

ANESTHESIOLOGY

Perioperative Opioid Administration

A Critical Review of Opioid-free *versus* Opioid-sparing Approaches

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Opioids are an integral part of perioperative care because of their high analgesic efficacy.^{1–3} They have well-known short-term adverse effects and the potential for long-term adverse effects for patients and society.^{3–5} The long-term harms are specifically responsible for the ongoing opioid epidemic in North America, as well as in some other parts of the world, and are related primarily to oral opioids prescribed for chronic pain.⁶ In the United States, Congress declared 2001 to 2011 the “Decade of Pain Control and Research.”⁷ Liberal opioid use was encouraged in an effort to gain higher patient satisfaction along with misguided efforts by the pharmaceutical industry acting as driving forces.⁸ This resulted in practice patterns favoring opioid overprescription with limited oversight. Several observational studies have demonstrated a clear disconnect between the prescriptions provided to the patients and opioids needed to manage pain.^{9,10} This increases the risk for persistent opioid use and opioid use disorder,¹¹ and the unused pills represent a reservoir feeding the opioid diversion market, leading to societal harms.^{12,13} Because a large proportion of literature clearly indicates inappropriate physician prescriptions as the contributing factor,^{10,11,14} interventions encouraging safer opioid prescriptions have a direct role to play. These interventions have the potential to decrease opioid utilization and overprescription without affecting the satisfaction of postdischarge analgesia.^{15–17} However, imposing strict opioid limits alone may not lead to appreciable reductions.¹⁸

ABSTRACT

Opioids form an important component of general anesthesia and perioperative analgesia. Discharge opioid prescriptions are identified as a contributor for persistent opioid use and diversion. In parallel, there is increased enthusiasm to advocate opioid-free strategies, which include a combination of known analgesics and adjuvants, many of which are in the form of continuous infusions. This article critically reviews perioperative opioid use, especially in view of opioid-sparing *versus* opioid-free strategies. The data indicate that opioid-free strategies, however noble in their cause, do not fully acknowledge the limitations and gaps within the existing evidence and clinical practice considerations. Moreover, they do not allow analgesic titration based on patient needs; are unclear about optimal components and their role in different surgical settings and perioperative phases; and do not serve to decrease the risk of persistent opioid use, thereby distracting us from optimizing pain and minimizing realistic long-term harms.

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At the same time, this seems to have precipitated a rethinking around the use of opioids during the perioperative period, and anesthesiologists are identifying the role they can play in decreasing the burden of the opioid crisis. With good intent, backed by strong enthusiasm but uncertain evidence, there is advocacy toward opioid-free perioperative care strategies, with ever more increasing publications.^{2,19–21} A quick search of PubMed indicates over 300 publications in the last 10 yr, of which more than 200 were published in the past 5 yr. Many suggest these strategies as a new paradigm that might help to solve the problem.² Others have quoted that there are alternative approaches to pain management that do not rely on opioids,²² without clarifying what these methods are and how they operate. There is a lack of understanding around these alternative approaches, their limitations and applicability, phases of care in which they can be effectively introduced and operate, and whether they truly lead to opioid-free care throughout the perioperative course, including after discharge from the surgical facility.^{21,23} The bigger and more relevant questions are whether these strategies influence overall opioid needs and pain resolution and whether this has any bearing on the potential for persistent opioid use after surgery.²⁴

Our review was informed by the existing literature around the theme of rational opioid use in the perioperative period, more specifically as it applies to opioid-reduction and -minimizing strategies. Because this is not a systematic review, we did not consider a specific methodologic criteria for study selection or analysis. However, a conscious

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attempt was made to keep the review current and comprehensive by searching within Medline and Embase databases *via* OVID platform using the terms “opioid-sparing” and “opioid-free” to look for studies and reviews focused on intraoperative anesthesia and postoperative analgesia. In addition, we looked into practice guidelines and recommendations published by recognized anesthesia societies and organization, relevant to this review. Keeping in mind the common anesthesia practitioner, we will review the feasibility, challenges, and practical considerations with the use of opioid-sparing and opioid-free techniques in different phases of perioperative care. Because a clear distinction needs to be made, we will separate the terms “opioid-free anesthesia” to denote avoidance of opioids in the intraoperative period and “opioid-free analgesia” to further extend opioid avoidance to the postoperative phase. We conclude by summarizing the important questions and the potential role for anesthesiologists in optimizing perioperative pain, opioid utilization and surgical recovery.

Perioperative Opioid Use

Traditionally, the perioperative phases in which analgesics are used include the intraoperative period, the postoperative in-hospital period, and the postdischarge period. However, the preoperative period also constitutes an important phase in which analgesics are to be managed within the context of enhanced recovery after surgery pathways.^{25,26} It is necessary to categorize into these phases because factors involved in the analgesic choices and available options differ. For example, the in-hospital period allows more analgesic options and modalities of administration as compared with the postdischarge period, in which the options are restricted to oral analgesics,⁴ unless there is a specific pathway to address such needs in the form of a transitional pain care or perioperative surgical home.²⁷

