ANESTHESIOLOGY

Perioperative Opioid Administration

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

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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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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 to lead to appreciable reductions.[18]

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 Glass[32] 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 advocation 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] Forget[45] 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

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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 White[57] used remifentanil 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

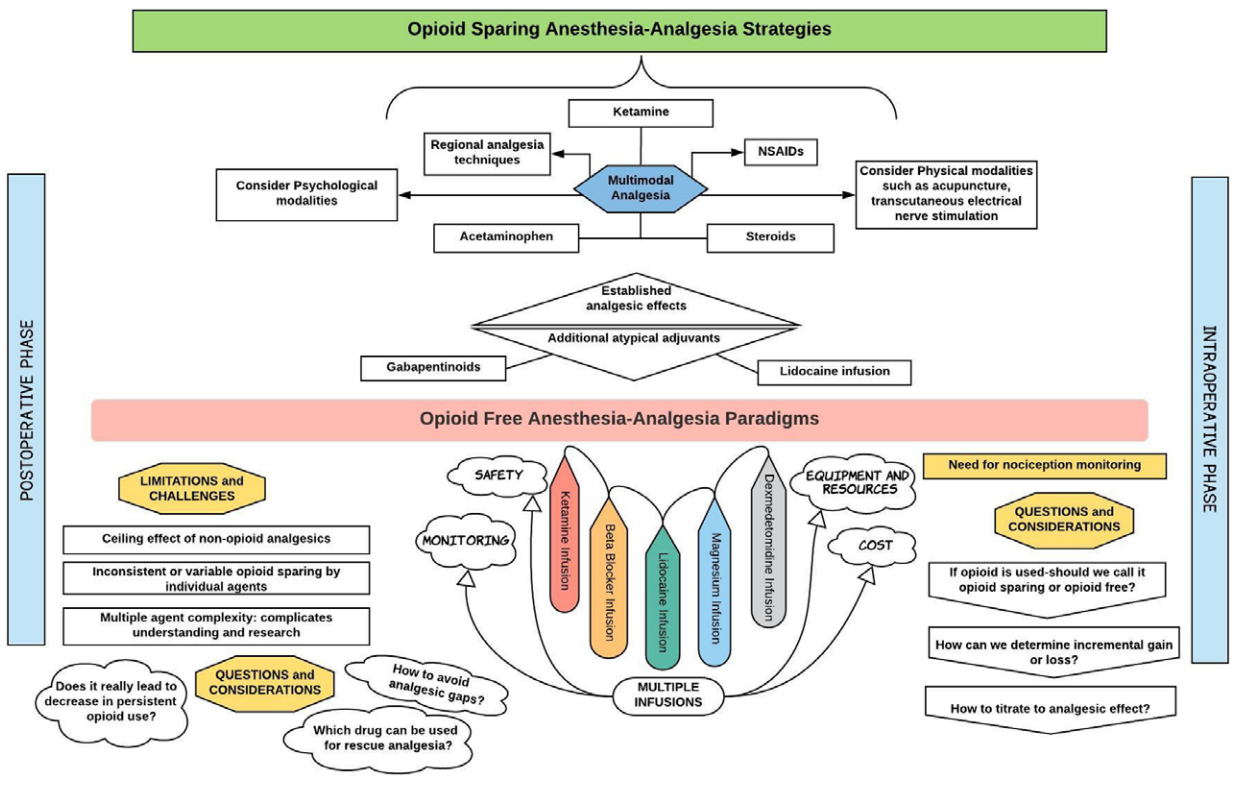

Fig. 1. A representation of intra- and postoperative care considerations and limitations in the context of opioid-sparing *versus* opioid-free strategies. Opioid-free paradigms include multimodal analgesia options indicated in the *top part* along with other infusion options in the *bottom part*. NSAID,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

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trials proposing opioid-free anesthesia for laparoscopic cholecystectomies. Toleska and Dimitrovski[61] 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 Dimitrovski[61] 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 remifentanil 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 blocker[63] 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 remifentanil.[82] In a systematic review and meta-analysis, Fletcher and Martinez[83] 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

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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 dose[97]; acetaminophen also has a daily maximum dose and cannot provide meaningful rescue analgesia in moderate to severe pain[98]; 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 salpingooophorectomy), 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

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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)

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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 μg/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

