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Rational Multimodal Analgesia for Perioperative Pain Management

Girish P. Joshi[1]

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Abstract

Purpose of Review A multimodal analgesic approach improves postoperative pain relief and reduces opioid use; however, it is not universally implemented. This review presents the evidence assessing multimodal analgesic regimens and recommends optimal analgesic combinations.

Recent Findings The evidence for best combinations of individual patients undergoing specific procedures is lacking. Nevertheless, an optimal multimodal regimen may be determined based on identifying efficacious, safe, and inexpensive analgesics interventions.

Summary Key components of an optimal multimodal analgesic regimen include the preoperative identification of patients at high risk for postoperative pain in addition to patient and caregiver education. Unless contraindicated, all patients should receive a combination of acetaminophen, non-steroidal anti-inflammatory drug or cycoxygenase-2-specific inhibitor, dexamethasone, and procedure-specific regional analgesic technique and/or surgical site local anesthetic infiltration. Opioids should be administered as rescue adjuncts. Non-pharmacological interventions are important components of an optimal multimodal analgesic technique. It is imperative to integrate multimodal analgesia regimens within a multidisciplinary enhanced recovery pathway.

Keywords Perioperative pain · Multimodal analgesia · Analgesics · Opioids · Opioid-related adverse events · Evidence-based medicine

Introduction

Adequate postoperative pain control is imperative for enhanced recovery after surgery because it facilitates early ambulation and rehabilitation [1••]. Although it is well-recognized that poorly controlled pain has negative short-term and long-term consequences, postoperative pain management remains inadequate [2]. The reasons for inadequate pain control are several including inappropriate clinical application of multimodal analgesic regimens [3], likely due to broad and conflicting guidelines [4–6]. For example, the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia jointly recommend almost all analgesic interventions that were evaluated [7]. Thus, there is a lack of guidance with regards to optimal drug combinations. Similarly, the American College of Surgeons guidelines for pain management after ambulatory abdominal surgery recommend non-steroidal anti-inflammatory drugs (NSAIDs) and gabapentinoids, alone or in combination preoperatively, local anesthetic wound infiltration intraoperatively, and NSAIDs, acetaminophen, and gabapentinoids, alone or in combination, postoperatively [8]. Based on these guidelines, one might assume that NSAIDs and gabapentinoids can be administered interchangeably. This is obviously not the case, as the analgesic efficacy and adverse effects of these drugs are not the same [1••]. Likewise, recently the consortium of 14 professional societies recently recommended multimodal analgesia but provided no specifics except to suggest the use of a variety of analgesics and techniques combined with non-pharmacological interventions [9]. Such vague recommendations are not useful in day-to-day clinical practice. Overall, although all guidelines recommend using a multimodal analgesic strategy, a procedure- and/

✉ Girish P. Joshi
girish.joshi@utsouthwestern.edu

[1] Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9068, USA

or patient-specific approach has not been provided. The aim of this narrative review is to present the current evidence assessing multimodal analgesic regimens and to recommend optimal analgesic combinations.

Multimodal Analgesia Concept and Evidence

Pain is a complex and multifactorial phenomenon that requires a multimodal analgesic regimen that includes combination of analgesics with different mechanisms of action and/or different sites of administration [10, 11]. A multimodal analgesic strategy should improve postoperative pain relief, reduce opioid use, and thus reduce opioid-related adverse events [12–15]. Despite the known benefits of multimodal analgesia, it is not appropriately used in day-to-day clinical practice [12, 13]. Analysis of an administrative database from 315 hospitals revealed that among patients ($n = \sim 800{,}000$) undergoing four common major surgical procedures (open lobectomy, open colectomy, total knee arthroplasty, and below-knee amputation), there was significant variability in the use of multimodal analgesia [3]. The authors concluded that multimodal analgesia was not universally implemented and that non-opioid analgesics were underutilized [3].

One of the reasons for inappropriate multimodal analgesic regimens is the lack of good evidence [12, 13]. Analgesic combinations are often irrational, and multimodal regimens do not always address the different types of pain responses (e.g., nociceptive and inflammatory pain) for a particular surgical procedure [16, 17]. Furthermore, the multimodal analgesic strategies are not always integrated in a multidisciplinary procedure-specific enhanced recovery pathway [1••, 18].

Components of Multimodal Analgesia

The analgesic components of perioperative pain management can be classified as pharmacological and non-pharmacological interventions (Table 1). In addition, preoperative identification of patients at high risk for postoperative pain and patient/caregiver education are also considered key elements of a multimodal approach to pain management.

Opioids

Opioids provide excellent pain relief; however, they should be used at the lowest effective dose and for the shortest possible duration because of their adverse risk–benefit profile [19–21]. High intraoperative opioid doses can increase postoperative pain and opioid consumption leading to an increase in opioid-related adverse events [22, 23, 24••]. Therefore, in recent years, there has been an increased interest in opioid-free anesthesia (defined as complete avoidance of intraoperative opioids) and analgesia (defined as complete avoidance of intra- and postoperative opioids). This approach often involves using intravenous infusions of analgesic adjuncts such as ketamine, dexmedetomidine, lidocaine, and magnesium [24••]; however, the analgesic benefits of this approach remain questionable. More importantly, there are concerns of adverse effects (e.g., ketamine-induced hallucinations, nightmares, and sleep disturbances, dexmedetomidine-induced bradycardia, hypotension, excessive sedation, delayed recovery and ambulation, lidocaine-induced local anesthetic systemic toxicity, and magnesium-induced potentiation of residual muscle paralysis) [24••], and the best drug combination, dosing, and duration of administration (i.e., timing of discontinuation) remain unclear. Furthermore, these drugs cannot be titrated to patient needs, they have a ceiling effect and a narrow therapeutic index of safety, and their use requires equipment that can be burdensome and costly. Importantly, currently there are no realistic options to completely avoid opioids in the postoperative period because existing non-opioid analgesics are not always adequate, particularly after major surgery [24••].

