Multimodal Pain Management and the Future of a Personalized Medicine Approach to Pain

RENEE C.B. MANWORREN, PhD, APRN, BC, FAAN

Purpose/Goal
To provide the learner with knowledge specific to using a multimodal approach for managing postoperative pain.

Objectives
1. Describe multimodal analgesia.
2. Identify nonpharmacological interventions that may help relieve pain.
3. Explain how pharmacological agents relieve pain.
4. Identify examples of polypharmacy.
5. Discuss advantages of a personalized medicine approach to managing postoperative pain.

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ABSTRACT
In the soon-to-be-released clinical practice guidelines from the American Pain Society, multimodal analgesia is recommended for pain management after all surgical procedures. Multimodal analgesia is a surgery-specific population-based approach to optimize pain relief by treating pain through multiple mechanisms along multiple sites of the nociceptive pathway. The reliance on multiple medications and therapies inherent to the multimodal approach also may address individual patient differences in analgesic pharmacogenetics (ie, the influence of allelic differences in single genes and the associated variability in specific medication responses). Perioperative nurses may see a shift from surgery-specific population-based multimodal analgesic protocols to a personalized medicine approach as knowledge of the genetic influences of analgesic metabolism and pain sensitivity is translated into clinical practice. Personalized medicine is proposed as an individualized pain management treatment plan that eventually may be based on each patient’s genetic coding for metabolism of analgesics and pain sensitivity.


Key words: postoperative pain, multimodal analgesia, personalized medicine, pharmacokinetic, pharmacodynamic, pharmacogenetic, pharmacogenomic.
The American Pain Society, in partnership with the American Society of Anesthesiologists, the US Department of Veterans Health Administration, and Department of Defense, convened an expert panel to perform a comprehensive review of scientific evidence and develop new clinical practice guidelines for postoperative pain management.1 The expert panel recommends multimodal analgesia for the treatment of postoperative pain in children and adults (Table 1). Multimodal analgesia is the use of a variety of analgesic medications and techniques combined with nonpharmacological (ie, biobehavioral) interventions. Multimodal analgesia allows for the use of lower doses of medications, yet potentially provides greater pain relief and fewer analgesic adverse effects than can be achieved with monomodal (ie, single medication or modality) therapy.2 Reliance on more than one method of relieving pain also may address individual genetic differences in analgesic metabolism and pain sensitivity.

The purpose of this article is to familiarize perioperative nurses with the essential concepts of multimodal analgesia and personalized medicine for translation of both approaches into clinical practice. This article reviews the mechanisms of action of traditional peroperative analgesics and other medications and therapies that are not traditionally considered perioperative analgesics but may be used to treat pain as part of multimodal analgesic plans. Multimodal analgesia is differentiated from polypharmacy, and the advantages of a multimodal approach are contrasted with the risks of polypharmacy. Finally, genetic differences in analgesic metabolism and pain sensitivity will be introduced to support a potential shift in perioperative pain management practice from multimodal analgesia to a personalized medicine approach.

MULTIMODAL ANALGESIA
Multimodal analgesia optimizes pain relief by treating pain through complementary mechanisms of action along multiple sites of the nociceptive pathway (ie, the pathway by which an individual is aware of pain caused by injury to body tissue [Figure 1].2-5 Multimodal analgesia includes pharmacological and nonpharmacological interventions. Pharmacological agents include traditional (eg, local anesthetics, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], opioids) and nontraditional (eg, anticonvulsants, N-methyl-D-aspartate [NMDA]-receptor antagonists, alpha-2 adrenergic agonists, antidepressants) analgesics. Nonpharmacological interventions, which have varying degrees of evidence regarding efficacy, include transcutaneous electrical nerve stimulation, cognitive behavioral therapies (eg, intraoperative suggestion, relaxation methods, guided imagery, hypnosis), acupuncture, heat therapy, massage, cold therapy, and touch therapy.

