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Perioperative use of opioids: Current controversies and concerns

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In the midst of an epidemic of opioid abuse and overdose-related morbidity and mortality, the use of opioids remains the most common means of providing analgesia in the perioperative period. In this article, we review the risks and benefits of opioid use in preoperative, intraoperative and post-operative phases of care. Furthermore, we describe the role that surgeons and anaesthesiologists can play in reducing perioperative opioid use and mitigate their adverse effects, from both an individual and a population health perspective.

Introduction

Opioids are commonly used in the perioperative period including during general anaesthesia to supplement sedation during regional anaesthesia and for treatment of acute pain in the post-operative period. Despite a wide range of benefits, opioids also have a well-described adverse effect profile that may delay recovery and return to activities of daily living. Furthermore, the increasing rate of opioid consumption and misuse in the United States has reached epidemic status in the past decade.

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Therefore, the role of opioid use in the perioperative period is being questioned. In this article, we discuss the current controversies and concerns and provide the optimal approach to opioid use in the perioperative period.

Opioid-related adverse events

Opioid-related adverse events most notably include respiratory depression, pruritus, ileus, nausea, vomiting, urinary retention and constipation [1–4]. The synergistic effect of opioids with sedative-hypnotic agents allows for lower doses of each drug, but this synergism can also exacerbate their hypotensive effect if drug dosage is not reduced [5]. Furthermore, the respiratory depressive effects of opioids can negatively impact attempts to maintain spontaneous ventilation in the anaesthetised patient and/or contribute to delayed emergence and tracheal extubation [6,7]. Some less common risks of intraoperative opioid use include bradycardia [8,9] and chest wall rigidity [10–12]. The development of opioid-related adverse effects may require use of opioid antagonists such as naloxone, which can be carefully titrated to reverse adverse effects while partially preserving analgesic effects. Rapid and complete reversal of opioid-mediated analgesia can result in sympathetic stimulation, resulting in hypertension, tachycardia, myocardial ischaemia or pulmonary oedema [13].

Another adverse effect of opioids is related to the potential for development of opioid-induced hyperalgesia (OIH). This phenomenon is characterised by greater than expected sensitivity to painful stimuli, or even a paradoxical allodynic response, in response to opioid administration [14–16]. While OIH has been most thoroughly described with high-dose intraoperative remifentanil infusions [17–19], it is possible with other opioids and outside the intraoperative period. Animal studies have indicated that preoperative and intraoperative morphine exposure can prolong post-operative pain [20]. One study showed that patients on chronic opioid therapy, when compared with opioid-naïve patients, displayed greater preoperative hyperalgesic responses as well as greater post-operative pain intensity and opioid consumption [21]. Given this, some have advocated for preoperative opioid weaning to improve perioperative analgesia and decrease the risk of persistent post-operative opioid use [22]. Other ameliorating factors for the development of OIH include gradual (rather than abrupt) withdrawal of remifentanil infusion [23]; maintenance of anaesthesia with propofol-based TIVA rather than inhalational anaesthetics [24,25] and perioperative use of co-analgesics such as ketamine [26,27], non-steroidal anti-inflammatory drugs (NSAIDs) [28], beta-adrenergic receptor antagonists (e.g. propranolol) [29], clonidine [30], naloxone [31] and nitrous oxide [32].

Tolerance is a phenomenon whereby administration of opioids has a diminishing effect, which can occur with both acute and chronic use [33]. Unlike OIH, tolerance can be overcome with higher doses, although the risk of opioid-related adverse effects is elevated [34–36]. Patients can also present to the operating room with acute opioid intoxication. While these patients tend to have lower anaesthetic requirements due to the concurrent intoxication, they also have an elevated risk of developing dose-dependent opioid-related adverse effects if additional opioids are utilised in the intraoperative period.

Overview of opioid use in the preoperative phase

Preoperative opioid use, misuse or abuse is associated with increased post-operative mortality and morbidity, which can increase length of hospital stay, 30-day readmission and health care expenditures [37–40]. Preoperative opioid use appears to be the strongest predictor of persistent post-operative pain [41]. In contrast, weaning opioids before surgery improves post-operative pain and other outcomes [42,43].

Given the myriad of opioid-related adverse effects and poor outcomes associated with their use, it is recommended that this population undergo analgesic planning beginning in the preoperative phase of care and utilise multiple pharmacologic and non-pharmacologic modalities throughout the perioperative period to address pain [44]. To this end, novel concepts such as the “transitional pain service” have been implemented by some institutions to provide coordinated, integrated analgesic care for this high-risk population [45].

Preoperative analgesics are sometimes used in an attempt to modulate the nociceptive response before the nociceptive stimulus. Preoperative opioid administration showed either no benefit or

worsened outcomes [46,47]. Thus, preoperative opioid administration is not recommended. Similarly, the use of long-acting or controlled-release opioids for acute pain is not recommended; hence, their use in the preoperative phase should be avoided [44,48,49]. Nevertheless, low-dose opioids (25–50 μg) are sometimes given if patients have immediate preoperative pain or are undergoing a pre-induction procedure, such as regional blocks.

Overview of opioid use in the intraoperative phase

Opioids are a commonly used adjuvant during induction of general anaesthesia to mitigate unwanted hyperdynamic responses (i.e. tachycardia and/or hypertension) to laryngoscopy and tracheal intubation. In addition, an opioid administered 3–5 min before induction reduces the dose of sedative-hypnotics (e.g. propofol) [50]. Opioids can also blunt cough/gag reflexes during airway manipulation [51–53].

