

# American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Perioperative Opioid Minimization in Opioid-Naïve Patients

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Surgical care episodes place opioid-naïve patients at risk for transitioning to new persistent postoperative opioid use. With one of the central principles being the application of multimodal pain interventions to reduce the reliance on opioid-based medications, enhanced recovery pathways provide a framework that decreases perioperative opioid use. The fourth Perioperative Quality Initiative brought together a group of international experts representing anesthesiology, surgery, and nursing with the objective of providing consensus recommendations on this important topic. Fourth Perioperative Quality Initiative was a consensus-building conference designed around a modified Delphi process in which the group alternately convened for plenary discussion sessions in between small group discussions. The process included several iterative steps including a literature review of the topics, building consensus around the important questions related to the topic, and sequential steps of content building and refinement until agreement was achieved and a consensus document was produced. During the fourth Perioperative Quality Initiative conference and thereafter as a writing group, reference applicability to the topic was discussed in any area where there was disagreement. For this manuscript, the questions answered included (1) What are the potential strategies for preventing persistent postoperative opioid use? (2) Is opioid-free anesthesia and analgesia feasible and appropriate for routine operations? and (3) Is opioid-free (intraoperative) anesthesia associated with equivalent or superior outcomes compared to an opioid minimization in the perioperative period? We will discuss the relevant literature for each questions, emphasize what we do not know, and prioritize the areas for future research. (Anesth Analg 2019;129:567–77)

The perioperative period may be an important time for the development of long-term and persistent opioid use particularly in opioid-naïve patients.<sup>1</sup> Despite the use of multimodal analgesia, surgical patients may be overprescribed opioid analgesics on discharge to home.<sup>2,3</sup> Each surgical care episode places patients at risk for transitioning to persistent postoperative opioid use. A recent study

reported rates of new persistent postoperative opioid use ranging from 5.9% to 6.5%, suggesting that new persistent opioid use after surgery is common.<sup>4</sup>

With one of its central principles being the application of multimodal pain interventions to reduce the reliance on opioid-based medications,<sup>5</sup> enhanced recovery pathways provide a framework that decreases the amount of perioperative

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opioids used. Compared with traditional care, enhanced recovery pathways have been shown to successfully reduce reliance on perioperative opioids while providing adequate analgesia without increasing complication rates.<sup>6</sup> Previously published guidelines have either not focused on acute postoperative pain or have not focused on opioid minimization.<sup>7</sup> This is particularly important in the opioid epidemic era because clinicians are looking for guidance on the management of postoperative pain and the appropriate use of opioids.

In light of this gap in the literature, specifically concerning opioid minimization for acute postoperative pain management, we were interested in answering the following questions: (1) What are the potential strategies for preventing persistent postoperative opioid use? (2) Is opioid-free anesthesia and analgesia feasible and appropriate for routine operations? and (3) Is opioid-free (intraoperative) anesthesia associated with equivalent or superior outcomes compared to an opioid minimization in the perioperative period? These questions are addressed in the context of surgical enhanced recovery, and because our intent was not to provide detailed recommendations for procedure-specific surgical enhanced recovery pathways, we instead provide broad guidance when addressing these questions, discuss the relevant literature for each question, and emphasize what we do not know and need to prioritize for future research.

## METHODS

On January 4–6, 2018, fourth Perioperative Quality Initiative was held in Nashville, TN. The fourth Perioperative Quality Initiative was convened in the light of recent developments in opioid minimization in the perioperative period with the aim of clarifying and advancing understanding of optimizing analgesia while minimizing perioperative opioid use. This report is the result of the fourth Perioperative Quality Initiative working subgroup charged with appraising the published evidence on opioid minimization and perioperative analgesia. Details describing the Perioperative Quality Initiative process have been published previously.<sup>8</sup>

A group of international experts was established including viewpoints representing anesthesiology, surgery, pain medicine, and nursing. Fourth Perioperative Quality Initiative was a consensus-building conference designed around a modified Delphi process in which the group alternately convened for plenary discussion sessions in between small group discussions. The recommendations were developed over 2 days, and consensus was reached around the main issues within each topic.

We used the Delphi method to achieve consensus surrounding the topic of perioperative opioid minimization and opioid-free anesthesia and analgesia in opioid-naïve patients (see Contributors for details).<sup>8</sup> The Delphi method has been used in various formats to obtain the perspectives and opinions of diverse groups.<sup>9</sup> The participants in the Perioperative Quality Initiative consensus were recruited based on their expertise in the principles of enhanced recovery after surgery and perioperative medicine. The process included several iterative steps including a literature review of the topics and building consensus around the important questions related to the topic. Content refinement continues until agreement is achieved and a consensus document is produced.

For content to be included in the manuscript, we searched PubMed from 1966 to December 2017. This should not be

considered a systematic but a narrative review. All coauthors conducted a search for  $\geq 1$  portion of the consensus document and shared those references with the other experts. The search was limited to human trials and limited to articles published in English. During the fourth Perioperative Quality Initiative conference and thereafter as a writing group, reference applicability to the topic was discussed in any area where there was disagreement. We did not provide a specific definition for “opioid-naïve” or persistent postoperative opioid use. Although the focus of the consensus is on enhanced recovery pathways, parts of the consensus may be applicable to all surgical procedures in general.

## RESULTS/DISCUSSION

### Question 1: What Are the Potential Strategies for Preventing Persistent Postoperative Opioid Use?

**Recommendation.** There are insufficient data to recommend a specific strategy for prevention of persistent postoperative opioid use. We recommend that patients be discharged home with a comprehensive multimodal analgesia care plan with the aim of minimizing or avoiding postdischarge opioid use.

Studies and meta-analyses involving multimodal analgesia have focused on immediate postoperative opioid reductions rather than long-term outcomes.<sup>10–16</sup> Although these findings are promising, one cannot draw conclusions on the long-term benefits of various perioperative treatments without deliberate longitudinal follow-up. Without a shift in focus to postoperative outcomes long after hospital discharge, the long-term efficacy of many perioperative interventions is left unexplored.

In the context of emerging awareness of the risk of new persistent opioid use after surgery, future research, extending longitudinal follow-up beyond the acute phase, is needed. Analysis to determine efficacy of perioperative interventions in preventing persistent postsurgical pain, minimizing opioid use, and promoting opioid cessation will be telling. At present, there are insufficient data to recommend a specific strategy for prevention of persistent postoperative opioid use.