Acetaminophen

Acetaminophen is a weak analgesic with a favorable efficacy-adverse effect profile [25]. The World Health Organization

Table 1 Analgesic options for perioperative pain management

Pharmacological Interventions
- Non-opioid analgesics: acetaminophen, non-steroidal anti-inflammatory drugs, cyclooxygenase-2-specific inhibitors
- Local/regional analgesic techniques: neuraxial analgesia (epidural analgesia, paravertebral blocks, intrathecal opioids), interfascial plane blocks, peripheral nerve blocks (local anesthetics, cryoneurolysis, percutaneous peripheral nerve stimulation), surgical site infiltration
- Analgesic adjuncts: dexamethasone, gabapentinoids (gabapentin, pregabalin), ketamine, alpha-2 receptor agonists (clonidine, dexmedetomidine), lidocaine infusion, magnesium, muscle relaxants
- Opioids

Non-pharmacologic interventions
- Physical modalities: transcutaneous electrical nerve stimulation, acupuncture, continuous passive movement and cryotherapy, lifestyle improvement (e.g., exercise, yoga, massage)
- Psychological modalities: stress reduction, attentional strategies, behavioral therapies (e.g., music therapy cognitive-behavioral therapies [relaxation, distraction, imaging, virtual reality], biofeedback [e.g., therapeutic touch], peer-to-peer or other peer support, case management, psychotherapy)

(WHO) considers acetaminophen as an essential medicine (i.e., the most efficacious, safe, and cost-effective medication) [26]. Importantly, acetaminophen enhances the analgesic effects of NSAIDs and cyclooxygenase (COX)-2-specific inhibitors, and their combination provides superior pain relief compared with either drug alone [27–30]. Therefore, acetaminophen should be used routinely for all patients unless there are contraindications such as severe liver dysfunction and severe alcoholism. In healthy patients, acetaminophen should be administered as a scheduled dosing of 1000 mg every 6 h, maximum 4000 mg per day. It is, however, necessary to exercise caution and educate patients who take medications containing acetaminophen such as opioids or cold medications. Of note, there are no clinically significant differences between the oral and intravenous formulations of acetaminophen [31].

Non-steroidal Anti-Inflammatory Drugs (NSAIDs) and Cyclooxygenase (COX)-2-Specific Inhibitors

Both NSAIDS and COX-2-specific inhibitors are potent analgesics and are considered a cornerstone of multimodal analgesic regimen [1••]. However, despite their well-described opioid-sparing effects, these group of drugs are underutilized, most likely due to concerns for potential adverse effects like increased perioperative bleeding, acute kidney injury, cardiovascular and gastrointestinal complications, and asthma exacerbation as well as increased anastomotic leak after colorectal surgery [1••, 32••, 33, 34]. However, recent evidence suggests that these concerns are unfounded particularly with short-term perioperative use [32••, 33–35, 36•]. Therefore, NSAIDs or COX-2-specific inhibitors should be administered unless there are contraindications such as the presence of renal risk factors (e.g., impaired renal function, nephrotoxic agents use, and hypovolemia), gastrointestinal bleeding risk factors, and acute cardiovascular disease. In addition, closed cavity procedures (e.g., neurosurgery) where even minimal bleeding can influence surgical outcome should preclude their administration. Interestingly, at equipotent doses, there are no differences between the analgesic efficacy of NSAIDs and COX-2-specific inhibitors, and except for lack of antiplatelet effects with COX-2-specific inhibitors, there are no differences in their adverse effect profiles. Of note, both NSAIDs and COX-2-specific inhibitors exhibit a "ceiling effect" with respect to their maximum analgesic effect.

Gabapentinoids

Gabapentinoids (i.e., gabapentin and pregabalin) have been used in surgical patients due to their potential benefits of reducing postoperative opioid consumption and/or pain scores; however, these benefits have been questioned [37•, 38, 39•]. In addition, there are increasing reports of adverse effects (e.g., sedation, dizziness, visual disturbances, falls, and respiratory depression), particularly with concomitant use of opioids and other sedatives [40, 41]. A recent retrospective cohort study analyzed an administrative database to assess gabapentin-related adverse effects in older patients (age ≥ 65 years) undergoing major surgery and receiving gabapentin for at least 2 days after surgery [42•]. Propensity matching showed that compared to non-users ($n = 118{,}936$), gabapentin users ($n = 118{,}936$) had increased risk of delirium, new antipsychotic use, and pneumonia. The risk of delirium was greater in patients with high comorbidity burden and chronic kidney disease [42•].

Given the questionable efficacy and potential adverse effects, the routine use of gabapentinoids is not recommended. Nevertheless, patients receiving preoperative gabapentinoids may continue them in the perioperative period, but with great caution, particularly with high-risk patients (i.e., elderly, morbidly obese, obstructive sleep apnea, and high opioid use). Also, gabapentinoids may be appropriate when NSAIDs or COX-2-specific inhibitors cannot be used or for surgical procedures associated with postoperative neuropathic pain. Although the dose and duration of gabapentinoid use remain controversial, most used gabapentin doses are between 300 and 600 mg, orally 1–2 h prior to surgery followed by 300–600 mg every 8 h, while the doses for pregabalin are between 50 and 100 mg, orally 1–2 h prior to surgery followed by 50–100 mg every 12 h.

Dexamethasone

A single intraoperative dose of dexamethasone provides excellent postoperative nausea and vomiting (PONV) prophylaxis and reduces postoperative pain [43, 44]. Large cohort studies and systematic reviews have reported that low-dose (8–10 mg, IV) dexamethasone does not increase the incidence of clinically significant hyperglycemia or delay wound healing [45–49], and intravenous dexamethasone has been shown to prolong regional block [50] and reduce breakthrough pain [51]. Therefore, a single intraoperative dose of dexamethasone 8–10 mg, IV is an important component of a multimodal analgesic regimen, unless contraindicated (e.g., presence of uncontrolled diabetes). Recent evidence suggests that relatively higher doses of corticosteroids enhance recovery [52, 53, 54•].

Ketamine

The analgesic effects of low-dose ketamine (0.5–1 mg/kg, IV bolus and/or continuous intraoperative infusion 0.1–0.2 mg/kg/h) are well-described in systematic reviews

and meta-analyses [55–57]. However, most studies are flawed because they did not include NSAIDs or COX-2-specific inhibitors, and thus, ketamine's benefits over these basic analgesics remain unknown. Also, even single low-dose ketamine is associated with postoperative hallucinations, nightmares, and sleep disturbances [58, 59]. Therefore, indiscriminate use of ketamine, particularly single bolus dose, should be avoided. Nevertheless, ketamine infusion may be appropriate in opioid-tolerant patients undergoing major surgery [56].