Careful titration of remifentanil has been used to assist in awake fibre-optic tracheal intubation to suppress airway reflexes and pain from intubation while maintaining spontaneous ventilation and allowing the patient to remain awake and able to follow commands [52,53]. Use of this technique is primarily limited by the respiratory depressant effect of remifentanil. Occasionally, high-dose remifentanil (3–5 μg/kg) has been used to avoid the use of a muscle relaxant, if the clinical scenario requires such management [54,55]. However, this approach is limited by development of hypotension during induction.

During general anaesthetic maintenance, opioids are mainly used as an adjuvant to attenuate the autonomic response to surgical stimulation [56–61] and reduce the sedative-hypnotic requirements [5,62,63]. Most often, delivery of opioids during this phase is through intermittent bolus, but a continuous infusion of an ultra-short-acting opioid (i.e. remifentanil) is also utilised, especially in TIVA techniques. Reduced sedative-hypnotic dose from opioid use contributes to more rapid emergence [64]. During emergence from general anaesthesia, shorter acting opioids (e.g. fentanyl or remifentanil) are often given in smaller boluses to provide analgesia and blunt airway reflexes without ablating spontaneous ventilation. In certain scenarios, avoidance of elevated intracranial or intraocular pressure is paramount; hence, a low-dose remifentanil infusion can be used to allow the patient to emerge from general anaesthesia and follow commands before the return of airway reflexes, resulting in an atraumatic extubation [65]. In addition, longer acting opioids (e.g. morphine or hydromorphone) may be administered to provide longer duration of analgesia in the immediate post-operative period.

Intraoperative opioid selection and dosing

Selection of the ideal opioid and dose depends on several factors including the intended use, desired speed of onset/offset, procedure-specific factors (e.g. anticipated duration of surgery and anticipated pain from surgery), patient-specific factors (e.g. age, comorbidities, opioid tolerance) and whether other anaesthetics or analgesics are co-administered.

Given that many of the adverse effects of opioids tend to be dose-related, it is necessary to limit intraoperative opioid dosing (i.e. opioid-sparing approach). This approach includes using lower opioid doses (e.g. fentanyl 0.5–1 μg/kg) at induction of anaesthesia. Of note, there is no role for 'opioid loading' (i.e. use of larger opioid doses) at induction of anaesthesia. In addition, care should be taken to dose opioids based on ideal body weight and consideration of other factors that may impact opioid effects. For example, elderly patients or those with renal or hepatic dysfunction should be given relatively lower doses of opioids, while patients with opioid tolerance due to chronic use may require relatively higher doses. Higher opioid doses are used in patients with impaired myocardial function because they have a relatively little direct myocardial depression, and the blunted airway reflexes and diminished sympathetic stimulation can help maintain haemodynamics during airway manipulation. Despite this benefit, however, other approaches should be used (e.g. use of esmolol) to avoid opioid-related adverse events and OIH.

Intraoperative opioid reduction strategies

Given the concerns of opioid-related adverse events, several efforts have been made to find a way to maintain adequate anti-nociception/analgesia while decreasing use of opioids throughout the

perioperative period. Such efforts, termed multimodal or balanced analgesia, have utilised multiple non-opioid analgesics or techniques. Perioperative analgesic alternatives to opioids include use of regional analgesia and non-opioid analgesics such as paracetamol (or acetaminophen), NSAIDs, dexamethasone and beta-adrenergic receptor antagonists (e.g. esmolol) [66–71]. These opioid-sparing techniques have been shown to be superior to opioid-only techniques [66] but remain woefully underutilised in clinical practice despite substantial literature supporting its use [72]. Furthermore, it is necessary to differentiate intraoperative hyperdynamic response from reasons other than pain (e.g. high intra-abdominal pressures during laparoscopy), which should not be treated with opioids.

Given the evidentiary success of opioid-sparing analgesia efforts, the desire to avoid the perioperative adverse effects of opioids and the growing concern that perioperative opioid use contributes to persistent post-operative opioid use, some have advocated to completely eliminate opioid use, particularly within the intraoperative phase of care. The ultimate goal is to avoid the short-term opioid-related adverse effects, as well as to reduce opioid dependence, addiction and overdose by never exposing patients to opioids in the first place. Such efforts have been labelled 'opioid-free anaesthesia' and tend to more extensively utilise analgesic adjuncts such as dexmedetomidine, ketamine, magnesium and lidocaine infusions [72,73]. Despite the intuitively beneficial effect, there remains significant controversy over the need for and feasibility of opioid-free anaesthesia for most surgical procedures with our current analgesic options [74]. Furthermore, there are concerns of adverse effects of analgesic adjuncts used to replace opioids. Currently, there seems to be consensus that, in addition to maximising use of multimodal analgesic options, it is best practice to use the lowest dose of opioid (opioid-sparing approach) for the shortest duration of time that is necessary to provide adequate pain control [72,74,75].

Nociception monitors

Pain is defined as an 'unpleasant sensory and emotional experience' [76], but the anaesthetised patient has no emotional experience, which begs the question whether it is possible to experience pain during general anaesthesia. Thus, it is more accurate to state that during the intraoperative period, anaesthesiologists work to ameliorate nociception, the physiological transduction of noxious stimuli in the peripheral and central nervous system. While the subjective experience of pain is difficult to assess in the conscious patient, it is that much more difficult for anaesthesiologists to discern the level of nociception in the anaesthetised patient. Given that this assessment will drive the intraoperative use of opioids, there has been significant effort to find a more accurate and objective way to determine the degree of nociception present intraoperatively.

