Pharmacotherapeutic pain management in patients undergoing laparoscopic cholecystectomy: A review

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Abstract

Laparoscopic cholecystectomy is widely performed because it results in a relatively easier pain management and shorter hospital stay. Although postoperative pain following laparoscopic cholecystectomy tends to be less intense compared to that following open cholecystectomy, early discomfort from operation after laparoscopy can be similar or even more intense than after open surgery. Consequently, it remains a source of apparent pain and surgical stress. Thus, proactive pain control is a priority for both patients and doctors. A considerable amount of new research about pain and pain management has been documented in the literature over the last 2 decades. In addition, novel medications and technologies for acute pain control after laparoscopic cholecystectomy have been investigated for patient care. Nevertheless, a significant proportion of patients still have excessively high pain levels after laparoscopic surgery. Acute pain after laparoscopic cholecystectomy is complicated in nature and has multiple causes; therefore, a single treatment modality is rarely sufficient. A combined approach to pain management is often the best option. In this review, the wide range of pharmacotherapeutic agents that have been used to control pain after laparoscopic surgery are critically assessed. The article also focuses on new techniques and medications that have been investigated in recent years to manage pain after laparoscopic surgery as quickly and safely as possible.

Key words: surgery, pain management, gallbladder, laparoscopic cholecystectomy, pharmacotherapeutics

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Introduction

The gallbladder is a small organ located in the upper right abdomen. Bile, which aids in food digestion, is stored in the gallbladder. Gallstones are solid pieces of bile that form as a result of alterations in bile composition and concentration induced by hormones, dietary changes, drugs, and rapid weight loss or gain. Gallstones can sometimes migrate out of the gallbladder, obstructing the normal flow of bile and causing gallbladder inflammation and infection. Continuous sharp abdominal discomfort, fever, nausea, and vomiting are all possible symptoms.[1] The gallbladder can be removed in a minimally invasive manner using laparoscopic cholecystectomy. The most common reasons for laparoscopic cholecystectomy are choledocholithiasis (gallstones in the bile duct), cholelithiasis (cholesterol stones) and acute cholecystitis (inflammation of the gallbladder wall).[2] Gallstones are divided into 2 types based on their composition: cholesterol stones and pigmented stones. Cholesterol stones are the more common type; they form when the amounts of cholesterol and bile salts in the gallbladder are out of equilibrium. Cholesterol can precipitate out of the bile salt-lecithin-cholesterol micelles when the concentration of bile salts drops, resulting in cholesterol stones.[3] There are 2 categories of pigmented stones: black pigment stones and brown pigment stones. Patients with high levels of unconjugated bilirubin, which are most often caused by hemolytic blood dyscrasias, and patients with bile stasis caused by gallbladder hypoactivity, which is common in patients on complete parenteral nutrition, can develop black pigment stones.[4,5] Brown pigment stones usually develop from infected bile, which causes high calcium concentrations in the bile to precipitate, resulting in stone formation. Brown stones are more likely to occur in the intrahepatic or extrahepatic ducts than in the gallbladder.[6] During a meal, the gallbladder releases bile into the small intestine to facilitate fat digestion. Gallstones can become caught in the thin conduit (cystic duct) that links the gallbladder to the main bile duct (common bile duct) during this process. Pain, nausea and vomiting can occur as the gallbladder contracts to force the bile past the blockage. This causes persistent sharp pain that primarily affects the upper abdomen, back and right shoulder. If the stone becomes entirely trapped and cannot be moved into the small intestine, it can cause cholecystitis, bile duct obstruction and pancreatic inflammation (gallstone pancreatitis).[7]

Gallstones are a common ailment in developed countries, but they are less common in developing communities that still eat traditional diets.[8] Intestinal hypomotility has recently been identified as a major contributor to cholesterol lithogenesis. Fiber may help prevent gallstone development by accelerating intestinal transit and decreasing the production of secondary bile acids, such as deoxycholate, which has been linked to a higher bile cholesterol saturation.[9–11] Gallbladder diseases can be affected by various factors, such as drugs,[12–14] diet (i.e., fried foods, fatty red meat, highly processed foods),[15] obesity,[16,17] physical activity,[18,19] gender and oral contraceptives,[20] rapid weight loss,[21,22] diabetes,[23,24] genetics,[25,26] and age,[27–29] which are presented in Fig. 1.

In this review, a wide range of pharmacotherapeutic agents that have been used to control pain after laparoscopic surgery are critically assessed. The article also focuses on new techniques and medications that have been investigated in recent years to manage pain after laparoscopic surgery as quickly and safely as possible.

Materials and methods

Sources for this review article were collected from electronic scientific databases, including ScienceDirect, PubMed, Scopus, and Google Scholar, as well as books and other reports. Various recent research and review papers were also studied to gain insight into pharmacotherapeutic treatments aimed at alleviating pain after laparoscopic surgery. Following an extensive literature survey, we collected relevant information on pain management after laparoscopic surgery. All of the collected information was classified into different sections according to the objective of the paper. To obtain the relevant articles, various keywords, namely "laparoscopic cholecystectomy", "gallbladder", "pain management", and "surgery", were used for the search. Among the 139 studies identified, 102 articles were shortlisted, and 37 articles were excluded due to insufficient data or not being suitable for the purposes of this review article. Of the 102 articles, 38 primarily focused on the introduction and factors influencing gallbladder diseases, 32 highlighted pharmacotherapeutic pain management in laparoscopic cholecystectomy using local anesthetics, 11 presented opioids used for pain management, and 21 investigated the role of non-opioids in pain management (Fig. 2).

Laparoscopic and open cholecystectomy

The gold standard for the treatment of benign gallbladder problems is laparoscopic cholecystectomy.[30] This approach can be used in 90% of elective cholecystectomies and 70% of emergency cholecystectomies.[31] Acute cholecystitis, particularly if it is thick, can alter the aforementioned paradigm, requiring conversion to open surgery or a technique adjustment. A difficult cholecystectomy is defined by the following criteria: need for conversion from laparoscopic to open surgery, length of the process greater than 180 min, blood loss greater than 300 mL, and urgent need for an experienced surgeon.[32] The gallbladder can be removed using one of two methods: open cholecystectomy or laparoscopic cholecystectomy. During an open cholecystectomy, a 10–15-cm long incision