Dexmedetomidine

Several RCTs and meta-analyses have reported reduced pain scores and opioid requirements with dexmedetomidine infusion [60]. However, like ketamine, there are significant flaws in the RCTs, including lack of use of basic analgesics and variability in the dose and duration of administration. Also, dexmedetomidine has several potential adverse effects (e.g., hypotension and sedation) that might delay ambulation and rehabilitation [61•, 62, 63]. Given the controversial analgesic benefits and concerns of adverse effects, there is no role for dexmedetomidine infusion as a component of multimodal analgesia.

Lidocaine

Intraoperative intravenous lidocaine infusion (1–2 mg/kg bolus followed by 1–2 mg/kg/h infusion) has been shown to reduce postoperative pain and opioid requirements after abdominal surgery [64, 65•, 66], but not for other surgical procedures. In recent years, concerns have been raised regarding the potential for local anesthetic systemic toxicity (LAST) when lidocaine infusion is combined with regional analgesic techniques [67•], which are increasingly being used.

Magnesium

Several systematic reviews and meta-analyses have found reduced postoperative pain and opioid requirements with intraoperative intravenous magnesium infusion [68, 69]. However, like other analgesic adjuncts, the studies are flawed. More importantly, there are concerns of adverse effects such as arrhythmias, hypotension, and increased risk of residual paralysis which has been shown to increase postoperative pulmonary complications and hospital length of stay [24••].

Muscle Relaxants

Muscle relaxants represent a broad category of medications that are increasingly being used for perioperative pain to avoid opioids. Perioperative muscle relaxant use has poor evidence for improvement in postoperative pain relief and opioid consumption. Due to the lack of evidence of the analgesic efficacy and risk of sedation, falls, and delirium, particularly when combined with opioids, routine use of muscle relaxants is not recommended [70, 71].

Local/Regional Analgesia

Local/regional analgesia techniques are key components of an optimal multimodal analgesic regimen and should be used whenever possible [1••], with the choice of the local/regional technique depending on the type of surgical procedure. However, single-injection regional nerve blocks have a short duration of action with an abrupt termination of analgesia that could result in rebound pain [51, 72]. The duration of regional analgesia can be prolonged with the use of catheters that provide flexibility [73], but their use is limited due to the relative technical difficulty in placement and the need for resources [74•]. The use of additives (e.g., dexamethasone and clonidine) combined with local anesthetic solution may also aid in prolonging the duration of regional analgesia. Despite this, clonidine is often avoided because it can cause bradycardia and hypotension, and intravenous dexamethasone is preferred because it prolongs analgesia like perineural dexamethasone [50].

Epidural and paravertebral blocks provide excellent pain relief and are generally considered a standard of care for major open thoracoabdominal surgery [1••]. However, their use is declining because of the potential for delayed ambulation, and similar pain relief can be achieved with distal regional blocks (e.g., interfascial plane blocks and/or surgical site infiltration) [75•, 76]. Similarly, although intrathecal morphine provides excellent pain relief for about 24 h, its use is also declining because of the high risk/benefit ratio attributed to an increased potential for adverse effects (e.g., nausea, vomiting, pruritus, urinary retention, and respiratory depression) and rebound increase in postoperative opioid requirements [77].

In recent years, interfascial plane blocks (e.g., transversus abdominis plane blocks, serratus plane blocks, quadratus lumborum blocks, and erector spinae plane blocks) have increased in popularity because of their ease of performance and their ability to administer in the presence of venous thromboembolism prophylaxis [75•, 76, 78••]. While peripheral nerve blocks reduce postoperative pain and opioid requirements after extremity surgery [79], interfascial plane blocks are optimal for torso surgery (e.g., thoracic, and abdominal wall and intrathoracic and intra-abdominal surgery). In contrast to peripheral nerve blocks that have the potential for motor blockade (e.g., femoral nerve block), which can delay ambulation and rehabilitation

[1••], the interfascial plane blocks provide no motor blockade. Recently, cryoneurolysis (use of low temperatures to reversibly ablate a peripheral nerve) and percutaneous peripheral nerve stimulation have been proposed as alternatives for local anesthetic-based techniques [80•]. The benefits if these techniques include prolonged duration of action. However, the evidence of risks/benefits of these techniques is limited [81, 82].

Another rapidly evolving technique providing an alternative analgesic strategy that is easy to perform, safe, and inexpensive is surgical site infiltration [83, 84•]. In fact, the analgesic efficacy of surgical site infiltration may be like interfascial plane blocks, although the evidence is sparse. For effective surgical site infiltration, it is necessary to meticulously infiltrate all layers of the surgical wound under direct visualization prior to closure of the incision. Local anesthetic solutions that could be used include bupivacaine 150–200 mg or ropivacaine 200–400 mg diluted with preservative-free normal (0.9%) saline to a total volume depending upon the size of the incision. Although local anesthetic solutions are often combined with additives such as epinephrine (0.5 mg), morphine (5 mg), clonidine (100 mcg), ketorolac (30 mg), and steroids (methylprednisolone 40 mg), the evidence for their benefits is lacking [83, 84•, 85, 86].

Pragmatic Approach to Multimodal Pain Management

An optimal analgesic strategy would reduce pain intensity to an acceptable level to improve functionality and permit ambulation. The first step in formulating a strategy is to screen all patients for risk factors of severe and persistent postoperative pain (i.e., high pain responders) and persistent postoperative opioid use as well as risk factors for opioid misuse or the potential for opioid-related adverse events (e.g., respiratory depression due to obstructive sleep apnea, morbid obesity, and sedative medications) (Table 2) [87, 88]. Once identified, these risk factors should be addressed. For example, chronic pain conditions should be optimized, and pain flare caused by discontinuation of analgesics (e.g., NSAIDs or opioid weaning) prior to surgery should be avoided. If NSAIDs are discontinued, they could be replaced by COX-2-specific inhibitors to maintain adequate pain control. Patients on chronic opioids should be asked to continue their regularly prescribed opioids in the preoperative period, and patients with psychological disorders could receive coaching with regard to coping strategies and cognitive-behavioral therapy.