**Preoperative Risk Assessment.** The first step in a tailored, patient-specific approach to preventing persistent postoperative opioid use entails accurate preoperative risk assessment although whether these risk factors can be modified to prevent persistent postoperative opioid use is unclear. Educating the patient on analgesic options and setting realistic expectations for postoperative pain may potentially decrease postoperative pain and opioid use. Patients exhibit a wide range in opioid needs after similar procedures.<sup>17,18</sup> This may imply a disconnect between the initial rationale to prescribe opioids for postoperative pain and the factors that continue to reinforce these behaviors such as depressed mood and postoperative insomnia. Previous research highlights preoperative tobacco use, alcohol and substance use disorders, mood disorders, anxiety, and pain diagnoses as risk factors for new persistent opioid use after surgery.<sup>4</sup> Interventions designed to optimize these presurgical risk factors may reduce the incidence

of new persistent postoperative opioid use. For example, preoperative depression and use of antidepressants are important risk factors for chronic opioid use after surgery.<sup>18</sup> Clinically diagnosed depression increases the odds of chronic opioid therapy after lumbar fusion, and 77% of patients with depression receive chronic opioid therapy after lumbar fusion compared to 50% without a depression diagnosis.<sup>19</sup> Similarly, depression is a risk factor for new chronic opioid use after total hip arthroplasty rather than anxiety or psychoses.<sup>20</sup> This mirrors trends in long-term opioid therapy for non-cancer pain because patients with a history of depression are more likely to receive chronic opioid therapy at higher daily doses and for extended durations.<sup>4</sup> As risk factors for new persistent postoperative opioid use become well-defined across surgical cohorts, evidence-based treatments to minimize the incidence of both persistent postoperative pain and opioid use must be developed.

**Opioids During Anesthesia.** In the context of the current opioid epidemic, anesthesiologists have begun to question the need for opioids as part of anesthetic regimens. Feasibility of opioid-free anesthesia in case/pilot studies has been reported<sup>21,22</sup>; however, patients are noted to receive opioids after discharge from the postanesthesia care unit even in the context of opioid-free anesthesia.<sup>23</sup> Several case series suggest that potential benefits of opioid-free anesthesia may include reduced time to discharge, fewer unplanned hospital admissions, and a significant decrease in postoperative opioid use in the postanesthesia care unit although longer-term opioid consumption (6 hours after surgery) may not be decreased.<sup>22-24</sup> Future work is needed to determine the impact of transient postoperative opioid reductions resulting from opioid-free anesthesia protocols.

An important consideration moving forward will be the utility of opioid minimization during anesthesia versus opioid-free anesthesia in preventing new persistent postoperative opioid use. Future clinical trials examining opioid requirements both during and after opioid-free anesthesia, not only during hospitalization but also after hospital discharge, are needed. Careful examination of postoperative pain intensity and trajectories is needed long after hospital discharge to influence a dramatic shift in clinical practice. Preliminary evidence demonstrates continued opioid prescribing despite implementation of an enhanced recovery pathway emphasizing multimodal analgesia and opioid-free anesthesia.<sup>25</sup>

**Postoperative Including Postacute Care.** Opioid prescribing at hospital discharge may be another key determinant of persistent postoperative opioid use. Surgery is an important stimulus for chronic opioid use even among those who are opioid naïve before surgery.<sup>18</sup> Prescribing opioids at hospital discharge to previously opioid-naïve patients is a risk factor for chronic opioid use 1 year after discharge.<sup>16</sup> Educating perioperative health care providers who prescribe postdischarge analgesics about multimodal analgesia and alternative options for postoperative pain management may potentially decrease the amount of opioid prescribed on hospital discharge. Implementation of an enhanced recovery pathway may not automatically decrease postdischarge

opioid prescribing, despite an in-hospital decrease in opioid use, as noted in one study where opioid prescribing practices at discharge did not decrease significantly after enhanced recovery pathway implementation.<sup>25</sup> Research to understand the impact of postoperative opioid prescribing at discharge to the development of new persistent postoperative opioid use is critical to developing evidence-based approaches to encourage opioid cessation. At present, the majority of patients undergoing surgery are prescribed opioids at discharge.<sup>26</sup> Longitudinal studies of perioperative pain and opioid use among a variety of surgical cohorts are needed to truly determine the need for continued opioid prescribing in the context of optimal, extended multimodal analgesic treatment plans.

Implementation of an evidence-based opioid prescribing guideline post-laparoscopic cholecystectomy reduced the total amounts of opioid prescribed without increasing pain or the number of refills requested.<sup>27</sup> A more patient-specific approach may yield greater precision. Among 333 inpatients undergoing general surgical procedures, post-discharge opioid use was associated with opioid consumption the day before discharge and younger age.<sup>28</sup> Thus, an approach based on inpatient opioid requirements could limit overprescribing and may decrease the incidence of persistent postoperative opioid use.

Given the increased attention to opioid prescribing, legislative bodies in certain states have begun to limit the duration of initial opioid prescriptions for acute pain. Research to support evidence-based opioid prescribing guidelines in a variety of surgical cohorts is urgently needed to help inform policy makers and key stakeholders in their efforts. In parallel, professional guidelines recommend tapering opioids by 6 weeks after most major surgeries to preoperative doses or lower in the absence of clinically meaningful improvements in function and pain with 20% weekly dose reductions.<sup>29</sup> Similarly, the clinical practice guidelines on the management of postoperative pain strongly recommend providing patient education regarding the outpatient postoperative pain treatment plan including opioid weaning with dose reductions of 20%–25% of the discharge dose every day or 2 if patients receive opioids for more than 1–2 weeks.<sup>7</sup> These recommendations are based largely on anecdotal experience and represent an important knowledge gap regarding the optimal duration and optimal tapering strategies of postoperative opioid treatment after hospital discharge.<sup>30</sup> Randomized trials evaluating postoperative opioid tapering and necessary psychosocial interventions are needed to support burgeoning expert opinions and opioid prescribing policy.<sup>31</sup>

Although much focus has shifted to opioid prescribing in the context of rising opioid-related overdoses and mortality in recent years, decisions to initiate and maintain postoperative opioid therapy should be considered in the context of optimizing postoperative pain management and similarly preventing persistent postsurgical pain. Focused efforts to optimize nonopioid multimodal analgesia after hospital discharge are needed to supplement restricted opioid prescribing.<sup>32</sup> Clearly, a shift in prescribing practices is needed not only to include opioid restriction but also to emphasize nonopioid analgesics and treatment strategies.