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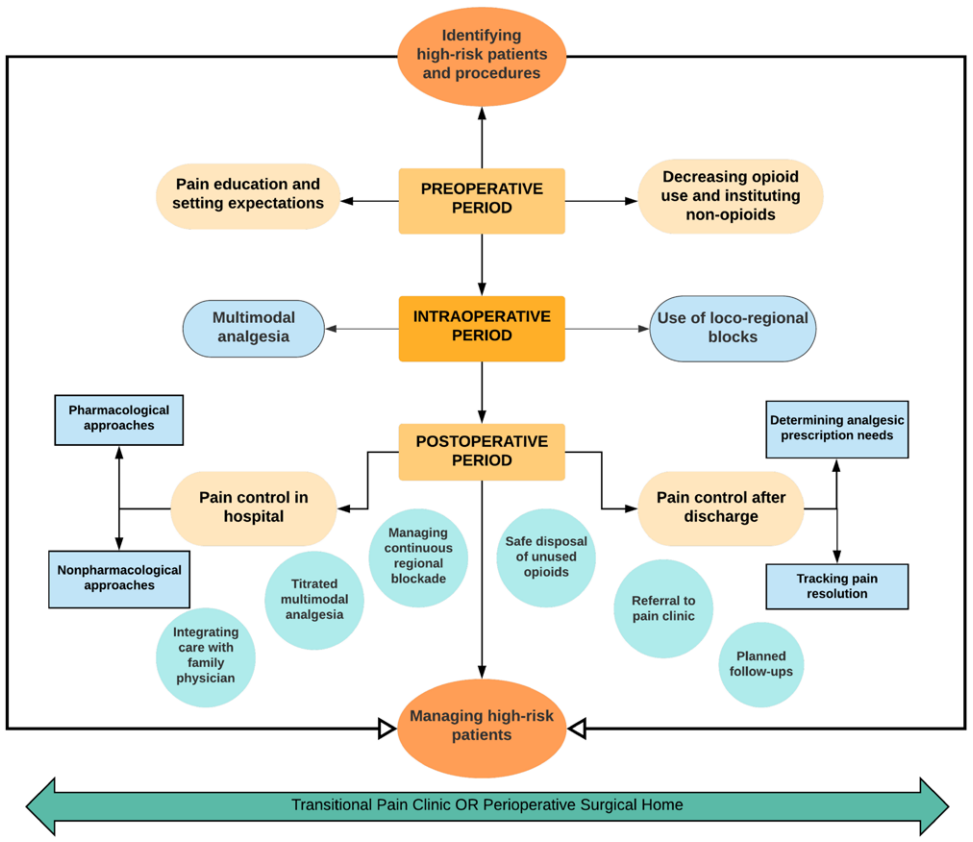

Fig. 2. Opportunities for anesthesiologists' in optimizing perioperative pain, opioid utilization, and improving recovery. Important elements in surgical phases are identified; use of a framework such as transitional pain service or perioperative surgical home can include specific roles for the anesthesiologist.

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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References

1. Egan TD: Are opioids indispensable for general anaesthesia? Br J Anaesth 2019; 122:e127–35
2. Lavand'homme P, Estebe JP: Opioid-free anesthesia: A different regard to anesthesia practice. Curr Opin Anaesthesiol 2018; 31:556–61
3. Alexander JC, Patel B, Joshi GP: Perioperative use of opioids: Current controversies and concerns. Best Pract Res Clin Anaesthesiol 2019; 33:341–51
4. Joshi GP, Kehlet H: Postoperative pain management in the era of ERAS: An overview. Best Pract Res Clin Anaesthesiol 2019; 33:259–67
5. Wheeler M, Oderda GM, Ashburn MA, Lipman AG: Adverse events associated with postoperative opioid analgesia: A systematic review. J Pain 2002; 3:159–80
6. Centers for Disease Control and Prevention: Prescription Opioid Data; 2019 Available at: https://www.cdc.gov/drugoverdose/data/prescribing.html. Accessed April 1, 2020.
7. Brennan F: The US Congressional "Decade on Pain Control and Research" 2001–2011: A Review. J Pain Palliat Care Pharmacother 2015; 29:212–27
8. Chidgey BA, McGinigle KL, McNaull PP: When a vital sign leads a country astray: The opioid epidemic. JAMA Surg 2019; 154:987–8
9. Feinberg AE, Chesney TR, Srikandarajah S, Acuna SA, McLeod RS; Best Practice in Surgery Group: Opioid use after discharge in postoperative patients: A systematic review. Ann Surg 2018; 267:1056–62
10. Page MG, Kudrina I, Zomahoun HTV, Croteau J, Ziegler D, Ngangue P, Martin E, Fortier M, Boisvert EE, Beaulieu P, Charbonneau C, Cogan J, Daoust R, Martel MO, Néron A, Richebé P, Clarke H: A systematic review of the relative frequency and risk factors for prolonged opioid prescription following surgery and trauma among adults. Ann Surg 2019; 271:845–54
11. Sun EC, Darnall BD, Baker LC, Mackey S: Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. JAMA Intern Med 2016; 176:1286–93
12. Rudd RA, Seth P, David F, Scholl L: Increases in drug and opioid-involved overdose deaths: United States, 2010–2015. MMWR Morb Mortal Wkly Rep 2016; 65:1445–52
13. Florence CS, Zhou C, Luo F, Xu L: The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. Med Care 2016; 54:901–6
14. Fujii MH, Hodges AC, Russell RL, Roensch K, Beynnon B, Ahern TP, Holoch P, Moore JS, Ames SE, MacLean CD: Post-discharge opioid prescribing and use after common surgical procedure. J Am Coll Surg 2018; 226:1004–12
15. Hartford LB, Van Koughnett JAM, Murphy PB, Vogt KN, Hilsden RJ, Clarke CF, Allen LJ, Gray SD, Parry NG, Gray DK, Leslie KA: Standardization of Outpatient Procedure (STOP) narcotics: A prospective non-inferiority study to reduce opioid use in outpatient general surgical procedures. J Am Coll Surg 2019; 228:81–88.e1
16. Losby JL, Hyatt JD, Kanter MH, Baldwin G, Matsuoka D: Safer and more appropriate opioid prescribing: A large healthcare system's comprehensive approach. J Eval Clin Pract 2017; 23:1173–9
17. Frazee R, Garmon E, Isbell C, Bird E, Papaconstantinou H: Postoperative opioid prescription reduction strategy in a regional healthcare system. J Am Coll Surg 2020; 230:631–5
18. Chua KP, Kimmel L, Brummett CM: Disappointing early results from opioid prescribing limits for acute pain. JAMA Surg 2020; 155:375–6
19. Sultana A, Torres D, Schumann R: Special indications for opioid free anaesthesia and analgesia, patient and procedure related: Including obesity, sleep apnoea, chronic obstructive pulmonary disease, complex regional pain syndromes, opioid addiction and cancer surgery. Best Pract Res Clin Anaesthesiol 2017; 31:547–60
20. Thota RS, Ramkiran S, Garg R, Goswami J, Baxi V, Thomas M: Opioid free onco-anesthesia: Is it time to convict opioids?: A systematic review of literature. J Anaesthesiol Clin Pharmacol 2019; 35:441–52
21. Wick EC, Grant MC, Wu CL: Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: A review. JAMA Surg 2017; 152:691–7
22. Guglielmi G: Opioid prescriptions: Striking differences in behaviour point to ways to combat abuse. Nature 2019. Available at: https://www.nature.com/articles/d41586-019-02572-x. Accessed April 1, 2020.
23. Lirk P, Rathmell JP: Opioid-free anaesthesia: Con: It is too early to adopt opioid-free anaesthesia today. Eur J Anaesthesiol 2019; 36:250–4

