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REVIEW

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Postoperative pain management following laparoscopic cholecystectomy-non-opioid approaches: a review

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Abstract

Background Gallstone disease with its consequences is a common clinical issue that may necessitate surgical removal. In comparison with traditional open procedures, laparoscopic cholecystectomy (LC) remains the mainstay treatment for symptomatic gallstone disease and can lead to a shorter recovery period, and a shorter hospital stay; yet, severe abdominal and shoulder pain may be experienced.

Main body Novel drugs and technology for acute and chronic pain management following LC have been studied to improve patient care. The review discusses innovative pain management strategies with non-opioid approaches for laparoscopic surgery, with an emphasis on ensuring speedy and safe recovery.

Conclusion The key findings state that IV paracetamol is a necessary part of multimodal postoperative pain management. There were several pharmacological interventions found to be effective in pain control: magnesium sulfate and dexamethasone showed anti-inflammatory benefits; ondansetron provided analgesic effects; gabapentinoids and alpha-2-agonists reduced central sensitization; local anesthetics offered targeted pain relief; antidepressants addressed neuropathic pain; NSAIDs proved effective for inflammatory pain. Similarly, non-pharmacological approaches, and emerging technologies, also contributed to the management of post-LC pain underscoring the need for a comprehensive approach to its management. More rigorous research is needed to guide pain management after LC. Future studies should compare multiple treatments simultaneously and involve larger patient groups. This approach will help identify optimal pain control strategies. It will also provide clearer insights into the safety and efficacy of various pain medications under comparable clinical conditions.

Keywords Laparoscopic cholecystectomy, Postoperative pain, Non-opioid strategies, Pain management, Gallstone, Gallbladder, Minimally invasive surgery, Analgesia

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Background

Gallstones are solid bile deposits that can occur in the gallbladder caused by various factors such as hormones, dietary changes, drugs, and rapid weight loss or obesity. These gallstones can cause gallbladder inflammation and infection by impeding normal bile flow. This is known as cholecystitis, and it can produce severe, continuous abdominal pain, fever, nausea, and vomiting

[1]. Regretfully, opinions differ about the best management approach for this condition. The sole novel route to the bile duct for a long time was a direct open surgical technique. Advanced endoscopic technology has made minimally invasive procedures possible [2]. An open cholecystectomy involves a 10–15 cm incision in the upper right quadrant of the abdomen. The surgeon removes the gallbladder through an incision. In contrast, the laparoscopic cholecystectomy (LC) operation requires only 3–4 extremely tiny incisions. This procedure makes use of a long, thin tube known as a laparoscope by introducing it through the incisions. One incision is made to remove the gallbladder [3].

LC is the current gold standard and less invasive therapy causing less postoperative pain, but it might be mild, moderate, or severe in certain people [4, 5]. Moreover, it results in reduced analgesic intake, reduced recovery time, and shorter hospital stays than open cholecystectomy [6, 7]. Visceral and shoulder pain are the most common types of pain experienced during LC. These pains are caused by diaphragmatic and peritoneal stretching, peritoneal irritation by CO_2, changes in intra-abdominal pH, and the release of inflammatory mediators [8]. Inadequate care of acute pain within the first 48 h following surgery increases the likelihood of chronic pain development; therefore, postoperative pain management is crucial [9, 10] with the use of both non-opioid and opioid treatments. During the immediate postoperative phase, opioid medication can cause a variety of adverse effects, including respiratory depression, pruritus, nausea, and vomiting. Due to the significant adverse effects of opioids, the non-opioid medication in conjunction with a multimodal regimen is strongly suggested due to the latter regimen's fewer adverse effects [11, 12]. It is therefore crucial to identify the different non-opioid modalities in the management of postoperative LC pain. This current review aims to comprehensively evaluate the current evidence on non-opioid strategies as well as assess the efficacy of various pharmacological and non-pharmacological non-opioid interventions for pain control after LC.