Traditional Analgesics
Analgesics relieve pain through a variety of mechanisms of action along multiple sites of the nociceptive pathway.
- Local anesthetic agents block conduction of nerve impulses by decreasing or preventing an increase in the permeability of excitable membranes to sodium either at the site of injury (eg, wound site) or centrally (eg, IV, nerve block, epidural).
- Acetaminophen inhibits prostaglandin synthesis in the central nervous system and has a weak anti-inflammatory activity in the peripheral nervous system.
- Nonsteroidal anti-inflammatory drugs inhibit prostaglandin production by blocking cyclooxygenase both peripherally and centrally.
- Opioids have multiple sites of action. In the brain, opioids activate descending pain inhibitors. In the periphery, they work by reducing the release of inflammatory products. In the spine, opioids decrease:
  - presynaptic calcium and sodium influx;
  - production and release of excitatory amino acids, such as substance P; and
  - postsynaptic excitability.

In combination, NSAIDs and opioids produce superior postoperative pain relief compared to use of either medication alone. For example, patients who received the perioperative NSAID ketorolac in addition to opioids reported statistically significantly lower mean pain intensity (mean [M] = 2.9, standard deviation [SD] = 1.7) in the first 24 hours after surgery compared with scores from patients who did not receive perioperative IV ketorolac (M = 3.7, SD = 1.7; t = 3.14, P = .002).6 They also received statistically significantly less morphine equivalent of postoperative opioids (M = 0.94, SD = 0.71) during the first 24 hours after surgery than those who did not receive perioperative IV ketorolac (M = 1.21, SD = 0.78; t = 2.41, P = .02). Thus, this multimodal approach to managing postoperative pain after an emergency surgical procedure resulted in improved analgesia despite the use of less opioids.

Nontraditional Analgesics
Many other classes of medications that are not traditionally considered analgesics may be included in a multimodal approach to postoperative pain management. These medications also alter the transduction, transmission, perception, or modulation of pain through their various mechanisms of action.
- Anticonvulsants inhibit high-frequency neuronal firing by blocking sodium channels and reducing neuron hyperexcitability.
NMDA-receptor antagonists, like ketamine, bind to the NMDA receptor, thereby inhibiting glutamate activation. Glutamate is an excitatory amino acid found in laminae I, II, and III of the dorsal horn of the spinal cord. Glutamate activates primary afferent neurons.

Alpha-2 adrenergic agonists act on the descending pain pathways supraspinally, activating receptors to stimulate acetylcholine release, and on the ascending pain pathways, by inhibiting substance P release. Substance P is a neuropeptide or neurotransmitter that is released from the primary afferent neuron and binds to the secondary neuron in the dorsal horn to create an action potential. Thus, inhibiting release of substance P reduces transmission of pain.

Antidepressants alter neurotransmitters that affect pain pathways by inhibiting presynaptic neuronal reuptake of neurotransmitters, thereby modulating the release of neurotransmitters. These medications are often used in combination with other analgesic therapies to achieve a balanced approach to pain management.
serotonin and norepinephrine at the descending pain pathway. By inhibiting the reuptake of serotonin and norepinephrine, there is more activation of the descending pain pathway, resulting in improved inhibition of pain.

Nonpharmacological Interventions

Nonpharmacological interventions are an important component of a perioperative multimodal pain management plan. Nonpharmacological interventions also work by a variety of mechanisms and sites to relieve postoperative pain; the

Figure 1. The effect of pharmacological and nonpharmacological pain management interventions along the nociceptive pain pathway where each type of intervention exerts its mechanism of action to relieve pain. *The mechanism of action of these nonpharmacological interventions is unclear; they are considered safe but lack evidence of benefits for postoperative pain relief.
Cognitive behavioral therapies, such as intraoperative sug-

Transcutaneous electrical nerve stimulation is thought to
than half of all prescription medications. A pharmacokinetic
P450 enzyme system. This same system metabolizes more
surgery. Most opioids are metabolized by the cytochrome
Opioids are the gold standard for the relief of acute pain of
concomitant use of two NSAIDs with the same mechanism
example of irrational analgesic polypharmacy would be the
appropriate and safe prescribing requires the use of the
avoid polypharmacy are based on the assumption that
Multimodal analgesia and polypharmacy are two distinctly
different concepts that are easily confused and therefore may
call into question the safety and efficacy of a multimodal
postoperative pain treatment plan. The multimodal approach
relies on the thoughtful use of analgesics in at least two
medication classes and therapies that target different pain
mechanisms. Polypharmacy has numerous definitions (eg,
multiple clinicians prescribing multiple medications with the
same mechanism of action for the same condition and filled at
several dispensing pharmacies). Ultimately, polypharmacy is a
poor measure of prescribing quality. Recommendations to
avoid polypharmacy are based on the assumption that
appropriate and safe prescribing requires the use of the
fewest possible number of medications to reduce the
potential for adverse drug-drug interactions (DDIs). An
example of irrational analgesic polypharmacy would be the
concomitant use of two NSAIDs with the same mechanism
of action. In this situation, clinicians would be concerned for
the patient’s increased risk for acute renal failure.