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24. Ladha KS, Patorno E, Liu J, Bateman BT: Impact of perioperative epidural placement on postdischarge opioid use in patients undergoing abdominal surgery. Anesthesiology 2016; 124:396–403
25. Edwards DA, Hedrick TL, Jayaram J, Argoff C, Gulur P, Holubar SD, Gan TJ, Mythen MG, Miller TE, Shaw AD, Thacker JKM, McEvoy MD; POQI-4 Working Group: American Society for Enhanced Recovery and Perioperative Quality Initiative joint consensus statement on perioperative management of patients on preoperative opioid therapy. Anesth Analg 2019; 129:553–66
26. Lee BH, Wu CL: Educating patients regarding pain management and safe opioid use after surgery: A narrative review. Anesth Analg 2020; 130:574–81
27. Vetter TR, Kain ZN: Role of the perioperative surgical home in optimizing the perioperative use of opioids. Anesth Analg 2017; 125:1653–7
28. Brown EN, Pavone KJ, Naranjo M: Multimodal general anesthesia: Theory and practice. Anesth Analg 2018; 127:1246–58
29. Cividjian A, Petitjeans F, Liu N, Ghignone M, de Kock M, Quintin L: Do we feel pain during anesthesia?: A critical review on surgery-evoked circulatory changes and pain perception. Best Pract Res Clin Anaesthesiol 2017; 31:445–67
30. Kehlet H: Surgical stress: The role of pain and analgesia. Br J Anaesth 1989; 63:189–95
31. Egan TD, Svensen CH: Multimodal general anesthesia: A principled approach to producing the drug-induced, reversible coma of anesthesia. Anesth Analg 2018; 127:1104–6
32. Fleischer LH, Glass PS: Can we prevent recall during anesthesia? Evidence Based Practice of Anesthesiology. Edited by Fleischer LA. Philadelphia, W.B. Saunders, 2004, pp. 223–7
33. Domino KB, Posner KL, Caplan RA, Cheney FW: Awareness during anesthesia: A closed claims analysis. Anesthesiology 1999; 90:1053–61
34. Lydic R, Baghdoyan HA: Sleep, anesthesiology, and the neurobiology of arousal state control. Anesthesiology 2005; 103:1268–95
35. Rabiner EA, Beaver J, Makwana A, Searle G, Long C, Nathan PJ, Newbould RD, Howard J, Miller SR, Bush MA, Hill S, Reiley R, Passchier J, Gunn RN, Matthews PM, Bullmore ET: Pharmacological differentiation of opioid receptor antagonists by molecular and functional imaging of target occupancy and food reward-related brain activation in humans. Mol Psychiatry 2011; 16:826–35, 785
36. Stein C: The control of pain in peripheral tissue by opioids. N Engl J Med 1995; 332:1685–90
37. Hendrickx JF, Eger EI 2nd, Sonner JM, Shafer SL: Is synergy the rule?: A review of anesthetic interactions producing hypnosis and immobility. Anesth Analg 2008; 107:494–506
38. Bouvet L, Stoian A, Rimmelé T, Allaouchiche B, Chassard D, Boselli E: Optimal remifentanil dosage for providing excellent intubating conditions when co-administered with a single standard dose of propofol. Anaesthesia 2009; 64:719–26
39. Kehlet H, Dahl JB: The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 1993; 77:1048–56
40. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, Rockall TA, Young-Fadok TM, Hill AG, Soop M, de Boer HD, Urman RD, Chang GJ, Fichera A, Kessler H, Grass F, Whang EE, Fawcett WJ, Carli F, Lobo DN, Rollins KE, Balfour A, Baldini G, Riedel B, Ljungqvist O: Guidelines for perioperative care in elective colorectal surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations: 2018. World J Surg 2019; 43:659–95
41. Koepke EJ, Manning EL, Miller TE, Ganesh A, Williams DGA, Manning MW: The rising tide of opioid use and abuse: The role of the anesthesiologist. Perioper Med (Lond) 2018; 7:16
42. Chavez JR, Ibancovichi JA, Sanchez-Aparicio P, Acevedo-Arcique CM, Moran-Muñoz R, Recillas-Morales S: Effect of acetaminophen alone and in combination with morphine and tramadol on the minimum alveolar concentration of isoflurane in rats. PLoS One 2015; 10:e0143710
43. Wasserman I, Poeran J, Zubizarreta N, Babby J, Serban S, Goldberg AT, Greenstein AJ, Memtsoudis SG, Mazumdar M, Leibowitz AB: Impact of intravenous acetaminophen on perioperative opioid utilization and outcomes in open colectomies: A claims database analysis. Anesthesiology 2018; 129:77–88
44. Soffin EM, Wetmore DS, Beckman JD, Sheha ED, Vaishnav AS, Albert TJ, Gang CH, Qureshi SA: Opioid-free anesthesia within an enhanced recovery after surgery pathway for minimally invasive lumbar spine surgery: A retrospective matched cohort study. Neurosurg Focus 2019; 46:E8
45. Forget P: Opioid-free anaesthesia: Why and how?: A contextual analysis. Anaesth Crit Care Pain Med 2019; 38:169–72
46. Ladha KS, Patorno E, Huybrechts KF, Liu J, Rathmell JP, Bateman BT: Variations in the use of perioperative multimodal analgesic therapy. Anesthesiology 2016; 124:837–45
47. Wu CL, King AB, Geiger TM, Grant MC, Grocott MPW, Gupta R, Hah JM, Miller TE, Shaw AD, Gan TJ, Thacker JKM, Mythen MG, McEvoy MD; Fourth Perioperative Quality Initiative Workgroup: American Society for Enhanced Recovery and Perioperative Quality Initiative joint consensus statement on perioperative opioid minimization in opioid-naïve patients. Anesth Analg 2019; 129:567–77