Methods

Randomized controlled trials that were published in English between 2005 and 2024 were obtained from multiple databases, such as PubMed, Web of Science, Science Direct, Scopus, EMBASE, Medline, and Cochrane Library. The trials evaluated non-opioid postoperative pain management after laparoscopic cholecystectomy and reported pain scores. The various components of the gathered data were categorized based on the medication classifications. The terms "Laparoscopic cholecystectomy," "postoperative pain," "non-opioid strategies," "pain management," "gallbladder," "minimally invasive surgery," and "analgesia" are used to get the relevant articles.

The retrieved studies were initially screened based on titles and abstracts to exclude irrelevant papers. Full texts of potentially eligible studies were then thoroughly reviewed to ensure they met the inclusion criteria. Studies were excluded if they focused solely on opioid interventions, did not report pain scores, or were not randomized controlled trials. The included studies were categorized based on the pharmacological class of the non-opioid interventions investigated. This categorization allowed for a systematic analysis of different types of non-opioid strategies. For each category, key information, including dosage, administration route, intervention timing, pain scores, and secondary outcomes, was extracted and summarized. The results of this analysis are presented in Table 1, which provides a comprehensive overview of the available evidence on non-opioid postoperative pain management strategies following LC.

Main text

Local anesthetics

Transversus abdominis plane block

The transversus abdominis plane (TAP) block enhances postoperative analgesia following abdominal surgery. A long-acting anesthetic is injected into the anterior abdominal wall's neurovascular plane to perform this procedure. This plane runs between the layers of the internal oblique and transversus abdominis muscles and passes the intercostal nerves from their spinal origins across the abdominal wall [88, 89]. This procedure can be done laparoscopically, under ultrasound (US) guidance, or utilizing a surface landmark-based method [3]. Overall, the data are positive, with the majority of studies showing clinically significant decreases in pain and postoperative opioid consumption. While it has been demonstrated that laparoscopic cholecystectomy (LC) patients can benefit from various TAP procedures, including US-guided TAP block and additional strategies, TAP blocking procedures are the most successful means of providing analgesia compared to general anesthesia and port infiltration. However, as US technology develops, TAP blockades are becoming more practicable and technically easier to execute. This has raised interest in TAP blocks as a therapeutic technique for analgesia following abdominal surgery [90]. Reducing opioid use with intraoperative laparoscopic transversus abdominis plane block (LC + TAP) is a safe and successful strategy, according to research that compared patients who underwent LC alone with patients who underwent a laparoscopic bilateral TAP block (LC + TAP) [17]. Accordingly, a randomized triple-blind study [52] compared the effectiveness of a laparoscopic TAP block versus port site local

Table 1 Pharmacotherapeutic pain management following laparoscopic cholecystectomy

Study (author)	Year	Time of administration	Number of patients (treatment/control)	Intervention	Main outcome
(Abdelraheem Mohamed et al.) [13]	2024	Intraoperative	25/25	20 mL of 0.5% bupivacaine + 480 mL of NS/20 mL of 0.5% bupivacaine	Diluted I.P bupivacaine reduces pain after surgery, reduces the need for rescue analgesia, and uses fewer analgesics in the first 24 h after surgery than non-diluted bupivacaine, with similar outcomes in terms of side effects, and hemodynamic parameter comparison
(Zheng et al.) [14]	2024	Preoperative	50/50	0.5 μg/kg dexmedetomidine infusion diluted in NS over 10 min/NS infusion over 10 min	Dexmedetomidine is a potentially safe and effective anesthetic protocol, that reduces the incidence of complications, provides hemodynamic stability, and reduces the stress response and postoperative pain
(Vishnuraj et al.)[15]	2024	Preoperative	44/44	0.5 mcg/kg/h dexmedetomidine infusion with 0.35 mg/kg I.V bolus ketamine/2 mcg/kg I.V bolus fentanyl administered with 0.5 mcg/kg maintenance doses were administered if the mean arterial pressure and heart rate were higher than the baseline by ± 20%	Opioid-free anesthesia with dexmedetomidine and ketamine combination was related to a lower PONV and a decreased need for analgesia during the first 2 h postoperatively
(Uzunay et al.) [16]	2024	Intraoperative	30/30	TAP / Ultrasound-guided TAP	There was no noticeable difference. Nonetheless, laparoscopic TAP block is quicker, simpler, and more effective than ultrasound-guided TAP block.
(Jeffrey et al.) [17]	2023	Intraoperative	100/100	Each TAP block solution contained a 100-mL mixture of 20 mL of 1% lidocaine, 30 mL of 0.5% bupivacaine, and 50 mL of injectable NS/LC alone	Laparoscopic TAP block is a safe and effective way to minimize postoperative opioid use for immediate pain relief
(Korkutata et al.) [18]	2023	Preoperative	32/32	Ultrasound-guided bilateral TAP block + 15 ml of 0.25%/bupivacaine and 25 ml of 1.5 mg/kg tramadol as adjuvant/15 ml of 0.25% bupivacaine and 25 ml of 0.5 mcg/kg dexmedetomidine	The adjuvant dexmedetomidine in the TAP block preoperatively resulted in more stable intraoperative hemodynamic outcomes
(Çevikkalp et al.) [19]	2023	Intraoperative	34/35/35/35	Standard analgesia/Local anesthesia/unilateral TAP block/bilateral TAP block	A four-quadrant bilateral TAP block is a useful and simple method for easing pain during the first hour. However, to sufficiently prevent post-laparoscopic cholecystectomy pain, the TAP block should be delivered to all four quadrants
(Abbasnia et al.) [20]	2023	Preoperative Postoperative	50/50/50	VR1 (distraction image)/VR2 (Patient education approach)/control	Preoperative anxiety and postoperative discomfort were significantly reduced due to the two strategies of patient education and distraction utilizing visual reality technology. In addition, there was a greater perception of postoperative pain among the control group members whose anxiety was uncontrolled before surgery. In the meantime, there was less main pain in the two VR groups