Opioids are the gold standard for the relief of acute pain of
moderate to severe intensity, such as that experienced after
surgery. Most opioids are metabolized by the cytochrome
P450 enzyme system. This same system metabolizes more
than half of all prescription medications. A pharmacokinetic

Alternately, pharmacodynamic DDIs (eg, sedation from the
coadministration of opioids and benzodiazepines) are the result
of alterations of the concentration-response curve of one or both
medications without a change in pharmacokinetics. Twenty-six
percent of patients with chronic noncancer pain who were
treated with opioids experienced pharmacodynamic DDIs.
Patients between the ages of 35 and 44 years had the highest
risk (46%) of pharmacodynamic DDIs. Polypharmacy is
not required for the occurrence of a pharmacodynamic DDI;
however, patients who had taken one other prescription in
the three months before the pharmacodynamic DDI had
times the risk of experiencing pharmacodynamic DDIs
compared with patients who were on single medication
therapy. Each additional prescription increases a patient’s risk
by more than 100%; patients taking opioids are at particular
risk. Results from one study estimated that 32% of patients
taking opioids are also taking more than five concurrent
medications and 21% are taking more than 10 medications.
However, multimodal therapy is recommended despite this
increased risk; hence, nurses should be aware of the potential
for pharmacokinetic and pharmacodynamic DDIs and
monitor patients accordingly for adverse effects. In the future,
a personalized medicine approach to postoperative
pain management may provide patient-specific guidance to
prevent pharmacokinetic DDIs and pharmacodynamic DDIs.

**PERSONALIZED MEDICINE**

There is tremendous variability in patients’ individual re-
ponses to medications and therapies used to treat post-
operative pain. Thus, patients who are very sensitive to an
intervention and patients who report no effect from an inter-
vention are at the greatest risk for poorly controlled post-
operative pain and/or adverse analgesic effects.

Personalized medicine is proposed as an individualized pain
management treatment plan based on each patient’s genetic
coding for analgesic metabolism and pain sensitivity. Per-
sonalized medicine may allow clinicians to better treat the pain of
patients who fall outside sample norms and advance a new
paradigm for treating acute postoperative pain.

Pharmacogenetics is the study of the influence of allelic dif-
fferences in single genes and the associated variability in specific
medication responses. Genetic variants correlate with aberrant analgesic metabolism phenotypes. Gene variants in
pharmacodynamic and pharmacokinetic genes (ie, \textit{CYP2D6}, \textit{CYP2C9}, \textit{CYP2C19}, \textit{CYP3A4}, \textit{CYP3A5}) may be useful for preoperatively identifying patients at risk for postoperative pain and analgesic adverse effects. For example, in August 2012, the US Food and Drug Administration (FDA) warned against prescribing codeine for tonsillectomy pain after the deaths of several children.\textsuperscript{16} Their deaths were attributed to an overdose as a result of their genetic variation of \textit{CYP2D6},\textsuperscript{17} which causes ultrarapid metabolism of codeine to morphine, resulting in toxic levels of morphine. Evidence-based guidelines are available for how genetic test results can be used to optimize therapy,\textsuperscript{15,18-20} and include guidelines for specific analgesics like codeine\textsuperscript{19} and other medications used to treat pain.\textsuperscript{20} Genetic variations can influence the effectiveness and increase the danger of using other analgesics and multimodal therapies to treat postoperative pain.