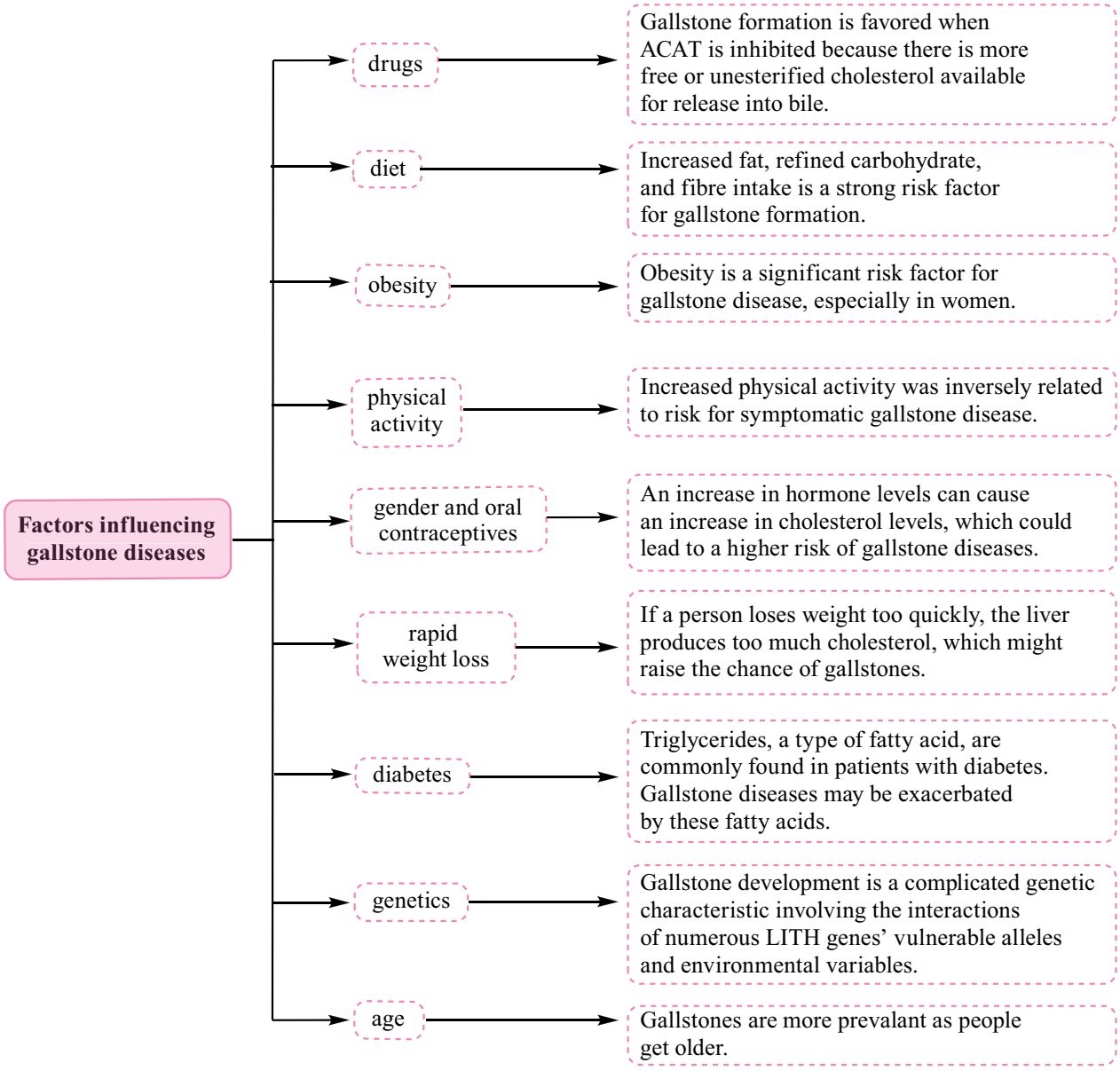


Fig. 1. Factors influencing gallstone diseases

is made in the right upper quadrant of the abdomen. The surgeon locates and removes the gallbladder through the incision. Conversely, in the laparoscopic cholecystectomy procedure, 3–4 very small incisions are performed. This technique employs a long, thin tube known as a laparoscope. A tiny video camera and surgical equipment are included in the tube. The tube, camera and instruments are inserted through the incisions. The surgeon can visualize the instruments and anatomy on video display monitors in real time. One of the incisions is used to remove the gallbladder (Fig. 3). A laparoscopic cholecystectomy is less invasive than a traditional open cholecystectomy because 3–4 tiny incisions are made in the abdomen rather than 1 large incision. There is less bleeding and, in most cases, the recovery time is shorter than following open operations. In some circumstances, the laparoscope may reveal that the gallbladder is severely diseased or unveil additional technical issues. The surgeon may then have to convert to open surgery to safely and securely remove the gallbladder. Because laparoscopic cholecystectomy has largely replaced open cholecystectomy for benign gallbladder disease, many gallbladder cancers are discovered incidentally during or after laparoscopic cholecystectomy.[33] The need for open cholecystectomies has diminished since the introduction of laparoscopic cholecystectomy. The most common reason for an open cholecystectomy (2–10% of the cases) is a conversion from a laparoscopic to an open procedure. This modification is elected for a number of reasons. Surgeons may switch to the open method if there is a concern about the anatomy of the gallbladder. Inflammation, adhesions, anatomical differences, bile duct injury, retained bile duct stones, and uncontrollable bleeding are all indications that the operation should be converted to open surgery.[34]

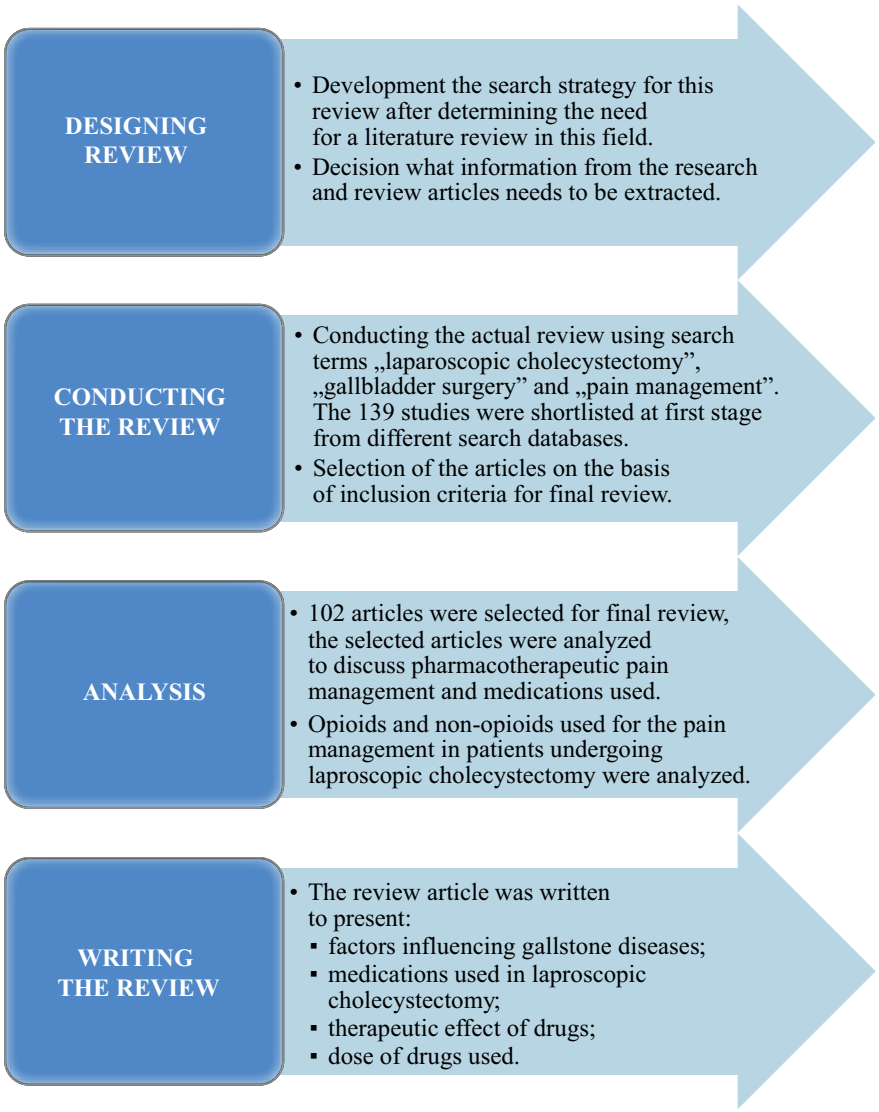


Fig. 2. The 4-step methodology adopted for conducting the literature review

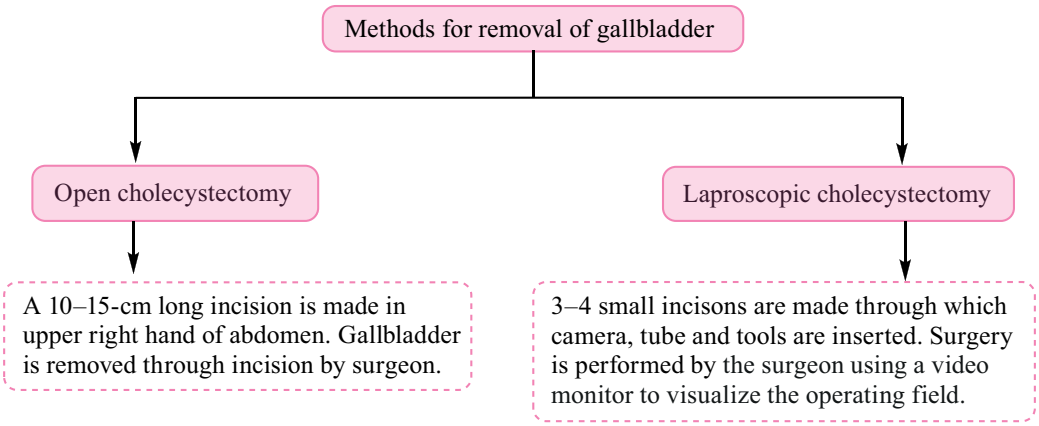


Fig. 3. Methods for gallbladder removal (open and laparoscopic cholecystectomy)

Inappropriate patient selection, surgical inexperience and technological limitations inherent in the less invasive procedure can all contribute to serious complications of laparoscopic cholecystectomy, including bile duct injury, bile leakage, hemorrhage, and intestine injury.[35,36] Diathermy burns are a common cause of ductal injuries that may go initially unreported; they mainly affect the right or common hepatic ducts. These considerations, as well as the inherent complications of biliary tract illnesses, such as inflammation and scarring, have led to the development of "stop rules" for surgeons performing this procedure. Specifically, when a safe dissection cannot be achieved laparoscopically, an early open approach should be considered the best option.[37,38]

Pharmacotherapeutic pain management during laparoscopic cholecystectomy

Laparoscopic surgery has several advantages over open surgery, including less postoperative pain, smaller incisions, shorter postoperative ileus, less blood loss, shorter hospital stay, faster recovery, and earlier return to preoperative activities and work.[39–41] Reduced postoperative pain is one of the most significant advantages of laparoscopy when compared to open surgery. However, a discomfort from the operation cannot be completely prevented, so several pharmacotherapeutic options are available.[42] Pain following laparoscopic cholecystectomy has been shown to increase morbidity and is the major cause of extended hospitalization.[43] Incisional pain may still be present at the laparoscopic port insertion sites. Abdominal discomfort can vary in intensity and is linked to the extent of surgery and manipulation.[44]

Patients commonly complain of upper abdominal, back and right shoulder pain, as well as discomfort from the port incision sites. Shoulder and subdiaphragmatic discomfort affect between 12% and 60% of patients. The level of discomfort peaks within the first few hours after surgery and usually decreases after 2 or 3 days.[45–47] Pain following laparoscopic cholecystectomy has a complex origin. Peritoneal insufflation with CO_2 and phrenic nerve irritation in the peritoneal cavity are 2 possible causes of discomfort after laparoscopy.[48–50] In fact, in laparoscopic cholecystectomy, the acidic environment formed by CO_2 gas dissolution can cause peritoneal irritation and phrenic nerve injury. Effective pain relief is of the utmost importance for anyone treating patients undergoing surgery.

One of the most important aspects of enhanced recovery after surgery (ERAS) programs, and indeed all anesthetic care, is effective analgesia. It is important for minimizing postoperative stress, encouraging a return to regular functions like breathing, eating and sleeping, and supporting early mobilization. It may also help reduce organ dysfunction and expedite hospital discharge.[51] Various medications are used to relieve pain during and after laparoscopic cholecystectomy.