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48. Gelineau AM, King MR, Ladha KS, Burns SM, Houle T, Anderson TA: Intraoperative esmolol as an adjunct for perioperative opioid and postoperative pain reduction: A systematic review, meta-analysis, and meta-regression. Anesth Analg 2018; 126:1035–49
49. Siu EY, Moon TS: Opioid-free and opioid-sparing anesthesia. Int Anesthesiol Clin 2020; 58:34–41
50. Edry R, Recea V, Dikust Y, Sessler DI: Preliminary intraoperative validation of the nociception level index: A noninvasive nociception monitor. Anesthesiology 2016; 125:193–203
51. Ledowski T, Ang B, Schmarbeck T, Rhodes J: Monitoring of sympathetic tone to assess postoperative pain: Skin conductance *vs.* surgical stress index. Anaesthesia 2009; 64:727–31
52. Ledowski T: Objective monitoring of nociception: A review of current commercial solutions. Br J Anaesth 2019; 123:e312–21
53. Meijer FS, Niesters M, van Velzen M, Martini CH, Olofsen E, Edry R, Sessler DI, van Dorp ELA, Dahan A, Boon M: Does nociception monitor-guided anesthesia affect opioid consumption?: A systematic review of randomized controlled trials. J Clin Monit Comput 2020; 34:629–41
54. Maheshwari K, Avitsian R, Sessler DI, Makarova N, Tanios M, Raza S, Traul D, Rajan S, Manlapaz M, Machado S, Krishnaney A, Machado A, Rosenquist R, Kurz A: Multimodal analgesic regimen for spine surgery: A randomized placebo-controlled trial. Anesthesiology 2020; 132:992–1002
55. Frauenknecht J, Kirkham KR, Jacot-Guillarmod A, Albrecht E: Analgesic impact of intra-operative opioids *vs.* opioid-free anaesthesia: A systematic review and meta-analysis. Anaesthesia 2019; 74:651–62
56. Inoue Y, Koga K, Sata T, Shigematsu A: Effects of fentanyl on emergence characteristics from anesthesia in adult cervical spine surgery: A comparison of fentanyl-based and sevoflurane-based anesthesia. J Anesth 2005; 19:12–6
57. Song D, White PF: Remifentanil as an adjuvant during desflurane anesthesia facilitates early recovery after ambulatory surgery. J Clin Anesth 1999; 11:364–7
58. Beloeil H: Opioid-free anesthesia. Best Pract Res Clin Anaesthesiol 2019; 33:353–60
59. Dahl JB: Pitfalls in trials of "multimodal analgesia." Pain 2016; 157:280–1
60. White PF, Kehlet H: Postoperative pain management and patient outcome: Time to return to work! Anesth Analg 2007; 104:487–9
61. Toleska M, Dimitrovski A: Is opioid-free general anesthesia more superior for postoperative pain *versus* opioid general anesthesia in laparoscopic cholecystectomy? Pril (Makedon Akad Nauk Umet Odd Med Nauki) 2019; 40:81–7
62. Bakan M, Umutoglu T, Topuz U, Uysal H, Bayram M, Kadioglu H, Salihoglu Z: Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: A prospective, randomized, double-blinded study. Braz J Anesthesiol 2015; 65:191–9
63. Pereira IT, Prado WA, Dos Reis MP: Enhancement of the epidural morphine-induced analgesia by systemic nifedipine. Pain 1993; 53:341–5
64. Eipe N, Gupta S, Penning J: Intravenous lidocaine for acute pain: An evidence-based clinical update. BJA Education 2016; 16:292–8
65. Avidan MS, Maybrier HR, Abdallah AB, Jacobsohn E, Vlisides PE, Pryor KO, Veselis RA, Grocott HP, Emmert DA, Rogers EM, Downey RJ, Yulico H, Noh GJ, Lee YH, Waszynski CM, Arya VK, Pagel PS, Hudetz JA, Muench MR, Fritz BA, Waberski W, Inouye SK, Mashour GA; PODCAST Research Group: Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: An international, multicentre, double-blind, randomised clinical trial. Lancet 2017; 390:267–75
66. Barends CRM, Driesens MK, Struys M, Visser A, Absalom AR: Intranasal dexmedetomidine in elderly subjects with or without beta blockade: A randomised double-blind single-ascending-dose cohort study. Br J Anaesth 2020; S0007-0912(19)31015-3
67. Demiri M, Antunes T, Fletcher D, Martinez V: Perioperative adverse events attributed to α2-adrenoceptor agonists in patients not at risk of cardiovascular events: Systematic review and meta-analysis. Br J Anaesth 2019; 123:795–807
68. Edokpolo LU, Mastriano DJ, Serafin J, Weedon JC, Siddiqui MT, Dimaculangan DP: Discharge readiness after propofol with or without dexmedetomidine for colonoscopy: A randomized controlled trial. Anesthesiology 2019; 131:279–86
69. Lodenius Å, Maddison KJ, Lawther BK, Scheinin M, Eriksson LI, Eastwood PR, Hillman DR, Fagerlund MJ, Walsh JH: Upper airway collapsibility during dexmedetomidine and propofol sedation in healthy volunteers: A nonblinded randomized crossover study. Anesthesiology 2019; 131:962–73
70. Grosu I, Lavand'homme P: Use of dexmedetomidine for pain control. F1000 Med Rep 2010; 2:90
71. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. Lancet 2008; 371:1839–47
72. Yu SK, Tait G, Karkouti K, Wijeysundera D, McCluskey S, Beattie WS: The safety of perioperative esmolol: A systematic review and meta-analysis of randomized controlled trials. Anesth Analg 2011; 112:267–81