Intraoperative Considerations and Challenges

Balanced Anesthesia and Opioids

The concept of balanced general anesthesia includes unconsciousness, amnesia, immobility, and antinociception.^{28,29} Under general anesthesia, although the patient does not suffer from pain (subjective experience), nociceptive signals are continuously generated and carry negative physiologic consequences,³⁰ as well as a higher risk of awareness. The nociceptive pathways have strong connections with arousal pathways and administering anti-nociceptive agents decreases arousal.^{28,31} Cividjian *et al.*²⁹ note that it would be wrong to assume that there is no interaction between the adequacy of hypnosis and the adequacy of antinociception under general anesthesia. Fleischer and Glass³² note the following regarding the link between nociceptive signals and awareness: “One of the most common pitfalls in the use of state-of-consciousness

monitoring in preventing awareness has been the failure to anticipate changing levels of noxious stimulus and their likely effect on the hypnotic state. During sleep, depending on how ‘light’ or ‘deep,’ one may be awakened by noise of a lesser or greater degree, so during general anesthesia, the hypnotic state will be affected by stronger or weaker stimuli, depending on the adequacy of the analgesic component of the anesthetic. It is this component that is not measured by the Bispectral Index or any other monitor currently available and that is most likely responsible for case reports of awareness at Bispectral Index levels generally accepted as synonymous with unconsciousness.” Within an analysis of the American Society of Anesthesiologists Closed Claims Project, intraoperative pain was the third most common event recalled by patients.³³ The adequacy of antinociception is assessed by autonomic changes such as blood pressure and heart rate, as well as patient movements in an unparalyzed patient.^{1,28,32} Opioids act as the primary agents of antinociception and decrease arousal by acting on receptors at several levels.^{1,28,34–36} As an adjuvant to other components of general anesthesia, they decrease the need for sedative-hypnotics during induction and maintenance^{31,37} and contribute to a significant decrease in the minimum alveolar concentration.¹ They mitigate hyperdynamic responses for laryngoscopy and intubation, and blunt cough and gag reflexes during airway manipulation.³⁸

Despite these benefits, it is clear that opioids should be used sparingly because they have recognized short-term adverse effects that can influence patient-important outcomes and cost.³ This can be achieved by using nonopioid analgesics. Although the initial advocacy of multimodal analgesia was toward the adequate control of postoperative pain and minimizing adverse effects from individual agents,³⁹ it has now been extended to the entire perioperative phases, including the intraoperative part, wherein the objective is to reduce opioid requirements (*i.e.*, opioid sparing).^{3,40,41} However, the amount of intraoperative opioid sparing could differ between surgical procedures, and not all analgesics may be safe in all procedures or patients.^{4,42,43}

Opioid-free Anesthesia and Its Challenges

Opioid-free anesthesia is a claim toward “no opioid use,” specifically to separate it from opioid sparing. Despite the claim, people differ in their interpretation regarding the need for opioids even within opioid-free anesthesia. For example, one definition suggests opioid-free anesthesia as a technique in which no intraoperative opioid is administered *via* any route, including systemic, neuraxial, or tissue infiltration.⁴⁴ Forget⁴⁵ defines it as “the combination of various opioids sparing techniques leading to the disappearance of the intraoperative opioids.”

The known nonopioid analgesic strategies include the use of acetaminophen, nonsteroidal anti-inflammatory drugs or cyclooxygenase-2-specific inhibitors, local/regional analgesic techniques and nonpharmacologic

adjuncts.⁴ Medications commonly considered as analgesic adjuncts include steroids, gabapentinoids, intravenous lidocaine infusion, and ketamine infusion.^{28,46,47} More recently, dexmedetomidine, magnesium, and β -blocker infusions were added.^{20,41,48} Paradigms of opioid-free anesthesia proposed include administration of several nonopioid analgesics, plus some or all of the above noted analgesic adjuncts, along with infusions of dexmedetomidine, magnesium, and β -blockers, in various combinations.^{2,19,20,41,48,49} There are some important considerations and limitations of these approaches (fig. 1).

All agents considered, excepting opioids, are limited by a ceiling effect and, with most agents, a small therapeutic index for safety. Most adjuncts are to be administered as a combination of fixed-dose infusions, and one cannot titrate them to an effect, which is a necessity during the intraoperative period. With an attempt to take out the reliance on opioids for anti-nociception, an objective and effective way to discern the level of nociception in a patient under general anesthesia becomes essential.^{3,28} Nociceptive monitoring relies on indirect measures of peripheral and central responses and depends either on single responses such as skin conductance or on indices combining multiple

measures such as the surgical stress index or nociception level index.^{50,51} However, because of technological limitations and potential inaccuracies, their present use is precluded.⁵² A recent systematic review looked at nociception monitor-guided anesthesia effects on opioid consumption and noted that no consistent effect of such monitoring on anesthesia could be established.⁵³ Optimal combination of these agents or their dosing remains unclear.⁵⁴ Frauenknecht *et al.*⁵⁵ recently published a systematic review and meta-analysis looking for analgesic impact of intraoperative opioids *versus* opioid-free anesthesia. They looked within PubMed and Google Scholar for trials that compared any type of intraoperative opioid administration with placebo injection or absence of opioids and included 23 trials for analysis. However, many included trials were not clearly opioid-free anesthesia as the name implied; Inoue *et al.*⁵⁶ used fentanyl for induction in all three groups, and Song and White⁵⁷ used remifentanyl in both groups. Other studies, some of which were not included in this review, involve the use of three or more adjuncts at varying doses,^{23,58} which makes it extremely difficult to tease out the incremental clinical value and cost considerations for individual agents.^{59,60} As an example, let us look at two recent randomized controlled

