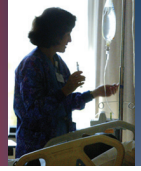


By Rosemary C. Polomano, PhD, RN, FAAN, Mechele Fillman, MSN, NP-C, Nicholas A. Giordano, BSN, RN, April Hazard Vallerand, PhD, RN, FAAN, Kelly L. Wiltse Nicely, PhD, CRNA, and Carla R. Jungquist, PhD, RN, ANP-BC, FAAN

Multimodal Analgesia for Acute Postoperative and Trauma-Related Pain

Current recommendations from evidence-based guidelines and expert consensus reports.

ABSTRACT: Multimodal analgesia, which combines analgesic drugs from different classes and employs analgesic techniques that target different mechanisms of pain, is recommended in the treatment of acute postoperative and trauma-related pain because its synergistic effect maximizes pain relief at lower analgesic doses, thereby reducing the risk of adverse drug effects. Using a case-based approach, this article reviews various multimodal analgesic therapies used in the treatment of acute pain; discusses their benefits; and summarizes findings from related research, recommendations from evidence-based practice guidelines, and expert consensus reports.

Keywords: acute pain, multimodal analgesia, nondrug measures for acute pain, opioids, postoperative pain

At 8 AM, MG, a 47-year old Hispanic man, arrives by ambulance at a level II trauma center ED, having been involved in a multivehicle accident. (This case is a composite based on our clinical experience.) MG is alert, oriented, and able to communicate. He is immediately taken to the trauma bay for triage. He reports pain, which he rates as a 9 on a 0-to-10-point pain scale, in his left upper arm and shoulder, lateral chest area, and anterior lower leg. He has a heart rate of 134 beats per minute, his blood pressure is 160/100 mmHg, and his respirations are shallow at a rate of 30 breaths per minute. He is obese, with a body mass index of 36.9 kg/m^2, and has no known drug allergies. The ED nurse promptly medicates him for pain with IV fentanyl 100 mcg given over one minute, delivers oxygen by nasal cannula at a rate of 4 L/min, initiates cardiac monitoring and continuous pulse oximetry, and draws blood for hematologic and chemistry profiles.

When removing his trousers, the nurse sees that his left tibia is protruding through the skin and applies a sterile pressure dressing to minimize bleeding and reduce risk of infection. Stat X-rays of the painful areas reveal a closed fracture of the upper left humerus, two left rib fractures, and an extensive compound left tibial fracture. Both injured extremities are immobilized with splints. The nurse accompanies MG to radiology for computed tomography scans of the head, cervical spine, chest, abdomen, and pelvis, which show no additional traumatic injuries.

After MG is returned to the ED, his wife arrives and informs the ED nurses that her husband takes nebivolol 10 mg once a day for poorly controlled hypertension and that his primary care physician has recently expressed concern about his kidneys. Since he was diagnosed with obstructive sleep apnea two years ago, MG has used a continuous positive airway pressure (CPAP) device for sleep. MG's wife accompanies him to the preoperative holding area where he is prepared for surgery to stabilize his fractured tibia.

The trauma team, preoperative nurse, and certified registered nurse anesthetist (CRNA) agree to start multimodal analgesia prior to surgery. MG's nurse cautions that his blood test shows a mildly elevated serum creatinine level of 2.1 mg/dL, which raises concerns about giving him a nonsteroidal anti-inflammatory drug (NSAID), such as IV ketorolac or ibuprofen. The team decides to administer IV acetaminophen 1,000 mg and IV fentanyl 75 mcg. MG's CRNA performs a left femoral nerve block, injecting 15 mL of the local anesthetic ropivacaine 0.5%. MG now rates his pain as a 4 on a 0-to-10-point pain scale. His heart rate is 90 beats per minute, his respiratory rate is 22 breaths per minute, and his blood pressure is 130/90 mm/Hg.

Multimodal analgesia or "balanced analgesia" combines analgesics from two or more drug classes or

analgesic techniques that employ different mechanisms of action, targeting different (peripheral or central) pain pathways, thus achieving a synergistic effect at lower analgesic doses.[1,2] This article reviews various multimodal analgesic interventions for acute pain, discusses their benefits, and summarizes expert consensus recommendations and evidence-based practices for using multimodal therapy.

HOW MULTIMODAL ANALGESIA WORKS

Multimodal analgesia may employ the following pharmacologic approaches[3]:

- analgesics, including opioids, nonopioid analgesics (such as acetaminophen and NSAIDs), the gabapentinoids (gabapentin and pregabalin), serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, and N-methyl-D-aspartate (NMDA) receptor antagonists
- neuraxial (epidural and intrathecal) interventions
- peripheral nerve block interventions
- intraarticular and wound infiltration with local analgesia

Physical and behavioral health interventions are also a part of multimodal analgesic strategies. Introduced more than two decades ago,[2] multimodal analgesia is currently recommended for treating both acute[1,3] and chronic[4] pain. The synergy created when multimodal regimens are used to target discrete components of the peripheral and central pain pathways provides effective analgesia at lower opioid dosing, reducing related risk and producing fewer adverse effects (see Figure 1).[5-8]

Each phase of the nociceptive pain process may be targeted by some type of analgesic:

- **Transduction,** in which activated nociceptors (the free nerve endings of primary afferent neurons that sense noxious stimuli) release an electric signal, may be disrupted by NSAIDs and membrane stabilizing agents, such as gabapentinoids.
- **Transmission,** in which the electric signal moves from the site of injury to the spinal cord and brain, may be interrupted by local anesthetics and gabapentinoids.
- **Perception,** the awareness of pain in the somatosensory cortex of the brain, may be moderated by systemic opioids and NMDA receptor antagonists.
- **Descending and local modulation,** the adaptive processes through which pain impulses may be enhanced or diminished either centrally (by descending pathways that originate in the brain and project to the spinal cord) or in the periphery, are responsive to such interventions as neuraxial therapy, peripheral nerve blocks, and local infiltration analgesia.

Because of their opioid-sparing effects, multimodal strategies are particularly useful and often indicated for patients who are opioid dependent or opioid tolerant.[9] Multimodal analgesic plans of care should be individualized to the

- patient.
- type of pain.
- mechanism of pain (inflammatory or neuropathic).
- type of surgical procedure.
- location of pain.
- expected duration of pain.

PREVENTIVE MULTIMODAL ANALGESIA

The timing of multimodal analgesia is an important consideration in its use. After consulting the surgical team and clinical nurses, MG's CRNA administers IV acetaminophen and fentanyl and performs a femoral nerve block prior to surgery. This preoperative analgesic strategy is part of MG's "preventive analgesia." Traditionally, preoperative analgesia has been called "preemptive analgesia," but Dahl and Kehlet contend that the term "preventive" better explains the assumption on which the practice is based—"that the only way to prevent central sensitization might be to completely block any pain and afferent signals from the surgical wound from the time of incision until final wound healing."[10] Preventing the likelihood of central sensitization is important because, in theory, it reduces the likelihood of chronic postsurgical pain syndrome (discussed in "Assessing and Managing Acute Pain: A Call to Action," on page S4).

There is evidence that the efficacy of systemic multimodal regimens is procedure-specific.[11] In their extensive review, Pozek and colleagues conclude that when multimodal approaches do not prevent central sensitization, it may be because of inadequate duration, as these therapies are often administered only intraoperatively and not continued throughout the postoperative period required for healing and recovery.[12] Nurses must ensure that patients receiving multimodal analgesia have a plan in place to manage pain effectively during hospitalization and following discharge.