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73. Soave PM, Conti G, Costa R, Arcangeli A: Magnesium and anaesthesia. Curr Drug Targets 2009; 10:734–43
74. Cavalcante AN, Sprung J, Schroeder DR, Weingarten TN: Multimodal analgesic therapy with gabapentin and its association with postoperative respiratory depression. Anesth Analg 2017; 125:141–6
75. Kharasch ED, Eisenach JC: Wherefore gabapentinoids?: Was there rush too soon to judgment? Anesthesiology 2016; 124:10–2
76. Kumar AH, Habib AS: The role of gabapentinoids in acute and chronic pain after surgery. Curr Opin Anaesthesiol 2019; 32:629–34
77. U.S. Food and Drug Administration: FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR), 2019. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin. Accessed April 1, 2020.
78. Verret M, Lauzier F, Zarychanski R, Perron C, Savard X, Pinard AM, Leblanc G, Cossi MJ, Neveu X, Turgeon AF; Canadian Perioperative Anesthesia Clinical Trials (PACT) Group: Perioperative use of gabapentinoids for the management of postoperative acute pain: A systematic review and meta-analysis. Anesthesiology 2020; 133:265–79
79. Martinez V, Carles M, Marret E, Beloeil H; Regional Anaesthesia and Pain Committee of the French Society of Anaesthesiology and Intensive Care Medicine: Perioperative use of gabapentinoids in France: Mismatch between clinical practice and scientific evidence. Anaesth Crit Care Pain Med 2018; 37:43–7
80. Anesthesia Patient Safety Foundation: Infusion Pumps and Their Safety in the OR, 2000. Available at: https://www.apsf.org/article/infusion-pumps-and-their-safety-in-the-or/. Accessed April 1, 2020.
81. Colvin LA, Bull F, Hales TG: Perioperative opioid analgesia: When is enough too much?: A review of opioid-induced tolerance and hyperalgesia. Lancet 2019; 393:1558–68
82. Lavand'homme P, Steyaert A: Opioid-free anesthesia opioid side effects: Tolerance and hyperalgesia. Best Pract Res Clin Anaesthesiol 2017; 31:487–98
83. Fletcher D, Martinez V: Opioid-induced hyperalgesia in patients after surgery: A systematic review and a meta-analysis. Br J Anaesth 2014; 112:991–1004
84. Byrne K, Levins KJ, Buggy DJ: Can anesthetic–analgesic technique during primary cancer surgery affect recurrence or metastasis? Can J Anaesth 2016; 63:184–92
85. Wall T, Sherwin A, Ma D, Buggy DJ: Influence of perioperative anaesthetic and analgesic interventions on oncological outcomes: A narrative review. Br J Anaesth 2019; 123:135–50
86. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, Mayers DB, Meyer-Treschan TA, Grady M, Tan EY, Ayad S, Mascha EJ, Buggy DJ; Breast Cancer Recurrence Collaboration: Recurrence of breast cancer after regional or general anaesthesia: A randomised controlled trial. Lancet 2019; 394:1807–15
87. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W: Pain intensity on the first day after surgery: A prospective cohort study comparing 179 surgical procedures. Anesthesiology 2013; 118:934–44
88. Joshi GP, Beck DE, Emerson RH, Halaszynski TM, Jahr JS, Lipman AG, Nihira MA, Sheth KR, Simpson MH, Sinatra RS: Defining new directions for more effective management of surgical pain in the United States: Highlights of the inaugural Surgical Pain Congress™. Am Surg 2014; 80:219–28
89. Coppes OJM, Yong RJ, Kaye AD, Urman RD: Patient and surgery-related predictors of acute postoperative pain. Curr Pain Headache Rep 2020; 24:12
90. Kehlet H: Postoperative opioid sparing to hasten recovery: What are the issues? Anesthesiology 2005; 102:1083–5
91. Ip HY, Abrishami A, Peng PW, Wong J, Chung F: Predictors of postoperative pain and analgesic consumption: A qualitative systematic review. Anesthesiology 2009; 111:657–77
92. Meissner W, Zaslansky R: A survey of postoperative pain treatments and unmet needs. Best Pract Res Clin Anaesthesiol 2019; 33:269–86
93. Brennan TJ: Pathophysiology of postoperative pain. Pain 2011; 152:S33–40
94. Borys M, Zyzak K, Hanych A, Domagała M, Gałkin P, Gałaszkiewicz K, Kłaput A, Wróblewski K, Miękina J, Onichimowski D, Czuczwar M: Survey of postoperative pain control in different types of hospitals: A multicenter observational study. BMC Anesthesiol 2018; 18:83
95. Katz J, Seltzer Z: Transition from acute to chronic postsurgical pain: Risk factors and protective factors. Expert Rev Neurother 2009; 9:723–44
96. Kharasch ED, Avram MJ, Clark JD: Rational perioperative opioid management in the era of the opioid crisis. Anesthesiology 2020; 132:603–5
97. Kaufman DW, Kelly JP, Battista DR, Malone MK, Weinstein RB, Shiffman S: Exceeding the daily dosing limit of nonsteroidal anti-inflammatory drugs among ibuprofen users. Pharmacoepidemiol Drug Saf 2018; 27:322–31
98. Mörwald EE, Poeran J, Zubizarreta N, Cozowicz C, Mazumdar M, Memtsoudis SG: Intravenous acetaminophen does not reduce inpatient opioid prescription or opioid-related adverse events among patients undergoing spine surgery. Anesth Analg 2018; 127:1221–8
99. Apfelbaum JL, Chen C, Mehta SS, Gan TJ: Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003; 97:534–40