Table 1 (continued)

Study (author)	Year	Time of administration	Number of patients (treatment/control)	Intervention	Main outcome
(Wang et al.) [21]	2023	Postoperative	21/21	Acupuncture 2 h after surgery/parecoxib sodium at request	Acupuncture has the potential to be a useful approach as one of the multimodal analgesia techniques to treat postoperative pain after LC since it can clinically improve the short-term treatment of POP and decrease the need for additional analgesics
(Sravanthi et al.) [23]	2023	Intraoperative	32/32	Pneumoperitoneum was created, and before beginning dissection, the subdiaphragmatic area was instilled with 50 mg/kg of 10% MgSO4 diluted in 100 mL/100 mL of 0.9% NS over 20 min	I.P MgSO4 lowers POP and vomiting after elective LC without causing additional adverse effects related to magnesium
(Akhondi & Sarkoohi et al.) [24]	2023	Intraoperative	32/32	50 mg/kg IV magnesium in 100 mL of NS/control (100 mL NS) within 1 h	MgSO4 is a safe and effective supplement that can help minimize postoperative pain and the need for opioids
(ElHoshy & El-Din Yacout et al.) [25]	2023	Intraoperative	30/30	loading dose of 1 mg/kg I.V esmolol was administered gradually over 10 min then given a maintenance dose of 30 µg/kg/min/loading dose of 40 mg/kg I.V $MgSO_4$ was administered over a ten-minute interval, followed by a 15 mg/kg/h maintenance infusion	Perioperative esmolol infusion results in a better and quicker recovery profile
(Gupta et al.) [26]	2023	Preoperative Intraoperative	26/26	1.5 mg/kg of IV bolus lidocaine gradually over 10 min before induction of anesthesia, followed by a continuous IV infusion of 1.5 mg/kg/h/1.5 mg/kg of IV bolus lidocaine gradually over 10 min before induction of anesthesia, followed by a continuous IV infusion of 2 mg/kg/h	Lidocaine at both infusion doses produced postoperatively clinically sufficient analgesia; however, the infusion at a rate of 2 mg/kg/h reduced the mean VAS score significantly than the infusion at a rate of 1.5 mg/kg/h
(Sarakatsianou et al.) [27]	2023	Intraoperative	49/49	1.5 mg/kg of IV bolus lidocaine, followed by a continuous IV infusion of 2 mg/kg/h/Equivalent placebo infusion of 0.9% NS	Lidocaine had no analgesia effect on laparoscopic cholecystectomy postoperative pain
(Kaur et al.) [28]	2023	Preoperative	30/30/30	600 mg oral gabapentin/300 mg oral pregabalin/placebo	For individuals having a laparoscopic cholecystectomy, a single preoperative dose of 300 mg of pregabalin or 600 mg of gabapentin can be used to effectively prevent pain
(Sane et al.) [29]	2023	Preoperative	25/25/25	100 mg pregabalin/4 mg tizanidine/placebo	Preoperative 100 mg pregabalin and 4 mg tizanidine significantly decreased the amount of analgesics used and the postoperative shoulder pain without resulting in any complications
(Vandana et al.) [30]	2023	Intraoperative	42/42	40 ml of 0.25% IP bupivacaine and 16 mg of IP dexamethasone/40 ml of 0.25% IP bupivacaine only	16 mg of IP dexamethasone with 0.25% IP bupivacaine considerably lowers postoperative pain and the need for rescue analgesia