MG's plan for preventive multimodal analgesia. With preoperative multimodal analgesia initiated, MG's team discusses plans for his postoperative pain control during surgery. He'll receive systemic therapy with opioid analgesics, a nonopioid (acetaminophen), and a gabapentinoid (gabapentin) to manage his postoperative pain and pain from his left humerus and rib fractures. A femoral nerve catheter will deliver a continuous infusion of the local anesthetic ropivacaine, providing a peripheral nerve block to alleviate pain from his tibial fracture surgery. Compared with bupivacaine, ropivacaine provides optimal continuous

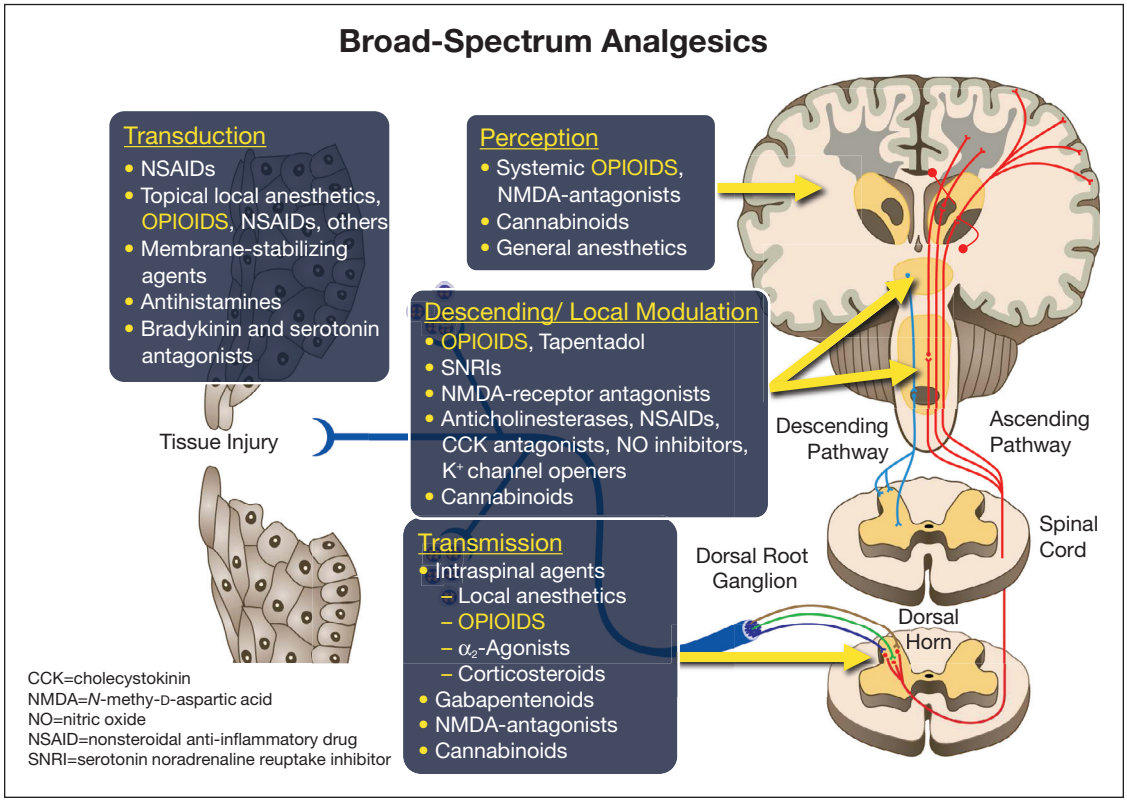


Figure 1. The broad-spectrum analgesics used in multimodal regimens can be used to target each phase of the nociceptive pain process. Opioids are highlighted to indicate their specific activity on pain signaling pathways. Reproduced from Gudin J. Opioid therapies and cytochrome p450 interactions. *J Pain Symptom Manage* 2012; 44(6 Suppl), S4-S14, with permission from Elsevier.

regional analgesia for preoperative, intraoperative, and postoperative pain control while producing a lower incidence and degree of motor blockade.[13] The team debates whether an NSAID should be added to MG's regimen, given the nature of his bone pain, but ultimately decides against that strategy on account of his mild renal impairment.

MG's initial pain management plan includes the following:

- IV hydromorphone 0.2 mg demand dose by patient-controlled analgesia (PCA) with a lock-out interval of 10 minutes (up to 1.2 mg per hour) to start immediately after surgery
- IV acetaminophen 1,000 mg every six hours for 24 hours to start immediately after surgery, then acetaminophen 650 mg by mouth every four hours
- gabapentin 200 mg by mouth every eight hours to start as soon as MG can tolerate sips of water
- ropivacaine 0.2% by continuous infusion through a left femoral nerve catheter at 6 mL per hour for up to 36 hours
- IV ondansetron 4 mg every four to eight hours for nausea and vomiting
- docusate sodium 100 mg by mouth twice a day as a stool softener, and senna 15 mg by mouth twice a day for preventing opioid-induced constipation (to be held if the patient has a loose stool or diarrhea)

SYSTEMIC MULTIMODAL ANALGESICS

Nonopioids. For acute pain management in the perioperative setting, the American Society of Anesthesiologists Task Force on Acute Pain Management advocates around-the-clock nonopioid analgesics, unless contraindicated, as first-line agents and as adjuvant agents to opioids.[14]

NSAIDs, which are indicated for pain from inflammation, are an integral part of multimodal acute pain management. NSAIDS inhibit cyclooxygenase (COX), an enzyme that synthesizes prostaglandins. The two most common forms of COX are COX-1, which synthesizes prostaglandins that are important

in such functions as platelet aggregation, gastric cytoprotection, and kidney function, and COX-2, which synthesizes prostaglandins that promote inflammation and pain at sites of injury.[15]

The extent of enzyme inhibition varies among the NSAIDs. Some are more potent inhibitors of prostaglandin synthesis, while others are more effective at mediating nonprostaglandin effects.[16] Patient response to different NSAIDs varies, which suggests that transitioning from one NSAID to another in a different class could provide improved pain relief. Preoperative COX inhibitors (primarily selective COX-2 inhibitors)[17] and postoperative nonselective and selective NSAIDs[18] have been associated with reduced postoperative opioid consumption. In patients undergoing bowel surgery, administering ketorolac (a nonselective NSAID) in addition to IV morphine by PCA was found to reduce morphine consumption by 18.3% and to speed the return of normal bowel function.[19]

Adverse events from NSAIDs include platelet inhibition (leading to bleeding), inhibition of prostaglandin formation required for normal gastrointestinal and renal function, cardiotoxicity (selective COX-2 inhibitors), hepatotoxicity, and drug-induced asthmatic responses (nonselective COX inhibitors).[15] NSAID toxicity profiles vary; nurses should refer to drug information resources specific to each. In general, NSAIDs should be avoided in patients who have or are at risk for bleeding, gastrointestinal ulceration, cardiovascular events, or renal or hepatic impairment that can significantly affect drug clearance and increase oral bioavailability.[1,20] The benefits of pain relief from NSAIDs must be weighed against risks of adverse effects, including impaired bone healing.[21,22] Evidence supports that ketorolac given in the first 24 hours after surgery does not affect time to healing or incidence of bone nonunion after a fracture.[23] While debates exist over whether NSAIDs cause anastomotic leaks after bowel surgery, data indicate that the risk of anastomotic leakage after colorectal surgery is no greater with the use of NSAIDs.[24]

Acetaminophen. Although acetaminophen's mechanism of action is not well understood, it is believed that its primary analgesic effect is induced by its inhibition of COX, interference with NMDA receptor activation, and promotion of descending inhibitory serotonergic pathways that interfere with spinal nociceptive processing.[25] IV acetaminophen is available in the United States, indicated for the treatment of mild to moderate pain and as an adjunct to opioid analgesics for the treatment of moderate to severe pain. For adults and adolescents weighing at least 50 kg (110 lb), recommended IV dosing is 1,000 mg every six hours or 650 mg every four hours, with a maximum single IV dose of 1,000 mg and a minimum dosing interval of four hours. The maximum daily dose of acetaminophen is 4,000 mg per day (including all routes of administration and all acetaminophen-containing products including combination products). A recent Cochrane review that included 75 studies of patients receiving IV acetaminophen (47 studies) or the prodrug form of IV acetaminophen (25 studies) or both (three studies) for postoperative pain showed that 36% of participants overall experienced at least 50% pain relief over four hours compared with 16% of participants receiving placebo.[26] In one of the studies reviewed, patients who had undergone either total knee or hip replacement surgery and were given adjuvant IV acetaminophen 1,000 mg at six-hour intervals in addition to opioid therapy reduced opioid consumption by 46% (8 mg morphine equivalent) over the first six hours ($P < 0.01$) and by 33% (19 mg morphine equivalent) over 24 hours ($P < 0.01$), compared with patients given opioid therapy and placebo.[27] Other than increased bioavailability, the IV formulation of acetaminophen has no clear advantage over the oral form in patients able to take oral medications, as both are effective and have similar safety profiles.[28]

Smith provides a table of studies showing that IV acetaminophen and NSAIDs are comparable in their analgesic effects.[29] Acetaminophen is contraindicated in patients with known hypersensitivity to acetaminophen or its excipients and in patients with severe hepatic impairment or severe active liver disease.