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100. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL: Incidence, patient satisfaction, and perceptions of post-surgical pain: Results from a US national survey. Curr Med Res Opin 2014; 30:149–60
101. Tyler MA, Lam K, Ashoori F, Cai C, Kain JJ, Fakhri S, Citardi MJ, Cattano D, Luong A: Analgesic effects of intravenous acetaminophen *vs.* placebo for endoscopic sinus surgery and postoperative pain: A randomized clinical trial. JAMA Otolaryngol Head Neck Surg 2017; 143:788–94
102. McDaid C, Maund E, Rice S, Wright K, Jenkins B, Woolacott N: Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: A systematic review. Health Technol Assess 2010; 14:1–153
103. Andersen LØ, Kehlet H: Analgesic efficacy of local infiltration analgesia in hip and knee arthroplasty: A systematic review. Br J Anaesth 2014; 113:360–74
104. Rawal N: Current issues in postoperative pain management. Eur J Anaesthesiol 2016; 33:160–71
105. Marhofer P, Hopkins PM: Anaesthesiologists *versus* surgeons, or regional anaesthesia *versus* local anaesthesia? Br J Anaesth 2020; 124:126–8
106. Joshi GP, Kehlet H, Rawal N: Surgeon-administered regional analgesia to replace anaesthetist-administered regional analgesia: Need for communication and collaboration. Br J Anaesth 2019; 123:707–9
107. Gabriel RA, Ilfeld BM: Use of regional anesthesia for outpatient surgery within the United States: A prevalence study using a nationwide database. Anesth Analg 2018; 126:2078–84
108. Schug SA, Palmer GM, Scott DA, Halliwell R, Trinca J: Acute pain management: Scientific evidence, fourth edition, 2015. Med J Aust 2016; 204:315–7
109. Nicholls JL, Azam MA, Burns LC, Englesakis M, Sutherland AM, Weinrib AZ, Katz J, Clarke H: Psychological treatments for the management of postsurgical pain: A systematic review of randomized controlled trials. Patient Relat Outcome Meas 2018; 9:49–64
110. Shanthanna H, Turan A, Vincent J, Saab R, Shargall Y, O'Hare T, Davis K, Fonguh S, Balasubramaniam K, Paul J, Gilron I, Kehlet H, Sessler DI, Bhandari M, Thabane L, Devereaux PJ: *N*-Methyl-D-aspartate antagonists and steroids for the prevention of persisting post-surgical pain after thoracoscopic surgeries: A randomized controlled, factorial design, international, multicenter pilot trial. J Pain Res 2020; 13:377–87
111. Mauermann E, Ruppen W, Bandschapp O: Different protocols used today to achieve total opioid-free general anesthesia without locoregional blocks. Best Pract Res Clin Anaesthesiol 2017; 31:533–45
112. Kehlet H, Joshi GP: Enhanced recovery after surgery: Current controversies and concerns. Anesth Analg 2017; 125:2154–5
113. Fiore JF Jr, Olleik G, El-Kefraoui C, Verdolin B, Kouyoumdjian A, Alldrit A, Figueiredo AG, Valanci S, Marquez-GdeV JA, Schulz M, Moldoveanu D, Nguyen-Powanda P, Best G, Banks A, Landry T, Pecorelli N, Baldini G, Feldman LS: Preventing opioid prescription after major surgery: A scoping review of opioid-free analgesia. Br J Anaesth 2019; 123:627–36
114. Mattila K, Toivonen J, Janhunen L, Rosenberg PH, Hynynen M: Postdischarge symptoms after ambulatory surgery: First-week incidence, intensity, and risk factors. Anesth Analg 2005; 101:1643–50
115. Ladha KS, Neuman MD, Broms G, Bethell J, Bateman BT, Wijeysundera DN, Bell M, Hallqvist L, Svensson T, Newcomb CW, Brensinger CM, Gaskins LJ, Wunsch H: Opioid prescribing after surgery in the United States, Canada, and Sweden. JAMA Netw Open 2019; 2:e1910734
116. Chapman CR, Stevens DA, Lipman AG: Quality of postoperative pain management in American *versus* European institutions. J Pain Palliat Care Pharmacother 2013; 27:350–8
117. van Dijk JF, Kappen TH, Schuurmans MJ, van Wijck AJ: The relation between patients' NRS pain scores and their desire for additional opioids after surgery. Pain Pract 2015; 15:604–9
118. van Boekel RLM, Vissers KCP, van der Sande R, Bronkhorst E, Lerou JGC, Steegers MAH: Moving beyond pain scores: Multidimensional pain assessment is essential for adequate pain management after surgery. PLoS One 2017; 12:e0177345
119. Chen EY, Marcantonio A, Tornetta P 3rd: Correlation between 24-hour predischarge opioid use and amount of opioids prescribed at hospital discharge. JAMA Surg 2018; 153:e174859
120. Thiels CA, Ubl DS, Yost KJ, Dowdy SC, Mabry TM, Gazelka HM, Cima RR, Habermann EB: Results of a prospective, multicenter initiative aimed at developing opioid-prescribing guidelines after surgery. Ann Surg 2018; 268:457–68
121. Smith RV, Havens JR, Walsh SL: Gabapentin misuse, abuse and diversion: A systematic review. Addiction 2016; 111:1160–74
122. Thiels CA, Habermann EB, Hooten WM, Jeffery MM: Chronic use of tramadol after acute pain episode: Cohort study. BMJ 2019; 365:l1849
123. Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, Kroenke K, Bair MJ, Noorbaloochi S: Effect of opioid *vs.* nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: The SPACE randomized clinical trial. JAMA 2018; 319:872–82
124. Goesling J, Moser SE, Zaidi B, Hassett AL, Hilliard P, Hallstrom B, Clauw DJ, Brummett CM: Trends and predictors of opioid use after total knee and total hip arthroplasty. Pain 2016; 157:1259–65