Table 1 (continued)

Study (author)	Year	Time of administration	Number of patients (treatment/control)	Intervention	Main outcome
(Nikoubakht et al.) [31]	2022	Intraoperative	20/19/19	NS/dissolved 5.7% intra-abdominal bicarbonate in 1000 cc normal saline/50 cc of 0.2% I.P bupivacaine spray	Both bupivacaine and bicarbonate are efficient in lowering the need for opioids and postoperative analgesia, which in turn reduces adverse effects and improves postoperative pain management
(Iqbal et al.) [32]	2022	Intraoperative	42/40	20 mL of 0.5% I.P bupivacaine/20 mL of NS	Bupivacaine irrigation does not relieve the pain
(Mansour et al.) [33]	2022	Preoperative	30/30	60 mg of oral duloxetine/placebo	Duloxetine significantly lowers postoperative pain compared to placebo. Additionally, its usage is linked to a decrease in PONV
(S. Jain et al.) [34]	2022	Preoperative	25/25	0.5 mg/kg I.V ketamine/2 ml I.V NS	A single bolus dosage of 0.5 mg/kg of I.V ketamine provided significant pain relief but only for up to 30 min after surgery
(Efe Mercanoglu et al.) [35]	2022	Preoperative	30/30/30	0.5 mg/kg I.V bolus ketamine followed by 10 µg/kg/min/1 µg/kg I.V bolus dexmedetomidine followed by 0.5 µg/kg/h/NS infusion as a control group	For complete intravenous anesthesia throughout the intraoperative phase, infusions of ketamine or dexmedetomidine may be appropriate additions. Additionally, incorporating both medications into the overall intravenous anesthetic procedure may enhance postoperative pain management and reduce the need for opioids
(Najam et al.) [36]	2022	Preoperative	27/33	150 mg oral pregabalin/placebo	Pregabalin effectively reduces pain in the acute postoperative period and leads to lower VAS scores
(Jamil & Qaisar et al.) [37]	2022	Preoperative	80/80	0.1 mg/kg I.V dexamethasone diluted in 5 mL of NS/5 mL of I.V NS	A single dosage of dexamethasone significantly lowers postoperative pain
(Nazemroaya et al.) [38]	2022	Intraoperative	29/29/29	8 mg I.V dexamethasone in combination with 2 cc of I.P NS as placebo/8 mg I.P dexamethasone in combination with 2 cc of I.V NS as placebo/control group (2 cc of I.P and I.V NS)	8 mg of IP dexamethasone reduces pain and nausea severity, but with no change in PONV
(Jijo et al.) [39]	2022	Intraoperative	30/30	30 mL of diluted I.P $MgSO_4$ at a dose of 30 mg/kg through the port. The patient was then placed in the Trendelenburg position for ten minutes. At every port site, 3 mL of 0.25% bupivacaine was administered locally after skin closure/in patients who did not receive I.P $MgSO_4$ port site infiltration was given using the same medication and dose	I.P MgSO4 significantly lowers nausea and vomiting and effectively manages postoperative pain in patients, all with no negative consequences
(Saliminia et al.) [40]	2022	Preoperative	30/30	Unilateral ultrasound-guided TAP block with 20ml of 0.5% bupivacaine/bupivacaine without TAP block	TAP Block reduces the requirement for analgesic medication administration, pain levels, and stress response indicators

