

# Multimodal Analgesia in the Era of the Opioid Epidemic



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## KEYWORDS

- Multimodal analgesia
- Appropriate opioid use
- Acute pain
- Acute postsurgical pain

## INTRODUCTION

A long introduction exposing the origins of the opioid crisis with its associated dismal mortality and morbidity rate should not be needed to encourage providers to adopt new analgesic strategies with less reliance on opioid medications. Unfortunately, we are in the midst of this crisis due to an overreliance on opioids. The thought that better pain control can be achieved with just adding more opioids was clearly wrong. It should be profoundly evident to all providers that a new paradigm is needed in order to curb this opioid crisis. Achieving good pain control with less or no opioid medications while minimizing complications should be our new goal. Multimodal analgesic regimens can achieve this new goal of reducing opioids while providing improved pain control. These regimens that should incorporate a more holistic approach to pain control are explored and discussed.

## PATIENT EVALUATION OVERVIEW

There is no silver bullet for good postoperative pain control. Historically, analgesic regimens focused on the postoperative period. However, contemporary pain control begins as soon as the preoperative period. Using strategies of enhanced recovery after surgery (ERAS) encapsulate the ideas of focusing on the patient's total perioperative timeline in order to affect positive outcomes for the surgical intervention. ERAS pathways have identified not only improved pain control and opioid reduction<sup>1,2</sup> but also other parameters such as decreasing length of stay and postoperative complications.<sup>3,4</sup> These pathways do not rely on one component but rather attempt to use evidence-based interventions to improve surgical outcomes including pain control. This multifaceted approach attempts to improve areas that may have not been directly linked to pain control but could certainly affect patient analgesia in a downstream manner. For instance, postoperative complications such as vomiting are associated with poor pain control.<sup>5</sup> Specific strategies used by ERAS pathways that may have

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direct or downstream effects on pain control include patient and family preoperative education, minimally invasive surgical techniques, standardized anesthesia regimens, goal directed fluid administration, use of postoperative regional anesthesia techniques, restrictive use of surgical site drains, and multimodal approach to opioid sparing pain control.<sup>6</sup> Even though these strategies were conceived for elective surgery, they can certainly be used in a nonelective setting when appropriate.

## PATIENT AND FAMILY PREOPERATIVE EDUCATION

It is helpful to identify patients at risk for poor postoperative pain control so that interventions may be tailored to the patient's individual needs. Several patient characteristics have been described as contributing to poor postoperative pain control: psychiatric illnesses such as depression, anxiety, catastrophizing,<sup>7-10</sup> younger age,<sup>8,11</sup> elevated preoperative pain scores,<sup>8-11</sup> longer operative times,<sup>11</sup> sole use of general anesthesia,<sup>9</sup> and chronic opioid use.<sup>12</sup> Many of these factors can be modified, for example, presurgical planning to include anesthesiology input to maximize the use of regional anesthetic techniques. Preoperative psychosocial interventions, especially patient education and relaxation techniques, have contributed to improved postoperative pain control.<sup>13</sup> Chronic opioid use will need to be addressed by consultation with the patient's chronic pain physician. Patient-specific opioid regimens may be determined or other helpful information such as identification of a provider narcotic agreement. Buprenorphine-containing products necessitate particular attention. Several regimens have been developed to address this unique medication that has become quite common for the treatment of chronic pain or opioid use disorder. The adoption of a buprenorphine management algorithm by all key providers will help prevent perioperative complications or surgical delays. A novel management pathway was reported by Acampora and colleagues.<sup>14</sup> This pathway allows for the continuation or titration down to 8 mg of buprenorphine twice daily, which does not interfere with full agonist opioids that will likely be required following a major surgery.

## STANDARDIZED ANESTHESIA REGIMENS

The anesthetic care that a patient receives can greatly affect postoperative analgesia. Regular consultation with your anesthesiologist will help ensure that anesthesia therapy is being delivered in a manner that maximizes analgesia and reduces opioid exposure; this can be achieved by developing expectations for optimization of regional anesthesia, minimizing agents such as remifentanyl that have been associated with hyperalgesia,<sup>15</sup> and increasing the utilization of agents such as ketamine,<sup>16</sup> which can improve analgesia and reduce opioid use. Indiscriminate use of intraoperative opioids should be avoided because it will not achieve improved postoperative pain but will certainly worsen postoperative complications.<sup>17</sup> Using the tenants of ERAS is an effective way of conducting an anesthetic in order to improve analgesia and reduce complications. However, these may be difficult to achieve in emergent surgical cases.