Patient and caregiver education is also an important component of a multimodal analgesic strategy because it will often reduce patient anxiety, improve pain control, and improve satisfaction [89, 90, 91•]. Patients and their caregivers should receive preoperative education, including possible options for pain management (both pharmacological and non-pharmacological) and their risks and benefits. Importantly, patients should be advised about the potential concerns with opioids and the importance of limiting their use. However, it is also important to emphasize that consuming opioids is appropriate if there is intolerable pain that is limiting function, and it is imperative to set realistic patient expectations regarding specific goals for adequate pain control. At discharge, patients and their caregivers should receive instructions that acetaminophen and NSAIDs/COX-2-specific inhibitors should be administered on a schedule even if there is no pain. Furthermore, patients with abnormal pain trajectory (i.e., persistent postoperative pain) or those with difficulty in weaning off opioids (i.e., persistent postoperative opioid use, and opioid use disorder) should be referred to a multidisciplinary transitional pain service [92]. Also, safe storage and proper disposal of opioids should always be emphasized.

The number and types of non-opioid analgesic combinations should depend upon patient characteristics and the surgical procedure (e.g., invasiveness, location, type [somatic versus visceral], and consequences of pain) [1••]. An ideal approach would match the analgesic technique with postoperative pain trajectory; however, the evidence for the best combinations for a particular patient

Table 2 Preoperative predictors of postoperative pain

- Presence of preoperative pain (preexisting chronic pain)
- Preoperative opioid use
- Preoperative medication assisted treatment (buprenorphine, methadone, naloxone)
- Substance use disorders
- Inappropriate patient expectations
- Inappropriate anxiety of surgical outcome
- Age and sex
- Psychological conditions (low self-esteem, severe anxiety, major depressive disorder, pain catastrophizing or hypervigilance [i.e., strong attention bias towards pain], functional pain states [e.g., fibromyalgia])
- Genetic variance in opioid receptors
- Acute opioid tolerance and opioid-induced hyperalgesia

undergoing a particular procedure is lacking. While optimal analgesic combinations remain elusive, unless there are contraindications, all patients should receive a combination of acetaminophen and NSAIDs or COX-2-specific inhibitors administered either preoperatively or intraoperatively and continued as scheduled dosing, postoperatively unless contraindicated. Considered as "basic analgesics," they have well-documented analgesic efficacy, and they are safe and inexpensive. Although at equipotent doses all NSAIDs and COX-2-specific inhibitors have similar efficacy, meloxicam may be preferred because it is administered once a day, improving patient compliance. Furthermore, meloxicam has greater affinity to COX-2 inhibition compared with COX-1 inhibition, like celecoxib. A single intraoperative dose of dexamethasone 8–10 mg, IV should be administered concomitantly with basic analgesics, unless there are contraindications.

All patients should receive surgical site infiltration and/or regional analgesia (interfacial plane block or peripheral nerve block) depending on the surgical procedure and site. Regional techniques should be performed preferably prior to surgery, while surgical site injections are performed at the end of the surgical procedure. If a regional block has not been performed prior to surgery, a rescue block may be administered if the patient has moderate-to-severe pain. The choice of regional analgesic technique requires several considerations. For example, even if an analgesic technique provides excellent pain relief (neuraxial blocks), it may not be clinically beneficial if the associated adverse events can delay ambulation. Similarly, although femoral nerve blocks and sciatic nerve blocks provide excellent pain relief after knee surgery, they can cause muscle weakness and delay ambulation and rehabilitation. Also, it is necessary to consider the balance between the intensity of postoperative pain and the invasiveness of the analgesic intervention. For example, even if epidural analgesia and intrathecal morphine provide excellent pain relief, they are unnecessary for laparoscopic procedures because postoperative pain can be managed adequately with basic analgesics. Patients receiving gabapentinoids preoperatively may continue them in the perioperative period; however, these drugs should be used with great caution and patients should be monitored for excessive sedation and respiratory depression. Other analgesic interventions (e.g., intravenous lidocaine and/or ketamine infusions) could be included only if basic analgesics, dexamethasone, and/or local/regional analgesia cannot be administered. Also, ketamine infusion may be appropriate in opioid-tolerant patients undergoing major surgery and when regional analgesia cannot be performed.

Intraoperative opioid doses should be reduced, but the role of opioid-free anesthesia remains controversial. In the acute postoperative period, opioids should be administered only as a rescue agent (i.e., when basic analgesics and local/regional analgesic techniques are insufficient in controlling pain) rather than as scheduled. Opioids should not be administered to achieve a specific pain score, but to improve patient comfort and postoperative function like ambulation and rehabilitation (e.g., deep breathing exercises and coughing after thoraco-abdominal surgery). The use of intravenous patient-controlled analgesia (IV-PCA) should be limited because pumps and tubing attached to the patient might impede early ambulation and rehabilitation, another critical component of enhanced recovery pathways. Patients complaining of severe pain that is limiting function may receive intravenous bolus doses of long-acting opioids (e.g., morphine, hydromorphone), while those with moderate pain could receive oral opioids, if appropriate. In fact, oral opioids should be preferred over parenteral opioids. This has become possible with the implementation of enhanced recovery pathways that emphasize early oral intake after surgery. Modified release (e.g., extended release) opioids should be avoided because they do not have any clinical benefits over immediate-release opioids and are associated with increased harm, including increased opioid-related adverse events such as opioid-induced ventilatory impairment and persistent postoperative opioid use, and increased hospital length of stay and readmission rates [93]. Postdischarge opioid prescription should be judicious, and caution should be exercised with older patients, patients with morbid obesity and/or obstructive sleep apnea, patients with significant unoptimized comorbid conditions, and those receiving other sedative medications (e.g., gabapentinoids, benzodiazepines, antihistamines, barbiturates) [94, 95••]. Limiting the opioid prescription should reduce the availability of opioids for diversion, and it is imperative that pharmacological approaches are supplemented with non-pharmacological techniques.