Current efforts to assess intraoperative nociception rely on proxy metrics of nociception, as there are currently no known ways to measure nociception [77]. As nociception induces increased sympathetic tone relative to parasympathetic tone, most purported nociceptive monitors aim to quantify the balance of these autonomic systems as a proxy measure of nociception [78]. One such proxy is skin conductance, as sympathetic stimulation induces sweating, which will lower electrical conductance due to the salt content of sweat [78], but studies have casted doubt as to whether it is a sufficiently accurate measure of nociception in anaesthetised adults [79].

As an increased sympathetic tone will lead to peripheral vasoconstriction, another monitor assesses variability of the pulse wave amplitude of photoplethysmography (PPG) used for pulse oximetry as well as heart rate variability to create a surgical stress index (SSI) or surgical Pleth index (SPI) and is a dimensionless scale rated from 0 to 100 [80,81]. It has been shown that the SSI/SPI increases in response to nociceptive stimulation [82], although not if the site of stimulation is in the distribution of a regional anaesthetic block [83], and SSI/SPI decreases after administration of opioids [84].

Another nociceptive monitor that has shown promising results is the pupillary pain index (PPI), which measures pupillary reflex dilation as a response to tetanic stimulation under the assumption that nociception from tetany will cause a pupillary response [85]. Another promising option is the Analgesia Nociception Index (ANI), which measures heart rate (HR) variability with respiration and provides a dimensionless scale of 0–100. This measurement is somewhat unique compared to other nociceptor monitors, as this physiological measurement is parasympathetically driven; thus, a nociceptive stimulus will result in a higher sympathetic tone relative to the parasympathetic tone and a

higher score. Thus, a higher ANI score indicates lower levels of nociception. Intraoperative ANI use has been shown to reduce pain in the immediate post-operative period without changing overall intraoperative opioid use, which is thought to be due to better matching of fentanyl dosing to nociceptive surgical stimulation [86]. The nociception level (NoL) index uses multiple measurements, including HR, HR variability, PPG wave amplitude, skin conductance and skin conductance fluctuations to assess intraoperative nociception and has shown promise in distinguishing between noxious and non-noxious stimuli, as well as a stronger response to more intense stimuli and a blunted response with analgesic administration [87]. Overall, presently, all the nociceptive monitors seem to have limitations, and thus, their routine use remains questionable.

Overview of opioid use in the acute post-operative phase (<30 days)

In the immediate post-operative period (i.e. in the post-anaesthesia care unit), patients complaining of intolerable pain should receive incremental doses of longer acting opioid (e.g. morphine or hydromorphone) assuming that the patient has received non-opioid analgesics either preoperatively or intraoperatively. In addition, a rescue regional analgesic block may be performed, if not done in the preoperative or intraoperative period. In the era of enhanced recovery after surgery approach, opioids may be administered orally if the pain is not severe. In addition, the use of intravenous patient-controlled analgesia (IV-PCA) with opioid is generally avoided because infusion pumps and tubing may make ambulation difficult. Therefore, patients may receive oral opioids for a moderate degree of pain and intravenous bolus doses for a severe degree of pain. It is imperative that non-opioid analgesics be administered continuously.

During the acute post-operative phase, analgesic management tends to transition from the anaesthesiologist to the surgical team as the patient moves away from the operating room environment to convalesce, whether in another healthcare setting or at home. In either case, this is a key time in which decisions regarding analgesic management can have far-reaching effects related to persistent post-operative pain and opioid use [39,40].

Several studies have shown wide variability among surgeons in the perioperative prescription of opioids, and there is a growing realisation that better management of this variability represents an opportunity to provide a public health benefit to the entire population by limiting the supply of opioids available for diversion without compromising post-operative analgesia for individual patients [88–91]. Recall that while most opioid-overdose-related deaths are due to heroin (with or without fentanyl-analogues) [91–94], most heroin users initially became dependent on prescription opioids [95]. Many patients also use only a fraction of the prescribed post-operative opioids; hence, the remaining opioids represent an immense reservoir available for diversion from the initial intended use [96–98]. System-level movement towards more conservative opioid-prescribing guidelines for acute pain conditions can decrease opioid utilisation without compromising analgesia [99,100]. Surgeons have also begun to advocate for procedure-specific opioid-prescribing guidelines to provide sufficient post-operative analgesia while limiting the opioid supply in the population available for diversion [101–103]. There is concern that poorly controlled acute post-operative pain can hasten the transition to chronic pain conditions and persistent post-operative opioid use [104–106]; therefore, it is imperative to balance the desire to limit opioid supply with the need to provide adequate analgesia.

For the anaesthesiologist, use of opioid-sparing (or even opioid-free), multimodal analgesic techniques can help contribute to this goal. Surgeons should take note that such techniques, especially regional anaesthesia, may require more time in the immediate preoperative period but will create outsized benefits for their patients in the post-operative period [107,108]. In addition, surgeons should strive to extend the use of multimodal analgesic practices in their post-operative analgesic plans. This may help to achieve the goal of using the lowest dose of opioid for the shortest duration necessary to establish adequate analgesia. It has been shown that even after implementation of procedure-specific post-operative opioid-prescribing guidelines, patients do not frequently require refills of such medications [102,109,110] and often have remaining opioids [111]. This may assuage the concerns of surgeons that patients will frequently request further refills of opioid analgesics due to inadequate analgesia. Another study used a shared decision-making process between surgeons and patients to guide opioid prescribing after caesarean delivery and resulted in a 50% reduction in prescribed post-

operative opioids [112]. In addition, pre- and post-operative teaching for patients regarding the risks of opioids and to reframe patients' expectations regarding post-operative pain have been shown to contribute to better overall patient outcomes [91,113]. Educational efforts have also been effective in increasing patient disposal of unused post-operative opioids [114] but are rarely implemented [96–98,115]. Institutions have also taken initiatives to assist with reducing opioid dispensing by setting up opioid educational programs before surgery. An inter-professional approach in reducing post-operative use was a consistent theme seen among studies noting interventions by physicians, nursing staff, pharmacists and physical therapists [116]. Some states have begun to mandate such educational efforts [117].