## APPROPRIATE USE OF OPIOIDS

Opioids have been used for centuries to treat acute pain, and unfortunately, they still play an important role in the management of acute pain. However, physicians must understand the many caveats that exist with this drug class in order to use opioids in an appropriate manner while being sensitive to the potential pitfalls. Namely, physicians must understand that all opioids are addictive, which is contrary to prior false

assumptions contributing to the current opioid epidemic.<sup>18</sup> Historically, the pharmaceutical industry has at times developed synthetic opioids or opioidlike drugs that are touted as less addictive or nonaddictive. One such drug is tramadol. It was approved by the US Food and Drug Administration (FDA) in 1995 as the only nonscheduled opioid available. The drug's use continued to increase since that time due to physicians' belief that it was less addictive and safer for patients. Tramadol ranked second in the total US opioid market sales in 2013.<sup>19</sup> Unfortunately, it became apparent that tramadol was addictive and was assigned to schedule IV by the Drug Enforcement Agency in 2014.<sup>20</sup> This oversight was likely because it was not well understood that there exists many genetic polymorphisms modulating CYP enzyme activity that are responsible for the ultimate activity of this prodrug. Patients with the gene CYP2D6 ultrametabolizers (UM) are most at risk of opioid addiction as well as other opioid side effects.<sup>19</sup> Tramadol is efficiently converted to the more active M1 metabolite in patients who are UM. Several factors make it a less attractive first-line opioid analgesic aside from its unpredictable analgesic response. Namely, tramadol has serotonin reuptake inhibition that can result in serotonin syndrome in patients already receiving serotonergic antidepressants, antipsychotics, anticonvulsants, anti-parkinsonian agents, or monoamine oxidase inhibitors.<sup>21</sup> Seizure is another limiting potential side effect because this drug can lower the seizure threshold.<sup>22</sup> Clearly, this drug lacks reliable analgesic response and has numerous potential nonopioid side effects. Therefore, tramadol does not meet the basic requirements for a first-line opioid analgesic in postoperative pain control, which is reliable analgesia with minimal drug side effects or interactions.

One must follow a few simple opioid-prescribing tenants that will help provide consistency, safety, and efficacy. These tenants are as follows: (1) select opioids with reliable analgesia and limited medication interactions. Understand the pharmacodynamics and pharmacogenomics related to these individual medications. (2) Reduce a patient's opioid exposure by providing the most effective individualized dose at the shortest duration. A reduction of overall opioid exposure throughout the entirety of a patient's surgical experience should be a goal. (3) Avoid range dosing orders. Many times providers place these types of orders to reduce nurse phone calls; however, range dosing makes it difficult for the provider to accurately determine dose responses if the patient is receiving variable doses at variable times. (4) Avoid long-acting agents or basal rates for acute pain issues. There are no long-acting agents that have indications for acute pain. These agents do have higher risk of opioid toxicity. (5) Avoid therapeutic duplication of opioids, which can be confusing for ancillary staff as well as a potential Joint Commission violation. An appropriate example would be to provide oxycodone, 5 mg, orally (PO) every 4 hours as needed for severe or moderate pain. Hydromorphone, 0.5 mg, intravenous (IV) every 2 hours as needed for breakthrough pain or physical therapy. This regimen will avoid a duplicate therapy citation but will also be effective by providing the patient with an IV drug (onset of 8–10 minutes) that will provide analgesia faster so that they can participate in physical therapy. (6) Avoid combined opioid analgesics. The combination of acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs) to opioids makes it confusing and difficult for patients or nurses to safely maximize nonopioid medications. (7) Attempt to maximize oral administration when appropriate. Oral opioid immediate release medications typically last 3–4 hours, whereas IV medication lasts on average 90 minutes. Oral medications are less costly and require far less work for nurses to administer. A patient moves much closer to disposition when they are not reliant on IV medications. However, oral opioids should not be used when enteric absorption is in question. (8) Consider patient-controlled analgesia (PCA) when the patient is