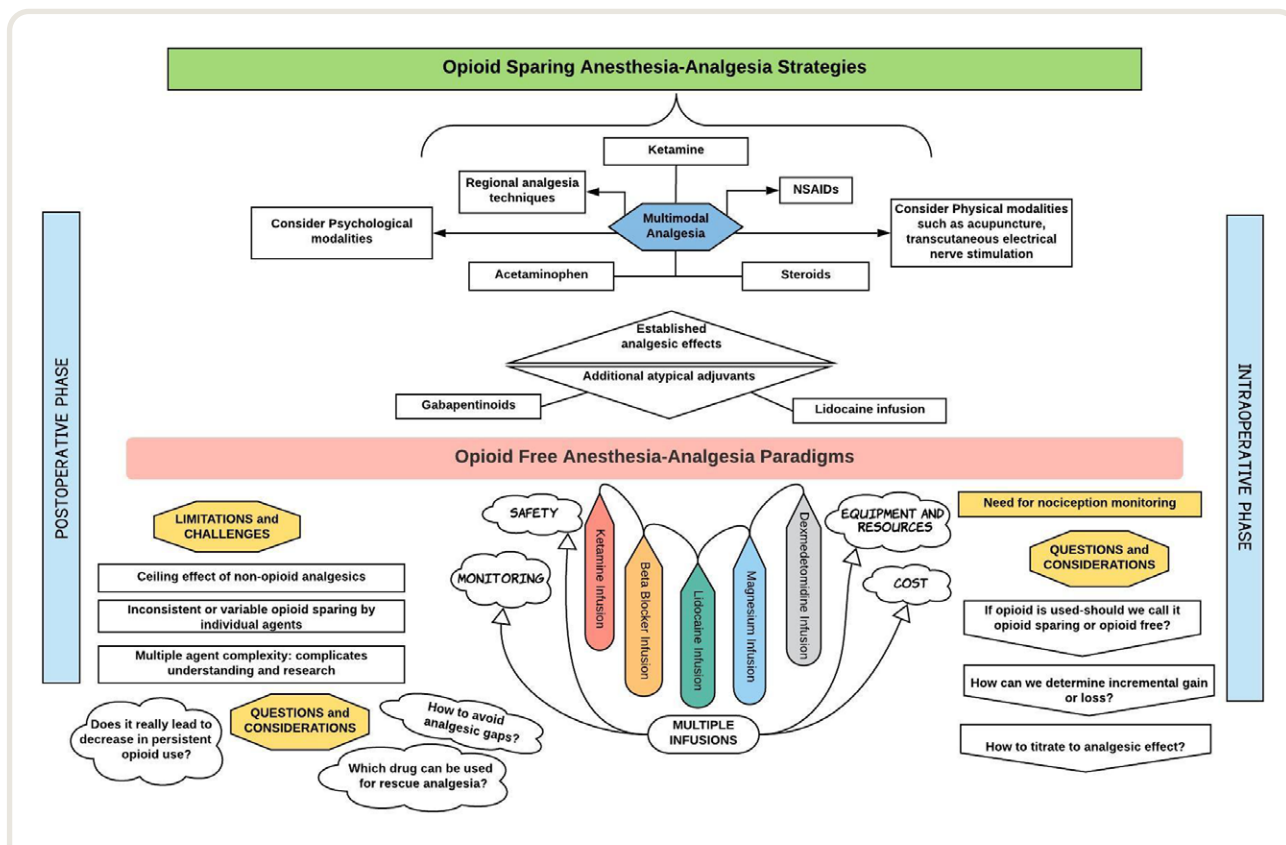


Fig. 1. A representation of intra- and postoperative care considerations and limitations in the context of opioid-sparing *versus* opioid-free strategies. Opioid-free paradigms include multimodal analgesia options indicated in the *top part* along with other infusion options in the *bottom part*. NSAID, nonsteroidal anti-inflammatory drug.

trials proposing opioid-free anesthesia for laparoscopic cholecystectomies. Toleska and Dimitrovski⁶¹ report a trial of 30 patients having fentanyl-based anesthesia compared with 30 patients having infusions of lidocaine and magnesium. There were methodologic limitations affecting internal validity with no prespecified primary outcome, and the fentanyl group did not have any multimodal analgesia compared with the opioid-free anesthesia group, who had dexamethasone, paracetamol, and an anti-inflammatory medication. Toleska and Dimitrovski⁶¹ only report pain scores for each hour throughout the recovery and do not report any outcome on opioid usage or adverse effects. In another trial, Bakan *et al.*⁶² report an 80-patient trial in which all patients had multimodal analgesia, with the opioid-free anesthesia group having a combination of lidocaine plus dexmedetomidine and propofol infusion during surgery compared with remifentanyl and fentanyl in the standard group. The primary outcome of opioid consumption within 6 h after extubation was not significantly different between the two groups. There was actually a significant increase in the discharge time from recovery in the opioid-free anesthesia group. If other studies propose adding other nonopioid adjuncts, such as calcium channel blocker⁶³ or β -blocker with potential analgesic properties, how do we determine whether it should be included in the opioid-free anesthesia combination?