Local anesthetics

Lidocaine

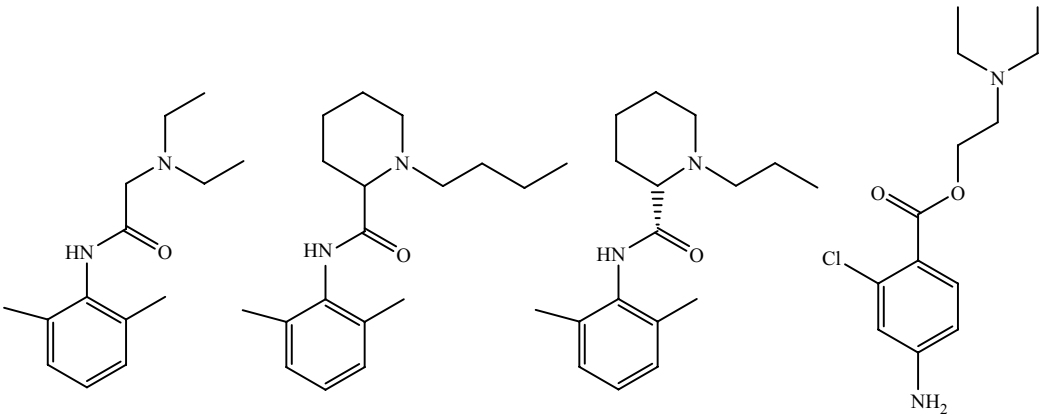
Lidocaine 1 (Fig. 4) is an amino-amide local anesthetic that reduces neuronal transmission by inhibiting sodium channels. It provides analgesia, reduces the need for opioids, and alleviates nausea and vomiting symptoms. It also reduces the risk of ileus when administered as a systemic infusion.[52] Local anesthetics block nociceptive input into the central nervous system, have anti-inflammatory properties and are often very helpful in neuropathic pain. Furthermore, selective sympathetic blockade can be particularly beneficial for visceral pain at lower local anesthetic dosages. Unfortunately, the therapeutic ratio of local anesthetics for pain management after laparoscopy is low. Intravenous local anesthetics are linked to neurological and tissue toxicity at higher tissue and systemic doses, and high plasma concentrations can have substantial negative central nervous system and cardiovascular consequences. Furthermore, interindividual variability in local anesthetic tolerance exists.[53] Intravenous lidocaine infusion (lidocaine is given at steady rate at low doses) is a good alternative for postoperative pain relief for these reasons.[54] Different doses have been used; typically, a bolus of 1–1.5 mg/kg is administered, followed by a 2–3 mg/kg/h infusion that lasts until the completion of surgery or for the first 24 h afterwards.[55] Neurological changes, such as lightheadedness, dizziness and visual disturbances, as well as cardiac dysrhythmias are extremely rare side effects of perioperative lidocaine infusion.[56]

Intraperitoneal instillation and nebulization

Intraperitoneal instillation of local anesthetics has been used in laparoscopic cholecystectomy to lessen postoperative pain and the need for postoperative analgesics.[57] After laparoscopic cholecystectomy, intraperitoneal instillation of bupivacaine 2 (Fig. 4) 100 mg with adrenaline was as efficacious as a similar volume (80 mL) of normal saline.[58] Surgical maneuvers, disturbance of the peritoneum and dissection of the viscera cause peritoneal nerve irritation, resulting in visceral and shoulder pain during and after laparoscopic cholecystectomy. Sedation, nausea, delayed stomach emptying, and respiratory depression are all adverse effects of using opioids to manage this pain. Therefore, according to various studies, instillation and nebulization of local anesthetics into the peritoneal cavity can be used to reduce discomfort following laparoscopic surgery as an alternative to opioids. Sandhya et al. investigated and employed ropivacaine 3 (Fig. 4) for intraperitoneal nebulization because it has lower toxicity and is as effective as bupivacaine.[59] Dose-finding research discovered that 50 mg of nebulized ropivacaine provided acceptable analgesia in individuals undergoing laparoscopic cholecystectomy. An increase in the ropivacaine dose did not result in any additional benefits. Pain alleviation was adequate for patients administered a smaller dose of 30 mg of ropivacaine.[59] (Fig. 4).

Central neuraxial blocks

Studies have found that epidural analgesia using bupivacaine 2 or chloroprocaine 4 (Fig. 4) was superior to intravenous opioid analgesia for pain control after laparoscopic surgery.[60] The use of epidural analgesia appears to be safe and



Lidocaine **1** Bupivacaine **2** Ropivacaine **3** Chloroprocaine **4**

Fig. 4. Local anesthetics for pain management during laparoscopic cholecystectomy

effective after major abdominal laparoscopic surgery. However, it is associated with longer hospital stays and higher rates of urinary tract infections; these are the consequences of urinary catheters, which often accompany this treatment method.[61] Anticoagulants and other drugs that impair hemostatic function are becoming more widely used, which may limit the use of epidural analgesia during laparoscopic surgery, despite its effectiveness in pain control. Intrathecal indwelling catheters are also linked to an increased risk of infectious problems, which is concerning given the multidrug-resistant bacterial outbreaks that have become common over the last 2 decades. As a result, following careful analysis of the risks and benefits, the decision to use epidural analgesia should be made on an individual basis.[62]

Transversus abdominis plane block

A transversus abdominis plane (TAP) block is a peripheral nerve block that achieves abdominal wall anesthesia. The procedure can be performed using a surface landmark-based technique, laparoscopically or with ultrasound guidance. Proponents believe that TAP blocks have a lower risk of complications and are more acceptable to patients than epidural analgesia. Research has examined the effects of TAP rectus sheath blocks on pain relief following abdominal surgery, but there is not enough information on the method of localization, timing, dosages, and volumes of local anesthetic. Transversus abdominis plane blocks are obviously influenced by operator skill and can be unpredictable.[63] Use of TAP blocks in colorectal surgery has been the subject of recent research. Transversus abdominis plane blocks plus intravenous acetaminophen in laparoscopic colorectal surgery resulted in earlier resumption of eating and discharge from hospital in an accelerated recovery regimen compared to patient-controlled analgesia (PCA) with morphine.[64] In an open right hemicolectomy study from 2012, TAP+PCA was compared with subcutaneous local infiltration+PCA.[65] In the TAP arm, there was less PCA morphine use and less sedation after 24 h. Similarly, Conaghan et al. found that TAP+PCA reduced intravenous opioid use in laparoscopic colorectal resections compared to PCA alone. Although there are data showing that TAP blocks improve pain scores and reduce opioid consumption following abdominal surgery, more research is needed to compare TAP blocks with other pain management methods, such as epidural anesthesia.[66]

Ultrasound-guided TAP nerve blocks have become a common analgesic method after abdominal wall surgery. Because TAP blocks are confined to somatic anesthesia of the abdominal wall and are heavily reliant on interfascial dissemination, a number of innovative approaches have been developed to improve analgesia, either in conjunction with TAP nerve blocks or as standalone modalities.[67]

Several trials have determined that ultrasound-guided TAP blocks, as a part of a multimodal analgesic approach to postoperative analgesia, increase patient satisfaction and reduce opioid use. Given that the greatest amount of pain during the 24 h after laparoscopic cholecystectomy occurs at the trocar sites, it is critical to determine the best time to perform TAP blocks (before or after surgery) to maximize block effectiveness. Rahimzadeh et al. found that ultrasound-guided TAP blocks reduced the use of pethidine in the postoperative group compared to the preemptive group, thus lowering opioid analgesic side effects, including nausea, vomiting, pruritus, and dizziness. A transversus abdominis plane block is an affordable, straightforward and easy-to-perform treatment that can be used as part of a multimodal analgesic strategy.[68]

Incisional infiltration of local anesthetic

Local anesthetics are widely used in numerous medical and surgical specialties, including anesthesia, ophthalmology, otorhinolaryngology, dentistry, urology, and aesthetic surgery. They cause superficial loss of pain sensation after direct injection. Their delivery and effectiveness can be enhanced by using free bases, increasing the drug concentration, lowering the melting point, employing physical and chemical permeation enhancers, and using lipid delivery vesicles. Several studies have found that local anesthesia reduces postoperative pain after laparoscopic procedures, but there are few data on the effect of local

anesthesia on nausea in the postoperative period.[69] Inan et al. examined the effects and timing of local anesthesia during laparoscopic surgery on postoperative pain, nausea, and opioid and antiemetic requirements. Their prospective study included 142 individuals who underwent laparoscopic cholecystectomy. Fifty-three individuals did not receive any local anesthetics during surgery (group A). In group B, 46 patients had their skin, subcutis, fascia and parietal peritoneum infiltrated with 0.5% bupivacaine hydrochloride at the trocar sites prior to insertion. At the conclusion of surgery, local anesthetic was administered in similar doses and in the same manner to the remaining 43 patients (group C). When compared to patients in groups B and C, group A had a statistically significantly higher requirement for analgesics. The mean analgesic doses were substantially higher in group B than in group C after surgery. In group A, the period between the first antiemetics was much shorter than in group C. Using trocar sites to administer local anesthetic to the skin, subcutis, fascia, and parietal peritoneum lowered the need for postoperative analgesics as well as pain severity.[70]

Opioids

Opioids are the most commonly recommended drugs for the treatment of acute and chronic postoperative pain. The greatest challenges to successful opioid analgesia are underestimation of pain, prolonged duration of action and fear of addiction. Opioid receptors in the cell membranes of the presynaptic nerve terminals in the central nervous system mediate the bulk of the pharmacological actions of opioids.[71] Opioids have long been considered an important aspect of postoperative pain management, but they have many negative effects, including urinary retention, ileus, nausea, vomiting, pruritus, respiratory depression, and central nervous system depression. In surgical patients, these side effects are linked to higher mortality, longer duration of stay, greater risk of readmission, and higher healthcare expenses. Therefore, constant monitoring of breathing and oxygen saturation in patients using opioids after surgery is critical.[72] Despite years of progress in pain management, opioids remain the basis of postoperative pain management in many situations. Numerous opioids used for postoperative pain management in laparoscopic cholecystectomy are discussed below (Fig. 5).

