Preoperative Optimization for Perioperative Analgesia



Nicole Matar, MD, Anna A. Pashkova, MD*

KEYWORDS

- Preoperative optimization
 Multimodal analgesia
 Acute on chronic pain
 Opioids
- Analgesic adjuncts

KEY POINTS

- Preoperative optimization of patients with chronic pain requires a multimodal and collaborative approach.
- Poor pain control is associated with increased morbidity, impaired physical function and quality of life, slowed recovery, prolonged opioid use during and after hospitalization, and increased costs.
- Current outpatient pain regimens and prescriptions should be reviewed and confirmed preoperatively. Methadone and buprenorphine management requires advanced planning.
- Any medical history or patient factors affecting postoperative analgesic choice should be noted.
- A focused social and psychiatric history must be taken with a focus on substance use disorder.

INTRODUCTION

The majority of patients meet their surgical team before entering the operating room. Just like other aspects of medical optimization, patients should undergo preoperative evaluation to optimize postoperative analgesia. This process includes obtaining a thorough pain history, setting expectations, screening for substance use disorders, developing a postoperative analgesia plan, and possibly involving a multidisciplinary team, including anesthesiology, pain medicine, palliative care, psychiatry, and/or addiction specialists. Waiting to consult the pain service team postoperatively misses an opportunity for valuable planning.

Inadequate postoperative pain control is undesirable, but inadequate pain control is cited in more than 80% of postoperative patients. Pain control directly correlates with patient satisfaction. Poor pain control is associated with increased morbidity, impaired physical function and quality of life, slowed recovery, prolonged opioid use during and

Department of Anesthesiology, Columbia University Medical Center, 622 West 168th Street, PH 5-505, New York, NY 10032, USA

* Corresponding author.

E-mail address: apashkova@gmail.com

after hospitalization, and increased cost of care. Postoperative pain may also lead to prolonged pain or chronic pain conditions. Although a multitude of factors contribute to inadequate postoperative pain control, limited physician understanding of strategies for pain prevention and control is a contributing factor. Preoperative pain is a risk factor for poorly controlled postoperative pain, and so appropriate analgesia for patients with chronic pain conditions requires additional planning.

The distinction between acute and chronic pain is essential to providing appropriate postoperative analgesia. Acute pain is self-limited, provoked by a particular disease or injury, and generally associated with a sympathetic nervous system activation. Chronic pain, in contrast, should be thought of as a disease state. Chronic pain extends beyond the normal healing time of an associated disease or injury. The prevalence of chronic pain is high with up to a quarter of the adult American population with chronic pain. The treatment of acute pain focuses on addressing the underlying cause. Chronic pain, however, requires a different approach aimed at both the physical and the psychosocial state of a patient. Studies have found that patients with various chronic pain conditions may tend to be more sensitive to injury than others. Additionally, patients with chronic pain may be more physically deconditioned than other patients in similar situations. Thus, those with chronic pain undergoing surgery require special care with respect to postoperative pain management. The perioperative period creates a state of acute on chronic pain for many patients, resulting in an increased complexity of treatment for practitioners.

A focused pain history should be part of the preoperative assessment to create an appropriate perioperative pain management plan (Box 1). Key aspects should include any history of chronic or acute pain conditions, the location of the patient's pain, and the patient's preoperative pain score. A thorough list of medications should be obtained. The surgeon should be aware of any opioid medications that the patient is taking, and because many medications are written on as as-needed basis ("PRN"), make note of the total daily dose the patient is actually taking. Adjuvant pain medications and doses must be covered. Patients on multiple sedating medications are at higher risk for respiratory depression and death when combined with opioids. Patients should be screened for medical comorbidities, such as obstructive sleep apnea (OSA), that confer a higher risk of postoperative respiratory depression. A psychosocial history should be obtained. Patients with a history of substance use disorder require special consideration if postoperative opioids are indicated, and patients on buprenorphine require advanced planning.