Future Consideration

Although the concept of multimodal analgesia is well-accepted, there are several areas of perioperative pain management where evidence is lacking or insufficient [96, 97]. There is a need to identify optimal patient- and procedure-specific analgesic combinations and duration of administration. The role of analgesic adjuncts (e.g., ketamine, lidocaine, dexmedetomidine) in supplementing best analgesic combinations (i.e., basic analgesics, dexamethasone, and local/regional analgesia) needs further investigation. In addition to assessing pain intensity at rest and movement-evoked pain and opioid consumption, it is necessary to measure procedure-specific functional outcomes (e.g.,

ability to ambulate or breathe deeply), psychological outcomes (e.g., psychological responses to pain experiences), and other patient-centered outcomes [98]. These outcomes should be evaluated for a prolonged period (e.g., up to one year). Resolution of pain (pain trajectory) and pain progression needs to be characterized. Also, it is necessary to report outcomes related to patient safety. Future research should include challenging patient populations (e.g., those at high risk of postoperative pain or postoperative persistent pain and persistent opioid use). It is necessary to understand the barriers to administering appropriate non-opioid analgesics (e.g., NSAIDs and regional analgesia) to all eligible patients. Non-pharmacological approaches to pain management could be used as adjuncts; however, further investigations addressing their cost-effectiveness are warranted to justify wider adoption.

Conclusions

Adequate pain management facilitates early ambulation and enhances patient recovery. Optimal pain management would be patient- and procedure-specific, initiated in the preoperative period and with identification and optimization of risk factors for severe and persistent postoperative pain as well as persistent postoperative opioid use. Patient education is imperative to improving postoperative pain control. Unless there are contraindications, all patients should receive basic analgesics (acetaminophen and NSAIDs or COX-2-specific inhibitors) supplemented with intraoperative dexamethasone and local/regional analgesia techniques (Table 3). Opioids should be administered as rescue on an "as needed" basis. Analgesic adjuncts such as intravenous ketamine and lidocaine infusion may be used in patients at high risk for postoperative pain or when basic analgesics are not able to be administered. In addition, non-pharmacological interventions should become a standard component of multimodal analgesia techniques. After discharge, patients with abnormal pain trajectory and those requiring high-dose opioids should have access to consultation with a pain specialist (transitional pain service). It is imperative to integrate multimodal analgesia regimens within a multidisciplinary enhanced recovery pathway [18]. This should improve postoperative recovery and facilitate transition from the anesthesiologist to the surgical team

Table 3 Optimal comprehensive multimodal analgesic strategy

Preoperative interventions
- Preoperative screening and optimization of high-risk patients
  - Severe postoperative pain (i.e., high pain responders), persistent postoperative pain, persistent postoperative opioid use, opioid misuse, and potential for opioid-related adverse events
- Patient and caregiver education
- Acetaminophen and COX-2-specific inhibitors, orally, unless contraindications
- Gabapentinoids (gabapentin or pregabalin): if receiving prior to surgery, caution in patients at risk of sedation and/or respiratory depression
- Regional analgesia techniques (procedure-specific and patient-specific)
  - Interfascial plane blocks: torso surgery (e.g., thoracic or abdominal wall and intrathoracic or intra-abdominal surgery)
  - Peripheral nerve blocks: major upper extremity and lower extremity surgery
  - Neuraxial analgesia (epidural analgesia or paravertebral blocks): high-risk patients undergoing open thoracic or open upper abdominal surgery, consider alternative regional analgesia technique, if possible
  - Intrathecal morphine: high-risk patients undergoing major lower limb surgery performed under spinal anesthesia, consider alternative regional analgesia technique, if possible

Intraoperative interventions
- Opioid-sparing (not opioid-free anesthesia)
- Acetaminophen and NSAIDs or COX-2-specific inhibitors, unless contraindications, if not administered preoperatively
- Analgesic adjuncts
  - Dexamethasone 8–10 mg, IV
  - Ketamine intravenous infusion: opioid-tolerant patients undergoing major surgical procedures associated with significant postoperative pain. No role for single bolus dose
  - Lidocaine intravenous infusion: open abdominal surgery when basic analgesics (e.g., acetaminophen and NSAIDs or COX-2-specific inhibitors) and regional analgesic techniques not used
  - Dexmedetomidine intravenous infusion: no role
  - Magnesium intravenous infusion: no role
- Surgical site local anesthetic infiltration: when possible

Postoperative interventions
- Acetaminophen and NSAIDs or COX-2-specific inhibitors, scheduled (round-the-clock)
- Gabapentinoids: if already receiving prior to surgery, caution in patients at risk of sedation and/or respiratory depression
- Opioids, immediate release, preferably oxycodone, as rescue (if needed)
- Non-pharmacological interventions (procedure-specific and patient-specific)
- Regional analgesia: as rescue, when appropriate

NSAIDs non-steroidal anti-inflammatory drugs, *COX-2-specific inhibitors* cyclooxygenase-2-specific inhibitors

and nurses on the ward, avoiding analgesic gaps. Finally, it is necessary to update analgesic regimens when new evidence becomes available.