Pharmacogenomics is the study of the entire genome and identification of variations in multiple genes that are associated with medication responses.\textsuperscript{13-17} In addition to the genetic associations with analgesic metabolism and individual response, scientists have identified more than 400 distinct genes that influence pain or nociception.\textsuperscript{21} Potential genetic mechanisms for pain have been identified in adults in experimental settings.\textsuperscript{22,23} For example, polymorphic variation in the gene coding for vanilloid receptor subtype 1 (\textit{TRPV1}), opioid receptor delta subtype 1 (\textit{OPRD1}), \mu-opioid receptor (\textit{OPRM1}), and catechol-O-methyltransferase (\textit{COMT}) influence pain processing and reports of pain.\textsuperscript{24-28} Other gene variants encoding pain receptors and neuromodulators may have roles in pain sensitivity (eg, \textit{FKBP5}, \textit{GCH1}, \textit{MC1R}, \textit{SCN9A}, \textit{KCNS1}, \textit{5-HTTLPR}).\textsuperscript{21,24} Researchers have investigated select genes for an increased risk for severe pain from trauma, persistent pain after trauma, and the development of chronic pain conditions.\textsuperscript{27-29} But a pharmacogenomics approach allows researchers to study the patient’s entire genome, including genes that alter pain sensitivity and those that alter medication response.

In the future, clinicians may be able to merely swab the inside of the patient’s cheek to analyze their genetic pain sensitivity status and pharmacogenomic profile. This approach to identifying risk for acute postoperative pain and guiding treatments to relieve this pain will acknowledge patients’ individuality by applying emerging knowledge of human pain genetics in clinical practice. Researchers may find that patients with alleles associated with increased pain sensitivity and genetic alterations in pharmacodynamic and pharmacokinetic genes report greater pain intensity, require more analgesics, and experience a higher incidence of adverse analgesic effects. Rather than have the patient experience these inadequate analgesic responses, preoperative testing would guide clinicians in administering an analgesic regimen that was genetically suited, individualized, and personalized to best relieve the patient’s postoperative pain.

However, more clinical research is needed to identify and characterize the genetic associations with pain and analgesic response and their relevance to surgical patients. This program of research will advance personalized medicine and the care of surgical patients. The pace of acquiring genetic knowledge is advancing rapidly and may soon allow translation of genetic pain sensitivity and pharmacogenetic findings for personalized medicine in perioperative clinical practice.

**CONCLUSION**

Currently, multimodal analgesia is the approach of choice for relieving postsurgical pain. By using analgesics in at least two medication classes and nonpharmacological therapies, clinicians are able to target different pain mechanisms along multiple sites of the nociceptive pathway. Perioperative nurses should anticipate treating patients’ postoperative pain with combinations of local anesthetics, acetaminophen, NSAIDs, opioids, anticonvulsants, antidepressants, alpha-2 adrenergic agonists, and biobehavioral interventions. Vigilant monitoring is necessary for the early detection of DDIs. Therapy selection will become more personalized as advancements are made in the translation of pain genetics, pharmacogenetics, and pharmacogenomics. Multimodal analgesia therefore may be replaced with a personalized medicine approach to postoperative pain in the near future. Perioperative nurses should be prepared to design or participate in studies to investigate the personalized medicine approach to include the effectiveness of nonpharmacological nursing interventions focused on pain management and studies of genetic-guided therapy.

**References**


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Continuing Education: Multimodal Pain Management and the Future of a Personalized Medicine Approach to Pain

PURPOSE/GOAL
To provide the learner with knowledge specific to using a multimodal approach for managing postoperative pain.

OBJECTIVES
1. Describe multimodal analgesia.
2. Identify nonpharmacological interventions that may help relieve pain.
3. Explain how pharmacological agents relieve pain.
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5. Discuss advantages of a personalized medicine approach to managing postoperative pain.

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QUESTIONS
1. As a method to manage postoperative pain, multimodal analgesia
   1. is the use of a variety of analgesic medications and techniques combined with nonpharmacological interventions.
   2. allows for the use of lower doses of medications.
   3. potentially provides greater pain relief and fewer analgesic adverse effects than can be achieved with monomodal therapy.
   4. may also address individual genetic differences in analgesic metabolism and pain sensitivity.
      a. 1 and 3  b. 2 and 4  
      c. 1, 2, and 4  d. 1, 2, 3, and 4

2. Nonpharmacological interventions include
   1. acupuncture.
   2. cognitive behavioral therapies.
   3. heat therapy.
   4. massage.