**Table. Analgesic Options for Multimodal Analgesia**

Class of Analgesic Agent/ Technique	Advantages	Disadvantages	References
Acetaminophen	↓ Pain, opioid-sparing effect, nonopioid analgesia	Liver toxicity	33–40
α-2 agonists (eg, clonidine and dexmedetomidine)	↓ Pain, opioid-sparing effect, nonopioid analgesia	Hypotension, bradycardia, sedation	41–45
Gabapentinoids (eg, gabapentin and pregabalin)	↓ Pain, opioid-sparing effect, nonopioid analgesia	Dizziness, sedation, peripheral edema, renally excreted, potential respiratory depression	46–58
IV lidocaine	↓ Pain, facilitates return of gastrointestinal function	Optimal dosage regimen uncertain	59–62
N-methyl-D-aspartate antagonists (eg, ketamine, magnesium, and dextromethorphan)	↓ Pain, opioid-sparing effect, nonopioid analgesia	Optimal dosage regimen uncertain	63–70
NSAIDs (eg, ibuprofen, ketorolac, meloxicam, and celecoxib)	↓ Pain, opioid-sparing effect, nonopioid analgesia	Platelet dysfunction, gastrointestinal irritation, renal dysfunction	71–76
Regional anesthesia/analgesia	↓ Pain, opioid-sparing effect, nonopioid analgesia	Failure of technique, local anesthetics: hypotension, motor block. Opioids: pruritus, potential respiratory depression	77–86
Steroids (eg, methylprednisolone and dexamethasone)	↓ Pain, ↓ length of recovery room stay	↑ Serum glucose levels (controversial)	87–91
Wound infiltration (local anesthetics)	Fast and simple technique, minimal risk	Duration of analgesia limited to duration of action of local	92–95

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There are many nonopioid analgesic options available for use in a comprehensive multimodal analgesic regimen (Table) which can be tailored for specific patients or practices, although, it must be recognized that there is no definitive, evidence-based multimodal regimen. We recommend that patients be discharged home with a comprehensive multimodal analgesia care plan aiming to minimize or avoid postdischarge opioid use.<sup>96–100</sup>

### Question 2: Is Opioid-Free Anesthesia and Analgesia Feasible and Appropriate for Routine Operations?

**Recommendation.** Opioid-free anesthesia and analgesia are feasible, and we suggest its use as an appropriate perioperative strategy. However, there are insufficient data to determine the benefits and harms of opioid-free intraoperative anesthesia and postoperative analgesia compared to perioperative opioid minimization.

Since the first published reports around the turn of the century, it has become increasingly clear that opioid-free anesthesia is feasible in carefully selected patients and procedures.<sup>101,102</sup> Increasingly, randomized studies in this area are appearing and their results are also in general supportive of this approach with reduced opioid-related adverse events and, on balance, a reduction in pain scores and rescue analgesia use.<sup>101,102</sup> Importantly, no apparent safety issues are emerging as experience of opioid-free anesthesia increases, and all of the studies demonstrate the feasibility of this approach in routine practice.

At present, terminology is inconsistent in this area. Different groups use terms including “opioid-free anesthesia, opioid-free analgesia, and non-narcotic anesthesia/analgesia.” It is often unclear which period of anesthetic/perioperative care is being alluded to. Consequently, the limited literature in this area is divided into studies that describe true opioid-free anesthetic care throughout the entire perioperative patient journey, and those that are

opioid-free immediately around the time of surgery (induction and maintenance of anesthesia and emergence) but do not encompass opioid-free postoperative analgesia as well. In this text, we have endeavored to be consistent in defining opioid-free “analgesia” as the absolute avoidance of opioids for pain relief in the pre- and postoperative periods, whereas opioid-free “anesthesia” is the absolute avoidance of opioids from induction of anesthesia until complete emergence, inclusive of these 2 events.

**Feasibility and Safety.** Ideally, there would be many large scale randomized controlled trials and meta-analyses of randomized controlled trials to assess the feasibility and safety of opioid-free anesthesia; however, the literature that is available consists of case reports, small observational studies, and a few relatively small randomized controlled trials. A number of case reports have described the feasibility of opioid-free anesthesia in specific clinical contexts where either (1) patients were particularly susceptible to the adverse effects of opioids or (2) patients were known to have a clinical condition where opioids were associated with particular risks. Horlocker et al<sup>101</sup> reported the use of opioid-free anesthesia/analgesia for total knee arthroplasty in a woman with severe opioid-associated nausea and vomiting using spinal anesthesia with postoperative psoas compartment lumbar plexus block plus acetaminophen and ketorolac.<sup>97</sup> Gaszynski<sup>103</sup> reported the use of opioid-free anesthesia/analgesia in a man with myotonic dystrophy undergoing laparoscopic cholecystectomy using propofol and rocuronium for anesthesia and dexmedetomidine for intra- and postoperative analgesia. Gaszynski et al<sup>104</sup> reported opioid-free anesthesia in a superobese woman undergoing obesity surgery with dexmedetomidine and topical anesthesia for “awake intubation” and sevoflurane with dexmedetomidine for maintenance of anesthesia and analgesia. Patil and Anitescu<sup>105</sup> reported opioid-free analgesia in a woman with opioid-induced delirium using epidural

local anesthetic infusion with dexmedetomidine infusion initially followed by neuraxial and transdermal clonidine. Plunkett et al<sup>106</sup> report opioid-free anesthesia/analgesia for cervical ganglionectomy in a woman 7 days after opioid detoxification using ketamine and dexmedetomidine plus nonopioid adjuncts. Matthes et al<sup>107</sup> report opioid-free anesthesia/analgesia for cholecystectomy using bilateral transversus abdominis plane blocks for analgesia. Successful conduct of such opioid-free anesthesia/analgesia in each case relied on a combination of approaches using regional/local/field blocks where possible and liberal use of acetaminophen and nonsteroidal anti-inflammatory agents combined with administration of  $\alpha$ -2 and *N*-methyl-D-aspartate antagonists in some cases. It is unclear from the available literature whether the choice of adjunctive therapies materially impacts pain after opioid-free anesthesia/analgesia or which nonopioid analgesics are most effective in this context.

More recently, larger case series have emerged supporting such opioid-free anesthetic strategies: reduction in opioid-related adverse events seems a realistic prospect with opioid-free anesthesia. For example, Tripathy et al<sup>108</sup> reported superior outcomes (reduced recovery room time, postoperative nausea, analgesic requirements, and visual analog pain scale scores) in 24 patients undergoing modified radical mastectomy with axillary dissection who received anesthesia with propofol induction and sevoflurane maintenance versus that seen in contemporary (nonrandomized) control patients. Parsa et al<sup>23</sup> reported the use of 2 different opioid-free approaches in comparison with “traditional” opioid-based analgesia during anesthesia for bilateral breast reduction surgery. The opioid-free groups experienced a shorter time to discharge home, fewer unplanned hospital admissions, and decreased postoperative opioid use. In addition, Keller et al<sup>109</sup> reported on an analysis of >50,000 patients from the Premier database and reported that length of stay was shorter and postdischarge nursing needs and total costs were lower in the “opioid-free” group in both open and laparoscopic approaches. Moreover, readmissions were increased by 14% with opioid use. These initial reports demonstrated that opioid-free anesthesia and analgesia are feasible.