Overview of opioid use in the transitional post-operative phase (30–180 days)

Chronic pain is defined as pain that persists beyond the expected healing time related to acute pain related to tissue injury [104]. In post-surgical patients, it is thought to occur in up to 10% of patients after certain operations [118]. Given the scope of the problem, chronic post-surgical pain (CPSP) will be included as a diagnosis for ICD-11 to better define and track this as a surgical outcome at a population level [119,120].

Although we have an incomplete understanding of why some patients develop CPSP while others do not, some risk factors are evident. These include severity of acute post-operative pain, presence of preoperative pain and psychosocial factors such as depression, anxiety or catastrophising attitudes [105]. In addition, surgical factors such as procedure length, more invasive surgical techniques and intraoperative nerve injury may contribute to CPSP [104,106]. With regard to anaesthetic factors, it is concerning that OIH may contribute to the development of CPSP while use of multimodal analgesia and regional anaesthesia techniques is thought to be protective but not completely preventative [105].

One novel potential solution is the creation of the transitional pain service, a multidisciplinary team committed to co-ordinating care for patients at high risk for CPSP. Such teams use both pre- and post-operative interventions to manage the analgesic plan, especially with regard to opioid use, and also incorporate psychosocial training to try to mitigate the transition from acute post-operative pain to CPSP [45]. Creation of such services would, of course, require substantial buy-in from multiple stakeholders across a health system, from primary care physicians, anaesthesiologists, surgical services, nursing staff and hospital administrators. Early case reports have shown substantial improvement in specific cases [121,122], but no long-term outcome data have been published to date showing use of transitional pain services to decrease the development of CPSP.

Practice points

- Opioids are the mainstay of treatment for perioperative pain; however, use of higher opioid doses during the perioperative period has been associated with greater length of hospital stay, 30-day readmission rate and overall cost of care.
- Opioids have a place in the perioperative care of patients, but there is a need to balance adequate post-operative pain control and mitigate adverse opioid-related health effects.
- The first step in reducing intraoperative opioid use starts with reducing the opioid dose during induction of general anaesthesia and avoiding the use of opioids to treat hyperdynamic responses due to reasons other than pain as well as use of non-opioid multimodal analgesic techniques.
- In the immediate post-operative period, opioids should be used at the lowest dose for the shortest possible time to obtain adequate analgesia and in conjunction with other non-opioid analgesic analgesics (e.g. paracetamol and NSAIDs).
- More widespread utilisation of procedure-specific post-operative opioid dosing guidelines by surgeons may be the low hanging fruit' to reduce persistent post-operative opioid use and reduce the supply of opioids available for diversion.

Research agenda

- Further research is needed to further elucidate the hyperalgesic and central sensitisation effects of opioids and strategies for mitigation of this process.
- Properly designed studies are necessary to confirm the long-term effects of opioids (e.g. higher 30-day readmission rates) observed in observational trials.
- Clinical research efforts should continue to validate procedure-specific multimodal analgesic strategies to further reduce perioperative opioid use while maintaining adequate analgesia.
- The usefulness of nociceptive monitors in reducing intraoperative opioid dosing needs further study.
- Collaboration with surgical colleagues should be pursued to create, study and validate procedure-specific analgesic plans that include the dose, frequency and duration of post-operative opioid prescriptions.

Summary

As knowledge of the range and magnitude of opioid-related adverse effects has grown, so has an effort to identify strategies to mitigate those effects. Aside from the acute adverse effect profile, such as respiratory depression, nausea, vomiting, ileus, delirium and others, we have become aware that our intraoperative use of opioids may contribute to post-operative pain and persistent opioid use. Therefore, it is imperative that intraoperative opioid doses are limited. The first step is to reduce the opioid dose administered during induction of anaesthesia. In addition, use of non-opioid analgesics in the preoperative and/or intraoperative period should further reduce opioid requirements. Moreover, because opioids are typically administered based on haemodynamic parameters (i.e. increased heart rate and/or blood pressure), opioids should administered only after eliminating other causes of hyperdynamic response. In the post-operative period, greater use of opioids may lead to worsened post-operative pain, but undertreatment of pain may also lead to persistent pain.