Table 1 (continued)

Study (author)	Year	Time of administration	Number of patients (treatment/control)	Intervention	Main outcome
(Kiany et al.) [41]	2022	Intraoperative Preoperative	41/41	2% of a 5-cc lidocaine + equivalent of distilled water sprayed on after removal of gallbladder/2% of a 1.5-cc S.C lidocaine + equivalent of distilled water was injected into the port sites prior to the incisions	Comparing I.P lidocaine instillation vs S.C injection at the port site, I.P lidocaine provides analgesic consumption reduction and gives postoperative pain alleviation
(Erdi et al.) [42]	2022	Intraoperative Postoperative	30/30/30	1gm I.V paracetamol/800 mg I.V ibuprofen/0.9% NS All the drugs administered at the operation, 8 h, and 16 h after the surgery	Reducing the need for opioids following surgery can be accomplished by using both intravenous acetaminophen and ibuprofen for pain management. For people who are unable to use NSAIDs, acetaminophen can also be a good substitute for managing pain following surgery
(Najam et al.) [36]	2022	Preoperative	27/33	150 mg pregabalin/placebo	Pregabalin effectively reduces pain showing lower VAS scores during the acute postoperative phase. Nevertheless, neither was effective in lowering postoperative nausea and vomiting
(Mulita et al.) [43]	2021	Postoperative	106/113/67	1g I.V paracetamol every 8 h and 50mg I.M pethidine every 12-h/1g I.V paracetamol every 8 h and 40mg I.V parecoxib every 12-h/1g I.V paracetamol every 8 h	the combination of I.V paracetamol and I.V parecoxib appears to be similar to the combination of I.V paracetamol and I.M pethidine for postoperative analgesic therapy and both combinations of postoperative analgesics should be chosen above paracetamol monotherapy. Additionally, the study supports the concept that parecoxib significantly reduces the need for opioids for managing postoperative pain
(Abdelaziz et al.) [44]	2021	Intraoperative	25/25	4 mg I.P ondansetron (2 mL)/2 mL of I.P NS	IP ondansetron may enhance acetaminophen's analgesic effectiveness Additionally, its antiemetic properties made it a unique and innovative option
(R. Jain et al.) [45]	2021	Preoperative	30/30	Oral gabapentin (1200 mg)/placebo	Preemptive gabapentin controls alterations in hemodynamic parameters with significant prolonging of pain and PONV-free duration
(Karri et al.) [46]	2021	Preoperative	22/22/22	Oral gabapentin (600 mg)/oral memantine (20 mg)/placebo	Gabapentin provided superior postoperative pain relief than memantine. However, the memantine group took 50.53 min longer to request rescue analgesia compared to the gabapentin and placebo groups
(Vijayaraghavalu & Bharti Sekar et al.) [47]	2021	Intraoperative	30/30	30 mL of 0.5% bupivacaine/30 mL of NS	Bupivacaine has advantages in lowering pain following surgery and in delaying the need for rescue analgesia. Additionally, it lessens the frequency of shoulder aches, although it has little effect on postoperative nausea or vomiting

Table 1 (continued)