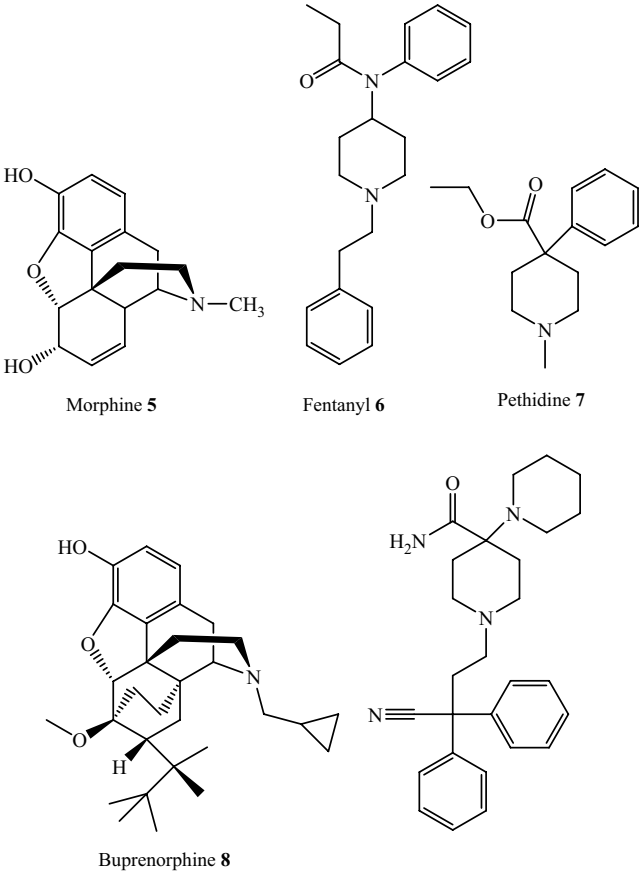


Fig. 5. Opioid drugs used in pain management during laparoscopic cholecystectomy

Morphine

Morphine 5 (Fig. 5) is the most common opiate. At one time, it was the gold standard for postoperative pain. It has a quick onset of action, with a peak effect of 1–2 h. Fentanyl and hydromorphone are synthetic derivatives of morphine that are more potent, have faster onsets of action and shorter half-lives. Only a few pain studies have compared morphine to other opioids following laparoscopy. Naguib et al. found that morphine is superior to tramadol in terms of perioperative pain control for patients undergoing laparoscopic cholecystectomy. In a small study of people who underwent laparoscopic colorectal surgery, epidural ropivacaine 2 mg/mL was contrasted with intravenous morphine for postoperative pain relief. Although epidural ropivacaine had significant opioid-sparing efficacy and sooner recovery of bowel movement, 20% of patients experienced motor block.[73] In addition, a low dose of intrathecal morphine appears to be particularly beneficial in controlling pain following laparoscopy. Patients undergoing laparoscopic colorectal surgery received a 15 mg bupivacaine spinal injection with or without 0.2 mg morphine. At this low dose, morphine was extremely effective. Throughout the first 24 postoperative hours, both rescue intravenous morphine use (10 mg compared to 30 mg) and dynamic pain levels were markedly lower in the bupivacaine and morphine group compared to the intrathecal bupivacaine only group.[74]

Fentanyl

Fentanyl 6 (Fig. 5) is an artificial opioid agonist that has a potency of 100 times that of morphine and 75 times that of oxycodone. Fentanyl is a lipophilic drug that quickly enters the central nervous system. Intravenous fentanyl

is commonly used for anesthesia and analgesia during surgery.[75] Fentanyl is mainly metabolized in the liver and intestinal mucosa, so it is not administered orally. Fentanyl, like oxycodone, is rapidly absorbed by mucosal membranes after intraoral and intranasal administration. Transmucosal fentanyl may be a viable approach to acute pain management. However, transmucosal delivery is only used to treat cancer pain that has become unbearable. The most important concern with the use of fentanyl for acute pain management is its low utility function, which means that the dosage required for effective pain relief is higher than the dose that can cause respiratory depression.[76]

Pethidine (meperidine)

Pethidine has been used for many years to relieve pain caused by laparoscopic surgery. However, because it contains an active metabolite (norpethidine) that is toxic to the central nervous system, it is not the ideal opioid. Norpethidine has a 14–21-hour elimination half-life, which can extend to 35 h in cases of renal failure. When pethidine 7 (Fig. 5) is administered in high doses, the level of norpethidine rises, putting vulnerable patients at risk of side effects.[77] Intraperitoneal pethidine with or without local anesthetic instillation was compared by Fogach et al. to intramuscular pethidine and intraperitoneal local anesthetic instillation. In addition to the toxicity of the metabolite norpethidine on the central nervous system, the parent chemical pethidine causes local discomfort.[78]

Buprenorphine

Buprenorphine 8 (Fig. 5) can operate as both an opioid agonist and antagonist. This chemical is a viable option for pain management in laparoscopy because both injectable and sublingual versions are available. It has 30 times the analgesic effectiveness of morphine in opioid-naïve patients. Buprenorphine has high transmucosal absorption, and the analgesia lasts substantially longer (6–8 h) than when morphine is used. No dose adjustments are required for elderly patients and patients with diminished renal function. Buprenorphine has a generally favorable safety profile; it rarely causes clinically significant respiratory depression, euphoria or sedation. Buprenorphine has a positive utility function.[79]

Piritramide

Piritramide 9 (Fig. 5), a 4-amino piperidine derivative, is used in several European countries and is structurally similar to pethidine. Piritramide has a wide volume of distribution (4.7 L/kg) and a long terminal half-life (7–8 h). It is almost entirely processed by the liver, with only approx. 1% being removed by the kidneys.[80] The analgesic potency of piritramide is comparable to that of morphine; a dose of 15–20 mg administered intramuscularly provides analgesia similar to 10–15 mg of morphine administered intramuscularly, and the analgesic ratio with oxycodone ranges between 1.6 and 2.2 (piritramide:oxycodone).[81]

Non-opioids

Opioid receptor agonist medications are being increasingly used for the treatment of a wide range of chronic pain problems. Tolerance and opioid-induced hyperalgesia can develop as a result of opioid use, which can contribute to long-term postsurgical pain. Furthermore, opioid use in the postoperative setting has been associated with a higher risk of persistent opioid addiction, which is particularly concerning considering the current national opioid abuse epidemic.[82] As a result, enhanced recovery pathways (ERPs) normally use opioid drugs sparingly, only when other therapies have failed, and only in conjunction with non-opioid analgesic treatments (Table 1).[83] Patients with chronic pain who are taking opioids before surgery are more likely to encounter significant postoperative pain, poor postoperative pain control, and opioid-related adverse effects. Hence, non-opioid analgesic modalities are especially important for this patient population. Several non-opioid medications used in pain management in patients undergoing laparoscopic cholecystectomy are discussed below (Fig. 6).

Nonsteroidal anti-inflammatory drugs

Ibuprofen, ketorolac and celecoxib are examples of nonsteroidal anti-inflammatory drugs (NSAIDs) that cause analgesia by blocking the cyclooxygenase enzyme and interrupting prostaglandin synthesis.[84–86] Nonsteroidal anti-inflammatory drugs are significant adjuncts in a multimodal analgesia regimen for the management of postoperative pain and are effective therapies for postoperative pain.[87] When NSAIDs and acetaminophen are used together, they have an additive or potentially synergistic analgesic effect. Furthermore, NSAID use has been linked to a reduced likelihood of opioid-related side effects, such as nausea, vomiting and drowsiness. Nonsteroidal anti-inflammatory drugs are associated with an increased risk of gastrointestinal ulcers, bleeding and renal impairment despite the fact that they are generally well tolerated. Celecoxib, an NSAID that selectively inhibits the cyclooxygenase-2 (COX-2) enzyme, may lessen the risk of gastrointestinal disturbances and bleeding. It should be noted, however, that COX-2 inhibitors are usually avoided following cardiac surgery because they increase the risk of negative cardiovascular consequences.[88] The inhibition of the enzyme cyclooxygenase is the principal mechanism of action of NSAIDs. Arachidonic acid is converted into thromboxane, prostaglandins and prostacyclin by the enzyme cyclooxygenase. The absence of these eicosanoids is thought to be responsible for the therapeutic effects of NSAIDs.[89]