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References

[1] Wheeler M, Oderda GM, Ashburn MA, et al. Adverse events associated with postoperative opioid analgesia: a systematic review. J Pain 2002;3:159–80.
[2] Zhao SZ, Chung F, Hanna DB, et al. Dose-response relationship between opioid use and adverse effects after ambulatory surgery. J Pain Symptom Manag 2004;28:35–46.
[3] Oderda GM, Gan TJ, Johnson BH, et al. Effect of opioid-related adverse events on outcomes in selected surgical patients. J Pain Palliat Care Pharmacother 2013;27:62–70.
[4] de Beer Jde V, Winemaker MJ, Donnelly GA, et al. Efficacy and safety of controlled-release oxycodone and standard therapies for postoperative pain after knee or hip replacement. Can J Surg 2005;48:277–83.
[5] Van Aken H, Meinshausen E, Prien T, et al. The influence of fentanyl and tracheal intubation on the hemodynamic effects of anesthesia induction with propofol/N2O in humans. Anesthesiology 1988;68:157–63.
[6] Gupta K, Prasad A, Nagappa M, et al. Risk factors for opioid-induced respiratory depression and failure: a review. Curr Opin Anaesthesiol 2018;31:110–9.
[7] Izrailtyan I, Qiu J, Overdyk FJ, et al. Risk factors for cardiopulmonary and respiratory arrest in medical and surgical hospital patients on opioid analgesics and sedatives. PLoS One 2018;13:e0194553.
[8] Liu W, Bidwai AV, Stanley TH, et al. Cardiovascular dynamics after large doses of fentanyl and fentanyl plus N2O in the dog. Anesth Analg 1976;55:168–72.
[9] DeSouza G, Lewis MC, TerRiet MF. Severe bradycardia after remifentanil. Anesthesiology 1997;87:1019–20.