**Randomized Evaluations.** Randomized studies suggest that opioid-related adverse events are reduced with opioid-free anesthesia with variable consequences for postoperative pain, with the most recent studies reporting that pain is unaffected or reduced. An early study by Callesen et al<sup>102</sup> studied patients undergoing total abdominal hysterectomy randomized to opioid-free epidural/spinal anesthesia plus continuous epidural bupivacaine after surgery or general anesthesia with continuous epidural bupivacaine and morphine after surgery. The opioid-free approach resulted in lower rates of postoperative nausea and vomiting but higher pain scores. Bakan et al<sup>110</sup> studied 80 patients undergoing elective laparoscopic cholecystectomy randomized to either propofol/remifentanyl anesthesia or the combination of dexmedetomidine, lidocaine, and propofol. Patients in the opioid-free group showed reduced postoperative fentanyl use for analgesia, fewer hypotensive events, and lower pain scores.<sup>110</sup> Ziemann-Gimmel et al<sup>111</sup> randomized 119 patients undergoing bariatric surgery to

anesthesia with opioids and volatile anesthesia or propofol, ketamine, and dexmedetomidine. Both the frequency and severity of postoperative nausea and vomiting were reduced in the opioid-free group. Becchi et al<sup>112</sup> compared opioid-free psoas compartment infusion of ropivacaine with IV infusion of morphine and ketorolac for patient receiving spinal anesthesia for total hip arthroplasty. The opioid-free group experienced lower pain scores at rest and, on mobilizing, less postoperative nausea and vomiting and lower use of rescue analgesia. Parsa et al<sup>23</sup> compared 39 patients undergoing bilateral breast reduction surgery with general anesthesia and opioids to 26 patients undergoing IV sedation and local anesthesia with local anesthesia and 18 patients who received general anesthesia alone. The opioid-free anesthesia groups received less postoperative opioids, were discharged from hospital more quickly, and had fewer unplanned hospital admissions. De Windt et al<sup>113</sup> studied 60 children undergoing minor hand surgery randomized to peripheral nerve block or opioids for intraoperative and postoperative analgesia. Pain scores and postoperative nausea and vomiting were reduced in the opioid-free group as well as times to first oral intake and discharge from hospital. Finally,  $\geq 1$  large prospective randomized controlled trial (enrollment goal of 400 patients) to assess the effect of opioid-free anesthesia on opioid-related adverse events is ongoing.<sup>114</sup>

In summary, the available literature of case reports, case series, and randomized studies is of low quality and small in size but indicates that opioid-free anesthesia is safe, feasible, and appears to effectively reduce opioid-related adverse events compared to traditional management strategies where opioids are a primary component of achieving analgesia. In addition, there appears to be no adverse effect on pain scores or the need for rescue analgesia with this approach. In fact, when taken as a whole, the prospective, randomized studies suggest that pain scores and rescue analgesia use are lower when opioid-free anesthesia techniques are used.

### **Questions 3: Is Opioid-Free (Intraoperative) Anesthesia Associated With Equivalent or Superior Outcomes Compared to an Opioid Minimization in the Perioperative Period?**

**Recommendation.** There are insufficient data to determine the benefits and harms of opioid-free intraoperative anesthesia and postoperative analgesia compared to perioperative opioid minimization.

While the feasibility, safety, and efficacy of opioid-free intraoperative anesthesia are relatively well supported by the available literature to date, there is no substantive literature comparing intraoperative opioid-free anesthesia to opioid minimization strategies (regimens that consciously attempt to decrease the amount of opioids used with the knowledge that some [small] amount of opioids will be given). As previously described, we have defined opioid-free anesthesia as the absolute avoidance of opioids from induction of anesthesia until complete emergence. In addition, we have defined opioid-free analgesia as the absolute avoidance of opioids for pain relief in the pre- and postoperative periods. Perioperative opioid minimization is a strategy to decrease the overall use of opioids both in the

intraoperative and postoperative period; it is clear that opioids are used, but there is a conscious effort to decrease the amount of opioids used. Although we are not advocating for the complete elimination of all perioperative opioid use (preoperatively, intraoperatively, postoperatively, and postdischarge), we were unable to identify experimental (clinical trial) data that would meet evidence-based medicine criteria for showing a comparative benefit for either of these 2 related but distinct approaches. The result of minimizing opioids should not be inadequately treated pain which may lead to chronic pain conditions and prolonged opioid use. In addition, achieving “opioid-free” anesthesia typically implies the use of nonopioid medications, all of which are associated with potential side effects and adverse events. For instance, each major class of nonopioid analgesics has several disadvantages that may limit or preclude its use in certain populations (Table). While opioid-free anesthesia has clearly been shown to be feasible, whether this practice will be embraced by the larger anesthesia community for surgical procedures in the “real world” is unclear. To do so will certainly require significant effort and a change of culture, but evidence would support moving in this direction.<sup>115,116</sup> Based on the available literature, we are unable to determine whether the benefits of opioid-free anesthesia outweigh its risks. The performance of such studies is a clear and urgent research priority.

### FUTURE RESEARCH/SUMMARY

Future research questions to be answered include (1) Are opioids necessary for routine anesthesia and analgesia? (2) Are there risks associated with opioid-free anesthesia and analgesia? (3) What are the effective strategies for prevention of persistent postoperative opioid use? (4) Does modifying current opioid prescription practices prevent persistent postoperative opioid use? (5) What is the optimal comprehensive multimodal analgesia plan? and (6) Can opioid-free or opioid minimization principles extend to the postdischarge period?

The question of whether an opioid-free anesthetic is appropriate is uncertain, although, preliminary evidence cited earlier suggests that opioid-free anesthetics may confer some advantages; however, a comprehensive analysis of the benefits and risks of an opioid-free anesthetic has not been undertaken. Thus, the question remains as to whether it is not only feasible, but is it safe and does it confer any benefit on the patient? In addition, the practice differences and risk/benefits between opioid-free analgesia and opioid minimization for postoperative and postdischarge pain control are unclear. Although ongoing trials are investigating the risks and benefits of opioid-free anesthesia,<sup>114</sup> we were unable to identify high-quality clinical trial data showing a comparative benefit for either of these 2 related (opioid-free anesthesia/analgesia and opioid minimization) but distinct approaches in either the intraoperative or postoperative period. The delivery of such studies is a clear and urgent research priority.