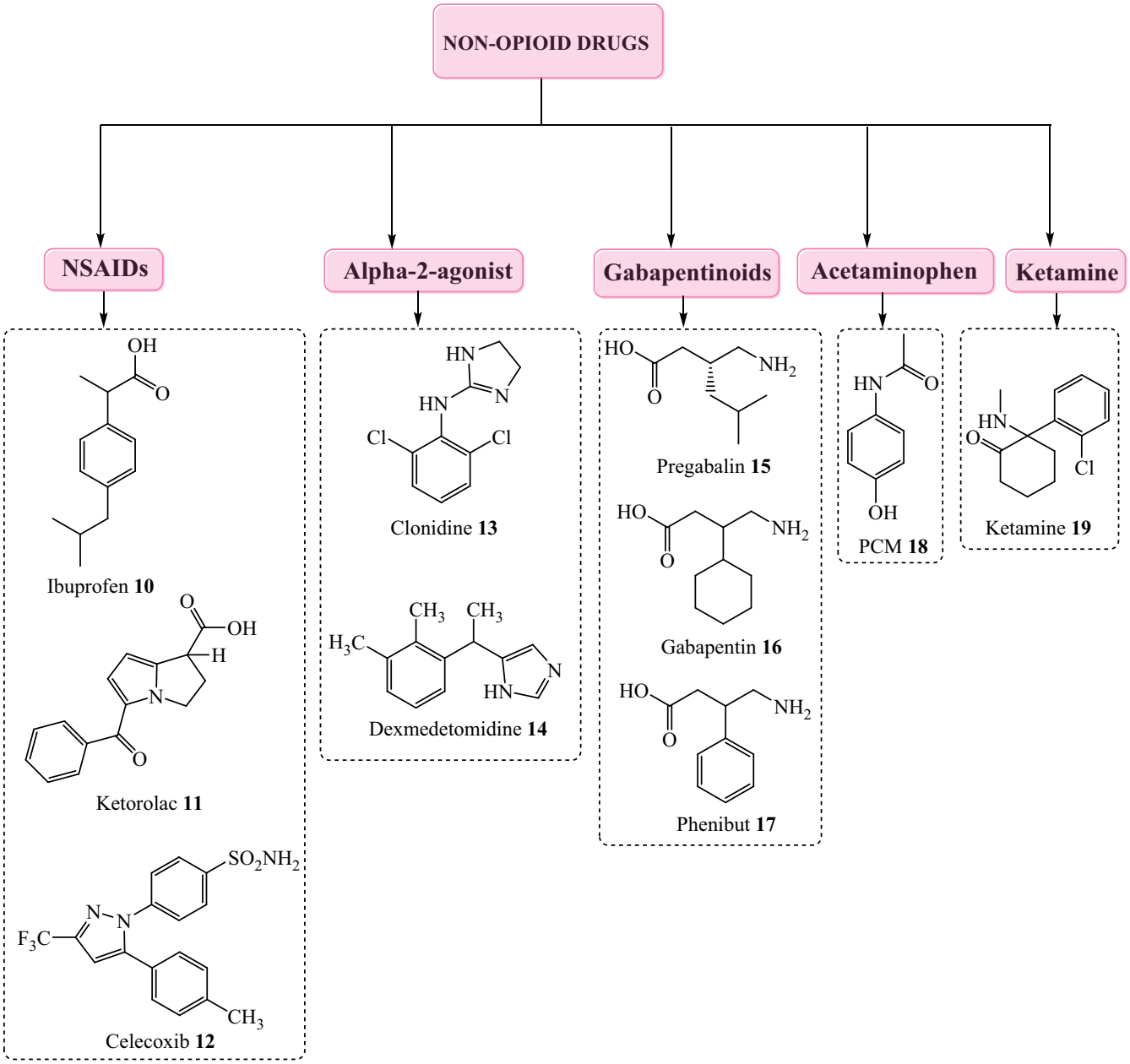


Fig. 6. Structures of non-opioid drugs used in pain management during laparoscopic cholecystectomy

Alpha-2 agonists

Analgesia can be produced by alpha-2 agonists, such as clonidine and dexmedetomidine, which stimulate alpha-2 receptors in the dorsal horn of the spinal cord and reduce nociceptive signal transmission. While these medications can be administered in a variety of ways, clonidine is usually administered intravenously or orally for postoperative pain relief, while dexmedetomidine is usually administered intravenously. Despite the lack of data to support these claims, clonidine and dexmedetomidine can be administered as adjuvants in epidurals and peripheral nerve plugs to potentially improve and prolong analgesia.[90] A study conducted by Rabie and Abdelfattah demonstrated that in patients undergoing laparoscopic cholecystectomy, an intravenous infusion of 0.6 g/kg/h dexmedetomidine before induction can minimize hemodynamic stress, incidence of cough, postoperative nausea and vomiting, as well as reduce postoperative analgesic requirements, without significantly prolonging the spontaneous respiratory recovery period.[91] Alpha-2 agonists work by stimulating presynaptic alpha-2 receptors, which activate inhibitory neurons in the central nervous system, resulting in a decrease in sympathetic output via a signaling pathway.[92]

Gabapentinoids

Gabapentinoids, such as gabapentin and pregabalin, are antiepileptic drugs that work by inhibiting voltage-gated calcium channels to generate analgesia. Traditionally, these

Table 1. Nonopioid drugs used in pain management in laparoscopic cholecystectomy

Nonopioid drugs	Description	Advantages	Disadvantages
NSAIDs	NSAIDs such as ibuprofen,[10] ketorolac[11] and celecoxib[12] produce analgesia by inhibiting prostaglandin synthesis through inhibiting the cyclooxygenase enzyme.	Better pain control, synergistic analgesic effect when paired with acetaminophen, reduced opioid consumption.	Gastrointestinal ulcers, bleeding, renal dysfunction, and cardiovascular problems are all possible side effects. After colorectal surgery, it may be associated with anastomotic leak.
Alpha-2 agonists	Analgesia is produced by alpha-2 agonists such as clonidine[13] and dexmedetomidine,[14] which stimulate alpha-2 receptors in the dorsal horn of the spinal cord and reduce nociceptive signal transmission.	Better pain control, reduced opioid usage; used as a supplement to regional anesthetic techniques.	Sedation, hypotension and bradycardia are all possible side effects. There is little evidence to support its usage in the postoperative situation.
Gabapentinoids	Gabapentinoids, such as pregabalin,[15] gabapentin[16] and phenibut,[17] are antiepileptic drugs that work by inhibiting voltage-gated calcium channels to generate analgesia.	Reduced reliance on opioids, improved pain control.	Sedation risk, vision impairment and respiratory depression. Cautious use required in patients with renal insufficiency. Available only in oral forms. Optimal dose regimen uncertain.
Acetaminophen	In ERPs, acetaminophen (PCM)[18] is a key component of multimodal postoperative pain management. Though the exact etiology is uncertain, its analgesic effect is thought to be mediated mostly by cyclooxygenase pathway inhibition.	When used with nonsteroidal anti-inflammatory medicines, it has a synergistic analgesic effect. Generally well-tolerated, better pain management, opioid needs are reduced.	Hepatotoxicity at larger doses should be avoided in persons with liver disease.
Ketamine	Ketamine[19] is a dissociative anesthetic that blocks the transmission of pain signals by antagonizing NMDA receptors in the brain and spinal cord.	Lower risk of opioid-induced hyperalgesia and tolerance, reduced opioid usage, better pain control.	Optimal dose regimen unknown in individuals with cardiovascular illness, hepatic impairment, high intracranial and intraocular pressure, active psychosis, and pregnancy. Neuropsychiatric symptoms are a possibility.

NSAIDs – nonsteroidal anti-inflammatory drugs; ERP – Enhanced Recovery Pathway; NMDA – N-methyl-D-aspartate.

medications have been used to treat chronic neuropathic pain. There is research suggesting that gabapentinoids may lower initial postoperative pain, opiate requirements, and postoperative nausea and vomiting when used perioperatively.[93] Gabapentinoids, however, have been linked to drowsiness, visual abnormalities and dizziness, all of which can impair early postoperative mobilization and delay recovery. Furthermore, perioperative gabapentin use has been linked to an increased risk of respiratory depression, particularly in older patients and those taking large opioid doses.[94] Gabapentinoids are commonly prescribed for neuropathic pain, restless legs syndrome and focal seizures. Their effectiveness in these conditions is due to their ability to inhibit the actions of the α2δ subunits of presynaptic voltage-gated calcium channels and thereby lower neurotransmitter release.[95]

Acetaminophen

Acetaminophen is a key component of multimodal postoperative pain management in ERPs. Although its exact mechanism of action is unknown, its analgesic impact is considered to be mediated mostly through suppression of the cyclooxygenase pathway. In nearly half of patients with mild to severe acute postoperative pain, a single dose of acetaminophen has been shown to offer 50% pain reduction for 4 h. When acetaminophen is used with NSAIDs, the analgesic effect can be additive or even synergistic. Furthermore, acetaminophen use has been linked to a lower need for opioids throughout the postoperative period.[96] Thus, oral acetaminophen is recommended in people who can tolerate it, while intravenous acetaminophen is effective in patients who cannot tolerate oral consumption or have reduced gastrointestinal tract function.[97] Acetaminophen works by inhibiting cyclooxygenases (COX-1, COX-2 and COX-3) as well as interfering with the endocannabinoid system and serotonergic pathways.[98] According to the study conducted by Mulita et al., the combinations of pethidine/acetaminophen and parecoxib/acetaminophen exhibited equivalent analgesic effectiveness and proved better than acetaminophen monotherapy for the management of postoperative pain following laparoscopic cholecystectomy. Reducing opioid doses by using postoperative non-opioid analgesics is a vital strategy to limit drowsiness, reduced pulmonary function and constipation in postsurgical patients.[99]

Ketamine

Ketamine is a dissociative anesthetic that blocks the transmission of pain signals by antagonizing N-methyl-D-aspartate (NMDA) receptors in the brain and spinal cord. Subanesthetic intravenous ketamine infusions have been found to minimize opiate usage and enhance pain control without creating significant side effects.[100] Ketamine is a glutamate and NMDA receptor antagonist that is noncompetitive. It works by blocking HCN1 receptors. The specific dissociative action and partial agonism of opiate μ-receptors allow for persistent sedation and patient

comfort throughout painful procedures.[101] Ketamine has also been proven to minimize the incidence of postoperative nausea and vomiting when combined with an opioid regimen. Ketamine could potentially assist in preventing opioid-induced hyperalgesia and tolerance from developing. However, it is uncertain if ketamine use during surgery lessens the likelihood of persistent postsurgical discomfort. Neuropsychiatric symptoms, such as hallucinations and nightmares, are the most common negative consequences linked to the use of subanesthetic dosages of ketamine in the postoperative environment.[102]

Limitations of the study

Despite the extensive research conducted in this review article on pain management in patients undergoing laparoscopic cholecystectomy, there are some limitations. The mechanisms of action of some treatments are not fully described. In addition, the article focuses solely on the medications used in pain management of laparoscopic cholecystectomy, as well as the doses used. However, the pharmacokinetics and side effects of these drugs are not explained in detail. There is no diagrammatic representation of the laparoscopic cholecystectomy procedure. Some articles were excluded because they did not meet our requirements.