The gabapentinoids, gabapentin and pregabalin, are anticonvulsants, often used orally, that are approved to treat neuropathic pain. They act as membrane stabilizers, presumably by inhibiting the transmission of painful stimuli, and also reduce the potential for central sensitization in the dorsal horn.[30] Optimal doses for preoperative and postoperative oral gabapentin and pregabalin have not been determined, with dose ranges varying, respectively, from 300 to 1,200 mg daily and from 50 to 300 mg daily.[31] The greater bioavailability of pregabalin makes it easier to titrate to effect for short-term use.

A meta-analysis of 17 randomized controlled trials that included a total of 1,793 inpatients undergoing elective surgery found that, regardless of dose, those receiving preoperative gabapentin (n = 895) within 24 hours of surgery had a significant reduction ($P < 0.001$) in opioid consumption compared with controls (n = 898).[32] This reduction was most pronounced in patients undergoing breast cancer surgery; cholecystectomy; and orthopedic, spinal, or thyroid surgeries. Others have documented 24-hour opioid-sparing effects and decreased pain with perioperative gabapentin for abdominal hysterectomy and spinal surgery.[33] Gabapentin 1.2 g per day by

mouth, administered one day before and two days after lower limb surgery, also had favorable effects on pain and analgesic consumption when used as an adjunct to epidural analgesia.[34] Compared with placebo, when oral pregabalin was administered to patients undergoing total hip arthroplasty at dosages of 150 mg before surgery and 75 mg twice a day after surgery, both during hospitalization and for seven days after discharge as an adjunct to the standard postsurgical regimen (oral celecoxib 200 mg every 12 hours for 72 hours and morphine, followed by an oral opioid–acetaminophen product), 24-hour opioid consumption and pain scores were significantly reduced ($P < 0.05$) in the first seven days after discharge.[35] There were no significant differences in pain scores between the pregabalin- and placebo-treated groups during hospitalization through postoperative day 4.

The NMDA receptor antagonists, IV ketamine and magnesium, and less commonly IV memantine, are used to treat acute pain. These drugs are potent antihyperalgesic agents that modulate central sensory processing of pain and potentiate opioid-induced analgesia.[36] NMDA receptor antagonists are thought to reduce central sensitization implicated in the development of postsurgical pain syndromes. When McNicol and colleagues reviewed studies in which intraoperative and postoperative subanesthetic IV and epidural ketamine was administered to patients undergoing a variety of different surgeries, including thoracotomy, mastectomy, hysterectomy, and various orthopedic surgeries, they concluded that perioperative IV, but not epidural, ketamine reduced postsurgical pain syndromes at three and six months.[37] Subanesthetic IV ketamine also has opioid-sparing effects. In a review of 34 efficacy studies of IV ketamine delivered at dosages of less than 1.2 mg/kg per hour with or without a bolus dose of 1 mg/kg to treat pain from various surgeries, 23 studies reported a 40% mean reduction in opioid consumption.[38] While no major adverse events were noted, minor ones included nausea, vomiting, dry mouth, and (rarely) hallucinations.

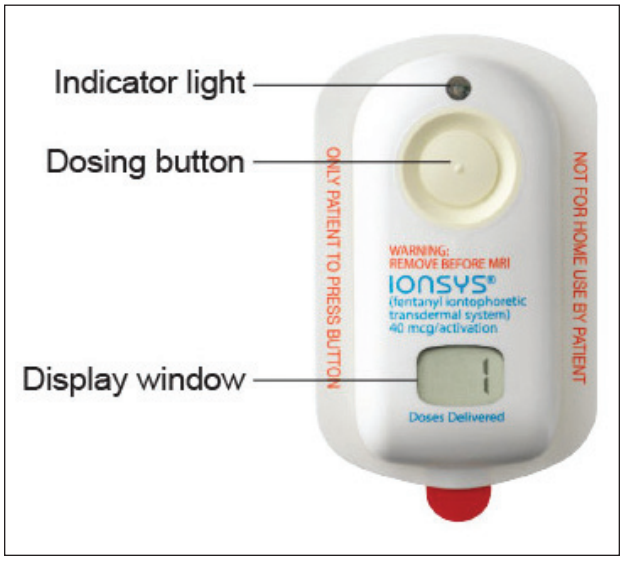


Figure 2. The IONSYS fentanyl iontophoretic transdermal system. Photograph reproduced with permission from The Medicines Company, Parsippany, NJ. The Medicines Company has not reviewed the content of this article for accuracy, and permission does not imply endorsement of any statements regarding IONSYS that may be contained within this article. The Medicines Company does not recommend the use of IONSYS in any manner other than as described in the full prescribing information, available at www.ionsys.com/pdfs/ionsys-prescribing-information.pdf.

Alpha-2 agonists, such as clonidine and dexmedetomidine, exert antinociceptive activity by stimulating alpha-2 adrenoreceptors located in the central nervous system.[39] When used to manage postoperative pain, these agents have demonstrated 24-hour opioid-sparing effects.[40] Clonidine can be administered by IV, epidural, intrathecal, perineural, intraarticular, oral, transdermal, and local infiltration routes; dexmedetomidine is more commonly administered by IV and neuraxial routes. Hypotension is a common adverse effect of perioperative multimodal regimens containing clonidine[39] and dexmedetomidine.[41] Dexmedetomidine also increases the risk of postoperative bradycardia[39] and is typically administered only during surgery and in settings in which patients are closely monitored, such as postanesthesia care or critical care units.

Opioids. There are several subtypes of opioids, of which the most common and potent for effective pain control are the pure opioid agonists, such as morphine, hydromorphone, fentanyl, and oxycodone. Opioid agonists[42]

- stimulate μ receptors found primarily in the peripheral and central nervous systems.
- inhibit nociception in the spinal cord.
- activate descending pain pathways controlled by circuits from the forebrain and midbrain.

For acute pain, opioids are generally administered by IV and oral routes. Bioavailability of opioid medications varies among the specific subtypes, with the route of administration, and among patients, making it difficult to determine milligram-to-milligram equianalgesic dose ratios.[43] Patanwala and colleagues provide suggested equianalgesic dose ratios for IV and oral opioids, but point out that when converting from IV to oral dosing and vice versa, especially

with repetitive dosing, clinicians should assess the active metabolite.[43]

Adverse events associated with μ-opioid agonists include confusion, sedation, hypotension, constipation, dizziness, pruritus, headache, nausea, vomiting, and respiratory depression.[44] In addition, the continued use of opioids, even for acute pain, can lead to physical dependence and addiction. For information on opioid prescribing, administration, and monitoring practices to reduce and address opioid abuse and addiction, nurses should consult the 2015 Washington State Agency Medical Directors' Group guidelines, available online at www.agencymeddirectors.wa.gov. Interactions between opioids and other medications can interfere with opioid metabolism, particularly when other medications are also metabolized via the cytochrome P-450 enzyme system. Nurses should be familiar with factors—such as multidrug regimens, advanced age, and impaired hepatic function—that can affect the cytochrome P-450 pathways, increasing the risk of opioid adverse effects and drug–drug interactions.[5,45] A rare occurrence with perioperative opioids is opioid-induced hyperalgesia (OIH), a nociceptive sensitization associated with opioid use.[46] It is often very difficult to diagnose OIH, which is frequently confused with acute opioid tolerance, a progressive decrease in the analgesic response to opioids. OIH can happen with any opioid, but it has been primarily associated with intraoperative remifentanil, though data on other intraoperative opioids are limited.[47] When OIH is suspected, opioid doses should be reduced or temporarily discontinued (unless the patient is opioid dependent) while clinicians determine whether pain lessens with the administration of other multimodal analgesic agents.