Future research to determine the impact of reduced perioperative opioid requirements on long-term postoperative opioid use after hospital discharge is needed. Although multimodal analgesia can clearly decrease perioperative opioid consumption, whether this actually leads to a decrease in postdischarge opioid use is uncertain and actual amount

of opioids a patient receives on discharge may be based on other factors.<sup>25</sup> More data are needed to determine whether nonopioid anesthesia will result in lower pain scores and less long-term impact on pain and postdischarge opioid use. It is clear that postdischarge opioids are generally not prescribed in a patient-specific manner and opioid overprescription is common after surgery.<sup>2,117</sup> The optimal timing and duration of treatment needed to reduce persistent postoperative opioid use are uncertain.<sup>115</sup> Discharge medication planning needs particular attention if the benefits of opioid-free and opioid minimization strategies are to be carried through beyond hospital discharge. Preliminary evidence shows significant decreases in postoperative opioids prescribed at discharge after implementation of state legislation restricting the quantity or duration of postoperative opioids prescribed for acute pain.<sup>118</sup> However, it is unclear whether institutional policies and state legislation will ultimately decrease the incidence of persistent postoperative opioid use.<sup>119</sup>

A Transitional Pain Service (which may include psychological assessment and behavioral interventions) has been used to identify patients at risk for persistent postsurgical pain, provide interdisciplinary pain management after hospital discharge, and transition care back to primary care providers which may reduce postoperative opioid use.<sup>46,120</sup> Future clinical trials examining the utility of extended postoperative pain management for preventing persistent postoperative pain and opioid use will provide a much needed evidence base for multimodal, interdisciplinary pain care.

The optimal postoperative and postdischarge multimodal analgesic regimens are not clear. Although there are many classes of nonopioid analgesics available, we often do not know the optimal dose, duration of postoperative use, or combinations for specific patient conditions or specific surgical procedures. Although many providers agree with general recommendations to discharge patients with opioid prescriptions sufficient for the expected duration of postoperative pain, further research is needed to determine whether opioids are necessary in the context of multimodal postdischarge pain treatment regimens and the necessary length of postoperative opioid prescriptions. In addition, research tracking the incidence of postoperative opioid misuse, diversion, and transition to opioid use disorders will additionally inform patients, providers, the public, and policymakers regarding the long-term risks of new persistent postoperative opioid use. ■■

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**DISCLOSURES**

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**Contribution:** This author helped conceive and design the study, analyze and interpret the data, draft the manuscript, critically revise the manuscript for important intellectual content.

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**REFERENCES**

1. Stone AB, Wick EC, Wu CL, Grant MC. The US opioid crisis: a role for enhanced recovery after surgery. *Anesth Analg*. 2017;125:1803–1805.

2. Bicket MC, Long JJ, Pronovost PJ, Alexander GC, Wu CL. Prescription opioid analgesics commonly unused after surgery: a systematic review. *JAMA Surg.* 2017;152:1066–1071.
3. Jones CM. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers - United States, 2002-2004 and 2008-2010. *Drug Alcohol Depend.* 2013;132:95–100.
4. Brummett CM, Waljee JF, Goesling J, et al. New persistent opioid use after minor and major surgical procedures in US adults. *JAMA Surg.* 2017;152:e170504.
5. Wick EC, Grant MC, Wu CL. Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: a review. *JAMA Surg.* 2017;152:691–697.
6. Grant MC, Sommer PM, He C, et al. Preserved analgesia with reduction in opioids through the use of an acute pain protocol in enhanced recovery after surgery for open hepatectomy. *Reg Anesth Pain Med.* 2017;42:451–457.
7. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain.* 2016;17:131–157.
8. Miller TE, Shaw AD, Mythen MG, Gan TJ; Perioperative Quality Initiative (POQI) I Workgroup. Evidence-Based Perioperative Medicine comes of age: the Perioperative Quality Initiative (POQI): the 1st consensus conference of the Perioperative Quality Initiative (POQI). *Perioper Med (Lond).* 2016;5:26.
9. von der Gracht H. Consensus measurement in Delphi studies: review and implications for future quality assurance. *Technol Forecast Soc Change.* 2012;79:1525–1536.
10. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *BMJ.* 2018;360:j5790.
11. Hill MV, McMahon ML, Stucke RS, Barth RJ Jr. Wide variation and excessive dosage of opioid prescriptions for common general surgical procedures. *Ann Surg.* 2017;265:709–714.
12. Bartels K, Mayes LM, Dingmann C, Bullard KJ, Hopfer CJ, Binswanger IA. Opioid use and storage patterns by patients after hospital discharge following surgery. *PLoS One.* 2016;11:e0147972.