Conclusions

Gallstones are solid pieces of bile that form as a result of changes in bile concentration and composition. They can cause sharp, constant abdominal pain, fever, nausea, and vomiting. Gallstones are divided into 2 types based on their composition: cholesterol stones and pigmented stones. Gallstones are a common ailment in developed countries but less common in developing communities that still eat traditional diets. Gallbladder diseases can be influenced by many factors, including age, genetics, diabetes, physical activity, drugs, obesity, rapid weight loss, gender, and oral contraceptives. Sedentary lifestyle is linked to an increased risk of cholecystectomy. Increased estrogen levels in the bile as a result of pregnancy or hormone therapy may cause gallstone formation. Gallbladder contraction is reduced during fasting associated with severely fat-restricted diets. The gallbladder can be removed using one of the two methods: open cholecystectomy or laparoscopic cholecystectomy. A laparoscope is a long, thin tube with a video camera and surgical equipment inserted into it. Three to four tiny incisions are made in the abdomen to introduce the surgical instruments. The need for an open cholecystectomy has diminished since the introduction of laparoscopic surgery, but the surgeon may convert to the open method if there is a concern about anatomy or other challenges.

Pain following laparoscopic cholecystectomy has a complex origin. Numerous medications are used to relieve pain during and after surgery. Local anesthetics block nociceptive input into the central nervous system, have anti-inflammatory properties, and are often very helpful in neuropathic pain. Morphine is superior to tramadol in terms of perioperative pain control. Fentanyl is a very powerful lipophilic opiate that quickly enters the central nervous system. The use of epidural ropivacaine resulted in considerable opioid sparing and faster bowel movement recovery. Pethidine is inadequate for pain reduction at a dose of 50 mg. Buprenorphine has 30 times the analgesic effectiveness of morphine in opioid-naïve patients. Piritramide resembles pethidine structurally. Tolerance and opioid-induced hyperalgesia can develop as a result of opioid use. Nonsteroidal anti-inflammatory drugs are significant supplements to a multimodal analgesic regimen for the management of postoperative pain. The COX-2 inhibitors are normally avoided following cardiac surgery. Gabapentinoids are antiepileptic medications that work by inhibiting voltage-gated calcium channels to generate analgesia. Acetaminophen is a key component of multimodal postoperative pain management. Ketamine has been proven to minimize the incidence of postoperative nausea and vomiting.

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References

1. Kim SS, Donahue TR. Laparoscopic cholecystectomy. *JAMA*. 2018; 319(17):1834. doi:10.1001/jama.2018.3438
2. Sartin J. Alterations in function of the gallbladder and exocrine pancreas. In: Copstead LE, Banasik JL, eds. *Study Guide for Pathophysiology*. 5th ed. London, UK: Elsevier Health Sciences; 2013:741–752. http://public.ebookcentral.proquest.com/choice/publicfullrecord.aspx?p=2074388. Accessed July 14, 2022.
3. Carey MC. Pathogenesis of gallstones. *Am J Surg*. 1993;165(4):410–419. doi:10.1016/S0002-9610(05)80932-8
4. Tazuma S. Gallstone disease: Epidemiology, pathogenesis, and classification of biliary stones (common bile duct and intrahepatic). *Best Pract Res Clin Gastroenterol*. 2006;20(6):1075–1083. doi:10.1016/j.bpg.2006.05.009
5. Trotman BW. Pigment gallstone disease. *Gastroenterol Clin North Am*. 1991;20(1):111–126. PMID:2022417.
6. Lammert F, Gurusamy K, Ko CW, et al. Gallstones. *Nat Rev Dis Primers*. 2016;2(1):16024. doi:10.1038/nrdp.2016.24
7. Baiu I, Hawn MT. Gallstones and biliary colic. *JAMA*. 2018;320(15):1612. doi:10.1001/jama.2018.11868
8. Schwesinger WH, Kurtin WE, Page CP, Stewart RM, Johnson R. Soluble dietary fiber protects against cholesterol gallstone formation. *Am J Surg*. 1999;177(4):307–310. doi:10.1016/S0002-9610(99)00047-1
9. LaMont JT, Smith BF, Moore JRL. Role of gallbladder mucin in pathophysiology of gallstones. *Hepatology*. 1984;4(5 Suppl):51S–56S. doi:10.1002/hep.1840040809
10. Marcus SN, Heaton KW. Effects of a new, concentrated wheat fibre preparation on intestinal transit, deoxycholic acid metabolism and the composition of bile. *Gut*. 1986;27(8):893–900. doi:10.1136/gut.27.8.893
11. Njeze GE. Gallstones. *Niger J Surg*. 2013;19(2):49–55. doi:10.4103/1117-6806.119236
12. Kurtin WE, Schwesinger WH, Diehl AK. Age-related changes in the chemical composition of gallstones. *Int J Surg Investig*. 2000; 2(4):299–307. PMID:12678532.
13. Diehl AK, Sugarek NJ, Todd KH. Clinical evaluation for gallstone disease: Usefulness of symptoms and signs in diagnosis. *Am J Med*. 1990; 89(1):29–33. doi:10.1016/0002-9343(90)90094-T