PCA, which allows self-administration of a prescribed opioid dosage on demand through a delivery device, is a common method of delivering opioids to treat acute postoperative pain, trauma-related pain, severe cancer-related pain, chemotherapy- or radiotherapy-induced mucositis, and pain from sickle cell crisis. PCA is recommended for patients who "require analgesia for more than a few hours and have adequate cognitive function to understand the device and its safety limitations."[1]

Morphine and hydromorphone are most frequently prescribed for IV PCA; fentanyl is also used, but less often. In one multicenter study comparing the three opioids, the incidences of opioid-induced respiratory depression, headache, confusion, agitation, and hallucination were not significantly different among the three, though IV fentanyl had a significantly lower rate of such common opioid-induced adverse reactions as nausea, vomiting, pruritus, urinary retention, and sedation.[48] Neto and colleagues suggest that

Figure 3. The Zalviso sufentanil sublingual tablet system. Photograph reproduced with permission from AcelRx Pharmaceuticals, Inc., Redwood City, CA.

methadone, which is rarely used with IV PCA for acute pain, may have advantages in alleviating postsurgical pain from total hip arthroplasty because it acts on pain pathways through NMDA receptor blockade, μ-opioid receptor activation, and norepinephrine and serotonin reuptake inhibition in the central nervous system,[49] possibly reducing the likelihood of central sensitization. In that study, methadone significantly reduced overall opioid consumption compared with morphine.[49] Because of methadone's highly variable elimination half-life, ranging from eight to 90 hours,[49] and its short analgesic duration (four to eight hours), which can lead to drug accumulation during titration, methadone should be prescribed only by clinicians experienced in its use.[49]

In setting up PCA devices and changing drug cartridges, nurses must verify that the correct drug is being administered to the correct patient at the correct dosage; a double check by two RNs is often hospital policy. A loading dose, which is generally higher than the demand dose, is typically given prior to the start of IV PCA. Evidence summarized in acute pain management guidelines issued by the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (available online at http://fpm.anzca.edu.au/documents/apmse4_2015_final) cautions against the use of a continuous background or basal infusion with opioid-naive patients, as this can increase the

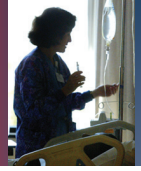
Table 1. Evidence-Based Guidelines for Managing Acute Pain

Authors/Professional Organization	Title	Major Recommendations	Recommendations Relevant to Multimodal Analgesia
American Society of Anesthesiologists Task Force on Acute Pain Management[14]	Practice guidelines for acute pain management in the perioperative setting	• Institutional policies and procedures for perioperative pain management must 1) prioritize continued pain education for providers, 2) utilize validated pain assessment instrumentation, and 3) promote around-the-clock pain consultations. • Take a preoperative, directed pain history on all patients. • Engage patients and families in preoperative pain management education. • Implement perioperative pain management techniques based on provider expertise and a discussion with the patient about risks and benefits. • Implement safe multimodal pain management. • Take extra precautions when managing pain in pediatric, geriatric, critically ill, and cognitively or communicatively impaired populations.	• When possible, implement multimodal pain management therapy in treatment across patient populations and procedures. • Unless contraindicated, deliver a continuous regimen of NSAIDs, selective COX-2 inhibitors, or acetaminophen to patients in acute pain. • Consider regional blockade to deliver multimodal local anesthetics in managing pain. • At all times, optimize dosing efficacy while minimizing the risk of adverse events. • Individualize medication, dose, route, and duration of pain management.
Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine[59]	Acute pain management: scientific evidence	• Provide continuous management of acute pain to prevent its transition to chronic pain, which has adverse effects on health outcomes. • Use patient self-reports of pain in conjunction with appropriate validated measures to assess the multiple dimensions of pain. • Optimal pain management requires patient education and health care team collaboration. • PCA is not appropriate for the delivery of all analgesics. • The patient's analgesia needs must be met prior to starting PCA. • Use nonpharmacologic techniques that have been proven safe and effective. • Certain populations, including children; patients with renal or hepatic impairment, opioid tolerance, addiction or substance use disorders, or sleep apnea; culturally or linguistically diverse populations; older adults; and pregnant women, require special assessment and pain management.	• Compared with mainly opioid-based analgesia, multimodal analgesia improves pain while reducing opioid consumption. • Burn injuries require aggressive multimodal analgesia and multidisciplinary treatment. • The patient's multifaceted pain experience requires individual management using diverse analgesics and routes of administration that all require evaluation and consideration of risks.

Table 1. Continued

Washington State Agency Medical Directors' Group[60]	Interagency guideline on prescribing opioids for pain	• Regularly evaluate clinically meaningful improvement in function related to pain in all patients, using validated tools and measures. • In addition to medications, pain therapies should include physical and behavioral health interventions. • Reserve opioids, prescribed at the lowest necessary dose, for acute pain resulting from severe injuries or medical conditions, surgical procedures, or when nonopioid options are ineffective or contraindicated. • Exercise caution when prescribing opioid analgesic therapy for patients with chronic noncancer pain and provide ongoing assessment to identify adverse outcomes. • At times, reducing or discontinuing chronic opioid analgesic therapy is necessary—especially when risk from continued treatment outweighs the benefit. • Assess patients for opioid use disorder in accordance with DSM-5 criteria. • Consider providing opioid-sparing analgesics as well as alternative treatments and behavioral therapies for pain control. • Precautions must be taken when managing chronic pain in special populations (children, pregnant women, older adults, or cancer survivors).	• Multimodal analgesics are most effective in controlling pain and in minimizing analgesic doses and their resultant adverse effects, which interfere with rehabilitation. • Set expectations with patients and family members about realistic pain management goals that include the potential need for multimodal treatment. • During the intraoperative period provide balanced multimodal analgesia. • Ketamine, lidocaine, and regional local anesthetic techniques may help minimize perioperative opioids and their adverse effects. • Use the lowest possible dose of opioid therapy as part of a multimodal regimen that includes NSAIDs, acetaminophen, and nonpharmacologic therapies, unless contraindicated.
American Pain Society; American Society of Regional Anesthesia and Pain Medicine; American Society of Anesthesiologists Committee on Regional Anesthesia[1]	Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council	• Preoperative education and pain management planning should be patient- and family-centered, and tailored to patient medical, psychological, or social needs. • Use validated pain assessment tools to track response to pain treatment and make appropriate adjustments. • Patients across the life span should receive multimodal analgesia that includes nonpharmacologic interventions. • Both physical modalities, such as TENS or acupuncture, and cognitive-behavioral approaches should be part of the pain management plan. • Organizational structure, policies, and procedures should provide clinicians with access to consultation with a pain specialist for patients with inadequately controlled postoperative pain. When patients are transitioning to outpatient care, patients, families, and primary care providers should be educated on the pain management plan.	• For procedures with evidence indicating efficacy, peripheral regional anesthesia should be implemented. • Use systemic pharmacologic therapies across medication classes and administrative routes while ensuring patient safety. • Offer and use multimodal analgesia—a variety of analgesic medications and techniques, combined with nonpharmacologic interventions—in the treatment of postoperative pain. • Be aware of the different adverse effect profiles of each medication and technique used in multimodal analgesia, so as to provide appropriate monitoring to identify and manage adverse effects.