requiring frequent IV administration due to poor absorption or severe pain. PCA has been shown to be safer and provides better patient and nurse satisfaction.<sup>23,24</sup> (9) Consider increasing doses by 50% to 100% when a patient is not experiencing analgesia at the current dose. An increase of less than 50% will likely not be appreciated by the patient. (10) Always monitor for signs of opioid toxicity before escalation of opioid regimen. Less overt signs of toxicity can include slurred speech, heavy eyelids, or drowsiness. (11) Consider switching from a prodrug opioid such as oxycodone to a parent compound opioid such as hydromorphone. The patient may have improved response to a lower equianalgesic dose when changing to a parent compound because specific cytochrome conversion is not required to obtain analgesic activity. Parent and prodrug opioids are listed in (Table 1). (12) Use equianalgesic dosing calculation to switch between different opioid formulations and classes. (13) Chronic opioid use requires more complex dosing regimens. One cannot simply place a patient on home dose of opioids and expect adequate pain control. Although opioid dosing for patients on chronic opioids can be quite complex and is outside of the focus of this manuscript, there are some simple guidelines that can be used to temporize care until further consultation with the pain service is obtained: continue long-acting opioids at the home dosing schedule. Immediate release opioids should be increased by 50% to 100%. For instance, a patient is consuming 5 mg of oral oxycodone every 4 hours and subsequently undergoes a total knee arthroplasty then a reasonable oxycodone dose would be 10 mg every 4 hours as needed. Breakthrough pain dosing is typically 10% to 15% of total 24-hour morphine equivalents.<sup>25</sup> These are general guidelines and should be tailored with the patient clinical response and in conjunction with the addition of multimodal regimens.

Deescalation of an opioid should always be considered and plans set in place to facilitate safe opioid titration; this can be achieved through numerous regimens including prepared discharge opioid titrated prescriptions, patient discharge education, pain service opioid titration clinics, counseling during follow-up surgical visits, and pharmacist-led deescalation.<sup>26</sup> The basis for timely reduction of opioid use without exacerbating pain can be achieved by a 25% weekly (or daily if tolerated) reduction of individual doses. The speed of deescalation should be based on the patient's motivation and clinical condition. A provider must be aware of local legislation dictating the total amount of opioids that can be prescribed on discharge so deescalation may need to occur within this time frame. Assistance on determining the amount of opioids prescribed may also be obtained from expert panel guidelines.<sup>27</sup> Difficulties with deescalation may require referral to psychiatric evaluation if there are signs of opioid use disorder.

<b>Parent Compounds</b>	<b>Prodrug Compounds</b>
Morphine	Tramadol
Oxymorphone	Hydrocodone
Hydromorphone	Oxycodone
Methadone	Codeine
Tapentadol	-
Fentanyl and analogues	-

## MULTIMODAL THERAPY

“Aggregation of marginal gains in cardiac surgery” was coined by Dr Fleming and colleagues<sup>28</sup> in his study, which embodies the intent of multimodal therapy, which is to provide improved outcomes while reducing complications. There is currently no “silver bullet” for postoperative analgesia; therefore, a provider must use therapies that reduce pain but do not cause undue side effects. For instance, prescribing high-dose gabapentin in the hopes of improved analgesia may result in oversedation of the patient. More is not necessarily better. Several medications and treatment options commonly identified as multimodal nonopioid therapies are explored in this article. This list is not all encompassing because there are other nonopioid medications that have been tried with variable results and evidence.

### *Acetaminophen and Nonsteroidal Antiinflammatory Drugs*

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Acetaminophen and NSAIDs have provided worldwide safe and effective analgesia for decades. However, these medications, as with any analgesic, have a therapeutic ceiling that may not be sufficient for some serious postsurgical pain issues. Regardless, these medications are appropriate for most analgesic regimens unless a medication contraindication exists. At the authors' institutions, most analgesic regimens include scheduled doses of acetaminophen  $\pm$  NSAIDs, which has helped ensure that the patient receives a maximized dose and if further analgesia is required then an opioid may be offered. They have found that this has reduced patient bias, which may include the belief that only opioids will be effective for pain control. Analgesia has improved since patients started receiving adequate acetaminophen  $\pm$  NSAIDs, which likely was improved by sole use or other augmented modalities. As well, patients no longer had to wait for a nurse reassessment to receive another class of medication if acetaminophen or NSAIDs were ineffective.

Typically, these medications are delivered and easily absorbed enterally. This mode of delivery is cost-effective. There is much evidence demonstrating no improved efficacy of IV delivery of these medications versus enteral delivery.<sup>29–33</sup> However, it may be imperative to use an IV route when poor enteral absorption states exist or oral intake is contraindicated.