Study (author)	Year	Time of administration	Number of patients (treatment/control)	Intervention	Main outcome
(H. Y. Kim et al.) [48]	2021	Preoperative	32/31	Lidocaine patch/control (dressing retention tape only) was applied on both shoulders	For female patients having LC, a 5% lidocaine patch decreased the frequency and intensity of shoulder pain following surgery. A straightforward, noninvasive, and safe analgesic technique for the shoulder is to use a 5% lidocaine patch
(Ye et al.) [49]	2021	Preoperative	30/30/30/30	10 ml I.V dexmedetomidine (4 µg/ml)/I.V dexmedetomidine (6 µg/ml)/I.V dexmedetomidine (8 µg/ml)/10 ml I.V NS	0.6µg/kg dexmedetomidine can stabilize hemodynamics, alleviate postoperative pain, and PONV, and reduce cough intensity during the emergence of patients undergoing LC
(Kaarthika et al.) [50]	2021	Intraoperative	34/33/35	0.5% bupivacaine/dexmedetomidine 1 µ/kg + 0.5% bupivacaine/1 µ/kg clonidine + 20 mL of 0.5% bupivacaine	Alpha-2 agonists combined with bupivacaine decrease the amount of opioids used after surgery, and dexmedetomidine seems to be more effective than clonidine at delaying the need for an initial analgesic prescription
(Arabzadeh et al.) [4]	2021	Intraoperative Preoperative Postoperative	30/30/30	40 mL bupivacaine (0.25%) I.P at the end of the operation/IV ketorolac (30 mg) a half hour before operation and every 8 h after surgery/NS (40 ml) I.P and (2ml) IV	Both intraperitoneal bupivacaine and intravenous ketorolac injections significantly reduced postoperative pain and PONV
(Jung et al.) [51]	2021	Intraoperative	39/39	Fentanyl (600 µg) used in combination with nefopam (120 mg)/nefopam (240 mg)	PCA that uses nefopam has a non-inferior and effective analgesic efficacy and creates a lower incidence of postoperative side effects
(Vindal et al.) [52]	2021	Intraoperative	50/50	The TAP block group would receive a syringe containing 10 ml of 0.25% bupivacaine at the TAP block site and a syringe containing 10 ml of saline at the port block site/the port site group would receive a syringe containing 10 ml of saline at TAP block site and syringe contains 10 ml of 0.25% bupivacaine at port block site	It is safe and simple to perform a TAP block with laparoscopic guidance. However, it assists with a speedy recovery, early release, and enhanced patient satisfaction following a laparoscopic cholecystectomy. It also lessens the intensity of postoperative pain
(Tekeli et al.) [53]	2020	Intraoperative	247/268	Ultrasound-guided TAP block after induction/dual analgesics (1 mg/kg of tramadol and 20 mg/kg of paracetamol) administered intravenously 30 min before the end of surgery	The TAP block approach could potentially lower the rate of analgesic-related adverse consequences by reducing the demand for further analgesics, effectively reducing postoperative analgesia, and lowering the rate of PONV. The TAP block group also experienced much reduced ICU need and overall hospital stays
(T. Singh et al.) [54]	2020	Preoperative	30/30/30	150 mg pregabalin/300 mg pregabalin/placebo	Pregabalin 150 mg is less likely than pregabalin 300 mg to have side effects like drowsiness and visual abnormalities after laparoscopic cholecystectomy, while still being effective in reducing postoperative pain

Table 1 (continued)