Suggested clinical approaches to opioid-free anesthesia seem to ignore the concerns about safety and drug interactions and do not appreciate the practical resource limitations.^{21,64} Even a single dose of intraoperative ketamine can cause hallucinations and nightmares;⁶⁵ dexmedetomidine can cause clinically important hypotension and prolong readiness to discharge, as well as an increased risk of airway collapse and prolonged hypoxia;^{62,66–70} β -blockers can increase the risk of death, stroke, and hypotension;^{71,72} and magnesium can cause arrhythmias and potentiate neuromuscular blockade and increase the risk of residual paralysis.⁷³ Although gabapentinoids have been used in many multimodal analgesia regimens,⁵⁴ their safety has been recently questioned.^{74–78} A recent French survey found a clear mismatch between existing evidence and clinical use of perioperative gabapentinoids.⁷⁹ This is an example of how widespread adoption of an analgesic adjunct in a fixed combination seeps into clinical practice without appropriate consideration of its individual risk–benefit ratio. Multiple intravenous medications necessitate equipment for infusions. This can be burdensome, apart from increased costs of using such equipment for every case.⁸⁰ It is unclear which of the adjuncts in the combination should be stopped for an observed adverse effect, and how will it impact on the subsequent delivery of opioid-free anesthesia? Similarly, which of these adjuncts would continue to provide analgesia that will extend beyond the operating room and discharge?

Two other considerations are pertinent to discuss: opioid-induced hyperalgesia and cancer recurrence.

Opioid-induced hyperalgesia has bigger implications in chronic pain practice, and it is very likely to be a real phenomenon even in acute care settings.⁸¹ Studies suggest that opioid-induced hyperalgesia is more pronounced, with short-acting or ultrashort-acting agents such as fentanyl and remifentanyl.⁸² In a systematic review and meta-analysis, Fletcher and Martinez⁸³ showed that patients with higher intraoperative opioid doses had higher pain scores than controls. The difference was less than 10 mm on a 100-mm scale at 1 h after surgery and decreased further over time. Whether the differences from opioid-induced hyperalgesia are big enough to make clinical relevance and offset limitations of not using them are important questions. Preclinical evidence and uncontrolled studies suggested that opioids can increase cancer recurrence by inhibiting the function of natural killer cells and by their effect on angiogenesis and tumor cell signaling pathways.⁸⁴ However, a recent review,⁸⁵ as well as a large ($n = 2,108$) multicenter randomized controlled trial, concluded that there was insufficient evidence to recommend any particular analgesic technique for patients undergoing cancer surgery.⁸⁶

Postoperative In-hospital Analgesia Considerations and Challenges

Patient-centered Pain Relief in the Context of Multimodal Analgesia

Although the nature of pain after surgery is to a large extent determined by the surgical procedure,^{87,88} the intensity of pain and the need for analgesics can vary even among patients having the same surgery.^{4,87,89} There is also individual variability in the amount of opioid sparing with known analgesics used for multimodal analgesia.^{90,91} The incidence of moderate to severe pain in-hospital and on the first postoperative day is reported in around 30 to 80% of patients.^{92–94} There is consistent evidence to suggest that a substantial proportion of patients continue to have inadequately managed postoperative pain with deleterious consequences, including persistent postsurgical pain.^{88,95,96} In summary, it is vital to recognize that a one-size-fits-all approach cannot be appropriate and runs against the tenet of personalized medicine, so allowance for analgesic titration is a much-needed necessity.

Opioid-free Analgesia and Its Challenges

Many protocols that have been suggested as opioid-free analgesia do not clarify their method of analgesia in the recovery unit.^{4,96} There is no literature on how these patients recover or about their postoperative trajectory in comparison with patients who receive opioids within a framework of good multimodal analgesia.²³ In the review by Frauenknecht *et al.*,⁵⁵ 15 of 23 trials used parenteral opioids in the postoperative period. With the absolute avoidance of opioids in opioid-free analgesia, there is no allowance

for any measures or analgesic to be titrated to individual patient requirements, other than the local/regional analgesic options. Nonsteroidal anti-inflammatory drugs have a maximum daily safe dose⁹⁷; acetaminophen also has a daily maximum dose and cannot provide meaningful rescue analgesia in moderate to severe pain⁹⁸; and gabapentinoids or other adjuvants are not pure analgesics and cannot be used as rescue analgesia by titration.⁷⁶ Within the context of treating postoperative pain in-hospital, we do not overtreat pain^{7,99,100}; more relevantly, do we overdepend on opioids? If so, why? Do we have realistic options to forego opioid use completely?

