Neural Localization</th>
<th>Area of Blockade</th>
<th>Duration of Blockade\textsuperscript{a}</th>
<th>Perioperative Outcomes\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar plexus</td>
<td>Neural stimulation, paresthesia</td>
<td>Femoral, partial lateral femoral cutaneous and obturator</td>
<td>12-18 h</td>
<td>Improved analgesia and joint range of motion, decreased hospital stay compared to PCA; fewer technical problems, less urinary retention, and hypotension than epidural analgesia (TKA)</td>
</tr>
<tr>
<td>Femoral</td>
<td>Loss of resistance</td>
<td>Femoral, partial lateral femoral cutaneous, obturator and sciatic (S1)</td>
<td>12-18 h</td>
<td>Improved analgesia and joint range of motion compared to PCA (TKA)</td>
</tr>
<tr>
<td>Fascia iliaca</td>
<td>Loss of resistance</td>
<td>Complete lumbar plexus; occasional spread to sacral plexus or neuraxis</td>
<td>12-18 h</td>
<td>Reduced morphine consumption, pain at rest compared to PCA (TKA, THA); reduced blood loss (THA); analgesia equivalent to continuous femoral block (TKA)</td>
</tr>
<tr>
<td>Psoas compartment</td>
<td>Neural stimulation, loss of resistance</td>
<td>Complete lumbar plexus; occasional spread to sacral plexus or neuraxis</td>
<td>18-30 h</td>
<td>Supplemental sciatic required (TKA); proximal approaches allow block of posterior femoral cutaneous nerve (TKA)</td>
</tr>
<tr>
<td>Sciatic</td>
<td>Neural stimulation, paresthesia</td>
<td>Posterior thigh and leg (except saphenous area)</td>
<td>18-30 h</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** PCA, patient-controlled analgesia; THA, total hip arthroplasty; TKA, total knee arthroplasty.

\textsuperscript{a}Duration of block performed with long-acting local anesthetic (bupivacaine or ropivacaine); intermediate acting agents (lidocaine or mepivacaine) will resolve after 4-6 h.

\textsuperscript{b}Outcomes most marked in patients who receive a continuous lumbar plexus catheter with infusion of 0.1%-0.2% bupivacaine or ropivacaine at 6-12 mL/h for 48-72 h.

nations are necessary to further advance the perioperative analgesic management of these complex patients.

**REFERENCES**