Patients may be on prescription opioids for acute or chronic pain. For patients on opioids for chronic pain, it is important to note the dose and the total amount the patient takes daily. The standard of comparing different opioids is converting the total daily dose to milligrams of oral morphine milligram equivalents (Table 1). Postoperatively, the patient should receive opioids to cover their baseline opioid requirement. For surgeries requiring postoperative opioids, higher opioid requirements will be likely. If it is necessary to switch the patient from their home opioid to a different opioid postoperatively, the managing physician should be versed in opioid conversion and take into account incomplete cross-tolerance. Incomplete cross-tolerance means that an opioid-tolerant patient will be most tolerant to the specific opioids they are chronically taking and slightly less tolerant to other opioids. As such, a dose decrease of 25% to 50% should occur when switching between different opioids. Fentanyl is available in a transdermal formulation via patch. Initiation and discontinuation should take into account onset time and offset time.

The home opioid dose may be confirmed via communication with outpatient physicians, pharmacies, or prescription drug monitoring systems. Patients on chronic

Box 1

Preoperative assessment

Pain medication history

- Does that patient have any contraindications to NSAIDs?
 - Kidney dysfunction
 - History of gastrointestinal bleed, peptic ulcers, or gastritis
 - Increased risk of bleeding
 - o Coronary artery disease
 - Stroke
- Does the patient have any contraindications to acetaminophen?
 - For patients with stable liver dysfunction, the maximum recommended dose of acetaminophen is 2000 mg/d²⁴
- Does the patient have any contraindications to gabapentinoids?
 - o Must be renally dosed
 - o Common side effects include dizziness and sedation
- Does the patient have an increased risk of opioid-induced respiratory depression?
 - Concurrent use of sedating medications (opioids, benzodiazepines, gabapentinoids)
 - o OSA or positive STOP-Bang questionnaire
 - Respiratory condition
 - o Cardiac condition
- Does the patient have any exacerbating or aggravating factors?
 - Anxietv
 - Sleep deprivation
 - Poor nutrition

Home medications

- Is the patient on chronic pain medications?
- What is the total dose of home opioid medications?
- Who is the outpatient prescribing provider?
- What is the dose of nonopioid pain medications?

Allergies or history of intolerances to pain medications

Social history

- Does the patient have a history of substance use disorder?
- Is the patient on medication-assisted treatment with methadone or buprenorphine?

opioids often have a controlled substance agreement with the prescriber that outlines that the patient should not receive opioid prescriptions from any other physicians, and so the patient should notify their opioid provider before any elective surgery. Methadone and buprenorphine are long-acting opioids that can be prescribed for chronic pain or substance use disorder, and are discussed elsewhere in this article.

Practitioners should be aware that patients on chronic opioids often have a tolerance to opioid medications, which consists of a rightward shift of the dose–response curve to opioids. As a result, patients require increasing amounts of the medication to maintain the same pharmacologic effect. Those patients who have developed tolerance are generally less responsive to standard protocols for postoperative pain control. Chapman and colleagues examined postoperative pain in surgical patients over the span of 6 days and found that those with chronic pain conditions prescribed opioids at baseline had a significantly greater difficulty with their postoperative pain control when compared with surgical patients without chronic pain conditions. The initial pain levels were higher and a decrease in postoperative pain was not found on average over a 6-day window. The study did not explain the cause behind the persistence of postoperative pain in patients with chronic pain. However, the concept of opioid-induced hyperalgesia has been discussed and studied by other researchers. The phrase is used to express the concept that

Table 1 Opioid equianalgesia table				
	Equianalgesic Dose		Conversion Factor	
Drug	Parenteral (mg)	Oral (mg)	Parenteral Opioid to MME	Oral Opioid to MME
Morphine	10	30	3	1
Hydromorphone	1.5	7.5	20	4
Oxycodone	_	20	_	1.5
Hydrocodone	_	30	_	1

Methadone conversion varies by dose. Fentanyl conversion rate of 2.4 is based on micrograms per hour of transdermal patch. Example: A patient on fentanyl patch $25\,\mu g/h$ is on a dose equivalent to approximately 60 mg oral morphine equivalents over 24 h. If converting between opioids, reduce dose by 25%-50% to account for incomplete cross tolerance. Example of conversion: A patient taking oxycodone 10 mg four times daily preoperatively is taking a total of 40 mg oxycodone daily. This is the equivalent of 60 mg oral morphine over 24 h. Accounting for incomplete cross-tolerance, the patient may be prescribed a total of 30 to 45 mg oral morphine in divided doses over 24 h with equianalgesic effect. This accounts for the patient's baseline opioid requirement, and supplemental analgesia may be needed postoperatively. Doses listed in this table are for comparison purposes only and do not constitute recommended doses.