The components of multimodal analgesia are chosen considering their (1) intrinsic analgesic potency, (2) opioid-sparing potential, and (3) potential side effects. The first two characteristics go in parallel: larger analgesic potency leads to higher opioid sparing. As highlighted within the PROCEDURE-SPECIFIC Postoperative Pain Management (PROSPECT) recommendations, not all medications carry the same potential in different surgeries,⁸⁸ such as the variation in the opioid-sparing effect of acetaminophen^{98,101,102} or the benefit of local infiltration analgesia observed in knee arthroplasties but not hip.¹⁰³ Despite broader acceptance of the concept of multimodal analgesia, there have been disappointing results, as observed by the proportion of surgical patients who continue to have inadequate pain relief.^{4,104} This is likely as a result of nonutilization or inconsistent application of available modalities rather than the nonavailability of newer modalities.^{23,46,90,104} Locoregional analgesia, whether delivered by surgeons or anesthesiologists, has been shown to have important effects for analgesia and opioid sparing.^{105,106} Despite this knowledge, in a recent study of nearly 13 million patients, only 3.3% among 25% patients considered eligible had nerve blocks.¹⁰⁷ In another study, only 29.8% of colectomy patients and 76.5% of knee arthroplasty patients received any nonopioid analgesic on the day of surgery.⁴⁶

There are several potential nonpharmacologic approaches to pain management that may reduce the use of medications and improve outcomes in the postoperative period. In clinical practice they are used as adjuncts rather than a primary analgesic and can be broadly categorized as physical and psychologic modalities. Physical modalities include transcutaneous electrical nerve stimulation, acupuncture, massage, yoga, continuous passive movement, and cryotherapy. Among these treatment options, systematic reviews and guidelines have determined that transcutaneous electrical nerve stimulation and acupuncture have demonstrated evidence to support their consideration.¹⁰⁸ However, the level of evidence and certainty is low, and the amount of analgesia provided is unclear. Other physical modalities are considered safe but are not supported by rigorous scientific studies. Psychologic modalities can be grouped into four categories: information provision, stress reduction, attentional strategies, and cognitive-behavioral

interventions.¹⁰⁸ These categories overlap and can be used in combination within a comprehensive intervention. Although initial evidence demonstrates significant potential of psychologic therapies for reducing postoperative pain, there is insufficient data to recommend a particular method or technique.¹⁰⁹ Given the relative safety of both physical and psychologic modalities, further investigations addressing their efficacy and cost effectiveness is warranted to justify wider adoption.

When we look at suggested regimens for opioid-free analgesia, many include continued infusions of lidocaine, magnesium, ketamine, and dexmedetomidine in various combinations,^{19,41} although some even include using fentanyl patient-controlled analgesia in postoperative wards.¹⁹ Apart from the limitations highlighted during the intraoperative phase, these infusion regimens necessitate monitoring, additional resources and equipment, and cost. For example, even for adjuncts with relatively better evidence such as ketamine and lidocaine infusions, more frequent and high-dependency monitoring, including continuous electrocardiogram, blood pressure, sedation level, and oxygen saturation, are required in most places.^{64,110} Given these considerations, the argument to include more modalities with little consideration to procedure or patient-specific needs in the ambit of opioid-free analgesia, seems counterintuitive.¹¹¹ Furthermore, the enthusiasm to implement these modalities can divert the attention from utilizing important components of multimodal analgesia. More importantly, the adverse effects of these approaches (*e.g.*, orthostatic hypotension) and the cumbersome infusions attached to the patient can delay ambulation, which is one of the key components of enhanced recovery.¹¹² Thus, there can be misguided attention toward areas with smaller gains and missed opportunities for larger gains, especially from the surgical community, who feel that newer opioid-free analgesia techniques are the way out of the present crisis. This is reflected in the systematic review by Fiore *et al.*,¹¹³ who set out to look for opioid-free prescriptions after surgery (where the real problem lies) and observed that a majority of randomized controlled trials ($n = 117$) compared opioid-free *versus* opioid analgesia during hospital stay, and only seven randomized controlled trials targeted analgesia postdischarge.

Postdischarge Analgesic Considerations and Challenges

It Is Not about Opioids but How We Use Them

Pain is a common complaint after surgery and can interfere with recovery.^{4,92} Surveys of mixed populations have shown that 70 to 80% of patients have moderate to severe pain during the first few days after surgery.^{93,99,100} In many common day surgeries (inguinal hernia, cholecystectomy, arthroscopies, laparoscopic salpingo-oophorectomy), postdischarge pain can be adequately controlled with a combination of nonopioid analgesics given round the clock, with opioids as a rescue analgesic.^{4,15,21,23} For major

surgeries, such as arthroplasty, laparotomy, or thoracotomy, opioids are included in the combination of analgesics, until such time as to allow appropriate resolution.^{3,4} Despite this knowledge, the practice of using two or more nonopioid analgesics is inconsistent and low.

In a large survey of 2,754 ambulatory surgery patients, only 14% of patients were prescribed a combination of two or more drugs, and 24% of adult patients continued to report pain even on day 7 after surgery.¹¹⁴ Interestingly, there seems to be a clear distinction in how postoperative opioids are used in reference to their geography.¹¹⁵ The per capita use of opioids in Scandinavian countries is half or less as compared with the United States.²³ Another observational study noted that postsurgical opioids are prescribed to 98.3% of patients in North America compared with 70.2% of patients in Europe; despite this, the mean worst pain scores were rated higher in North American patients (7.4 of 10) compared with patients from Europe (5.4 of 10).¹¹⁶ There may also be cultural differences in pain expectations and limitations of pain intensity measures used to reflect the need for analgesics.^{117,118} As pertinent to North America, there is abundance of literature suggesting that inappropriate opioid prescriptions, in the form of prolonged prescriptions with minimal oversight, have contributed to the ongoing opioid crisis.^{9,10} A large observational study in 18,343 patients attempting to find the basis on which discharge prescriptions were made found no correlation between opioids prescribed at discharge with the opioids consumed in the last 24 h before discharge.¹¹⁹ Other studies have shown that around 90% or more patients are provided with opioid prescriptions but only 20 to 30% actually used them^{14,120} and less than 20% received instructions for safe disposal.¹⁴ This overprescribing could lead to diversion and potentially to persistent opioid use.^{9,120}