COX = cyclooxygenase; DSM = Diagnostic and Statistical Manual of Mental Disorders; NSAID = nonsteroidal antiinflammatory drug; PCA = patient-controlled analgesia; TENS = transcutaneous electrical nerve stimulation.



likelihood of opioid-induced respiratory depression. Moreover, no convincing data demonstrate increased efficacy with basal infusions for opioid-naive patients, though there may be a stronger rationale for use of basal infusions in opioid-tolerant patients.[1] As reported in the recent American Pain Society *Principles of Analgesic Use*, basal rates for postoperative pain may not improve the quality of analgesia and may increase the incidence and severity of opioid-induced adverse effects, including respiratory depression.[50] A meta-analysis of randomized controlled trials comparing the same postoperative opioid (usually morphine) by PCA versus non-PCA, primarily by IV bolus but also by intramuscular, subcutaneous, and oral routes, demonstrated that PCA was more effective than non-PCA for pain control and was associated with greater patient satisfaction; however, PCA was also associated with greater overall opioid consumption and a higher incidence of pruritus.[51]

Novel PCA technologies. Newer PCA drug delivery technologies have been developed and tested. A transdermal fentanyl patient-controlled iontophoretic delivery system is now approved by the U.S. Food and Drug Administration and indicated for hospital treatment of acute postoperative pain (see Figure 2). It delivers fentanyl 40 mcg transdermally when activated by the patient and is restricted by a 10-minute lockout interval, allowing up to six doses per hour for up to 24 hours, or 80 doses, whichever comes first, at which point a new device must be applied for continued therapy. Maximum duration of therapy is three days (72 hours). Information on the safety and efficacy of the fentanyl iontophoretic transdermal system for postoperative pain is reported in a review by Scott and a meta-analysis by Poon and colleagues.[52, 53] Another novel drug delivery system that is approved for use in 33 European countries but not yet in the United States is a sufentanil sublingual tablet system (see Figure 3). This system is a handheld, preprogrammed, noninvasive, patient-activated device that delivers sufentanil 15-mcg microtablets on demand. Safety and efficacy information compiled from numerous studies and randomized, placebo-controlled trials comparing the system to morphine delivery by IV PCA are summarized by Frampton.[54] As these novel technologies that require no IV line become available in hospital settings, nurses will require training in their use and education on patient instructions and monitoring.

NEURAXIAL AND PERIPHERAL REGIONAL ANESTHESIA

Multimodal analgesia also includes the use of neuraxial anesthesia, which involves local administration of an anesthetic or opioid into the spinal cord's neuraxial (epidural or intrathecal) space.[4] A local anesthetic and opioid combination work synergistically to relieve pain, but no single combination has proven superior to another.[3] Strong, high-quality evidence supports the use of epidural analgesia for major thoracic and abdominal procedures specifically in patients at risk for cardiac complications, pulmonary complications, or prolonged ileus.[1] Decisions to use epidural analgesia either by single injection or by continuous infusion are often based on research on specific types and locations of pain, ability to closely monitor patients, and availability of anesthesia providers or pain service experts to oversee therapy. Rawal argues that less invasive, regional analgesic techniques may be as good as or better than neuraxial techniques in achieving optimal pain control.[55] Duch and Møller, however, found little quality evidence demonstrating the benefit or harm of continuous epidural analgesia for traumatic rib fractures.[56] Risks associated with epidural analgesia include hypoventilation, atelectasis, and pneumonia owing to the effects of local anesthetics on respiratory muscles and diaphragmatic excursion. Consequently, epidural analgesia is not used to manage MG's rib fracture pain; instead systemic analgesics are administered.

Regional analgesia also includes peripheral nerve blocks (PNBs) with or without a continuous peripheral nerve block (CPNB) infusion directed toward an isolated nerve or plexus through the injection of a local anesthetic near the neural targets. These techniques allow a localized delivery of analgesia to specific painful areas and augment multimodal regimens. The military has published an extensive manual that illustrates multiple anatomical locations for PNBs and describes ultrasound-guided procedures to accomplish these blocks.[57] The manual is available online at www.dvcipm.org/clinical-resources/dvcipm-maraa-book-project. In 2005, the authors of that manual, Buckenmaier and Bleckner, published a comprehensive review of anesthetic agents used with PNBs and CPNBs.[58] The delivery of both neuraxial and PNB therapies requires the expertise and oversight of anesthesia providers and pain service experts.

EVIDENCE-BASED PRACTICE GUIDELINES AND EXPERT CONSENSUS

Several evidence-based practice guidelines from professional associations and organizations endorse the use of multimodal analgesia for acute pain. Four of the most recent guidelines were developed by the American Society of Anesthesiologists; the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine; the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia; and the Washington State Agency Medical Directors'

Group (see Table 1).[1, 14, 59, 60] To reduce adverse effects from opioids and expand biological targets for pain management, these guidelines recommend the use of both pharmacologic and nonpharmacologic opioid-sparing interventions.

Wound infiltration with local anesthetics is one strategy often recommended as a component of multimodal analgesia.[14, 59] This practice can be accomplished by directly injecting an anesthetic into wound sites or joints, or by wound catheter infusions. Rawal summarized the benefits of such techniques in specific surgeries.[61]

Nonpharmacologic interventions for acute pain should be incorporated into multimodal pain management regimens for acute pain. These interventions, which include cold compresses, massage, physical activity coaching, graded exercise therapy, and behavioral health interventions, act synergistically to relieve pain. A recent study that included 56 nurses demonstrated that music, patient education, and deep breathing relaxation were judged favorably by nurses as evidence-based practice interventions, with nurse comfort levels being moderate to high using these interventions.[62] Nurses in this study were less comfortable with acupressure, guided imagery, and massage, viewing these techniques as having limited applicability in practice. Nurses need to understand the benefits of nonpharmacologic measures for acute pain, their mechanisms of action, and how to implement these practices effectively and in accordance with patient preferences, their own willingness to try these measures, and their skill in delivering these interventions (see Table 2).[63-84] All of these techniques can be used in hospital, ambulatory, and home settings.

MG'S RECOVERY

MG leaves the operating room with his left arm in a cast and an external fixation device stabilizing his tibial fracture. Because of his uncontrolled hypertension, obstructive sleep apnea, and fractured ribs, he is transferred to the surgical critical care unit and placed on a cardiac and end-tidal carbon dioxide ($ETCO_2$) monitor. A nurse initiates the preventive postoperative pain control plan the care team discussed during surgery. Pain is assessed every one to two hours at all injured sites (left upper arm, left ribs, and lower left leg). Respiratory status (rate, depth, and regularity of respirations) and level of sedation are monitored and documented every hour. Every two hours, when nurses perform neurovascular checks of MG's left lower extremity and left hand (assessing the surgical and femoral catheter sites for bleeding, skin color and temperature, swelling or edema, capillary refill of toenail beds, and motor and sensory function), they ensure that his femoral catheter is patent and that his left lower leg is supported by a pillow. MG is encouraged to use his IV PCA 15 minutes before coughing, turning, deep breathing, and using the incentive spirometer, which he is to do every two hours. His nurse encourages him to use music and TV as sources of distraction, and teaches him to use visual imagery—recalling pleasant moments on his recent vacation—during respiratory care. Other than the mild sedation from general anesthesia and gabapentin, MG remains stable, rating his pain intensity between 2 and 4 at rest and as high as 7 when taking a deep breath. His $ETCO_2$ is occasionally elevated (50 to 55 mmHg), but returns to normal (35 to 45 mmHg) after respiratory care. His wife brings his CPAP device from home for use overnight.