14. Liddle RA, Goldstein RB, Saxton J. Gallstone formation during weight-reduction dieting. *Arch Intern Med*. 1989;149(8):1750–1753. PMID:2669662.
15. Raghu T. Dietary factors influencing the pathogenesis of gallstone disease in Kerala, India. *IJARS*. 2021;10(2):SO01–SO04. https://www.ijars.net/article_fulltext.asp?issn=0973-709x&year=2021&month=April&volume=10&issue=2&page=SO01-SO04&id=2615. Accessed May 29, 2022.
16. Bonfrate L, Wang DQH, Garruti G, Portincasa P. Obesity and the risk and prognosis of gallstone disease and pancreatitis. *Best Pract Res Clin Gastroenterol*. 2014;28(4):623–635. doi:10.1016/j.bpg.2014.07.013
17. Trotman BW, Petrella EJ, Soloway RD, Sanchez HM, Morris TA, Miller WT. Evaluation of radiographic lucency or opaqueness of gallstones as a means of identifying cholesterol or pigment stones: Correlation of lucency or opaqueness with calcium and mineral. *Gastroenterology*. 1975;68(6):1563–1566. PMID:1093922.
18. Donovan JM, Carey MC. Physical-chemical basis of gallstone formation. *Gastroenterol Clin North Am*. 1991;20(1):47–66. PMID:2022425.
19. Aune D, Leitzmann M, Vatten LJ. Physical activity and the risk of gallbladder disease: A systematic review and meta-analysis of cohort studies. *J Phys Act Health*. 2016;13(7):788–795. doi:10.1123/jpah.2015-0456
20. Valdivieso V, Covarrubias C, Siegel F, Cruz F. Pregnancy and cholelithiasis: Pathogenesis and natural course of gallstones diagnosed in early puerperium. *Hepatology*. 1993;17(1):1–4. PMID:8423030.
21. Gebhard RL, Prigge WF, Ansel HJ, et al. The role of gallbladder emptying in gallstone formation during diet-induced rapid weight loss. *Hepatology*. 1996;24(3):544–548. doi:10.1002/hep.510240313
22. Capron JP, Delamarre J, Herve MA, Dupas JL, Poulain P, Descombes P. Meal frequency and duration of overnight fast: A role in gall-stone formation? *Br Med J (Clin Res Ed)*. 1981;283(6304):1435. doi:10.1136/bmj.283.6304.1435
23. Aune D, Vatten LJ. Diabetes mellitus and the risk of gallbladder disease: A systematic review and meta-analysis of prospective studies. *J Diabetes Complications*. 2016;30(2):368–373. doi:10.1016/j.jdiacomp.2015.11.012
24. Koppisetti S, Jenigiri B, Terron MP, et al. Reactive oxygen species and the hypomotility of the gall bladder as targets for the treatment of gallstones with melatonin: A review. *Dig Dis Sci*. 2008;53(10):2592–2603. doi:10.1007/s10620-007-0195-5
25. Nakeeb A, Comuzzie AG, Martin L, et al. Gallstones: Genetics versus environment. *Ann Surg*. 2002;235(6):842–849. doi:10.1097/00000658-200206000-00012
26. Chuang SC, Hsi E, Lee KT. Genetics of gallstone disease. *Adv Clin Chem*. 2013;60:143–185. doi:10.1016/b978-0-12-407681-5.00005-2
27. Lopushinsky SR, Urbach DR. Gallstone disease in the elderly: Diagnosis and management. *Aging Health*. 2005;1(3):441–447. doi:10.2217/1745509X.1.3.441
28. Paumgartner G, Gerok W, Bertolotti M, Bortolotti S, Menozzi D. Ageing and bile acid metabolism: Studies on 7α hydroxylation of cholesterol in humans. In: Paumgartner G, Stiehl A, Gerok W, eds. *Trends in Bile Acid Research*. Proceedings of the 52nd Falk Symposium held in Freiburg, Federal Republic of Germany, June 9–11, 1988. Dordrecht, the Netherlands: Kluwer Academic Publishers; 1989:75–78. ISBN: 0746201125.
29. Einarsson K, Nilsell K, Leijd B, Angelin B. Influence of age on secretion of cholesterol and synthesis of bile acids by the liver. *N Engl J Med*. 1985;313(5):277–282. doi:10.1056/NEJM198508013130501
30. Purzner RH, Ho KB, Al-Sukhni E, Jayaraman S. Safe laparoscopic subtotal cholecystectomy in the face of severe inflammation in the cystohepatic triangle: A retrospective review and proposed management strategy for the difficult gallbladder. *Can J Surg*. 2019;62(6):402–411. doi:10.1503/cjs.014617
31. Taki-Eldin A, Badawy AE. Outcome of laparoscopic cholecystectomy in patients with gallstone disease at a secondary level care hospital. *Arq Bras Cir Dig*. 2018;31(1):e1347. doi:10.1590/0102-672020180001e1347
32. Maehira H, Kawasaki M, Itoh A, et al. Prediction of difficult laparoscopic cholecystectomy for acute cholecystitis. *J Surg Res*. 2017;216:143–148. doi:10.1016/j.jss.2017.05.008
33. Zhao X, Li X, Ji W. Laparoscopic versus open treatment of gallbladder cancer: A systematic review and meta-analysis. *J Min Access Surg*. 2018;14(3):185–191. doi:10.4103/jmas.JMAS_223_16
34. Jones MW, Guay E, Deppen JG. Open cholecystectomy. In: *StatPearls*. Treasure Island, USA: StatPearls Publishing; 2022. http://www.ncbi.nlm.nih.gov/books/NBK448176/. Accessed July 14, 2022.
35. Khan MH, Howard TJ, Fogel EL, et al. Frequency of biliary complications after laparoscopic cholecystectomy detected by ERCP: Experience at a large tertiary referral center. *Gastrointest Endosc*. 2007;65(2):247–252. doi:10.1016/j.gie.2005.12.037
36. Binenbaum SJ, Goldfarb MA. Inadvertent enterotomy in minimally invasive abdominal surgery. *JSLS*. 2006;10(3):336–340. PMID:17212891.
37. Strasberg SM. Biliary injury in laparoscopic surgery. Part 1. Processes used in determination of standard of care in misidentification injuries. *J Am Coll Surg*. 2005;201(4):598–603. doi:10.1016/j.jamcollsurg.2005.05.009
38. Strasberg SM. Biliary injury in laparoscopic surgery. Part 2. Changing the culture of cholecystectomy. *J Am Coll Surg*. 2005;201(4):604–611. doi:10.1016/j.jamcollsurg.2005.04.032
39. Buanes T, Mjåland O. Complications in laparoscopic and open cholecystectomy: A prospective comparative trial. *Surg Laparosc Endosc*. 1996;6(4):266–272. PMID:8840447.
40. Mendoza-Sagaon M, Hanly EJ, Talamini MA, et al. Comparison of the stress response after laparoscopic and open cholecystectomy. *Surg Endosc*. 2000;14(12):1136–1141. doi:10.1007/s004640020035
41. Jatzko GR, Lisborg PH, Pertl AM, Stettner HM. Multivariate comparison of complications after laparoscopic cholecystectomy and open cholecystectomy. *Ann Surg*. 1995;221(4):381–386. doi:10.1097/00000658-199504000-00008
42. Boddy AP, Mehta S, Rhodes M. The effect of intraperitoneal local anesthesia in laparoscopic cholecystectomy: A systematic review and meta-analysis. *Anesth Analg*. 2006;103(3):682–688. doi:10.1213/01.ane.0000226268.06279.5a
43. Bisgaard T, Kehlet H, Rosenberg J. Pain and convalescence after laparoscopic cholecystectomy. *Eur J Surg*. 2001;167(2):84–96. doi:10.1080/110241501750070510
44. Sen S, Morrison B, O'Rourke K, Jones C. Analgesia for enhanced recovery after surgery in laparoscopic surgery. *Dig Med Res*. 2019;2:25. doi:10.21037/dmr.2019.08.09
45. Morsy K, Mohamad Abdalla E. Postoperative pain relief after laparoscopic cholecystectomy: Intraperitoneal lidocaine versus nalbuphine. *Ain Shams J Anaesthesiol*. 2014;7(1):40–44. doi:10.4103/1687-7934.128402
46. Alkhamesi NA, Peck DH, Lomax D, Darzi AW. Intraperitoneal aerosolization of bupivacaine reduces postoperative pain in laparoscopic surgery: A randomized prospective controlled double-blinded clinical trial. *Surg Endosc*. 2007;21(4):602–606. doi:10.1007/s00464-006-9087-6
47. Dey A, Malik VK. Shoulder tip pain following laparoscopic cholecystectomy: A randomized control study to determine the cause. *Indian J Surg*. 2015;77(Suppl 2):381–384. doi:10.1007/s12262-013-0849-9
48. Jackson SA, Laurence AS, Hill JC. Does post-laparoscopy pain relate to residual carbon dioxide? *Anaesthesia*. 1996;51(5):485–487. doi:10.1111/j.1365-2044.1996.tb07798.x
49. Tsimoyiannis EC, Siakas P, Tassis A, Lekkas ET, Tzourou H, Kambili M. Intraperitoneal normal saline infusion for postoperative pain after laparoscopic cholecystectomy. *World J Surg*. 1998;22(8):824–828. doi:10.1007/s002689900477
50. Wills VL, Hunt DR. Pain after laparoscopic cholecystectomy. *Br J Surg*. 2002;87(3):273–284. doi:10.1046/j.1365-2168.2000.01374.x
51. Saadati K, Razavi MR, Nazemi Salman D, Izadi S. Postoperative pain relief after laparoscopic cholecystectomy: Intraperitoneal sodium bicarbonate versus normal saline. *Gastroenterol Hepatol Bed Bench*. 2016;9(3):189–196. PMID:27458511.
52. Kranke P, Jokinen J, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. *Cochrane Database Syst Rev*. 2015;(7):CD009642. doi:10.1002/14651858.CD009642.pub2
53. Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol*. 1998;46(3):245–249. doi:10.1046/j.1365-2125.1998.00775.x
54. McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: A systematic review of randomized controlled trials. *Drugs*. 2010;70(9):1149–1163. doi:10.2165/10898560-000000000-00000