We would be shortsighted if we assume that the risk of misuse or diversion exists only with opioids or with certain opioids. The risk of misuse exists in 40 to 65% patients prescribed gabapentinoids.¹²¹ Tramadol is a weak μ -opioid receptor agonist and is used as a schedule IV drug in the United States and an unscheduled drug in Canada, and many consider it to be a much safer drug with less addictive properties.¹²² With this reasoning, physicians have used it in studies aimed to reduce opioid use,¹⁵ and one randomized controlled trial even included it under nonopioid prescribing.¹²³ However, Thiels *et al.*¹²² recently noted that patients receiving tramadol alone after surgery had similar or even higher risks of persistent opioid use compared with other patients receiving short-acting opioids.

Recognizing and Dealing with the Twin Issues of Persistent Opioid Use and Persistent Postsurgical Pain

The observed incidence and the definition of persistent opioid use varies.^{10,11,124} Brummett *et al.*¹²⁵ quoted an incidence of 5.9 to 6.5% in both minor and major surgeries. Goesling *et al.*¹²⁴ observed that among patients who were

opioid-naïve at surgery, 8.2% of knee arthroplasty and 4.3% of hip arthroplasty patients were using opioids at 6 months. In another database study of 641,941 opioid-naïve surgical patients, the odds ratio of persistent opioid use (more than 90 days after surgery) ranged between 1.28 (95% CI, 1.12 to 1.46) for cesarean delivery to 5.10 (95% CI, 4.67 to 5.58) for knee arthroplasty.¹¹ Jivraj *et al.*¹²⁶ observed that among 39 studies, 29 different definitions of persistent opioid use were used with an incidence varying from 0.01 to 14.7% and a median of 0.7%. Although ideally persistent opioid use should reflect actual use of opioids, prescriptions or pharmacy claims have been considered as proxy to indicate persistent opioid use in major reviews or studies using large databases.^{10,127} Most of them also do not report the reasons for persistent opioid use and if indeed an analgesic was needed for continuing pain.¹²⁸

Let us now consider whether opioid reduction during surgery or in the hospital decreases persistent opioid use. Although studies do show reduction in inpatient opioid consumption, especially with implementation of enhanced recovery after surgery pathways,^{129,130} there is no evidence to suggest that limiting intraoperative opioids influences the risk of persistent opioid use. In fact, even for regional analgesia, with nearly complete opioid avoidance, existing studies show no association with their use and persistent opioid use.^{24,131,132} If there is any such possibility, the more relevant question would be how much opioid reduction makes a difference for the risk of persistent opioid use? Suzan *et al.*¹³³ present a concept of crucial timing that separates the beneficial and negative effects of opioids. They hypothesize that if an opioid effect is present in the central pain pathways during injury (surgery), opioids augment postoperative pain. Although this may give additional credence to opioid-induced hyperalgesia, there is no rationale presented to support the risk of persistent opioid use.

As much as we appreciate the need to tackle increased opioid use, we cannot ignore the issue of inadequately treated pain and its consequences, including persistent postsurgical pain.^{17,27,96} Importantly, as pointed out by Kharasch and Clark,¹²⁸ “how do we interpret a 2 to 3% overall median frequency of persistent opioid use in the context of 10 to 60% frequency of” persistent postsurgical pain, in terms of overall priority and approach? There are also many features intricately linked between them, from pathophysiological, organizational, and health delivery perspectives.^{128,134} For example, the presence of preoperative pain and being on preoperative opioids independently increase the risk of persistent postsurgical pain and persistent opioid use.^{135, 136} The burden of acute pain intensity and duration have been associated with persistent postsurgical pain development.¹³⁷ Murphy *et al.*¹³⁸ report persistent pain outcomes of two different study populations receiving intraoperative methadone. In their first trial on spinal fusion surgery, the patients were randomized to receive 0.2 mg/kg methadone (n = 62) at induction or 2 mg of hydromorphone (n = 53)