The next morning, MG is transferred to the orthopedic unit. Since he used a total of 8.6 mg of IV hydromorphone by PCA within the first 24 hours after surgery and was expected to experience either constant or episodic pain from his fractures and surgical site over the next week, he is transitioned to a usual starting dose of controlled-release oxycodone, 20 mg every 12 hours, and to oral acetaminophen 650 mg every six hours, along with oxycodone 5 to 10 mg every four to six hours as needed. His femoral catheter is removed at 10 AM by the acute pain service.

The physical therapist helps MG get out of bed using special crutches for his casted left arm and bearing no weight on his left leg. He goes to the physical therapy unit two times for one-hour instruction sessions on crutch walking and safely using stairs. Nurses continue to monitor his vital signs and sedation level, performing neurovascular checks every four hours. He uses his incentive spirometer every four hours, and remains on continuous $ETCO_2$ monitoring. His recovery progresses, and his pain is well controlled.

The following day, MG is discharged to home with an analgesic regimen of controlled-release oxycodone 10 mg every 12 hours, gabapentin 200 mg every eight hours around the clock, oxycodone 5 mg every four to six hours, and acetaminophen 650 mg every six hours as needed. A bowel regimen with senna 15 mg twice a day is continued to prevent opioid-induced constipation. Arrangements are made for a home health nurse to visit him daily for five consecutive days to assess pain, check his respiratory and neurovascular status, and inspect his external fixation site for wound healing and signs of infection. A follow-up appointment in one week is arranged with the trauma service.

MG has a successful outcome with his aggressive multimodal plan of care. One week following discharge, he no longer needs controlled-release oxycodone and is taking only short-acting oxycodone 5 mg two to three times daily. He is tapering off gabapentin,

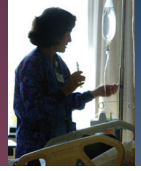
Table 2. Nondrug Measures for the Treatment of Pain

Nondrug Measures	Mechanism of Action/Benefits of Therapy	Intervention Methods	Nursing Implications
Cryotherapy	Cryotherapy involves cooling the skin surface with ice packs or similar methods. Cold therapy can temporarily reduce muscle temperature, induce vasoconstriction, and inhibit pain sensation,[63] and reduce tissue metabolism, oxygen utilization, inflammation, and muscle spasm.[64] Cryotherapy can reduce analgesic consumption.[65, 66]	Apply a bag of ice directly over the incisional area before the procedure or during the first 24 hours after the procedure. Wrap ice bag in a thin towel and apply no longer than 20 minutes.	• Frequent inspection of the skin is essential throughout therapy to assess tissue perfusion and check for signs of frostbite.
Massage Therapy	The mechanism of action of massage therapy to reduce pain is thought to be threefold: 1) physical and mental relaxation, 2) release of endorphins, and 3) stimulation of large-diameter inhibitory nerve fibers.[67, 68] Massage therapy elicits the body's relaxation response, decreasing the level of psychophysiologic arousal produced by stress and such physiologic changes as lowered blood pressure and heart rate, decreased muscle tension, lower levels of cortisol and norepinephrine, and reduced alpha motor neuron activity.[71] Massage plays an important role in reducing the inflammation and pain of muscle injuries.[72]	Techniques include Swedish effleurage or petrissage, acupressure, craniosacral therapy, deep tissue massage, trigger point therapy, or reflexology.[69, 70] Therapeutic massage regimens vary based on the primary goal (to reduce pain or anxiety, or to promote relaxation) and the area of the body being treated, with session duration ranging from 15 to 45 minutes.[69]	• Massage therapy can be self-referred and taught to both patient and caregivers by the nurse. • Strength and intensity of the intervention are tailored to the patient's response and tolerance for the massage stimulation.
Guided Imagery	Guided imagery involves using auditory stimuli, such as positive suggestions or biorhythmic music, to induce a state of relaxation and a sense of physical and emotional well-being. It promotes a sense of control over the helplessness of having distressing symptoms and can in turn interrupt the hypothalamic pituitary adrenal axis–signaling pathways.[73] Using guided imagery in the perioperative period can decrease anxiety and pain,[74] analgesic intake, psychological well-being,[75] and postanesthesia care unit length of stay for ambulatory patients.[76]	Imagining scenes, images, or experiences that are visually pleasing and conducive to healing.	• Nurses can teach and assist patients with guided imagery while simultaneously assessing vital signs and pain level.

Table 2. Continued

Distraction	With distraction, patients perform a cognitively demanding task to direct attention away from the pain.[77]	Distraction from a painful stimulus or procedure can include engaging in virtual or augmented realities,[78] playing with toys, watching TV, or listening to music.	• Distraction techniques should be appropriate to the patient's age and physical condition. • Goal-directed cognitive restructuring and distraction should be used to prioritize what patients wish to achieve from practicing distraction techniques. Kohl and colleagues provide an instructional guide with practical tips and exercises.[79]
Psychological Interventions	By redirecting or changing negative or dysfunctional beliefs about and attitudes toward pain, interventions such as CBT can improve patient outcomes. CBT has been found to reduce pain intensity, emotional distress, perceived disability, and use of health care resources.[80]	In CBT, the patient can practice relaxation training, goal setting, activity pacing, and problem-solving.	• Nurses must assess patients' understanding of CBT goals. • Assign patients "homework" to practice new techniques for managing behaviors toward pain and beliefs about pain management. • Training in the use of psychoeducational and cognitive-behavioral interventions, as well as skill-checking sessions, are recommended for quality assurance.[81]
TENS	TENS stimulates large-diameter afferent fibers, which activate inhibitory pain pathways in the central and peripheral nervous systems,[82] and overrides input from small-diameter pain fibers, thereby preventing or reducing painful stimuli from reaching the brain. TENS has been used effectively and safely on intact skin in such conditions as angina, back pain, fractures, procedural pain, postpartum pain, and phantom pain after amputation.[83, 84]	TENS units deliver electrical stimulation to the underlying peripheral nerves through electrodes placed over the intact skin surface.	• Patient teaching on effective and safe dosing of TENS is critical to prevent injury. • Nurses should regularly assess skin integrity at the application sites and teach patients to do the same and to rotate sites.

CBT = cognitive behavioral therapy; TENS = transcutaneous electrical nerve stimulation.



reducing the dosage by 100 mg per day. Two weeks after discharge, he is only taking acetaminophen 650 mg as needed and walking with crutches without any difficulty.

ENHANCED POSTOPERATIVE RECOVERY AND FUNCTION

Research demonstrates that multimodal analgesia not only reduces pain, opioid use, and opioid-related adverse effects, but also enhances postoperative recovery and function, and increases patient satisfaction. When regional analgesia was added to a systemic regimen of acetaminophen, gabapentin, and systemic opioids for operative repair of tibial and ankle fractures (similar to MG's regimen and surgery), patients receiving regional analgesia reported significantly higher satisfaction with pain management ($P = 0.005$) and a higher mean quality of recovery score at 24 hours ($P = 0.04$) compared with those who received no regional analgesia.[85] Similarly, Lee and colleagues found that, for patients undergoing upper extremity surgery, a multimodal analgesic regimen—which included preoperative and postoperative ibuprofen 800 mg, celecoxib 400 mg, and pregabalin 75 mg daily—added to the standard postoperative regimen of oral oxycodone 10 mg every 12 hours and acetaminophen 650 mg three times daily, significantly improved satisfaction at discharge ($P = 0.001$) compared with IV PCA postoperatively up to day 3 and the standard postoperative oxycodone and acetaminophen regimen.[86]

IMPLICATIONS FOR NURSES

To make the case for multimodal analgesia for acute pain, nurses in all health care settings must be knowledgeable about classes of analgesics, mechanisms of action in the peripheral and central nervous systems, routes of administration, recommended dosing, adverse effect profiles, drug-to-drug synergistic effects and interactions, and contraindications. Likewise, nurses should be familiar with research and evidence-based practice guidelines for specific types of pain. While multimodal analgesia should be considered for all patients with acute pain, attention should be given to patients at elevated risk for developing chronic postsurgical pain syndrome and other opioid-related adverse effects. In tailoring multimodal regimens to individual patients, interprofessional collaboration with pain experts (anesthesiologists, pain management nurses, and pharmacists) is important. In addition, nurses should be provided competency-based education that emphasizes multimodal analgesic approaches for acute pain management and clinical decision making in designing analgesic regimens and developing nursing plans of care. Competencies in delivering multimodal therapies and monitoring patients should be evaluated.