[10] Coruh B, Tonelli MR, Park DR. Fentanyl-induced chest wall rigidity. Chest 2013;143:1145–6.
[11] Afshan G. Are we anesthesiologists, aware about the incidence of muscle stiffness associated with remifentanil? Anesthesiol Pain Med 2012;1:218.
[12] Dimitriou V, Zogogiannis I, Liotiri D, et al. Impossible mask ventilation after an unusually low dose fentanyl-induced muscle rigidity in a patient with essential tremor: a case report and review of the literature. Middle East J Anaesthesiol 2014;22:619–22.
[13] Clarke SF, Dargan PI, Jones AL. Naloxone in opioid poisoning: walking the tightrope. Emerg Med J 2005 Sep;22(9): 612–6.
[14] Lee M, Silverman SM, Hansen H, et al. A comprehensive review of opioid-induced hyperalgesia. Pain Physician 2011; 14:145–61.
[15] Ramasubbu C, Gupta A. Pharmacological treatment of opioid-induced hyperalgesia: a review of the evidence. J Pain Palliat Care Pharmacother 2011;25:219–30.
[16] Weber L, Yeomans DC, Tzabazis A. Opioid-induced hyperalgesia in clinical anesthesia practice: what has remained from theoretical concepts and experimental studies? Curr Opin Anaesthesiol 2017;30:458–65.
[17] Guignard B, Bossard AE, Coste C, et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology 2000;93:409–17.
[18] Yu EH, Tran DH, Lam SW, et al. Remifentanil tolerance and hyperalgesia: short-term gain, long-term pain? Anaesthesia 2016;71:1347–62.
[19] Angst MS. Intraoperative use of remifentanil for TIVA: postoperative pain, acute tolerance, and opioid-induced hyperalgesia. J Cardiothorac Vasc Anesth 2015;29(Suppl 1):S16–22.
[20] Grace PM, Galer EL, Strand KA, et al. Repeated morphine prolongs postoperative pain in male rats. Anesth Analg 2019; 128:161–7.
[21] Hina N, Fletcher D, Poindessous-Jazat F, et al. Hyperalgesia induced by low-dose opioid treatment before orthopaedic surgery: an observational case-control study. Eur J Anaesthesiol 2015 Apr;32:255–61.
[22] McAnally H. Rationale for and approach to preoperative opioid weaning: a preoperative optimization protocol. Perioper Med (Lond) 2017;6:19.
[23] Comelon M, Raeder J, Stubhaug A, et al. Gradual withdrawal of remifentanil infusion may prevent opioid-induced hyperalgesia. Br J Anaesth 2016;116:524–30.
[24] Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Br J Anaesth 2014;112:991–1004.
[25] Shin SW, Cho AR, Lee HJ, et al. Maintenance anaesthetics during remifentanil-based anaesthesia might affect post-operative pain control after breast cancer surgery. Br J Anaesth 2010;105:661–7.
[26] Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology 2010;113:639–46.
[27] Joly V, Richebe P, Guignard B, et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. Anesthesiology 2005;103:147–55.
[28] Lenz H, Raeder J, Draegni T, et al. Effects of COX inhibition on experimental pain and hyperalgesia during and after remifentanil infusion in humans. Pain 2011;152:1289–97.
[29] Chu LF, Cun T, Ngai LK, et al. Modulation of remifentanil-induced postinfusion hyperalgesia by the beta-blocker propranolol in humans. Pain 2012;153:974–81.
[30] Koppert W, Sittl R, Scheuber K, et al. Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. Anesthesiology 2003;99:152–9.
[31] Koo CH, Yoon S, Kim BR, et al. Intraoperative naloxone reduces remifentanil-induced postoperative hyperalgesia but not pain: a randomized controlled trial. Br J Anaesth 2017;119:1161–8.
[32] Echevarria G, Elgueta F, Fierro C, et al. Nitrous oxide (N(2)O) reduces postoperative opioid-induced hyperalgesia after remifentanil-propofol anaesthesia in humans. Br J Anaesth 2011;107:959–65.
[33] Hayhurst CJ, Durieux ME. Differential opioid tolerance and opioid-induced hyperalgesia: a clinical reality. Anesthesiology 2016;124(2):483–8.
[34] Vadivelu N, Mitra S, Kaye AD, et al. Perioperative analgesia and challenges in the drug-addicted and drug-dependent patient. Best Pract Res Clin Anaesthesiol 2014;28:91–101.
[35] Pulley DD. Preoperative evaluation of the patient with substance use disorder and perioperative considerations. Anesthesiol Clin 2016;34:201–11.
[36] Bryson EO. The perioperative management of patients maintained on medications used to manage opioid addiction. Curr Opin Anaesthesiol 2014;27:359–64.
*[37] Waljee JF, Cron DC, Steiger RM, et al. Effect of preoperative opioid exposure on healthcare utilization and expenditures following elective abdominal surgery. Ann Surg 2017;265:715–21.
*[38] Cron D, Englesbe M, Bolton C, et al. Preoperative opioid use is independently associated with increased costs and worst outcomes after major abdominal surgery. Ann Surg 2017;265:695–701.
*[39] Menendez ME, Ring D, Bateman BT. Preoperative opioid misuse is associated with increased morbidity and mortality after elective orthopaedic surgery. Clin Orthop Relat Res 2015;473:2402–12.
*[40] Overdyk FJ, Dowling O, Marino J, et al. Association of opioids and sedatives with increased risk of in-hospital cardiopulmonary arrest from an administrative database. PLoS One 2016;11:e0150214.
[41] Rozet I, Nishio I, Robbertze R, et al. Prolonged opioid use after knee arthroscopy in military veterns. Anesth Analg 2014;119:454–9.
[42] Nguyen LC, Sing DC, Bozic KJ. Preoperative reduction of opioid use before total joint arthroplasty. J Arthroplast 2016;31: 282–7.
[43] Goplen CM, Verbeek W, Kang SH, et al. Preoperative opioid use is associated with worse outcomes after total joint arthroplasty: a systematic review and meta-analysis. BMC Musculoskelet Disord 2019;20:234.
[44] Chou R, Gordon DB, de Leon-Casasola OA, et al. Guidelines on the 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.
*[45] 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.
[46] Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology 2002;96:725–41.
[47] Ong CK, Lirk P, Seymour RA, et al. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg 2005;100:757–73.
[48] Schug SA, Palmer GM, Scott DA, et al. Acute pain management: scientific evidence. 4th ed. 2015. http://fpm.anzca.edu.au/documents/apmse4_2015_final. [Accessed 14 June 2019].
[49] Levy N, Mills P. Controlled-release opioids cause harm and should Be avoided in management of postoperative pain in opioid-naïve patients. Br J Anaesth 2019;122:e86–90.
[50] Smith C, McEwan AI, Jhaveri R, et al. The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. Anesthesiology 1994;81:820–8.
[51] Kelly HE, Shaw GM, Brett CN, et al. The effect of titrated fentanyl on suppressed cough reflex in healthy adult volunteers. Anaesthesia 2016;71:529–34.
[52] Johnston KD, Rai MR. Conscious sedation for awake fibreoptic intubation: a review of the literature. Can J Anaesth 2013;60:584–99.
[53] Zhang X, He W, Wu X, et al. TCI remifentanil vs. TCI propofol for awake fiber-optic intubation with limited topical anesthesia. Int J Clin Pharmacol Ther 2012;50:10–6.
[54] Bouvet L, Stoian A, Rimmele T, et al. Optimal remifentanil dosage for providing excellent intubating conditions when co-administered with a single standard dose of propofol. Anaesthesia 2009;64:719–26.
[55] Trabold F, Casetta M, Duranteau J, et al. Propofol and remifentanil for intubation without muscle relaxant: the effect of the order of injection. Acta Anaesthesiol Scand 2004;48:35–9.
[56] Chung KS, Sinatra RS, Halevy JD, et al. A comparison of fentanyl, esmolol, and their combination for blunting the haemodynamic responses during rapid-sequence induction. Can J Anaesth 1992;39:774–9.
[57] Cork RC, Weiss JL, Hameroff SR, et al. Fentanyl preloading for rapid-sequence induction of anesthesia. Anesth Analg 1984;63:60–4.
[58] Pouraghaei M, Moharamzadeh P, Soleimanpour H, et al. Comparison between the effects of alfentanil, fentanyl and sufentanil on hemodynamic indices during rapid sequence intubation in the emergency department. Anesthesiol Pain Med 2014;4:e14618.
[59] Casati A, Fanelli G, Albertin A, et al. Small doses of remifentanil or sufentanil for blunting cardiovascular changes induced by tracheal intubation: a double-blind comparison. Eur J Anaesthesiol 2001;18:108–12.
[60] O'Hare R, McAtamney D, Mirakhur RK, et al. Bolus dose remifentanil for control of haemodynamic response to tracheal intubation during rapid sequence induction of anaesthesia. Br J Anaesth 1999;82:283–5.
[61] Dahlgren N, Messeter K. Treatment of stress response to laryngoscopy and intubation with fentanyl. Anaesthesia 1981;36:1022–6.
[62] Hendrickx JF, Eger EI, Sonner JM, et al. Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. Anesth Analg 2008;107:494–506.
[63] Mertens MJ, Olofsen E, Engbers FH, et al. Propofol reduces perioperative remifentanil requirements in a synergistic manner: response surface modeling of perioperative remifentanil-propofol interactions. Anesthesiology 2003;99:347–59.
[64] Miller TE, Gan TJ. Total intravenous anesthesia and anesthetic outcomes. J Cardiothorac Vasc Anesth 2015;29(Suppl 1):S11–5.
[65] Lee JH, Koo BN, Jeong JJ, et al. Differential effects of lidocaine and remifentanil on response to the tracheal tube during emergence from general anaesthesia. Br J Anaesth 2011;106:410–5.
[66] Kumar K, Kirksey MA, Duong S, et al. A review of opioid-sparing modalities in perioperative pain management: methods to decrease opioid use postoperatively. Anesth Analg 2017;125:1749–60.
[67] Wick EC, Grant MC, Wu CL. Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: a review. JAMA Surg 2017;152:691–7.
[68] Mitrovic I, Margeta-Mitrovic M, Bader S, et al. Contribution of GIRK2-mediated postsynaptic signaling to opiate and alpha 2-adrenergic analgesia and analgesic sex differences. Proc Natl Acad Sci U S A 2003;100:271–6.
[69] De Kock M, Crochet B, Morimont C, et al. Intravenous or epidural clonidine for intra- and postoperative analgesia. Anesthesiology 1993;79:525–31.
[70] Gelineau AM, King MR, Ladha KS, et al. Intraoperative esmolol as an adjunct for perioperative opioid and postoperative pain reduction: a systematic review, meta-analysis, and meta-regression. Anesth Analg 2018;126:1035–49.
[71] Liang DY, Shi X, Li X, et al. The beta2 adrenergic receptor regulates morphine tolerance and physical dependence. Behav Brain Res 2007;181:118–26.
*[72] Mauermann E, Ruppen W, Bandschapp O. Different protocols used today to achieve total opioid-free general anesthesia without locoregional blocks. Best Pract Res Clin Anaesthesiol 2017;31:533–45.
[73] 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;125:1784–92.
[74] Lirk P, Rathmell JP. Opioid-Free Anaesthesia: con: it is too early to adopt opioid-free anaesthesia today. Eur J Anaesthesiol 2019;36:250–4.
*[75] Veyckemans F. Opioid-free anaesthesia: still a debate? Eur J Anaeshtesiol 2019;36:245–6.
[76] Loeser JD, Treede RD. The Kyoto protocol of IASP basic pain terminology. Pain 2008;137:473–7.
[77] Constant I, Nghe MC, Boudet L, et al. Reflex pupillary dilatation in response to skin incision and alfentanil in children anaesthetized with sevoflurane: a more sensitive measure of noxious stimulation than the commonly used variables. Br J Anaesth 2006;96:614–9.
[78] Constant I, Sabourdin N. Monitoring depth of anesthesia: from consciousness to nociception. A window on subcortical brain activity. Paediatr Anaesth 2015;25:73–82.