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125. Brummett CM, Waljee JF, Goesling J, Moser S, Lin P, Englesbe MJ, Bohnert ASB, Kheterpal S, Nallamothu BK: New persistent opioid use after minor and major surgical procedures in US adults. JAMA Surg 2017; 152:e170504
126. Jivraj NK, Raghavji F, Bethell J, Wijeysundera DN, Ladha KS, Bateman BT, Neuman MD, Wunsch H: Persistent postoperative opioid use: A systematic literature search of definitions and population-based cohort study. Anesthesiology 2020; 132:1528–39
127. Kent ML, Hurley RW, Oderda GM, Gordon DB, Sun E, Mythen M, Miller TE, Shaw AD, Gan TJ, Thacker JKM, McEvoy MD; POQI-4 Working Group: American Society for Enhanced Recovery and Perioperative Quality Initiative-4 joint consensus statement on persistent postoperative opioid use: Definition, incidence, risk factors, and health care system initiatives. Anesth Analg 2019; 129:543–52
128. Kharasch ED, Clark JD: Persistent postoperative opioid use: Perception, progress, and promise. Anesthesiology 2020
129. Page AJ, Gani F, Crowley KT, Lee KH, Grant MC, Zavadsky TL, Hobson D, Wu C, Wick EC, Pawlik TM: Patient outcomes and provider perceptions following implementation of a standardized perioperative care pathway for open liver resection. Br J Surg 2016; 103:564–71
130. Talboys R, Mak M, Modi N, Fanous N, Cutts S: Enhanced recovery programme reduces opiate consumption in hip hemiarthroplasty. Eur J Orthop Surg Traumatol 2016; 26:177–81
131. Mueller KG, Memtsoudis SG, Mariano ER, Baker LC, Mackey S, Sun EC: Lack of association between the use of nerve blockade and the risk of persistent opioid use among patients undergoing shoulder arthroplasty: Evidence from the Marketscan database. Anesth Analg 2017; 125:1014–20
132. Sun EC, Bateman BT, Memtsoudis SG, Neuman MD, Mariano ER, Baker LC: Lack of association between the use of nerve blockade and the risk of postoperative chronic opioid use among patients undergoing total knee arthroplasty: Evidence from the Marketscan database. Anesth Analg 2017; 125:999–1007
133. Suzan E, Pud D, Eisenberg E: A crucial administration timing separates between beneficial and counterproductive effects of opioids on postoperative pain. Pain 2018; 159:1438–40
134. Bicket MC, Brat GA, Hutfless S, Wu CL, Nesbit SA, Alexander GC: Optimizing opioid prescribing and pain treatment for surgery: Review and conceptual framework. Am J Health Syst Pharm 2019; 76:1403–12
135. Cook DJ, Kaskovich SW, Pirkle SC, Mica MAC, Shi LL, Lee MJ: Benchmarks of duration and magnitude of opioid consumption after total hip and knee arthroplasty: A database analysis of 69,368 patients. J Arthroplasty 2019; 34:638–644.e1
136. Hah JM, Bateman BT, Ratliff J, Curtin C, Sun E: Chronic opioid use after surgery: Implications for perioperative management in the face of the opioid epidemic. Anesth Analg 2017; 125:1733–40
137. Correll D: Chronic postoperative pain: Recent findings in understanding and management. F1000Res 2017; 6:1054
138. Murphy GS, Avram MJ, Greenberg SB, Shear TD, Deshur MA, Dickerson D, Bilimoria S, Benson J, Maher CE, Trenk GJ, Teister KJ, Szokol JW: Postoperative pain and analgesic requirements in the first year after intraoperative methadone for complex spine and cardiac surgery. Anesthesiology 2020; 132:330–42
139. Chapman CR, Donaldson GW, Davis JJ, Bradshaw DH: Improving individual measurement of postoperative pain: The pain trajectory. J Pain 2011; 12:257–62
140. Althaus A, Arránz Becker O, Moser KH, Lux EA, Weber F, Neugebauer E, Simanski C: Postoperative pain trajectories and pain chronification: An empirical typology of pain patients. Pain Med 2018; 19:2536–45
141. Hah JM, Cramer E, Hilmoe H, Schmidt P, McCue R, Trafton J, Clay D, Sharifzadeh Y, Ruchelli G, Goodman S, Huddleston J, Maloney WJ, Dirbas FM, Shrager J, Costouros JG, Curtin C, Mackey SC, Carroll I: Factors associated with acute pain estimation, postoperative pain resolution, opioid cessation, and recovery: Secondary analysis of a randomized clinical trial. JAMA Netw Open 2019; 2:e190168
142. Houle TT, Miller S, Lang JE, Booth JL, Curry RS, Harris L, Aschenbrenner CA, Eisenach JC: Day-to-day experience in resolution of pain after surgery. Pain 2017; 158:2147–54
143. Pagé MG, Katz J, Romero Escobar EM, Lutzky-Cohen N, Curtis K, Fuss S, Clarke HA: Distinguishing problematic from nonproblematic postsurgical pain: A pain trajectory analysis after total knee arthroplasty. Pain 2015; 156:460–8
144. Nilsson U, Gruen R, Myles PS: Postoperative recovery: The importance of the team. Anaesthesia 2020; 75:e158–64
145. Smit-Fun VM, Cox PBW, Buhre WF: Role of the anaesthetist in postoperative care. Br J Surg 2020; 107:e8–e10
146. Eisenach JC, Brennan TJ: Pain after surgery. Pain 2018; 159:1010–1
147. Carli F, Feldman LS: From preoperative risk assessment and prediction to risk attenuation: A case for prehabilitation. Br J Anaesth 2019; 122:11–3
148. Soffin EM, Lee BH, Kumar KK, Wu CL: The prescription opioid crisis: Role of the anaesthesiologist in reducing opioid use and misuse. Br J Anaesth 2019; 122:e198–208