Compliance with Ethical Standards

Conflict of Interest Received honoraria from Baxter International Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Joshi GP, Kehlet H. Postoperative pain management in the era of ERAS: an overview. Best Pract Res Anaestheisiol. 2019;33:259–67. **[Comprehensive review article].**
2. Gerbershagen HJ, Aduckathil S, van Wijck AJ, et al. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology. 2013;118:934–44.
3. Ladha KS, Patorno E, Huybrechts KF, et al. Variations in the use of perioperative multimodal analgesic therapy. Anesthesiology. 2016;124:837–45.
4. Joshi GP, Kehlet H. Procedure-specific pain management: the road to improve postsurgical pain management? Anesthesiology. 2013;118:780–2.
5. Joshi GP, Kehlet H, et al. Guidelines for perioperative pain management: need for re-evaluation. Br J Anaesth. 2017;119:703–6.
6. Kehlet H, Joshi GP. Systematic reviews and meta-analyses of randomized controlled trials on perioperative outcomes: an urgent need for critical reappraisal. Anesth Analg. 2015;121:1104–7.
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;17:131–57.
8. Hu QL, Dworsky JQ, Beck AC, et al. Perioperative pain management after ambulatory abdominal surgery: an American College of Surgeons systematic review. Ann Surg. 2020;231:572–601.
9. Mariano ER, Dickerson DM, Szokol JW, et al. A multisociety organizational consensus process to define guiding principles for acute perioperative pain management. Reg Anesth Pain Med. 2022;47:118–27.
10. Woolf CJ. Pain: moving from symptom control towards mechanism-specific pharmacologic management. Ann Int Med. 2004;140:441–51.
11. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg. 1993;77:1048–56.
12. Joshi GP. Multimodal analgesia techniques and postoperative rehabilitation. Anesthesiol Clin N Am. 2005;23:185–202.
13. Rosero EB, Joshi GP. Preemptive, preventive, multimodal analgesia: what do they really mean? Plast Reconstr Surg. 2014;134(4 Suppl 2):85S-93S.
14. Barker JC, Joshi GP, Janis JE. Basics and best practices of multimodal pain management for the plastic surgeon. Plast Reconstr Surg Glob Open. 2020;8:e2833.
15. Schoenbrunner AR, Joshi GP, Janis JE. Multimodal analgesia in the aesthetic plastic surgery: concepts and strategies. Plast Reconstr Surg Glob Open. 2022;10(5):e4310.
16. Investigators TNP. Effect of a postoperative multimodal opioid-sparing protocol vs standard opioid prescribing on postoperative opioid consumption after knee or shoulder arthroscopy a randomized clinical trial. JAMA. 2022;328:1326–35.
17. Petrikovets A, Sheyn D, Sun HH, et al. Multimodal opioid-sparing postoperative pain regimen compared with standard postoeprative pain regimen in vaginal pelvic reconstructive surgery: a multicenter randomized controlled trial. Am J Obstet Gynec. 2019;221(511):e1-10.
18. El-Boghdadly K, Jack JM, Heaney A, et al. Role of regional anesthesia and analgesia in enhanced recovery after colorectal surgery: a systematic review of randomized controlled trials. Reg Anesth Pain Med. 2022;47:282–92.
19. Fawcett WJ, Ljungqvist O, Lobo DN. Perioperative opioids-reclaiming lost ground. JAMA Surg. 2021;156:997–8.
20. Kharasch ED, Clark JD, Adams JM. Opioids and public health: the prescription opioid ecosystem and need for improved management. Anesthesiology. 2022;136:10–30.
21. Colvin LA, Bull F, Hales TG. Perioperative opioid analgesia–when is enough too much? A review of opioi-induced tolerance and hyperalgesia. Lancet. 2019;393:1558–68.
22. Alexander JC, Patel B, Joshi GP. Perioperative use of opioids: current controversies and concerns. Best Pract Res Clin Anaesthesiol. 2019;33:341–51.
23. Joshi GP. General anesthetic technique for enhanced recovery after surgery: current controversies. Best Pract Res Anaestheisiol. 2021;35:531–41.
24.•• Shanthanna H, Ladha K, Kehlet H, Joshi GP. Perioperative opioid administration: a critical review of opioid-free versus opioid-sparing approaches. Anesthesiology. 2021;134:645–59. **[Comprehensive narrative review on opioid-free anesthesia/analgesia].**
25. Freo U, Ruocco C, Valerio A, Scanol I, Nisoli E. Paracetamol: a review of guideline recommendations. J Clin Med. 2021;10:3420.
26. World Health Organization. WHO model list of essential medicines, 21st list. July 2019. https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06 (viewed February 2023).
27. Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effects of paracetamol, NSAIDs or their combination in postoperative pain management: a quantitative review. Br J Anaesth. 2002;88:199–214.
28. Ong CKS, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal anti-inflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg. 2010;110:1170–9.
29. Martinez V, Beloeil H, Marret E, et al. Non-opioid analgesics in adults after major surgery: systematic review with network meta-analysis of randomized trials. Br J Anaesth. 2017;118:22–31.
30. Thybo KH, Hagi-Pedersen D, Dahl JB, et al. Effect of combination of paracetamol (acetaminophen) and ibuprofen vs either alone on patient-controlled morphine consumption in the first 24 hours after total hip arthroplasty: the PANSAID Randomized Clinical Trial. JAMA. 2019;321:562–71.
31. Teng Y, Zhang Y, Li B. Intravenous versus oral acetaminophen as an adjunct on pain and recovery after total knee