[79] Ledowski T, Ang B, Schmarbeck T, et al. Monitoring of sympathetic tone to assess postoperative pain: skin conductance vs surgical stress index. Anaesthesia 2009;64:727–31.
*[80] Huiku M, Uutela K, van Gils M, et al. Assessment of surgical stress during general anaesthesia. Br J Anaesth 2007;98:447–55.
[81] Thee C, Ilies C, Gruenewald M, et al. Reliability of the surgical Pleth index for assessment of postoperative pain: a pilot study. Eur J Anaesthesiol 2014;32:4–48.
[82] Gruenewald M, Herz J, Schoenherr T, et al. Measurement of the nociceptive balance by anaglesia nociceptive index (ANI) and surgical Pleth index (SPI) during sevoflurane-remifentanil anaesthesia. Minerve Anestesiol 2015;81:480–9.
[83] Wennervirta J, Hynynen M, Koivusalo AM, et al. Surgical stress index as a measure of nociception/antinociception balance during general anesthesia. Acta Anaesthesiol Scand 2008;52:1038–45.
[84] Gruenewald M, Meybohm P, Ilies C, et al. Influence of different remifentanil concentrations on the performance of the surgical stress index to detect a standardized painful stimulus during sevoflurane anaesthesia. Br J Anaesth 2009;103:586–93.
*[85] Sabourdin N, Diarra C, Wolk R, et al. Pupillary pain index changes after a standardized bolus of alfentanil under sevoflurane anesthesia: first evaluation of a new pupillometric index to assess the level of analgesia during general anesthesia. Anesth Analg 2019;128:467–74.
[86] Upton HD, Ludbrook GL, Wing A, et al. Intraoperative "analgesia nociceptive index"-guided fentanyl administration during sevoflurane anesthesia in lumber discectomy and laminectomy: a randomized clinical trial. Anesth Analg 2017;125:81–90.
[87] Edry R, Recea V, Dikust Y, et al. Preliminary intraoperative validation of the nociception level index: a noninvasive nociception monitor. Anesthesiology 2016;125:193–203.
[88] Blay Jr E, Nooromid MJ, Bilimoria KY, et al. Variation in post-discharge opioid prescriptions among members of a surgical team. Am J Surg 2018;216:25–30.
[89] Thiels CA, Anderson CC, Ubl DS, et al. Wide variation and overprescription of opioids after elective surgery. Ann Surg 2017;266:564–73.
[90] Chen EY, Marcantonio A, Tornetta 3rd P, et al. Correlation between 24-hour predischarge opioid use and amount of opioids prescribed at hospital discharge. JAMA Surg 2018;153:e174859.
[91] Hartford LB, Van Koughnett JAM, Murphy PB, et al. Standardization of outpatient procedure (STOP) narcotics: a prospective non-inferiority study to reduce opioid use in outpatient general surgical procedures. J Am Coll Surg 2019;228:81–8.
[92] Rudd RA, Aleshire N, Zibbell JE, et al. Increases in drug and opioid overdose deaths - United States, 2000-2014. MMWR Morb Mortal Wkly Rep 2016;64:1378–82.
[93] Rudd RA, Seth P, David F, et al. Increases in drug and opioid-involved overdose deaths – United States 2010-2015. MMWR Morb Mortal Wkly Rep 2016;65:1445–52.
[94] Lin LA, Peltzman T, McCarthy JF, et al. Changing trends in opioid overdose deaths and presciption opioid receipt among veterans. Am J Prev Med 2019;57:106–10.
[95] https://www.samhsa.gov/data/sites/default/files/DR006/DR006/nonmedical-pain-reliever-use-2013.htm. [Accessed 14 June 2019].
[96] Volkow ND, McLellan AT. Opioid abuse in chronic pain - misconceptions and mitigation strategies. N Engl J Med 2016;374:1253–63.
[97] Fujii MH, Hodges AC, Russell RL, et al. Post-discharge opioid prescribing and use after common surgical procedure. J Am Coll Surg 2018;226:1004–12.
[98] Bicket MC, Long JJ, Pronovost PJ, et al. Prescription opioid analgesics commonly unused after surgery: a systemic review. JAMA Surg 2017;152:1066–71.
*[99] Losby JL, Hyatt JD, Kanter MH, et al. Safer and more appropriate opioid prescribing: a large healthcare system's comprehensive approach. J Eval Clin Pract 2017;23:1173–9.
[100] Garcia MC, Dodek AB, Kowalski T, et al. Declines in opioid prescribing after a private insurer policy change — Massachusetts, 2011–2015. MMWR Morb Mortal Wkly Rep 2016;65:1125–31.
[101] https://www.stvincent.org/-/media/Files/ININD/Medical-Education/CME/opioids/2019_opioid_prescribing_recommendations.pdf. [Accessed 14 June 2019].
[102] Hill MV, Stucke RS, McMahon ML, et al. An educational intervention decreases opioid prescribing after general surgical operations. Ann Surg 2018;267:468–72.
[103] Wyles CC, Hevesi M, Trousdale ER, et al. The 2018 chitranjan S. Ranawat, MD award: developing and implementing a novel institutional guideline strategy reduced postoperative opioid prescribing after TKA and THA. Clin Orthop Relat Res 2019;477:104–13.
[104] Chapman CR, Vierck CJ. The transition of acute postoperative pain to chronic pain: an integrative overview of research on mechanisms. J Pain 2017;18:359.e1–359.e38.
[105] Lavand'homme P. Transition from acute to chronic pain after surgery. Pain 2017;158(Suppl 1):S50–4.
[106] Pozek JP, Beausang D, Baratta JL, et al. The acute to chronic pain transition: can chronic pain Be prevented? Med Clin North Am 2016;100:17–30.
[107] Memtsoudis SG, Poeran J, Cozowicz C, et al. The impact of peripheral nerve blocks on perioperative outcome in hip and knee arthroplasty-a population-based study. Pain 2016;157:2341–9.
[108] Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis. Br J Anaesth 2013;111:711–20.
[109] Howard R, Alameddine M, Klueh M, et al. Spillover effect of evidence-based postoperative opioid prescribing. J Am Coll Surg 2018;227:374–81.
[110] Sekhri S, Arora NS, Cottrell H, et al. Probability of opioid prescription refilling after surgery: does initial prescription dose matter? Ann Surg 2018;268:271–6.
[111] Kumar K, Gulotta LV, Dines JS, et al. Unused opioid pills after outpatient shoulder surgeries given current perioperative prescribing habits. Am J Sports Med 2017;45:636–41.