Abbreviations: MG, milligrams; MME, oral morphine milligram equivalents.

Data from CDC: Calculating Total Daily Dose of Opioids for Safer Dosage. https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf.

chronic opioid users have lower pain thresholds and exaggerated pain levels after acute injuries. Previous studies have demonstrated that animals chronically exposed to morphine have enhanced proinflammatory cytokine levels postoperatively. It has been postulated that patients with chronic pain enter a state of hypersensitivity in their central nervous systems owing to the impaired function in endogenous opioid analgesic systems. 4

Patients on opioids for chronic noncancer pain scheduled for elective procedures may benefit from opioid tapering preoperatively. Preoperative opioid tapering to the lowest tolerated dose may mitigate opioid tolerance and opioid-induced hyperalgesia, resulting in improved postoperative analgesia. There are data that patients on highdose opioids have worse outcomes.² Hospitalized patients with opioid use have higher rates of hypoxemia, ileus, nausea, pruritis, and cognitive impairment, as well as an increased length of stay, which may also contribute to the higher cost of care. 8 Opioid tapering requires time and advanced planning, which may act as a barrier preoperatively. Another potential barrier is a patient's willingness to taper.8 However, studies support that opioid tapering for chronic pain leads to unchanged or improved pain scores and better function. 9,10 The reason for tapering should be explained to the patient. The duration of a taper varies based on a patient's need and the complexity of the initial opioid regimen. For those patients who have been taking opioids for weeks to months, the Centers for Disease Control and Prevention recommend a decrease of 10% per week as a reasonable starting point. 11 Abrupt discontinuation of opioids should be avoided. There is not enough data to support preoperative opioid tapering for all patients, and so the surgeon should contact the patient's outpatient opioid prescriber to discuss whether a preoperative taper would be helpful and appropriate. The opioid prescriber can then implement an individualized taper for the patient. The surgeon should also coordinate a tentative postoperative opioid and analgesic plan with the outpatient opioid prescriber. This strategy may help to set expectations for postoperative analgesia with the patient.

Adjuvant chronic pain medications should most often be continued if no contraindications arise. It is important to take into consideration which medications can be administered via additional routes, because select surgeries may preclude patients from taking pills orally in the immediate postoperative period. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be held based on anticipated intraoperative or post-operative blood loss. The management of aspirin prescribed as anticoagulation for a chronic medical condition should be coordinated with the patient's outpatient prescriber. Fluctuations in a patient's renal function may occur in the perioperative period. Practitioners must be cognizant of which medications need to be adjusted for variable renal function (Box 2). In the postoperative period, patients often have an increased risk of respiratory depression and apnea with sedating medications. The surgeon should make note of whether a patient is on multiple sedating medications, such as opioids, benzodiazepines, and gabapentinoids, because this will increase the patient's risk of respiratory depression. Opioid overdose mortality is increased 4-fold with concurrent use of opioids and benzodiazepines.

Patients should be screened for conditions that increase risk of postoperative respiratory depression. A meta-analysis by Gupta and colleagues⁵ noted that the incidence of postoperative opioid-induced respiratory depression is approximately 0.5%. Patients with preexisting cardiac disease, pulmonary disease, and OSA are at higher risk for respiratory complications.⁵ Patients should be screened for OSA and, if necessary, referred to a sleep medicine specialist. The STOP-Bang questionnaire is a common screening tool used for OSA. One study showed a 3.75-fold increased risk of perioperative complications with an STOP-Bang score of 3 or higher. 13 In a study on OSA-related malpractice, 22% of claims alleged that inappropriate medication administration resulted in respiratory depression.¹⁴ Because the majority of opioid-induced respiratory depression events occur within 24 hours of surgery, patients should be counseled on continuous positive airway pressure use postoperatively. If within hospital protocol, patients should be instructed to bring their home continuous positive airway pressure for use in the postanesthesia care unit and for sleep postoperatively. A multimodal analgesia plan should be implemented to minimize sedating medications postoperatively. A meta-analysis by Gupta and colleagues⁵ noted that patients who had respiratory events received a higher 24-hour morphine equivalent dose (average of 24.7 mg vs 18.9 mg). Put in perspective, 25 mg of oral morphine is approximately the equivalent of 5 tablets of hydrocodone

Box 2

Medication considerations for patients with renal insufficiency

- NSAIDs^a avoid use
- Gabapentin renally dose
- Pregabalin renally dose
- Tramadol renally dose
- Morphine avoid in severe renal dysfunction
- Meperidine avoid use
- Duloxetine avoid use if creatine clearance is less than 30 mL/min

Care should be made when prescribing the following medications in the setting of renal injury or failure. Discontinuation or dosing adjustment may be recommended.^a Coordination of aspirin continuation should be discussed with outpatient provider.