at surgical closure, along with routine anesthetic management. In the second trial, fast-track cardiac surgery patients were randomized to receive 0.3 mg/kg of methadone ($n = 77$) or 12 $\mu\text{g}/\text{kg}$ of fentanyl ($n = 79$) before cardiopulmonary bypass. In both trials, patients received multimodal analgesia postoperatively. Methadone improved postoperative pain control and also decreased the weekly frequency of chronic pain in spine-fusion patients at 3 months and for cardiac surgery patients at 1 month after surgery, indicating that better control of perioperative pain has the potential to decrease persistent postsurgical pain and the number of patients using opioids at 3 months after surgery.¹³⁸ The issues of persistent opioid use and persistent postsurgical pain are better understood by recognizing the trajectory of pain in surgical patients.^{92,139} Studies have observed significant variation within the pain-resolution patterns among patients^{10,140–142} and note that analgesic consumption during the acute postoperative period is dynamic and changes with time.⁹² In a mixed surgical cohort of 371 patients, Hah *et al.*¹⁴¹ observed that the average pain trajectory significantly predicted not only prolonged pain (hazard ratio, 0.63; 95% CI, 0.50 to 0.80; $P < 0.001$) but also delayed opioid cessation (hazard ratio, 0.52; 95% CI, 0.41 to 0.67; $P < 0.001$). It is very likely that at this time patients predisposed to persistent postsurgical pain and persistent opioid use are not clearly separable within the surgical cohorts until they establish themselves, which means it may be difficult to identify them at the time of discharge.¹⁴³

Maximizing Opportunities for Anesthesiologists in Optimizing Perioperative Pain, Opioid Utilization, and Recovery

The perioperative period presents a unique opportunity for both anesthesiologists and surgeons to collaborate to improve patient outcomes and surgical recovery.^{144,145} There is increasing recognition of different roles the anesthesiologist can play within the perioperative team.¹⁴⁵ A team approach allows healthcare providers and physicians to put the patient in the center, with a greater emphasis on patient-centered care and shared decision-making.¹⁴⁴ Several preoperative (patient) factors have been recognized to play a role in postoperative pain control, persistent opioid use, persistent postsurgical pain, and overall recovery.^{27,146} Existing literature identifies anxiety, depression, catastrophizing-coping, preexisting opioid use, chronic pain, smoking, and frailty as some of the important factors that could be potentially addressed.^{4,134,146,147} The preoperative phase gives an opportunity to assess, triage, and modify some of these factors, whenever possible (fig. 2). This engagement with the patient also provides an opportunity for the perioperative team to educate patients on pain control and in setting realistic expectations for the patient and the family.²⁶ This is a clear example of how patients, previously considered a passive recipient of information, can now be included as an active participant in their clinical process. At the same time,

it is also suggested to manage anticipation of pain, decrease opioid use, and optimize and allow nonopioids for pain control.^{4,25,148} Identifying patients at risk preoperatively allows the perioperative team to categorize and identify a framework to adapt intraoperative and postoperative care needs.

It is critical to maximize the role of locoregional analgesia during the intraoperative period, apart from utilizing multimodal analgesia (components are shown in fig. 1) taking into consideration patient- and procedure-specific factors.^{4,148} Compared with systemic agents, regional blockade is most effective for controlling movement-evoked pain,¹⁴⁹ and every patient should receive some form of locoregional analgesia. With a wide variety of options available, there is a need for communication, planning, and collaboration with the surgical team to choose a technique that is feasible, effective, and safe and that improves recovery.¹⁰⁶

Postoperatively, individual variation in postoperative pain resolution may necessitate further adjustments and additional options for pain management. Engagement of the patient, either in-person or by telemedicine, provides continued support and an opportunity to improve satisfaction. As part of the perioperative team, anesthesiologists can work with the surgical team to determine discharge prescription needs.^{150–152} Although not directly relevant as part of this article, anesthesiologists playing a role as perioperative physician goes beyond managing anesthesia and pain needs and supports the emerging concept of continued postoperative care and monitoring to decrease the morbidity and mortality that can occur after discharge.¹⁴⁵ Specific to pain, patients at high risk or with an abnormal pain trajectory can be routed through a framework or care paradigm similar to a transitional pain service or perioperative surgical home that is patient-centered and includes management of analgesia using a multipronged approach of education, prehabilitation, and multimodal pharmacologic and nonpharmacologic approaches (fig. 2).^{23,27,153} In a small observational study of 61 patients, Shechter *et al.*¹⁵⁰ report positive results from their perioperative pain program that focused on patients with chronic preoperative opioid therapy and reported reductions in opioid use and improvement in pain control and functions. Trials evaluating such combinations of interventions are being considered to address persistent opioid use.¹⁵⁴ Although such paradigms require involvement from many stakeholders,^{23,154} they not only create opportunities for anesthesiologists to lead and participate in coordinated care but also lead to more sustainable gains on two different but contextually similar and challenging health problems.

Conclusions

Do Opioid-free Strategies Have Benefits beyond and above Opioid-sparing Strategies?

To date, there is no evidence. Multimodal analgesia can lead to significant opioid sparing. At this time, the clinical