Patient education is an integral part of multimodal pain management. Patients need to understand the rationale for their treatment and for the use of all medications and interventions both during and after hospitalization. It is critical that patients receiving multimodal analgesia be provided both oral and written instructions about the medications they are using. This should include

- the names of all pain medications.
- how each medication works.
- dosages and dosing schedules.
- common and serious adverse effects.

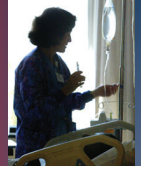
Patients should also be told to notify their health care providers if they are not deriving acceptable pain relief or if they experience any adverse effects, including constipation. If taking opioids or agents that produce sedation, patients should be advised to avoid alcohol, operating machinery, and driving. ▼

Rosemary C. Polomano is a professor of pain practice at the University of Pennsylvania School of Nursing, Philadelphia. Mechele Fillman is an NP for the acute pain service in the Division of Pain Medicine at Stanford Hospital and Clinics, Stanford, CA. Nicholas A. Giordano is a PhD student and Hillman Scholar in Nursing Innovation at the University of Pennsylvania School of Nursing. April Hazard Vallerand is associate dean for research and director of the PhD program at Wayne State University College of Nursing, Detroit. Kelly L. Wiltse Nicely is an assistant professor of nurse anesthesia in the Department of Biobehavioral Health Sciences, University of Pennsylvania School of Nursing. Carla R. Jungquist is an assistant professor in the University at Buffalo School of Nursing, Buffalo, NY. Contact author: Rosemary C. Polomano, polomanr@nursing.upenn.edu.
Rosemary C. Polomano has served on the advisory boards of Salix Pharmaceuticals, Daiichi Sankyo, and Mallinckrodt Pharmaceuticals; April Hazard Vallerand is on the speaker's bureaus of AstraZeneca and Purdue Pharma and is a consultant for Shionogi, Inc.; and Carla R. Jungquist has served on the advisory board of Mallinckrodt Pharmaceuticals. The authors have disclosed no potential conflicts of interest, financial or otherwise.

REFERENCES

1. Chou R, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain* 2016;17(2):131-57.
2. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg* 1993; 77(5):1048-56.
3. Gritsenko K, et al. Multimodal therapy in perioperative analgesia. *Best Pract Res Clin Anaesthesiol* 2014;28(1):59-79.
4. Argoff CE. Recent management advances in acute postoperative pain. *Pain Pract* 2014;14(5):477-87.
5. Gudin J. Opioid therapies and cytochrome p450 interactions. *J Pain Symptom Manage* 2012;44(6 Suppl):S4-S14.
6. Jarzyna D, et al. American Society for Pain Management Nursing guidelines on monitoring for opioid-induced sedation and respiratory depression. *Pain Manag Nurs* 2011; 12(3):118-45.e10.
7. Kelly DJ, et al. Preemptive analgesia I: physiological pathways and pharmacological modalities. *Can J Anaesth* 2001; 48(10):1000-10.

8. Weinbroum AA. Non-opioid IV adjuvants in the perioperative period: pharmacological and clinical aspects of ketamine and gabapentinoids. *Pharmacol Res* 2012;65(4):411-29.
9. Vadivelu N, et al. Review of perioperative pain management of opioid-dependent patients. *J Opioid Manag* 2016;12(4): 289-301.
10. Dahl JB, Kehlet H. Preventive analgesia. *Curr Opin Anaesthesiol* 2011;24(3):331-8.
11. Joshi GP, et al. Procedure-specific pain management and outcome strategies. *Best Pract Res Clin Anaesthesiol* 2014;28(2): 191-201.
12. Pozek JP, et al. The acute to chronic pain transition: can chronic pain be prevented? *Med Clin North Am* 2016;100(1): 17-30.
13. Simpson D, et al. Ropivacaine: a review of its use in regional anaesthesia and acute pain management. *Drugs* 2005;65(18): 2675-717.
14. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2012;116(2):248-73.
15. Bozimowski G. A review of nonsteroidal anti-inflammatory drugs. *AANA J* 2015;83(6):425-33.
16. Solomon DH. NSAIDs: therapeutic use and variability of response in adults. *UpToDate* 2016. https://www.uptodate.com/contents/nsaids-therapeutic-use-and-variability-of-response-in-adults.
17. Nir RR, et al. Preoperative preemptive drug administration for acute postoperative pain: a systematic review and meta-analysis. *Eur J Pain* 2016;20(7):1025-43.
18. Maund E, et al. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. *Br J Anaesth* 2011;106(3):292-7.
19. Chen JY, et al. Opioid-sparing effects of ketorolac and its correlation with the recovery of postoperative bowel function in colorectal surgery patients: a prospective randomized double-blinded study. *Clin J Pain* 2009;25(6):485-9.
20. Murphy EJ. Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. *Anaesth Intensive Care* 2005;33(3):311-22.
21. Giannoudis PV, et al. Inflammation, bone healing, and anti-inflammatory drugs: an update. *J Orthop Trauma* 2015;29 Suppl 12:S6-S9.
22. Pountos I, et al. Do nonsteroidal anti-inflammatory drugs affect bone healing? A critical analysis. *ScientificWorldJournal* 2012;2012:606404.
23. Donohue D, et al. Ketorolac administered in the recovery room for acute pain management does not affect healing rates of femoral and tibial fractures. *J Orthop Trauma* 2016;30(9): 479-82.
24. Paulasir S, et al. Nonsteroidal anti-inflammatory drugs: do they increase the risk of anastomotic leaks following colorectal operations? *Dis Colon Rectum* 2015;58(9):870-7.
25. Smith HS. Potential analgesic mechanisms of acetaminophen. *Pain Physician* 2009;12(1):269-80.
26. McNicol ED, et al. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. *Cochrane Database Syst Rev* 2016(5):CD007126.
27. Sinatra RS, et al. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiology* 2005;102(4):822-31.
28. Jibril F, et al. Intravenous versus oral acetaminophen for pain: systematic review of current evidence to support clinical decision-making. *Can J Hosp Pharm* 2015;68(3):238-47.
29. Smith HS. Perioperative intravenous acetaminophen and NSAIDs. *Pain Med* 2011;12(6):961-81.
30. Schmidt PC, et al. Perioperative gabapentinoids: choice of agent, dose, timing, and effects on chronic postsurgical pain. *Anesthesiology* 2013;119(5):1215-21.
31. Tiippana EM, et al. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg* 2007;104(6):1545-56.
32. Arumugam S, et al. Use of preoperative gabapentin significantly reduces postoperative opioid consumption: a meta-analysis. *J Pain Res* 2016;9:631-40.
33. Mathiesen O, et al. Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure. *BMC Anesthesiol* 2007;7:6.
34. Turan A, et al. Effect of oral gabapentin on postoperative epidural analgesia. *Br J Anaesth* 2006;96(2):242-6.
35. Clarke H, et al. Pregabalin reduces postoperative opioid consumption and pain for 1 week after hospital discharge, but does not affect function at 6 weeks or 3 months after total hip arthroplasty. *Br J Anaesth* 2015;115(6):903-11.
36. Suzuki M. Role of N-methyl-D-aspartate receptor antagonists in postoperative pain management. *Curr Opin Anaesthesiol* 2009;22(5):618-22.
37. McNicol ED, et al. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. *Acta Anaesthesiol Scand* 2014;58(10):1199-213.
38. Jouguelet-Lacoste J, et al. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. *Pain Med* 2015;16(2):383-403.
39. Blaudszun G, et al. Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. *Anesthesiology* 2012;116(6):1312-22.
40. Chan AK, et al. Alpha-2 agonists in acute pain management. *Expert Opin Pharmacother* 2010;11(17):2849-68.
41. Jessen Lundorf L, et al. Perioperative dexmedetomidine for acute pain after abdominal surgery in adults. *Cochrane Database Syst Rev* 2016;2:CD010358.
42. Krenzischek DA, et al. Pharmacotherapy for acute pain: implications for practice. *J Perianesth Nurs* 2008;23(1 Suppl): S28-S42.
43. Patanwala AE, et al. Opioid conversions in acute care. *Ann Pharmacother* 2007;41(2):255-66.
44. Vallerand AH, et al. *Davis's drug guide for nurses*. 15th ed. Philadelphia: F.A. Davis Company; 2017.
45. Smith HS. The metabolism of opioid agents and the clinical impact of their active metabolites. *Clin J Pain* 2011;27(9): 824-38.
46. Yu EH, et al. Remifentanil tolerance and hyperalgesia: short-term gain, long-term pain? *Anaesthesia* 2016;71(11):1347-62.
47. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth* 2014;112(6):991-1004.
48. Hutchison RW, et al. A comparison of a fentanyl, morphine, and hydromorphone patient-controlled intravenous delivery