Acetaminophen has been generally accepted as safe with limited side effects. Yet, providers are more hesitant to use concomitant NSAIDs for fear of potential side effects such as bleeding, acute renal failure, cardiovascular events, or bone regeneration impairment. However, these potential side effects can be ameliorated by using the lowest effective dose at a short duration, careful patient selection, coadministration of proton pump inhibitor, and renal function monitoring in at-risk patients. At the institution, the authors use celecoxib when the patient is receiving thoracic epidural analgesia with concomitant heparin or enoxaparin thromboprophylaxis. Celecoxib as a cyclooxygenase-2 selective NSAID has theoretically less risk of bleeding and platelet dysfunction. Although this drug was assigned a black box warning for increased cardiovascular events (stroke and myocardial infarction), subsequent trials have identified that there is no increased risk with respect to nonselective NSAIDs.<sup>34</sup> Providers as with any drug therapy should always conduct a risk/benefit analysis when prescribing any NSAID.

### *Gabapentenoïds*

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Gabapentenoïds (gabapentin and pregabalin) have been used for decades to treat chronic neuropathic pain. Over the past decade, these medications have gained attention as opioid sparing analgesics. A wide range of dosing has occurred with

variable evidence of analgesia effect. Unfortunately, this medication is limited by sedation and central nervous system (CNS) effects especially in elderly patients. A research trend seems to be developing identifying no benefit of this drug class for postoperative pain.<sup>35-37</sup> However, the validity of the body of past work conducted on this topic can be questioned.<sup>38</sup> If a provider chooses to administer this drug for postoperative pain then the lowest effective dose for this medication should be used. The medication should also be avoided in patients at risk for CNS side effects such as the frail and elderly.

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### ***Ketamine***

This N-methyl-D-aspartate receptor antagonist has gained significant interest as an opioid sparing analgesic. Consensus guidelines developed by the American Academy of Pain Medicine (AAPM) support the use of subanesthetic doses for acute pain therapy. Because ketamine subanesthetic versus anesthetic dosing differs significantly, the AAPM guidelines were also developed to help providers administer this medication in an appropriate manner for acute pain control. Recent randomized, double-blind, placebo-controlled trials have demonstrated significant reduction in pain scores and opioid consumption.<sup>39,40</sup> Postoperative subanesthetic ketamine infusions were used in these trials, which is likely more beneficial for providing sustained opioid sparing analgesia rather than intermittent bolus dosing. Although the benefits of ketamine have been demonstrated, its safe use requires knowledge of subanesthetic dosing regimens. As well, local restrictions on administration of this dissociative drug may impede widespread hospital use. Local hospital guidelines with combined nursing education should be established and executed in order to safely administer this medication.

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### ***Lidocaine***

Lidocaine infusion for acute pain is another modality of nonopioid analgesia that is gaining popularity. Unfortunately, the evidence for its benefits have been equivocal at best due to poor methodology of prior studies.<sup>41</sup> Safety concerns for the potential of local anesthetic systemic toxicity have not been clearly defined because lidocaine dosing has varied widely and serum lidocaine levels are inconsistently monitored. Further investigation of this regimen should be conducted before its acceptance as a safe opioid alternative.

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### ***Skeletal Muscle Relaxants***

This drug class has surprisingly not received significant scrutiny is skeletal muscle relaxants. These agents were introduced in the United States as early as 1957. Carisoprodol, chlorzoxazone, metaxalone, and methocarbamol were all approved by the FDA before the Kefauver-Harris Amendment of 1962. This amendment required manufacturers to document safety and efficacy before allowing medication approval to enter the market place. Many of these medications would likely not achieve the market under current FDA standards. As well, most of these medications have mechanism of action that are unknown but they all consistently cause CNS depression. CNS depression can be potentiated with the identified risk of opioid overdose.<sup>42</sup> To date there is only one study in younger adults suffering rib fractures that identified some opioid reduction with methocarbamol use.<sup>42</sup> However, these findings must be taken cautiously because this was a limited retrospective study (n = 50) with low evidence methodology. Routine use of these medications should be discouraged due to potential medication interactions, side effects, and lack of evidence especially in a critical care or postsurgical setting.