13. McLaughlin DC, Cheah JW, Aleshi P, Zhang AL, Ma CB, Feeley BT. Multimodal analgesia decreases opioid consumption after shoulder arthroplasty: a prospective cohort study. *J Shoulder Elbow Surg.* 2018;27:686–691.
14. Yung EM, Brull R, Albrecht E, Joshi GP, Abdallah FW. Evidence basis for regional anesthesia in ambulatory anterior cruciate ligament reconstruction: part III: local instillation analgesia: a systematic review and meta-analysis. *Anesth Analg.* 2019;128:426–437.
15. Hooten WM, St Sauver JL, McGree ME, Jacobson DJ, Warner DO. Incidence and risk factors for progression from short-term to episodic or long-term opioid prescribing: a population-based study. *Mayo Clin Proc.* 2015;90:850–856.
16. Calcaterra SL, Yamashita TE, Min SJ, Keniston A, Frank JW, Binswanger IA. Opioid prescribing at hospital discharge contributes to chronic opioid use. *J Gen Intern Med.* 2016;31:478–485.
17. Waljee JF, Zhong L, Hou H, Sears E, Brummett C, Chung KC. The use of opioid analgesics following common upper extremity surgical procedures: a national, population-based study. *Plast Reconstr Surg.* 2016;137:355e–364e.
18. 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;176:1286–1293.
19. Anderson JT, Haas AR, Percy R, Woods ST, Ahn UM, Ahn NU. Chronic opioid therapy after lumbar fusion surgery for degenerative disc disease in a workers' compensation setting. *Spine (Phila Pa 1976).* 2015;40:1775–1784.
20. Inacio MC, Hansen C, Pratt NL, Graves SE, Roughead EE. Risk factors for persistent and new chronic opioid use in patients undergoing total hip arthroplasty: a retrospective cohort study. *BMJ Open.* 2016;6:e010664.
21. Kim DJ, Bengali R, Anderson TA. Opioid-free anesthesia using continuous dexmedetomidine and lidocaine infusions in spine surgery. *Korean J Anesthesiol.* 2017;70:652–653.
22. Jebaraj B, Ramchandran R, Rewari V, et al. Feasibility of dexmedetomidine as sole analgesic agent during robotic urological surgery: a pilot study. *J Anaesthesiol Clin Pharmacol.* 2017;33:187–192.
23. Parsa FD, Cheng J, Stephan B, et al. Bilateral breast reduction without opioid analgesics: a comparative study. *Aesthet Surg J.* 2017;37:892–899.
24. Bakan M, Umutoglu T, Topuz U, et al. Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study. [Article in Portuguese]. *Rev Bras Anesthesiol.* 2015;65:191–199.
25. Brandal D, Keller MS, Lee C, et al. Impact of enhanced recovery after surgery and opioid-free anesthesia on opioid prescriptions at discharge from the hospital: a historical-prospective study. *Anesth Analg.* 2017;125:1784–1792.
26. Hanson KT, Thiels CA, Polites SF, et al. The opioid epidemic in acute care surgery-characteristics of overprescribing following laparoscopic cholecystectomy. *J Trauma Acute Care Surg.* 2018;85:62–70.
27. Howard R, Waljee J, Brummett C, Englesbe M, Lee J. Reduction in opioid prescribing through evidence-based prescribing guidelines. *JAMA Surg.* 2018;153:285–287.
28. 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.
29. McCarberg B. Washington State Opioid Prescribing Guidelines. *Pain Med.* 2015;16:1455–1456.
30. Gordon DB, de Leon-Casasola OA, Wu CL, Sluka KA, Brennan TJ, Chou R. Research gaps in practice guidelines for acute postoperative pain management in adults: findings from a review of the evidence for an American Pain Society Clinical Practice Guideline. *J Pain.* 2016;17:158–166.
31. Berna C, Kulich RJ, Rathmell JP. Tapering long-term opioid therapy in chronic noncancer pain: evidence and recommendations for everyday practice. *Mayo Clin Proc.* 2015;90:828–842.
32. Nooromid MJ, Blay E Jr, Holl JL, et al. Discharge prescription patterns of opioid and nonopioid analgesics after common surgical procedures. *Pain Rep.* 2018;3:e637.
33. Doleman B, Read D, Lund JN, Williams JP. Preventive acetaminophen reduces postoperative opioid consumption, vomiting, and pain scores after surgery: systematic review and meta-analysis. *Reg Anesth Pain Med.* 2015;40:706–712.
34. McNicol ED, Ferguson MC, Haroutounian S, Carr DB, Schumann R. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. *Cochrane Database Syst Rev.* 2016;5:CD007126.
35. Apfel CC, Turan A, Souza K, Pergolizzi J, Hornuss C. Intravenous acetaminophen reduces postoperative nausea and vomiting: a systematic review and meta-analysis. *Pain.* 2013;154:677–689.
36. Salihoglu Z, Yildirim M, Demiroglu S, et al. Evaluation of intravenous paracetamol administration on postoperative pain and recovery characteristics in patients undergoing laparoscopic cholecystectomy. *Surg Laparosc Endosc Percutan Tech.* 2009;19:321–323.
37. Apfel C, Jahr JR, Kelly CL, Ang RY, Oderda GM. Effect of i.v. acetaminophen on total hip or knee replacement surgery: a case-matched evaluation of a national patient database. *Am J Health Syst Pharm.* 2015;72:1961–1968.
38. Memis D, Inal MT, Kavalci G, Sezer A, Sut N. Intravenous paracetamol reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in intensive care unit. *J Crit Care.* 2010;25:458–462.
39. Hansen RN, Pham A, Strassels SA, Balaban S, Wan GJ. Comparative analysis of length of stay and inpatient costs for orthopedic surgery patients treated with IV acetaminophen and IV opioids vs IV opioids alone for post-operative pain. *Adv Ther.* 2016;33:1635–1645.