arthroplasty: a systematic review and meta-analysis. J Med. 2020;99:e23515.
32.•• Bosch DJ, Nieuwenhuijs-Moeke GJ, van Meurs M, Struys MMRF. Immune modulatory effects of nonsteroidal anti-inflammatory drugs in the perioperative period and their consequence on postoperative outcome. Anesthesiology. 2022;136:843–60. **[A comprehenssive review article].**
33. EuroSurg Collaborative. Safety of non-steroidal anti-inflammatory drugs after colorectal surgery: centre-level analysis of the IMAGINE study. BJS. 2022; 1–3.
34. STARSurg Collaborative. Perioperative nonsteroidal anti-inflammatory drugs (NSAID) administration and acute kidney injury (AKI) in major gastrointestinal surgery. A prospective, multicenter, propensity matched cohort study. Ann Surg. 2022;275:904–10.
35. Chang RW, Tompkins DM, Cohn SM. Are NSAIDs Safe? Assessing the risk-benefit profile of nonsteroidal anti-inflammatory drug use in postoperative pain management. The Am Surg. 2021;87:872–9.
36.• Bongiovanni T, Lancaster E, Ledesma Y, et al. Systematic review and meta-analysis of the association between non-steroidal anti-inflammatory drugs and operative bleeding in the perioperative period. J Am Coll Surg. 2021;232:765–90. **[Meta-analysis reporting lack of bleeding complications with short-term NSAID use].**
37.• Verret M, Lauzier F, Zarychanski R, Canadian Perioperative Anesthesia Clinical Trials (PACT) Group, et al. Perioperative use of gabapentinoids for the management of postoperative acute pain: a systematic review and meta- analysis. Anesthesiology. 2020; 133:265–79. **[Meta-analysis showing lack of analgesic effects of gabapentinoids].**
38. Kharasch ED, Clark JD, Kheterpal S. Perioperative gabapentinoids: deflating the bubble. Anesthesiology. 2020;133:251–4.
39.• Joshi GP, Kehlet H. Meta-analyses of gabapentinoids for pain management after knee arthroplasty-a caveat emptor? A narrative review Acta Anaesthesiol Scand. 2021;65:865–9. **[Critical analysis of meta-analyses of gabapentinoids for management of pain after total knee arthroplasty].**
40. American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67:674–94.
41. Bykov K, Bateman BT, Franklin JM, Vine SM, Patorno E. Association of gabapentinoids with the risk of opioid-related adverse events in surgical patients in the United States. JAMA Netw Open. 2020;3:e2031647.
42.• Park CM, Inouye SK, Marcantonio ER, Metzger E, Bateman BT, Lie JJ, et al. Perioperative gabapentin use and in-hospital adverse clinical events among older adults after major surgery. JAMA Intern Med. 2022;182:1117–27. **[Study showing increased adverse effects of gabapentinoids in older patients].**
43. De Oliveira GS Jr, Almeida MD, Benzon HT, et al. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2011;115:575–88.
44. Waldron NH, Jones CA, Gan TJ, et al. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth. 2013;110:191–200.
45. Herbst RA, Telford OT, Hunting J, et al. The effects of perioperative dexamethasone on glycemic control and postoperative outcomes. Endocr Pract. 2020;26:218–25.
46. Toner AJ, Ganeshanathan V, Chan MT, et al. Safety of perioperative glucocorticoids in elective noncardiac surgery: a systematic review and meta-analysis. Anesthesiology. 2017;126:234–48.
47. Asehnoune K, Le Moal C, Lebuffe G, et al. Effect of dexamethasone on complications or all cause mortality after major non-cardiac surgery: multicentre, double blind, randomised controlled trial. BMJ. 2021;373:n1162.
48. Corcoran TB, Myles PS, Forbes AB, et al. Dexamethasone and surgical-site infection. N Engl J Med. 2021;384:1731–41.
49. Feeley AA, Feeley TB, Feeley IH, et al. Postoperative infection risk in total joint arthroplasty after perioperative IV corticosteroid administration: a systematic review and meta-analysis of comparative studies. J Arthroplasty. 2021;36:3042–53.
50. Baeriswyl M, Kirkham KR, Jacot-Guillarmod A, et al. Efficacy of perineural vs systemic dexamethasone to prolong analgesia after peripheral nerve block: a systematic review and meta-analysis. Br J Anaesth. 2017;119:183–91.
51. Barry GS, Bailey JG, Sardinha J, Brousseau P, Uppal V. Factors associated with rebound pain after peripheral nerve block for ambulatory surgery. Br J Anaesth. 2021;126:862–71.
52. Kehlet H, Lindberg-Larsen V. High-dose glucocorticoid before hip and knee arthroplasty: to use or not to use-that's the question. Acta Orthop. 2018;89:477–9.
53. Jorgensen CC, Pitter FT, Kehlet H, Lundbeck Foundation Center for Fast- track H, Knee Replacement Collaborative Group. Safety aspects of preoperative high-dose glucocorticoid in primary total knee replacement. Br J Anaesth. 2017;119:267–75.
54.• Nielsen NI, Kehlet H, Gromov K, et al. High-dose steroids in high pain responders undergoing total knee arthroplasty: a randomized double-blind trial. Br J Anaesth. 2022;128:150–8. **[A study showing benefits of high dose steroids].**
55. Brinck ECV, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, et al. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane Database Syst Rev. 2018;(12):CD012033.
56. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43:456–66.
57. Zeballos JL, Lirk P, Rathmell JP. Low-dose ketamine for acute pain management: a timely nudge toward multimodal analgesia. Reg Anesth Pain Med. 2018;43:453–5.
58. Avidan MS, Maybrier HR, Abdallah AB, et al. 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.
59. Vlisides PE, Bel-Bahar T, Nelson A, et al. Subanaesthetic ketamine and altered status of consciousness in humnas. Br J Anaesth. 2018;121:249–59.
60. Kaye AD, Chernobylsky DJ, Thakur P, et al. Dexmedetomidine in enhanced recovery after surgery (ERAS) protocols for postoperative pain. Curr Pain Headache Rep. 2020;24:21.
61.• Demiri M, Antunes T, Fletcher D, Martinez V. Perioperative adverse events attributed to a2-adrenoceptor agonists in patients not at risk of cardiovascular events: systematic review and meta-analysis. Br J Anaesth. 2019;123:795–807. **[Meta-analysis suggesting significant cardiovascular complications with intraoperative use of dexmedetomidine].**
62. Lodenius A, Maddison KJ, Lawther BK, et al. Upper airway collapsibility during dexmedetomidine and propofol sedation in healthy volunteers: a nonblinded randomized crossover study. Anesthesiology. 2019;131:962–73.
63. Edokpolo LU, Mastriano DJ, Serafin J, et al. Discharge readiness after propofol with or without dexmedetomidine for colonoscopy: a randomized controlled trial. Anesthesiology. 2019;13:279–86.
64. Weibel S, Jelting Y, Pace NL, Helf A, Eberhart LHJ, Hahnenkamp K, et al. Continuous intravenous perioperative lidocaine infusion

for postoperative pain and recovery in adults. Cochrane Database Syst Rev. 2018;(6):CD009642.

65.• Foo I, Macfarlane AJR, Srivastava D, et al. The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety. Anaesthesia. 2021;76:238–50. **[Guidelines for perioperative use of lidocaine infusion].**

66. Shanthanna H, Weinberg G. Intravenous lidocaine, regional blockade, or both: considerations for multiple interventions involving local anaesthetics. Br J Anaesth. 2021;127:497–501.

67.• Pandit JJ, McGuire N. Unlicensed intravenous lidocaine for postoperative pain: always a safer 'licence to stop' than to start. Anaesthesia. 2021;76:156–60. **[Article emphasizing caution with the use of perioperative lidocaine infusion].**

68. Rodriguez-Rubio L, Nava E, Del Pozo JSG, et al. Influence of the perioperative administration of magnesium sulfate on the total dose of anesthetics during general anesthesia. A systematic review and meta-analysis. J Clin Anesth. 2017;39:129–38.

69. Bujalska-Zadrozny M, Tatarkiewicz J, Kulik K, et al. Magnesium enhances opioid-induced analgesia - what we have learnt in the past decades? Eur J Pharm Sci. 2017;99:113–27.