3. ______________________________ block conduction of nerve impulses by decreasing or preventing an increase in the permeability of excitable membranes to sodium either at the site of injury or centrally.
   a. Benzodiazapines  b. Local anesthetic agents  
   c. Muscle relaxants  d. GABA_B receptors

4. ______________________________ inhibit prostaglandin production by blocking cyclooxygenase, both peripherally and centrally.
   a. Antidepressants  b. Local anesthetic agents  
   c. Nonsteroidal anti-inflammatory drugs  d. Sedative-hypnotic anesthetics

5. touch therapy.
6. transcutaneous electrical nerve stimulation.
   a. 1, 2, and 3  b. 3, 4, and 5  
   c. 1, 2, 4, 5, and 6  d. 1, 2, 3, 4, 5, and 6
5. Opioids work by
   1. activating descending pain inhibitors.
   2. decreasing postsynaptic excitability.
   3. decreasing presynaptic calcium and sodium influx.
   4. decreasing production and release of excitatory amino acids.
   5. inhibiting prostaglandin synthesis in the central nervous system.
   6. reducing release of inflammatory products.
      a. 1, 3, and 5  b. 2, 4, 5, and 6
      c. 1, 2, 3, 4, and 6  d. 1, 2, 3, 4, 5, and 6

6. Antidepressants alter neurotransmitters that affect pain pathways by ___________ at the descending pain pathway.
   a. activating receptors to stimulate acetylcholine release
   b. inhibiting presynaptic neuronal reuptake of serotonin and norepinephrine
   c. blocking sodium channels and reducing neuron hyperexcitability
   d. reducing the release of inflammatory products

7. An example of irrational analgesic polypharmacy would be concomitant use of two NSAIDs with the same mechanism of action
   a. true  b. false

8. A _______________ drug-drug interaction (DDI) occurs when the use of one medication results in a change in the absorption, distribution, metabolism, and/or elimination of another medication.
   a. pharmacokinetic  b. physiogenic
   c. pharmacogenetic  d. pharmacogenomic

9. _______________ DDIs (eg, sedation resulting from the coadministration of opioids and benzodiazepines) is the result of alteration of the concentration-response curve of one or both medications without a change in pharmacokinetics.
   a. Physiogenic  b. Pharmacodynamic
   c. Pharmacogenetic  d. Pharmacogenomic

10. Personalized medicine
    1. is proposed as an individualized pain management treatment plan.
    2. is based on each patient’s genetic coding for analgesic metabolism and pain sensitivity.
    3. may allow clinicians to better treat the pain of patients who fall outside sample norms.
    4. may advance a new paradigm for treating acute postoperative pain.
       a. 1 and 3  b. 2 and 4
       c. 1, 2, and 4  d. 1, 2, 3, and 4
Continuing Education: Multimodal Pain Management and the Future of a Personalized Medicine Approach to Pain 1.4 CE

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OBJECTIVES
To what extent were the following objectives of this continuing education program achieved?
1. Describe multimodal analgesia.
   Low 1. 2. 3. 4. 5. High
2. Identify nonpharmacological interventions that may help relieve pain.
   Low 1. 2. 3. 4. 5. High
3. Explain how pharmacological agents relieve pain.
   Low 1. 2. 3. 4. 5. High
4. Identify examples of polypharmacy.
   Low 1. 2. 3. 4. 5. High
5. Discuss advantages of a personalized medicine approach to managing postoperative pain.
   Low 1. 2. 3. 4. 5. High

CONTENT
6. To what extent did this article increase your knowledge of the subject matter?
   Low 1. 2. 3. 4. 5. High
7. To what extent were your individual objectives met?
   Low 1. 2. 3. 4. 5. High
8. Will you be able to use the information from this article in your work setting?
   1. Yes 2. No
9. Will you change your practice as a result of reading this article? (If yes, answer question #9A. If no, answer question #9B.)
   9A. How will you change your practice? (Select all that apply)
       1. I will provide education to my team regarding why change is needed.
       2. I will work with management to change/implement a policy and procedure.
       3. I will plan an informational meeting with physicians to seek their input and acceptance of the need for change.
       4. I will implement change and evaluate the effect of the change at regular intervals until the change is incorporated as best practice.
5. Other: __________________________________

9B. If you will not change your practice as a result of reading this article, why? (Select all that apply)
1. The content of the article is not relevant to my practice.
2. I do not have enough time to teach others about the purpose of the needed change.
3. I do not have management support to make a change.
4. Other: __________________________________

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