40. Shaffer EE, Pham A, Woldman RL, et al. Estimating the effect of intravenous acetaminophen for postoperative pain management on length of stay and inpatient hospital costs. *Adv Ther*. 2017;33:2211–2228.
41. Naik BI, Nemergut EC, Kazemi A, et al. The effect of dexmedetomidine on postoperative opioid consumption and pain after major spine surgery. *Anesth Analg*. 2016;122:1646–1653.
42. Jessen Lundorf L, Korvenius Nedergaard H, Møller AM. Perioperative dexmedetomidine for acute pain after abdominal surgery in adults. *Cochrane Database Syst Rev*. 2016;2:CD010358.
43. Sanchez Munoz MC, De Kock M, Forget P. What is the place of clonidine in anesthesia? Systematic review and meta-analyses of randomized controlled trials. *J Clin Anesth*. 2017;38:140–153.
44. Sun R, Zhao W, Hao Q, et al. Intra-articular clonidine for postoperative analgesia following arthroscopic knee surgery: a systematic review and meta-analysis. *Knee Surg Sports Traumatol Arthrosc*. 2014;22:2076–2084.
45. Pöpping DM, Elia N, Marret E, Wenk M, Tramèr MR. Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: a meta-analysis of randomized trials. *Anesthesiology*. 2009;111:406–415.
46. Hah J, Mackey SC, Schmidt P, et al. Effect of perioperative gabapentin on postoperative pain resolution and opioid cessation in a mixed surgical cohort: a randomized clinical trial. *JAMA Surg*. 2018;153:303–311.
47. Wang L, Dong Y, Zhang J, Tan H. The efficacy of gabapentin in reducing pain intensity and postoperative nausea and vomiting following laparoscopic cholecystectomy: a meta-analysis. *Medicine (Baltimore)*. 2017;96:e8007.
48. Peng C, Li C, Qu J, Wu D. Gabapentin can decrease acute pain and morphine consumption in spinal surgery patients: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2017;96:e6463.
49. Mao Y, Wu L, Ding W. The efficacy of preoperative administration of gabapentin/pregabalin in improving pain after total hip arthroplasty: a meta-analysis. *BMC Musculoskelet Disord*. 2016;17:373.
50. Han C, Li XD, Jiang HQ, Ma JX, Ma XL. The use of gabapentin in the management of postoperative pain after total knee arthroplasty: a PRISMA-compliant meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2016;95:e3883.
51. Yao Z, Shen C, Zhong Y. Perioperative pregabalin for acute pain after gynecological surgery: a meta-analysis. *Clin Ther*. 2015;37:1128–1135.
52. Grant MC, Lee H, Page AJ, Hobson D, Wick E, Wu CL. The effect of preoperative gabapentin on postoperative nausea and vomiting: a meta-analysis. *Anesth Analg*. 2016;122:976–985.
53. Lunn TH, Husted H, Laursen MB, Hansen LT, Kehlet H. Analgesic and sedative effects of perioperative gabapentin in total knee arthroplasty: a randomized, double-blind, placebo-controlled dose-finding study. *Pain*. 2015;156:2438–2448.
54. Monks DT, Hoppe DW, Downey K, Shah V, Bernstein P, Carvalho JC. A perioperative course of gabapentin does not produce a clinically meaningful improvement in analgesia after cesarean delivery: a randomized controlled trial. *Anesthesiology*. 2015;123:320–326.
55. Siddiqui NT, Fischer H, Guerina L, Friedman Z. Effect of a preoperative gabapentin on postoperative analgesia in patients with inflammatory bowel disease following major bowel surgery: a randomized, placebo-controlled trial. *Pain Pract*. 2014;14:132–139.
56. Paul JE, Nantha-Aree M, Buckley N, et al. Gabapentin does not improve multimodal analgesia outcomes for total knee arthroplasty: a randomized controlled trial. *Can J Anaesth*. 2013;60:423–431.
57. Doleman B, Heinink TP, Read DJ, Faleiro RJ, Lund JN, Williams JP. A systematic review and meta-regression analysis of prophylactic gabapentin for postoperative pain. *Anaesthesia*. 2015;70:1186–1204.
58. Fabritius ML, Geisler A, Petersen PL, et al. Gabapentin for postoperative pain management: a systematic review with meta-analyses and trial sequential analyses. *Acta Anaesthesiol Scand*. 2016;60:1188–1208.
59. Kranke P, Jokinen J, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. *Cochrane Database Syst Rev*. 2015;7:CD009642.
60. Ventham NT, Kennedy ED, Brady RR, et al. Efficacy of intravenous lidocaine for postoperative analgesia following laparoscopic surgery: a meta-analysis. *World J Surg*. 2015;39:2220–2234.
61. Swenson BR, Gottschalk A, Wells LT, et al. Intravenous lidocaine is as effective as epidural bupivacaine in reducing ileus duration, hospital stay, and pain after open colon resection: a randomized clinical trial. *Reg Anesth Pain Med*. 2010;35:370–376.
62. Sun Y, Li T, Wang N, Yun Y, Gan TJ. Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. *Curr Med Res Opin*. 2015;31:575–581.
63. Jouguelet-Lacoste J, La Colla L, Schilling D, Chelly JE. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. *Pain Med*. 2015;16:383–403.
64. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. *Can J Anaesth*. 2011;58:911–923.
65. Assouline B, Tramèr MR, Kreienbühl L, Elia N. Benefit and harm of adding ketamine to an opioid in a patient-controlled analgesia device for the control of postoperative pain: systematic review and meta-analyses of randomized controlled trials with trial sequential analyses. *Pain*. 2016;157:2854–2864.
66. Wang L, Johnston B, Kaushal A, Cheng D, Zhu F, Martin J. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials. *Can J Anaesth*. 2016;63:311–325.
67. Carstensen M, Møller AM. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. *Br J Anaesth*. 2010;104:401–406.
68. De Oliveira GS Jr, Castro-Alves LJ, Khan JH, McCarthy RJ. Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology*. 2013;119:178–190.
69. Guo BL, Lin Y, Hu W, et al. Effects of systemic magnesium on post-operative analgesia: is the current evidence strong enough? *Pain Physician*. 2015;18:405–418.
70. King MR, Ladha KS, Gelineau AM, Anderson TA. Perioperative dextromethorphan as an adjunct for postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology*. 2016;124:696–705.
71. Elia N, Lysakowski C, Tramèr MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology*. 2005;103:1296–1304.
72. Straube S, Derry S, McQuay HJ, Moore RA. Effect of preoperative Cox-II-selective NSAIDs (coxibs) on postoperative outcomes: a systematic review of randomized studies. *Acta Anaesthesiol Scand*. 2005;49:601–613.
73. Lee A, Cooper MG, Craig JC, Knight JF, Keneally JP. Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. *Cochrane Database Syst Rev*. 2007;2:CD002765.
74. Kelley BP, Bennett KG, Chung KC, Kozlow JH. Ibuprofen may not increase bleeding risk in plastic surgery: a systematic review and meta-analysis. *Plast Reconstr Surg*. 2016;137:1309–1316.
75. Gobble RM, Hoang HL, Kachniarz B, Orgill DP. Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials. *Plast Reconstr Surg*. 2014;133:741–755.
76. Strom BL, Berlin JA, Kinman JL, et al. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. A postmarketing surveillance study. *JAMA*. 1996;275:376–382.
77. Brogi E, Kazan R, Cyr S, Giunta F, Hemmerling TM. Transversus abdominal plane block for postoperative analgesia: a systematic