## INTERVENTIONAL TREATMENT OPTIONS

### *Regional Anesthesia*

Regional anesthesia represents 2 distinct categories: peripheral and neuroaxial anesthesia. Both of these techniques can be introduced into a multimodal regimen. Historically, thoracic or lumbar epidural analgesia has been considered the gold-standard regional analgesia. However, this standard is quickly changing with the improvement of technology namely ultrasound technology, and this has allowed the expanded use of peripheral nerve blocks as well as improved the safety of this technique. The list of effective ultrasound-guided peripheral nerve blocks (**Box 1**) has grown significantly in the past decade. Peripheral nerve blocks have surpassed or replaced neuroaxial techniques that have been contraindicated due to a patient coagulation status, cardiovascular instability, or traumatic spinal cord injury; this is particularly evident in the critical care arena in which patients may not be candidates for epidural analgesia yet are suffering from significant painful injuries. Peripheral nerve blocks in critically ill patients typically do not affect central sympathetic tone similar to thoracic epidural analgesia; therefore, hypotension likely will not occur. As well, a peripheral nerve block technique is not necessarily contraindicated in patients suffering coagulopathy or who are receiving aggressive thromboprophylaxis.<sup>43</sup> All peripheral nerve blocks can be performed using single shot or continuous catheter techniques. A continuous catheter can provide extended pain relief for up to 7 days. Regional anesthesia has demonstrated robust evidence of its opioid sparing effects and should be maximized in all multimodal regimens.

### MULTIDISCIPLINARY APPROACH

Providing a multidisciplinary approach to complex acute pain issues may be necessary in many patients. An evidence-based approach such as ERAS protocols can incorporate a multidisciplinary approach to patient care in the setting of surgery. Similarly, utilization of guidelines such the American College of Critical Care Medicine's pain, agitation, and delirium guidelines in an intensive care setting may facilitate optimized analgesic care in a critically injured patient.<sup>44</sup> These guidelines take into account the downstream effects of poor pain control on other entities such as delirium. As well, incorporating these guidelines with ventilator weaning, early mobility, and sleep hygiene protocols may provide improved outcomes.<sup>45</sup> The local development of guidelines to facilitate treatment options is important to effectively use a systems resource such as physical therapy, psychiatric services, or medical

#### **Box 1**

##### **Peripheral nerve blocks**

Peripheral nerve block and coverage areas

##### Truncal Blocks:

Transversus thoracis plane, serratus anterior plane, erector spinae, parasternal

##### Abdominal Blocks:

Transversus abdominis, rectus sheath, erector spinae

##### Upper Extremities:

Supraclavicular, infraclavicular, interscalene, axillary

##### Lower Extremities:

Subgluteal sciatic, popliteal sciatic, adductor canal, femoral, fascia iliaca

comanagement teams. These guidelines can incorporate a more broad approach to pain management because a strong relationship exists between effective pain management and a patient's ultimate outcome.

## NONPHARMACEUTICAL THERAPY

These treatment options are often times overlooked due to lack of evidence or reimbursement issues. They can range from simple measures such as warm and cold compresses that require little effort but may safely provide analgesia.<sup>46,47</sup> Distraction therapies such as guided imagery, meditation,<sup>48</sup> and music<sup>49</sup> have also shown benefits in improving analgesia. Nurse education can include training for instituting these types of techniques. Transcutaneous electrical nerve stimulation is another modality with some evidence of improved analgesia in various pain syndromes including post-surgical pain from inguinal herniorrhaphy.<sup>50</sup> Although TENS units are relatively inexpensive, in a hospital setting utilization of TENS therapy can be cost prohibitive. Even though evidence is lacking in many of these modalities, they do represent a devotion to the patient to "do everything possible" to treat pain that certainly will not go unappreciated by a suffering patient or family.

## SUMMARY

The opioid crisis has certainly brought attention to the use of opioids to treat pain. This crisis has helped reveal that analgesic regimens should not be heavily relied on opioids to deliver pain control. The potential risk of overutilization of opioids has been self-evident. Unfortunately, until a new class of drug is discovered these medications will still play an important role in analgesia especially in critically injured patients. Even though these medications are still used, they should be used in an adjunct fashion in conjunction with other evidence-based multimodal therapies. Scrutiny and caution should be applied when introducing nonopioid analgesics to a regimen because these medications may have an unintended delirious impact on patient care. There may be increased time and costs to achieve a robust opioid-minimized or opioid-free multimodal regimen but as providers we must accept this cost in order to prevent further negative impacts on the current opioid crisis.

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