[112] Prabhu M, McQuaid-Hanson E, Hopp S, et al. A shared decision- making intervention to guide opioid prescribing after cesarean delivery. Obstet Gynecol 2017;130(1):42–6.
[113] Long DR, Lihn AL, Friedrich S, et al. Association between intraoperative opioid administration and 30-day readmission: a pre-specified analysis of registry data from a healthcare network in New England. Br J Anaesth 2018;120:1090–102.
[114] Hasak JM, Roth Bettlach CL, Santosa KB, et al. Empowering post-surgical patients to improve opioid disposal: a before and after quality improvement study. J Am Coll Surg 2018;226:235–40.
[115] Feinberg AE, Chesney TR, Srikandarjah S, et al. Opioid use after discharge in postoperative patients: a systematic review. Ann Surg 2018;267:1056–62.
[116] Lovecchio F, Premkumar A, Stepan J, et al. Fighting back: institutional strategies to combat the opioid epidemic: a systematic review. HSS J 2019;15:66–71.
[117] https://capitol.texas.gov/BillLookup/Text.aspx?LegSess=86R&Bill=HB2088. [Accessed 14 June 2019].
[118] Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. Lancet 2019;393:1537–46.
[119] Schug SA, Lavand'homme P, Barke A, et al. The IASP classification of chronic pain for ICD-11: chronic postsurgical and posttraumatic pain. Pain 2019;160:45–52.
[120] Treede RD, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the ISAP classification of chronic pain for the international classification of diseases (ICD-11). Pain 2019;160:19–27.
[121] Weinrib AZ, Burns LC, Mu A, et al. A case report on the treatment of complex chronic pain and opioid dependence by a multidisciplinary transitional pain service using the ACT matrix and buprenorphine/naloxone. J Pain Res 2017;10:747–55.
[122] Meng H, Hanlon JG, Katznelson R, et al. The prescription of medical cannabis by a transitional pain service to wean a patient with complex pain from opioid use following liver transplantation: a case report. Can J Anaesth 2016;63:307–10.