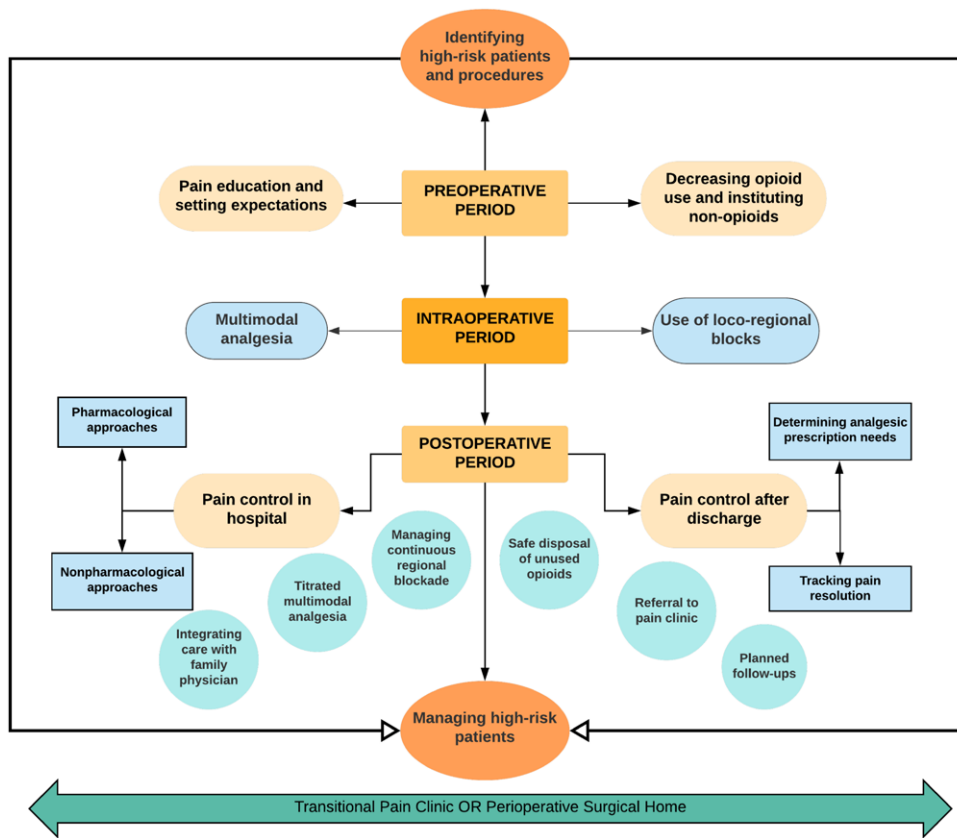


Fig. 2. Opportunities for anesthesiologists’ in optimizing perioperative pain, opioid utilization, and improving recovery. Important elements in surgical phases are identified; use of a framework such as transitional pain service or perioperative surgical home can include specific roles for the anesthesiologist.

benefits of such limited opioid use do not outweigh the challenges and limitations associated with the suggested opioid-free strategies.

Is Complete Opioid Sparing Possible in the Context of Existing Multimodal Opioid-sparing Strategies?

Yes, but only in some contexts and procedures. Opioid use during surgery is not a must; for example, surgeries can be performed under neuraxial anesthesia or effective regional analgesia. Similarly, some outpatient procedures can be opioid-free in their postoperative period and after discharge. However, individual titration of analgesics based on patient needs is important.

Do Opioid-free Strategies Prevent Persistent Opioid Use or Overprescription?

No. The existing literature does not support the hypothesis that avoidance of opioids will prevent persistent opioid use. They also have no bearing on the kind or amount of opioids prescribed at discharge.

Summary

In this article, we critically reviewed the considerations of using opioids during the perioperative period, as well as the limitations of the suggested opioid-free anesthesia and opioid-free analgesia approaches. Effective perioperative analgesia is not only a humane necessity but is important to prevent short- and long-term complications. We should avoid terminology that could be misinterpreted and temper our enthusiasm toward eliminating opioids completely with practical considerations, realistic expectations, and appropriate evidence. More importantly, we should focus on minimizing opioid use with known, safe, feasible options, adapted to individual patient needs. A framework that involves patient education, preoperative opioid minimization, use of multimodal analgesia strategies, and postoperative analgesia titrated to transitional pain needs can decrease the risk of persistent opioid use and persistent postsurgical pain.

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Competing Interests

Dr. Joshi has received honoraria from Baxter Pharmaceuticals (Deerfield, Illinois) and Pacira Pharmaceuticals (Parsippany, New Jersey). The other authors declare no competing interests.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Ambu: The Reanimating Invention of a *Bon Vivant*



In the mid-1950s, a whimsical Danish anaesthetist fashioned the first self-inflating Air-Mask Bag Unit (Ambu, *left*) around a re-expanding frame of bicycle-wheel spokes. The multitalented Henning Ruben (1914 to 2004) had originally funded his dental school education by performing the tango in dance halls throughout Denmark (*right*). A nationally ranked fencer, he had also delighted audiences with his swordsmanship. His piercing prowess even extended to mind-reading; he belonged to *Magisk Circle*, an elite corps of illusionists. When he started medical school, the Nazi occupation of Denmark forced Ruben, an Orthodox Jew, to vanish to Sweden as a dentist-magician. When he finally became an anaesthetist, he applied his *joie de vivre* to creating revitalizing contraptions. In 1952, the Danish polio epidemic prompted anaesthetist Bjørn Ibsen, “Father of Intensive Care,” to popularize the wonders of positive-pressure ventilation. That same calamity, along with a truck-driver strike that curtailed oxygen delivery to Danish hospitals, paved the way for Ruben’s two greatest inventions: his namesake nonbreathing valve, which obviated the need for portable soda lime; and his glorious Ambu bag, which could self-inflate with or without a gas supply. (Copyright © the American Society of Anesthesiologists’ Wood Library-Museum of Anesthesiology, Schaumburg, Illinois.)

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