5 mg administered over the span of 1 day. Patients who are at increased risk of postoperative respiratory depression may require longer periods or an increased level of monitoring. Approximately 20% of claims regarding OSA alleged inappropriate monitoring of the patient.¹⁴ The surgery should be booked at an appropriate location for monitoring duration and care.

In the extended postoperative period, patients often have exacerbating factors that contribute to a worse subjective sensation of pain. Special attention should be given to the anxiety, sleep deprivation, and poor nutrition that may arise in the postoperative period. ¹⁵

Patients with a history of substance use disorder require advanced planning. Methadone or buprenorphine are long-acting opioids that are often used as part of medication-assisted treatment to prevent relapse of substance abuse. It is important to note that some patients take methadone or buprenorphine for pain with no history of addiction, and so the indication for these medications is important to clarify. Methadone for substance use disorder is often acquired at a methadone clinic, which will not show up on prescription drug monitoring programs. In this case, the patient's dose should be confirmed with the methadone clinic preoperatively. If a patient recalls a dose lower than what is prescribed, their opioids may be underdosed postoperatively, which may lead to inadequate pain control. If a patient reports a dose higher than prescribed and this higher dose is administered, they are at risk for respiratory depression and opioid overdose. In general, the patient's methadone should be continued preoperatively.

Buprenorphine (commonly combined with naloxone as buprenorphine-naloxone) is a partial agonist of the opioid mu receptor and an antagonist at the opioid kappa and delta receptors. The naloxone is inactive when taken orally, but acts as an opioid antagonist in case the buprenorphine-naloxone is injected intravenously in an abuse attempt. Buprenorphine binds tightly to the opioid receptor and competitively displaces traditional opioids from the opioid receptor. Through this mechanism, the pharmacokinetic properties of buprenorphine interfere with the effectiveness of postoperative opioids. Owing to the long half-life of buprenorphine (20-70 hours reported), it is important to contact the buprenorphine provider to establish a periopplan. 16 Different formulations of buprenorphine pharmacokinetic properties. For procedures with expected minimal to no pain, it is generally recommended that patients continue taking their buprenorphine without a change in dose and with an avoidance of supplemental opioids. For those procedures expected to result in moderate to severe pain, consideration should be given to weaning off buprenorphine preoperatively. Patients who have discontinued buprenorphine may require tolerant doses of opioids in the perioperative period. If it is discovered that a patient is taking buprenorphine on the day of surgery, and moderate to severe postoperative pain is expected requiring opioids, consideration should be given to postponing an elective procedure. Anderson and colleagues¹⁷ suggests a dose-dependent timeline for the discontinuation of buprenorphine (Box 3). The discontinuation of buprenorphine puts the patient at risk for substance abuse relapse, and so should be done only at the discretion of the buprenorphine provider. Other studies recommend continuation of buprenorphine and the use of higher dose opioids postoperatively. 17 In such cases, admission to the intensive care unit may be required for respiratory monitoring. Hospital guidelines should be followed regarding buprenorphine recommendations. Regardless of the decision of continuation or discontinuation of buprenorphine, multimodal analgesia should play a prominent role in the perioperative analgesia plan. The inclusion of NSAIDs, acetaminophen, local anesthetics, and membrane stabilizers will contribute to an overall decrease

Box 3

Preoperative buprenorphine discontinuation

- 0-4 mg discontinue 24 hours before surgery
- >4-8 mg discontinue 48 hours before surgery
- >8–12 mg discontinue 72 hours before surgery

Suggested discontinuation time for buprenorphine based on totally daily preoperative dose prior to surgeries with anticipated moderate to severe pain requiring postoperative opioids. Decision to continue or discontinue buprenorphine preoperatively must be coordinated with outpatient prescriber.