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149. Gilron I, Carr DB, Desjardins PJ, Kehlet H: Current methods and challenges for acute pain clinical trials. Pain Rep 2019; 4:e647
150. Shechter R, Speed TJ, Blume E, Singh S, Williams K, Koch CG, Hanna MN: Addressing the opioid crisis one surgical patient at a time: Outcomes of a novel perioperative pain program. Am J Med Qual 2020; 35:5–15
151. Yorkgitis BK, Brat GA: Postoperative opioid prescribing: Getting it RIGHTT. Am J Surg 2018; 215:707–11
152. Hill MV, Stucke RS, Billmeier SE, Kelly JL, Barth RJ Jr: Guideline for discharge opioid prescriptions after inpatient general surgical procedures. J Am Coll Surg 2018; 226:996–1003
153. Katz J, Weinrib A, Fashler SR, Katznelzon R, Shah BR, Ladak SS, Jiang J, Li Q, McMillan K, Santa Mina D, Wentlandt K, McRae K, Tamir D, Lyn S, de Perrot M, Rao V, Grant D, Roche-Nagle G, Cleary SP, Hofer SO, Gilbert R, Wijeysundera D, Ritvo P, Janmohamed T, O'Leary G, Clarke H: The Toronto General Hospital Transitional Pain Service: Development and implementation of a multidisciplinary program to prevent chronic postsurgical pain. J Pain Res 2015; 8:695–702
154. Stulberg JJ, Schäfer WLA, Shallcross ML, Lambert BL, Huang R, Holl JL, Bilimoria KY, Johnson JK: Evaluating the implementation and effectiveness of a multi-component intervention to reduce post-surgical opioid prescribing: Study protocol of a mixed-methods design. BMJ Open 2019; 9:e030404

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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 nonrebreathing 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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