for acute postoperative analgesia: a multicenter study of opioid-induced adverse reactions. *Hosp Pharm* 2006;41(7):659-63.

49. Neto JO, et al. Methadone patient-controlled analgesia for postoperative pain: a randomized, controlled, double-blind study. *J Anesth* 2014;28(4):505-10.
50. Herndon CM, et al., editors. *Principles of analgesic use*. 7th ed. Chicago: American Pain Society; 2016.
51. McNicol ED, et al. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. *Cochrane Database Syst Rev* 2015(6):CD003348.
52. Poon KH, et al. Efficacy of fentanyl iontophoretic transdermal system in postoperative pain—a meta-analysis. *Acute Pain* 2009;11(2):65-74.
53. Scott LJ. Fentanyl iontophoretic transdermal system: a review in acute postoperative pain. *Clin Drug Investig* 2016;36(4):321-30.
54. Frampton JE. Sublingual sufentanil: a review in acute postoperative pain. *Drugs* 2016;76(6):719-29.
55. Rawal N. Epidural technique for postoperative pain: gold standard no more? *Reg Anesth Pain Med* 2012;37(3):310-7.
56. Duch P, Møller MH. Epidural analgesia in patients with traumatic rib fractures: a systematic review of randomised controlled trials. *Acta Anaesthesiol Scand* 2015;59(6):698-709.
57. Buckenmaier CC, 3rd, Bleckner LL. *Military advanced regional anesthesia and analgesia handbook*. Washington, DC: Office of the Surgeon General at TMM Publications, Borden Institute, Walter Reed Army Medical Center; 2008. Textbook of military medicine; http://www.dvcipm.org/clinical-resources/dvcipm-maraa-book-project.
58. Buckenmaier CC, III, Bleckner LL. Anaesthetic agents for advanced regional anaesthesia. *Drugs* 2005;65(6):745-59.
59. Schug SA, et al. *Acute pain management: scientific evidence*. Melbourne, Australia: Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine; 2015. http://fpm.anzca.edu.au/documents/apmse4_2015_final.
60. Washington State Agency Medical Directors' Group (AMDG). *Interagency guideline on prescribing opioids for pain*. Olympia, WA; 2015 Jun. http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf.
61. Rawal N. Current issues in postoperative pain management. *Eur J Anaesthesiol* 2016;33(3):160-71.
62. Sidani S, et al. Nurses' perceptions of interventions for the management of patient-oriented outcomes: a key factor for evidence-based practice. *Worldviews Evid Based Nurs* 2016;13(1):66-74.
63. Tiidus PM. Alternative treatments for muscle injury: massage, cryotherapy, and hyperbaric oxygen. *Curr Rev Musculoskelet Med* 2015;8(2):162-7.
64. Nadler SF, et al. The physiologic basis and clinical applications of cryotherapy and thermotherapy for the pain practitioner. *Pain Physician* 2004;7(3):395-9.
65. Kol E, et al. Evaluation of the outcomes of ice application for the control of pain associated with chest tube irritation. *Pain Manag Nurs* 2013;14(1):29-35.
66. Watkins AA, et al. Ice packs reduce postoperative midline incision pain and narcotic use: a randomized controlled trial. *J Am Coll Surg* 2014;219(3):511-7.
67. Furlan AD, et al. Massage for low-back pain. *Cochrane Database Syst Rev* 2015(9):CD001929.
68. Ucuzal M, Kanan N. Foot massage: effectiveness on postoperative pain in breast surgery patients. *Pain Manag Nurs* 2014;15(2):458-65.
69. Adams MHA, et al. The effects of massage therapy on pain management in the acute care setting. *Int J Ther Massage Bodywork* 2010;3(1):4-11.
70. Bauer BA, et al. Effect of massage therapy on pain, anxiety, and tension after cardiac surgery: a randomized study. *Complement Ther Clin Pract* 2010;16(2):70-5.
71. Field T. Massage therapy research review. *Complement Ther Clin Pract* 2014;20(4):224-9.
72. Waters-Banker C, et al. Investigating the mechanisms of massage efficacy: the role of mechanical immunomodulation. *J Athl Train* 2014;49(2):266-73.
73. Lewandowski W, Jacobson A. Bridging the gap between mind and body: a biobehavioral model of the effects of guided imagery on pain, pain disability, and depression. *Pain Manag Nurs* 2013;14(4):368-78.
74. Sears SR, et al. Evaluation of "Steps to Surgical Success" (STEPS): a holistic perioperative medicine program to manage pain and anxiety related to surgery. *Holist Nurs Pract* 2013;27(6):349-57.
75. Nelson EA, et al. Systematic review of the efficacy of presurgical mind-body based therapies on post-operative outcome measures. *Complement Ther Med* 2013;21(6):697-711.
76. Gonzales EA, et al. Effects of guided imagery on postoperative outcomes in patients undergoing same-day surgical procedures: a randomized, single-blind study. *AANA J* 2010;78(3):181-8.
77. Gard T, et al. Pain attenuation through mindfulness is associated with decreased cognitive control and increased sensory processing in the brain. *Cereb Cortex* 2012;22(11):2692-702.
78. Loreto-Quijada D, et al. Differential effects of two virtual reality interventions: distraction versus pain control. *Cyberpsychol Behav Soc Netw* 2014;17(6):353-8.
79. Kohl A, et al. Acceptance, cognitive restructuring, and distraction as coping strategies for acute pain. *J Pain* 2013;14(3):305-15.
80. Burns JW, et al. Specific and general therapeutic mechanisms in cognitive behavioral treatment of chronic pain. *J Consult Clin Psychol* 2015;83(1):1-11.
81. Koranyi S, et al. Psychological interventions for acute pain after open heart surgery. *Cochrane Database Syst Rev* 2014(5):CD009984.
82. Vance CG, et al. Using TENS for pain control: the state of the evidence. *Pain Manag* 2014;4(3):197-209.
83. Johnson MI, et al. Transcutaneous electrical nerve stimulation (TENS) for phantom pain and stump pain following amputation in adults. *Cochrane Database Syst Rev* 2015;8:CD007264.
84. Johnson MI, et al. Transcutaneous electrical nerve stimulation for acute pain. *Cochrane Database Syst Rev* 2015(6):CD006142.
85. Elkassabany N, et al. Does regional anesthesia improve the quality of postoperative pain management and the quality of recovery in patients undergoing operative repair of tibia and ankle fractures? *J Orthop Trauma* 2015;29(9):404-9.
86. Lee SK, et al. Is multimodal analgesia as effective as postoperative patient-controlled analgesia following upper extremity surgery? *Orthop Traumatol Surg Res* 2013;99(8):895-901.