Data from T. Anthony Anderson, Aurora N. A. Quaye, E. Nalan Ward, et. al; To Stop or Not, That Is the Question: Acute Pain Management for the Patient on Chronic Buprenorphine. Anesthesiology 2017;126(6):1180-1186. doi: https://doi.org/10.1097/ALN.000000000001633.

in opioid requirements for postoperative patients. Regional techniques should be used when possible. 17

For patients on methadone or buprenorphine for substance use disorder, a discharge plan should be implemented. Although the surgeon may continue these home medications while the patient is an inpatient, a DEA-X license is required for initiation or outpatient prescription of these medications. Thus, the patient should not be discharged home with a prescription. Instead, coordination and appropriate follow-up with the patient's outpatient provider must be established. Patients with a history of substance use disorder are at higher risk for opioid overdose.¹⁸

After a focused pain history is obtained, patients should be counseled on expectations regarding postoperative pain management. Patient satisfaction may be increased with a preoperative discussion of pain management expectations. Expectations of pain levels too high or unrealistic expectations of zero pain may be detrimental. ¹⁹

For those patients with implanted pain devices such as intrathecal pump or spinal cord stimulators, it is necessary to formulate a plan for continuation/discontinuation with the patient's chronic pain provider. Intrathecal drug delivery systems, for example, should be continued during the operative period if possible.²⁰ If there may be consideration of MRI, the compatibility of the device should be confirmed.

For the uncomplicated patient, enhanced recovery after surgery guidelines exist for select surgeries, and may guide the surgeon in developing an analgesic plan. Enhanced recovery after surgery guidelines have been shown to decrease complications, costs, and opioid use postoperatively. For the more complex patient, the surgeon should coordinate with the patient's outpatient pain provider. The anesthesiologist will also be instrumental in preoperative, intraoperative, and postoperative strategies to optimize pain control.

Intraoperative analgesia strategies often are managed by the anesthesiologist. However, it is important to ensure a multidisciplinary discussion as to the course of action. Regional anesthetic techniques should be considered and discussed between the surgical and anesthesia teams. Depending on hospital protocol, either the surgical team or anesthesiology team may order analgesics in the preoperative area to aid with postoperative analgesia. Common premedications include NSAIDs, acetaminophen, and gabapentinoids. Home medication reconciliation should be performed so the patient does not receive redundant medications (eg, preoperative gabapentin for a patient taking pregabalin). Preoperative acetaminophen and NSAIDs have been shown to reduce postoperative opioid consumption for a number of different surgeries.²³

Preoperative gabapentin has been shown to be effective in decreasing acute pain by blocking the development of hyperalgesia and decreasing central sensitization.²⁴ For those patients with chronic pain, a number of intraoperative strategies have been found to have benefits that extend into the postoperative period. Dosing long-acting opioids intraoperatively and adjuvant medication infusions, such as ketamine or lidocaine, can offer a multimodal plan for postoperative pain relief.²⁵

SUMMARY

Preoperative optimization of patients with chronic pain requires a multimodal and collaborative approach. Providers must assess individuals on a case-by-case basis. This approach includes a focused assessment of current outpatient pain regimens and prescriptions, any past medical history that may create contraindications to additional prescriptions, any pertinent psychiatric and social history with a focus on substance use disorder, and a general assessment of pain. The provider must be cognizant of medical conditions, such as OSA, respiratory disease, and cardiac disease, that will put the patient at higher risk for postoperative opioid induced respiratory depression. Special care must be paid to those patients on long-term outpatient opioid prescriptions, especially buprenorphine and methadone. Multimodal analgesia should be used to aid postoperative analgesia and minimize the amount of opioid required for postoperative care. For patients with chronic pain, providers should reach out to the patient's outpatient prescribers and pain specialists to ensure a safe and effective analgesic plan.