55. Yang SY, Kang H, Choi GJ, et al. Efficacy of intraperitoneal and intravenous lidocaine on pain relief after laparoscopic cholecystectomy. *J Int Med Res*. 2014;42(2):307–319. doi:10.1177/0300060513505493
56. Beaussier M, Delbos A, Maurice-Szamburski A, Ecoffey C, Mercadal L. Perioperative use of intravenous lidocaine. *Drugs*. 2018;78(12): 1229–1246. doi:10.1007/s40265-018-0955-x
57. Sharan R, Singh M, Kataria A, Jyoti K, Jarewal V, Kadian R. Intraperitoneal instillation of bupivacaine and ropivacaine for postoperative analgesia in laparoscopic cholecystectomy. *Anesth Essays Res*. 2018;12(2):377–380. doi:10.4103/aer.AER_6_18
58. Joris J, Thiry E, Paris P, Weerts J, Lamy M. Pain after laparoscopic cholecystectomy: Characteristics and effect of intraperitoneal bupivacaine. *Anesth Analg*. 1995;81(2):379–384. doi:10.1097/00000539-199508000-00029
59. Sandhya S, Puthenveettil N, Vinodan K. Intraperitoneal nebulization of ropivacaine for control of pain after laparoscopic cholecystectomy: A randomized control trial. *J Anaesthesiol Clin Pharmacol*. 2021;37(3):443–448. doi:10.4103/joacp.JOACP_358_19
60. Liu H, Hu X, Duan X, Wu J. Thoracic epidural analgesia (TEA) vs. patient controlled analgesia (PCA) in laparoscopic colectomy: A meta-analysis. *Hepatogastroenterology*. 2014;61(133):1213–1219. PMID:25436285.
61. Halabi WJ, Kang CY, Nguyen VQ, et al. Epidural analgesia in laparoscopic colorectal surgery: A nationwide analysis of use and outcomes. *JAMA Surg*. 2014;149(2):130–136. doi:10.1001/jamasurg.2013.3186
62. Christie IW, McCabe S. Major complications of epidural analgesia after surgery. Results of a six-year survey: Epidural complications. *Anaesthesia*. 2007;62(4):335–341. doi:10.1111/j.1365-2044.2007.04992.x
63. Charlton S, Cyna AM, Middleton P, Griffiths JD. Perioperative transversus abdominis plane (TAP) blocks for analgesia after abdominal surgery. *Cochrane Database Syst Rev*. 2010;(12):CD007705. doi:10.1002/14651858.CD007705.pub2
64. Zafar N, Davies R, Greenslade GL, Dixon AR. The evolution of analgesia in an 'accelerated' recovery programme for resectional laparoscopic colorectal surgery with anastomosis. *Colorectal Dis*. 2010; 12(2):119–124. doi:10.1111/j.1463-1318.2009.01768.x
65. Brady R, Ventham N, Roberts D, Graham C, Daniel T. Open transversus abdominis plane block and analgesic requirements in patients following right hemicolectomy. *Ann R Coll Surg Engl*. 2012;94(5): 327–330. doi:10.1308/003588412X13171221589856
66. Conaghan P, Maxwell-Armstrong C, Bedforth N, et al. Efficacy of transversus abdominis plane blocks in laparoscopic colorectal resections. *Surg Endosc*. 2010;24(10):2480–2484. doi:10.1007/s00464-010-0989-y
67. Elsharkawy H, Bendtsen TF. Ultrasound-Guided Transversus Abdominis Plane and Quadratus Lumborum Nerve Blocks. New York, USA: The New York School of Regional Anesthesia. https://www.nysora.com/topics/regional-anesthesia-for-specific-surgical-procedures/abdomen/ultrasound-guided-transversus-abdominis-plane-quadratus-lumborum-blocks/. Accessed May 29, 2022.
68. Rahimzadeh P, Faiz SHR, Latifi-Naibin K, Alimian M. A comparison of effect of preemptive versus postoperative use of ultrasound-guided bilateral transversus abdominis plane (TAP) block on pain relief after laparoscopic cholecystectomy. *Sci Rep*. 2022;12(1):623. doi:10.1038/s41598-021-04552-6
69. Lee IO, Kim SH, Kong MH, et al. Pain after laparoscopic cholecystectomy: The effect and timing of incisional and intraperitoneal bupivacaine. *Can J Anaesth*. 2001;48(6):545–550. doi:10.1007/BF03016830
70. Inan A, Sen M, Dener C. Local anesthesia use for laparoscopic cholecystectomy. *World J Surg*. 2004;28(8):741–744. doi:10.1007/s00268-004-7350-3
71. Heinke B, Gingl E, Sandkuhler J. Multiple targets of μ-opioid receptor-mediated presynaptic inhibition at primary afferent Aδ- and C-fibers. *J Neurosci*. 2011;31(4):1313–1322. doi:10.1523/JNEUROSCI.4060-10.2011
72. Shafi S, Collinsworth AW, Copeland LA, et al. Association of opioid-related adverse drug events with clinical and cost outcomes among surgical patients in a large integrated health care delivery system. *JAMA Surg*. 2018;153(8):757–763. doi:10.1001/jamasurg.2018.1039
73. Naguib M, Seraj M, Attia M, Samarkandi AH, Seet M, Jaroudi R. Perioperative antinociceptive effects of tramadol: A prospective, randomized, double-blind comparison with morphine. *Can J Anaesth*. 1998;45(12):1168–1175. doi:10.1007/BF03012458
74. Kong SK, Onsiong SMK, Chiu WKY, Li MKW. Use of intrathecal morphine for postoperative pain relief after elective laparoscopic colorectal surgery: Postoperative pain relief after laparoscopic colorectal surgery. *Anaesthesia*. 2002;57(12):1168–1173. doi:10.1046/j.1365-2044.2002.02873.x
75. Sjövall S, Kokki M, Kokki H. Laparoscopic surgery: A narrative review of pharmacotherapy in pain management. *Drugs*. 2015;75(16): 1867–1889. doi:10.1007/s40265-015-0482-y
76. Boom M, Olofsen E, Neukirchen M, et al. Fentanyl utility function: A risk-benefit composite of pain relief and breathing responses. *Anesthesiology*. 2013;119(3):663–674. doi:10.1097/ALN.0b013e31829ce4cb
77. Latta KS, Ginsberg B, Barkin RL. Meperidine: A critical review. *Am J Ther*. 2002;9(1):53–68. doi:10.1097/00045391-200201000-00010
78. Forgach L, Ong BY. Failure of meperidine wound infiltration to reduce pain after laparoscopic tubal ligation. *Can J Anaesth*. 1995;42(12): 1085–1089. doi:10.1007/BF03015093
79. Heel RC, Brogden RN, Speight TM, Avery GS. Buprenorphine: A review of its pharmacological properties and therapeutic efficacy. *Drugs*. 1979; 17(2):81–110. doi:10.2165/00003495-197917020-00001
80. Kumar N, Rowbotham DJ. Piritramide. *Br J Anesth*. 1999;82(1):3–5. doi:10.1093/bja/82.1.3
81. Stamer UM, Zhang L, Book M, Lehmann LE, Stuber F, Musshoff F. *CYP2D6* genotype dependent oxycodone metabolism in postoperative patients. *PLoS One*. 2013;8(3):e60239. doi:10.1371/journal.pone.0060239
82. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008;11(2 Suppl):S105–S120. PMID:18443635.
83. Cheung CK, Adeola JO, Beutler SS, Urman RD. Postoperative pain management in enhanced recovery pathways. *J Pain Res*. 2022;15: 123–135. doi:10.2147/JPR.S231774
84. Sehajpal S, Prasad DN, Singh RK. Prodrugs of non-steroidal anti-inflammatory drugs (NSAIDs): A long march towards synthesis of safer NSAIDs. *Mini Rev Med Chem*. 2018;18(14):1199–1219. doi:10.2174/1389557518666180330112416
85. Sehajpal S, Prasad DN, Singh RK. Novel ketoprofen–antioxidants mutual codrugs as safer nonsteroidal anti-inflammatory drugs: Synthesis, kinetic and pharmacological evaluation. *Arch Pharm (Weinheim)*. 2019;352(7):e1800339. doi:10.1002/ardp.201800339
86. Sehajpal S, Prasad DN, Singh RK. Synthesis and evaluation of prodrugs of ketoprofen with antioxidants as gastroprotective NSAIDs. *Asian J Chem*. 2018;30(9):2145–2150. doi:10.14233/ajchem.2018.21495
87. Gupta A, Bah M. NSAIDs in the treatment of postoperative pain. *Curr Pain Headache Rep*. 2016;20(11):62. doi:10.1007/s11916-016-0591-7
88. Benarroch EE. What is the mechanism of therapeutic and adverse effects of gabapentinoids? *Neurology*. 2021;96(7):318–321. doi:10.1212/WNL.0000000000011424
89. Przybyła GW, Szychowski KA, Gmiński J. Paracetamol: An old drug with new mechanisms of action. *Clin Exp Pharmacol Physiol*. 2021; 48(1):3–19. doi:10.1111/1440-1681.13392
90. Rosenbaum SB, Gupta V, Palacios JL. Ketamine. In: *StatPearls*. Treasure Island, USA: StatPearls Publishing; 2022. http://www.ncbi.nlm.nih.gov/books/NBK470357/. Accessed July 15, 2022.
91. Edwards DA, Hedrick TL, Jayaram J, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative joint consensus statement on perioperative management of patients on preoperative opioid therapy. *Anesth Analg*. 2019;129(2):553–566. doi:10.1213/ANE.0000000000004018
92. McNicol ED, Ferguson MC, Schumann R. Single-dose intravenous ketorolac for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2021;5(5):CD013263. doi:10.1002/14651858.CD013263.pub2
93. Bell S, Rennie T, Marwick CA, Davey P. Effects of peri-operative non-steroidal anti-inflammatory drugs on post-operative kidney function for adults with normal kidney function. *Cochrane Database Syst Rev*. 2018;11(11):CD011274. doi:10.1002/14651858.CD011274.pub2
94. Schnabel A, Reichl SU, Weibel S, et al. Efficacy and safety of dexmedetomidine in peripheral nerve blocks: A meta-analysis and trial sequential analysis. *Eur J Anesthesiol*. 2018;35(10):745–758. doi:10.1097/EJA.0000000000000870
95. Rabie A, Abdelfattah M. Outcome of intraoperative dexmedetomidine infusion in laparoscopic cholecystectomy. *Egypt J Anesth*. 2022; 38(1):16–22. doi:10.1080/11101849.2021.2004501
96. Verret M, Lauzier F, Zarychanski R, et al. Perioperative use of gabapentinoids for the management of postoperative acute pain. *Anesthesiology*. 2020;133(2):265–279. doi:10.1097/ALN.0000000000003428
97. Cavalcante AN, Sprung J, Schroeder DR, Weingarten TN. Multimodal analgesic therapy with gabapentin and its association with postoperative respiratory depression. *Anesth Analg*. 2017;125(1):141–146. doi:10.1213/ANE.0000000000001719

98. McNicol ED, Ferguson MC, Haroutounian S, Carr DB, Schumann R. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. *Cochrane Database Syst Rev*. 2016;2016(5): CD007126. doi:10.1002/14651858.CD007126.pub3
99. Jibril F, Sharaby S, Mohamed A, Wilby KJ. Intravenous versus oral acetaminophen for pain: Systematic review of current evidence to support clinical decision-making. *Can J Hosp Pharm*. 2015;68(3): 238–247. doi:10.4212/cjhp.v68i3.1458
100. Mulita F, Karpetas G, Liolis E, Vailas M, Tchabashvili L, Maroulis I. Comparison of analgesic efficacy of acetaminophen monotherapy versus acetaminophen combinations with either pethidine or parecoxib in patients undergoing laparoscopic cholecystectomy: A randomized prospective study. *Med Glas (Zenica)*. 2021;18(1): 27–32. doi:10.17392/1245-21
101. Pendi A, Field R, Farhan SD, Eichler M, Bederman SS. Perioperative ketamine for analgesia in spine surgery: A meta-analysis of randomized controlled trials. *Spine (Phila Pa 1976)*. 2018;43(5): E299–E307. doi:10.1097/BRS.0000000000002318
102. Ding X, Jin S, Niu X, et al. Morphine with adjuvant ketamine versus higher dose of morphine alone for acute pain: A meta-analysis. *Int J Clin Exp Med*. 2014;7(9):2504–2510. PMID:25356103.