70. Al Yafi MN, ElHawary H, Al-Halabi B, et al. Pain control following alloplastic breast reconstruction with muscle relaxant: a randomized controlled trial. J Plast Reconstr Aesthet Surg. 2021;74:407–47.

71. Li Y, Delcher C, Wei YJJ, et al. Risk of opioid overdose associated with concomitant use of opioids and skeletal muscle relaxants: a population-based cohort study. Clin Pharmacol Ther. 2020;108:81–9.

72. Lavand'homme P. Rebound pain after regional anesthesia in the ambulatory patient. Curr Opin Anaesthesiol. 2018;31:679–84.

73. Ilfeld BM. Continuous peripheral nerve blocks: an update of the published evidence and comparison with novel, alternative analgesic modalities. Anesth Analg. 2017;124:308–35.

74.• Hauritz RW, Hannig KE, Balocco AL, et al. Peripheral nerve catheters: a critical review of the efficacy. Best Prac Res Clin Anesthesiol. 2019;33:325–39. **[Critical assessment of the analgesic efficacy and limitations of peripheral nerve catheters].**

75.• Machi A, Joshi GP. Interfascial plane blocks. Best Pract Res Clin Anaesthesiol. 2019;33:303–15. **[Comprehensive review of interfacial plane blocks].**

76. ElHawary H, Joshi GP, Janis JE. Practical review of abdominal and breast regional analgesia for plastic surgeons: evidence and techniques. Plast Reconstr Surg Glob Open. 2020;8:e3224.

77. Olive DJ, Barrington MJ, Simone SA, et al. A randomised controlled trial comparing three analgesia regimens following total knee joint replacement: continuous femoral nerve block, intrathecal morphine or both. Anaesth Intensive Care. 2015;43:454–60.

78.•• Kietaibl S, Ferrandis R, Godier A, Llau J, Lobo C, Macfarlane AJR, et al. Regional anaesthesia in patients on antithrombotic drugs Joint ESAIC/ESRA guidelines. Eur J Anaesthesiol. 2022;39:100–32. **[Guidelines for regional anesthesia in patients on antithrombotic drugs].**

79. Joshi GP, Gandhi G, Shah N, et al. Peripheral nerve blocks in the management of postoperative pain: challenges and opportunities. J Clin Anesth. 2016;35:524–9.

80.• Ilfeld BM, Finneran JJ. Cryoneurolysis and percutaneous peripheral nerve stimulation to treat acute pain: a narrative review. Anesthesiology. 2020;133:1127–49. **[Comprehensive review of cryoneurolysis and percutaneous peripheral nerve stimulation].**

81. Ilfeld BM, Finneran JJ, Swisher MW, et al. Preoperative ultrasound-guided percutaneous cryoneurolysis for the treatment of pain after mastectomy: a randomized, participant- and observer-masked, sham-controlled study. Anesthesiology. 2022;137:529–42.

82. Rathmell JP, Forrester JD, Schreiber K. Cryoneurolysis: Interest and caution. Anesthesiology. 2022;137:521–3.

83. Joshi GP, Haas E, Janis J, Ramshaw BJ, Nihira MA, Dunkin BJ. Surgical site infiltration for abdominal surgery: a novel neuroanatomical-based approach. Plastic Reconstructive Surg Global Open. 2016;4: e1181.

84.• Joshi GP, Machi A. Surgical site infiltration: a neuroanatomical approach. Best Pract Res Clin Anaesthesiol. 2019;33:317–24. **[Comprehensive review of surgical site infiltration].**

85. Lavand'homme PM, Kehlet H, Rawal N, Joshi GP, PROSPECT Working Group of the European Society of Regional Anaesthesia and Pain Therapy (ESRA). Pain management after total knee arthroplasty: procedure specific postoperative pain management recommendations. Eur J Anaesthesiol. 2022;39:743–57.

86. Munoz-Leyva F, Jack JM, Bhatia A, et al. No benefits of adding dexmedetomidine, ketamine, dexamethasone, and nerve blocks to an established multimodal analgesic regimen after total knee arthroplasty. Anesthesiology. 2022;137:459–70.

87. Yang MMH, Hartley RL, Leung AA, et al. Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis. BMJ Open. 2019;9:e025091.

88. Coppes OJM, Yong RJ, Kaye AD, et al. Patient and surgery-related predictors of acute postoperative pain. Curr Pain Headache Rep. 2020;24:1–8.

89. Lee BH, Wu CL. Educating patients regarding pain management and safe opioid use after surgery: a narrative review. Anesth Analg. 2020;130:574–81.

90. Horn A, Kaneshiro K, Tsui BCH. Preemptive and preventive pain psychoeducation and its potential application as a multimodal perioperative pain control option: a systematic review. Anesth Analg. 2020;130:559–73.

91.• Aglio LS, Mezzalira E, Mendez-Pino L, et al. Surgical prehabilitation: strategies and psychological intervention to reduce postoperative pain and opioid use. Anesth Analg. 2022;134:1106–11. **[Comprehensive review pain prehabilitaion].**

92. Admiral M, Hermanides J, Meinsma SL, et al. Current multidisciplinary approaches to preventing chronic postoperative pain. Br J Anaesth. 2021;127:331–5.

93. Quinlan J, Levy N, Lobo DN, Macintyre PE. No place for routine use of modified-release opioids in postoperative pain management. Br J Anaesth. 2022;129:290–3.

94. Overton HN, Hanna MN, Bruhn WE, et al. Opioid-prescribing guidelines for common surgical procedures: an expert panel consensus. J Am Coll Surg. 2018;227:411–8.

95.•• Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain — United States, 2022. MMWR Recomm Rep. 2022;71:1–95. **[Guidelines for opioid prescription for pain].**

96. Gilron I, Kehlet H, Pogatzki-Zahn E. Current status and future directions of pain-related outcome measures for post-surgical pain trials. Can J Pain. 2019;3:36–43.

97. Gilron I, Carr DB, Desjardins PJ, Kehlet H. Current methods and challenges for acute pain clinical trials. Pain Reports. 2019;4:e647.

98. Pogatzki-Zahn E, Schnaber K, Kaiser U. Patient-reported outcome measures for acute and chronic pain: current knowledge and future directions. Curr Opin Anesthesiol. 2019;32:616–22.