REFERENCES

- 1. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. J Pain Res 2017;10:2287–98.
- 2. Pivec R, Issa K, Naziri Q, et al. Opioid use prior to total hip arthroplasty leads to worse clinical outcomes. Int Orthop 2014;38(6):1159–65.
- 3. Grichnik KP, Ferrante FM. The difference between acute and chronic pain. Mt Sinai J Med 1991;58(3):217–20.
- 4. Richard Chapman C, Donaldson G, Davis J, et al. Postoperative pain patterns in chronic pain patients: a pilot study. Pain Med 2009;10(3):481–7.
- Gupta K, Nagappa M, Prasad A, et al. Risk factors for opioid-induced respiratory depression in surgical patients: a systematic review and meta-analyses. BMJ Open 2018;8(12):e024086.
- 6. Smith HS, Peppin JF. Toward a systematic approach to opioid rotation. J Pain Res 2014;7:589–608.
- Mitra S, Sinatra RS. Perioperative management of acute pain in the opioiddependent patient. Anesthesiology 2004;101(1):212–27.
- 8. Blum JM, Biel SS, Hilliard PE, et al. Preoperative ultra-rapid opiate detoxification for the treatment of post-operative surgical pain. Med Hypotheses 2015;84(6): 529–31.
- 9. Fishbain DA, Pulikal A. Does opioid tapering in chronic pain patients result in improved pain or same pain vs increased pain at taper completion? a structured evidence-based systematic review. Pain Med 2019;20(11):2179–97.
- 10. Berna C, Kulich RJ, Rathmell JP. Tapering long-term opioid therapy in chronic noncancer pain: evidence and recommendations for everyday practice. Mayo Clin Proc 2015;90(6):828–42.

- 11. CDC Pocket Guide. Tapering opioids for chronic pain. Available at: https://www.cdc.gov/drugoverdose/pdf/clinical_pocket_guide_tapering-a.pdf. Accessed December 12, 2019.
- 12. Park TW, Saitz R, Ganoczy D, et al. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ 2015;350:h2698.
- 13. Nagappa M, Liao P, Wong J, et al. Validation of the STOP-Bang questionnaire as a screening tool for obstructive sleep apnea among different populations: a systematic review and meta-analysis. PLoS One 2015;10:e0143697.
- Svider PF, Pashkova AA, Folbe AJ, et al. Obstructive sleep apnea: strategies for minimizing liability and enhancing patient safety. Otolaryngol Head Neck Surg 2013;149(6):947–53.
- 15. Borsook D, George E, Barry K, et al. Anesthesia and perioperative stress: consequences on neural networks and postoperative behaviors. Prog Neurobiol 2010; 92(4):601–12.
- 16. Urman RD, Jonan A, Kaye AD. Buprenorphine formulations: clinical best practice strategies recommendations for perioperative management of patients undergoing surgical or interventional pain procedures. Pain Physician 2018;21:E1–12.
- 17. Anderson TA, Quaye ANA, Nalan Ward E, et al. To stop or not, that is the question: acute pain management for the patient on chronic buprenorphine. Anesthesiology 2017;126(6):1180–6.
- Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1):1–49.
- 19. Geurts JW, Willems PC, Lockwood C, et al. Patient expectations for management of chronic non-cancer pain: a systematic review. Health Expect 2017;20(6): 1201–17.
- 20. Grider JS, Brown RE, Colclough GE. Perioperative management of patients with an intrathecal drug delivery system for chronic pain. Anesth Analg 2008;107: 1393–6.
- 21. Haase GM. Embracing early recovery after surgery (ERAS) protocols: is it time for otolaryngology to join the parade? Am J Otolaryngol 2018;39(5):652–3.
- 22. Nelson G, Kiyang LN, Crumley ET, et al. Implementation of Enhanced Recovery After Surgery (ERAS) Across a Provincial Healthcare System: the ERAS Alberta Colorectal Surgery experience. World J Surg 2016;40:1092.
- 23. Kochhar A, Banday J, Ahmad Z, et al. Pregabalin in monitored anesthesia care for ear-nose-throat surgery. Anesth Essays Res 2017;11(2):350–3.
- 24. Qiu R, Perrino AC Jr, Zurich H, et al. Effect of preoperative gabapentin and acetaminophen on opioid consumption in video-assisted thoracoscopic surgery: a retrospective study. Rom J Anaesth Intensive Care 2018;25(1):43–8.
- 25. Murphy GS, Szokol JW, Avram MJ, et al. Intraoperative methadone for the prevention of postoperative pain: a randomized, double-blinded clinical trial in cardiac surgical patients. Anesthesiology 2015;122(5):1112–22.