- review and meta-analysis of randomized-controlled trials. *Can J Anaesth*. 2016;63:1184–1196.
78. Baeriswyl M, Kirkham KR, Kern C, Albrecht E. The analgesic efficacy of ultrasound-guided transversus abdominis plane block in adult patients: a meta-analysis. *Anesth Analg*. 2015; 121:1640–1654.
  79. De Oliveira GS Jr, Castro-Alves LJ, Nader A, Kendall MC, McCarthy RJ. Transversus abdominis plane block to ameliorate postoperative pain outcomes after laparoscopic surgery: a meta-analysis of randomized controlled trials. *Anesth Analg*. 2014;118:454–463.
  80. Terkawi AS, Mavridis D, Sessler DI, et al. Pain management modalities after total knee arthroplasty: a network meta-analysis of 170 randomized controlled trials. *Anesthesiology*. 2017;126:923–937.
  81. Jiang X, Wang QQ, Wu CA, Tian W. Analgesic efficacy of adductor canal block in total knee arthroplasty: a meta-analysis and systematic review. *Orthop Surg*. 2016;8:294–300.
  82. Chan EY, Fransen M, Parker DA, Assam PN, Chua N. Femoral nerve blocks for acute postoperative pain after knee replacement surgery. *Cochrane Database Syst Rev*. 2014;5:CD009941.
  83. Terkawi AS, Tsang S, Sessler DI, et al. Improving analgesic efficacy and safety of thoracic paravertebral block for breast surgery: a mixed-effects meta-analysis. *Pain Physician*. 2015;18: E757–E780.
  84. Pendi A, Acosta FL, Tuchman A, et al. Intrathecal morphine in spine surgery: a meta-analysis of randomized controlled trials. *Spine (Phila Pa 1976)*. 2017;42:E740–E747.
  85. Pöpping DM, Elia N, Marret E, Wenk M, Tramèr MR. Opioids added to local anesthetics for single-shot intrathecal anesthesia in patients undergoing minor surgery: a meta-analysis of randomized trials. *Pain*. 2012;153:784–793.
  86. Meylan N, Elia N, Lysakowski C, Tramèr MR. Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. *Br J Anaesth*. 2009;102:156–167.
  87. Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. *Br J Anaesth*. 2013;110:191–200.
  88. De Oliveira GS Jr, Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology*. 2011;115:575–588.
  89. Shen S, Gao Z, Liu J. The efficacy and safety of methylprednisolone for pain control after total knee arthroplasty: a meta-analysis of randomized controlled trials. *Int J Surg*. 2018;57:91–100.
  90. Liu G, Gong M, Wang Y, Xiang Z. Effect of methylprednisolone on pain management in total knee or hip arthroplasty: a systematic review and meta-analysis of randomized controlled trials. *Clin J Pain*. 2018;34:967–974.
  91. Bjerregaard LS, Jensen PF, Bigler DR, et al. High-dose methylprednisolone in video-assisted thoracoscopic surgery lobectomy: a randomized controlled trial. *Eur J Cardiothorac Surg*. 2018;53:209–215.
  92. Bamigboye AA, Hofmeyr GJ. Local anaesthetic wound infiltration and abdominal nerves block during caesarean section for postoperative pain relief. *Cochrane Database Syst Rev*. 2009;3:CD006954.
  93. Gupta A, Favaio S, Perniola A, Magnuson A, Berggren L. A meta-analysis of the efficacy of wound catheters for postoperative pain management. *Acta Anaesthesiol Scand*. 2011;55: 785–796.
  94. Kahokehr A, Sammour T, Soop M, Hill AG. Intraperitoneal local anaesthetic in abdominal surgery: a systematic review. *ANZ J Surg*. 2011;81:237–245.
  95. Kahokehr A, Sammour T, Srinivasa S, Hill AG. Systematic review and meta-analysis of intraperitoneal local anaesthetic for pain reduction after laparoscopic gastric procedures. *Br J Surg*. 2011;98:29–36.
  96. Garson LM, Vakharia S, Edwards AF, Maze M. “A time of opportunity”: patient safety and the perioperative surgical home. *Anesth Analg*. 2016;123:1348–1350.
  97. Desai K, Carroll I, Asch SM, et al. Utilization and effectiveness of multimodal discharge analgesia for postoperative pain management. *J Surg Res*. 2018;228:160–169.
  98. Memtsoudis SG, Poeran J, Zubizarreta N, et al. Association of multimodal pain management strategies with perioperative outcomes and resource utilization: a population-based study. *Anesthesiology*. 2018;128:891–902.
  99. Urman RD, Böing EA, Khangulov V, et al. Analysis of predictors of opioid-free analgesia for management of acute post-surgical pain in the United States. *Curr Med Res Opin*. 2018;26:1–7.
  100. McEvoy MD, Scott MJ, Gordon DB, et al; Perioperative Quality Initiative (POQI) I Workgroup. American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) joint consensus statement on optimal analgesia within an enhanced recovery pathway for colorectal surgery: part 1—from the preoperative period to PACU. *Perioper Med (Lond)*. 2017;6:8.
  101. Horlocker TT, Hebl JR, Kinney MA, Cabanela ME. Opioid-free analgesia following total knee arthroplasty—a multimodal approach using continuous lumbar plexus (psoas compartment) block, acetaminophen, and ketorolac. *Reg Anesth Pain Med*. 2002;27:105–108.
  102. Callesen T, Schouenborg L, Nielsen D, Guldager H, Kehlet H. Combined epidural-spinal opioid-free anaesthesia and analgesia for hysterectomy. *Br J Anaesth*. 1999;82:881–885.
  103. Gaszynski T. Opioid-free general anesthesia in patient with Steinert syndrome (myotonic dystrophy): case report. *Medicine (Baltimore)*. 2016;95:e4885.
  104. Gaszynski T, Gaszynska E, Szewczyk T. Dexmedetomidine for awake intubation and an opioid-free general anesthesia in a superobese patient with suspected difficult intubation. *Drug Des Devel Ther*. 2014;8:909–912.
  105. Patil SK, Anitescu M. Opioid-free perioperative analgesia for hemicolectomy in a patient with opioid-induced delirium: a case report and review of the analgesic efficacy of the alpha-2 agonist agents. *Pain Pract*. 2012;12:656–662.
  106. Plunkett A, Fahlgren M, McLean B, Munday D. Opioid-free balanced anesthesia for cervical ganglionectomy subsequent to recent ultra rapid opioid detoxification. *Pain Med*. 2009;10:767–770.
  107. Matthes K, Gromski MA, Schneider BE, Spiegel JE. Opioid-free single-incision laparoscopic (SIL) cholecystectomy using bilateral TAP blocks. *J Clin Anesth*. 2012;24:65–67.
  108. Tripathy S, Rath S, Agrawal S, et al. Opioid-free anesthesia for breast cancer surgery: an observational study. *J Anaesthesiol Clin Pharmacol*. 2018;34:35–40.
  109. Keller DS, Zhang J, Chand M. Opioid-free colorectal surgery: a method to improve patient & financial outcomes in surgery. *Surg Endosc*. 2018 [Epub ahead of print].
  110. Bakan M, Umutoglu T, Topuz U, et al. Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study. *Braz J Anesthesiol*. 2015;65:191–199.
  111. Ziemann-Gimmel P, Goldfarb AA, Koppman J, Marema RT. Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis. *Br J Anaesth*. 2014;112:906–911.
  112. Becchi C, Al Malyan M, Coppini R, Campolo M, Magherini M, Boncinelli S. Opioid-free analgesia by continuous psoas compartment block after total hip arthroplasty. A randomized study. *Eur J Anaesthesiol*. 2008;25:418–423.
  113. De Windt AC, Asehnoune K, Roquilly A, et al. An opioid-free anaesthetic using nerve blocks enhances rapid recovery after minor hand surgery in children. *Eur J Anaesthesiol*. 2010;27:521–525.
  114. Beloeil H, Laviolle B, Menard C, et al; SFAR Research Network. POFA trial study protocol: a multicentre, double-blind, randomised, controlled clinical trial comparing opioid-free versus opioid anaesthesia on postoperative opioid-related adverse events after major or intermediate non-cardiac surgery. *BMJ Open*. 2018;8:e020873.

115. Lavand'homme P, Estebe JP. Opioid-free anesthesia: a different regard to anesthesia practice. *Curr Opin Anaesthesiol*. 2018;31:556–561.
116. King AB, Spann MD, Jablonski P, Wanderer JP, Sandberg WS, McEvoy MD. An enhanced recovery program for bariatric surgical patients significantly reduces perioperative opioid consumption and postoperative nausea. *Surg Obes Relat Dis*. 2018;14:849–856.
117. Chen EY, Marcantonio A, Tornetta P III. Correlation between 24-hour pre-discharge opioid use and amount of opioids prescribed at hospital discharge. *JAMA Surg*. 2018;153:e174859.
118. MacLean CD, Fujii M, Ahern TP, et al. Impact of policy interventions on postoperative opioid prescribing. *Pain Med*. 2018 [Epub ahead of print].
119. Reid DB, Shah KN, Ruddell JH, et al. Effect of narcotic prescription limiting legislation on opioid utilization following lumbar spine surgery. *Spine J*. 2019;19:717–725.
120. Katz J, Weinrib A, Fashler SR, et al. 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.