Study (author)	Year	Time of administration	Number of patients (treatment/control)	Intervention	Main outcome
(Chilkoti et al.) [55]	2020	Preoperative Postoperative	40/40	0.5 µg/kg/h. IV infusion dexmedetomidine in 30 ml/h. NS/control (30 ml/h. NS)	0.5 µg/kg/hr. of I.V infusion dexmedetomidine is efficient in delivering postoperative analgesia, as evidenced by a significant decline in analgesic use within 24 h and the successful obtundation of hemodynamic alterations induced by pneumoperitoneum
(Chilkoti et al.) [56]	2019	Intraoperative	25/25/25	0.5 µg/kg of I.V infusion dexmedetomidine diluted in 30 ml NS + 40 ml of I.P 0.25% bupivacaine/30 ml of I.V infusion NS + dexmedetomidine (0.5 µg/kg) in 40 ml of I.P 0.25% bupivacaine/30 ml of I.V infusion NS + 40 ml of I.P 0.25% bupivacaine	I.P bupivacaine combined with a low bolus dose of dexmedetomidine is equally effective as IV 0.5 µg/kg dexmedetomidine
(Du et al.) [57]	2019	Preoperative Intraoperative	20/20/20/20	40 mg of I.V parecoxib preoperatively/0.6 µg/kg/h of I.V dexmedetomidine intraoperatively/combined group (40 mg of I.V parecoxib preoperatively + 0.6 µg/kg/h of I.V dexmedetomidine intraoperatively)/control group (equivalent amount of NS)	Parecoxib and dexmedetomidine used in combination may help patients with laparoscopic cholecystectomy experience less pain following surgery, as well as better postoperative drowsiness and cognitive outcomes
(Johnson et al.) [58]	2019	Preoperative Intraoperative	319/260	1g of I.V paracetamol intraoperative/1g of oral paracetamol preoperative	For postoperative analgesia in patients undergoing laparoscopic cholecystectomy at ambulatory surgical centers, single-dose oral paracetamol is not less effective than intravenous paracetamol
(Ghadami et al.) [59]	2019	Preoperative	30/30	150 mg oral gabapentin/100 mg I.V hydrocortisone	During the first 4 h, gabapentin proved to be more beneficial than hydrocortisone. Furthermore, 24 h after surgery, gabapentin was demonstrated to be a more effective pain reliever
(Von Plato et al.) [60]	2019	Preoperative	30/30	150 mg oral pregabalin/placebo	150 mg pregabalin shows no reduction in postoperative pain intensity
(Arif et al.) [61]	2019	Perioperative	21/21	1.5 mg/kgBW bolus lidocaine prior to endotracheal intubation, followed by lidocaine IV infusion 1.25 mg/kgBW/h for 2-h following surgery/1.5 mg/kgBW bolus lidocaine prior to endotracheal intubation, followed by 0.9% NaCl I.V infusion for 2-h following surgery	I.V lidocaine infusion at a rate of 1.25 mg/kgBW/h reduces the intensity of pain, and the requirement for postoperative opioids also speeds up the recovery of bowel sounds
(Surender et al.) [62]	2018	Preoperative	33/34	0.1 mg/kg of I.V dexamethasone diluted in NS for 10 ml/2 mg/kg of I.V lignocaine diluted in NS for 10 ml	Dexamethasone treatment improved pain and quality of recovery and reduced opioid consumption
(Kamali et al.) [22]	2018	Intraoperative Postoperative	66/66	1gm paracetamol intraoperatively followed by 500mg paracetamol every 6 h for 24-h/1µg/kg stat of dexmedetomidine intraoperatively followed by 0.5µg/kg/h for 6 h	Both medication regimes can regulate their hemodynamic state, allowing for efficient postoperative pain relief

Table 1 (continued)

Study (author)	Year	Time of administration	Number of patients (treatment/control)	Intervention	Main outcome
(Bielka et al.) [63]	2018	Intraoperative	30/30	0.5 µg/kg/h dexmedetomidine/NS infusion as control group	Enhancing analgesia with intraoperative dexmedetomidine infusion is a safe and efficient treatment option. The number of patients who experience severe postoperative pain, the amount of opioids taken after surgery, and the amount of time it takes before using rescue analgesia all seem to be considerably decreased by dexmedetomidine
(Zaman et al.) [64]	2018	Postoperative	25/25	75 mg of IV diclofenac/100 mg of IV tramadol given three times daily	Injectable tramadol is a more effective option for pain management and a comfortable recovery period than diclofenac
(Tuvayanon et al.) [65]	2018	Intraoperative	47/48/47	Passive gas released by the opening of a subdiaphragmatic port valve at the end of surgery/active gas released by the opening of a subdiaphragmatic port valve at the end of surgery/control group (release of gas from a surgical incision without using a port)	Reducing postoperative abdominal distension and shoulder pain can be achieved by either actively aspirating remaining CO2 from the intra-abdominal cavity or by using a passive-valve release approach
(Song et al.) [66]	2017	Perioperative	36/35	I.V bolus injection of 1.5 mg/kg lidocaine followed by a continuous IV infusion of 2 mg/ corresponding volume of NS	Low dosages of I.V lidocaine given during surgery can lessen pain after surgery, enhance healing, and delay the onset of an exaggerated inflammatory response after LC
(Medina-Vera & Novoa et al.) [67]	2017	Preoperative	49/49	1gm paracetamol diluted in 100 mL solution/30 mg ketorolac in NS with oral volume 100 mL solution	Paracetamol reduced intraoperative and postoperative opioid demand as effectively as ketorolac and had no adverse effects. For this reason, paracetamol works well as an analgesic in the treatment of postoperative pain
(Eidy et al.) [68]	2017	Preoperative	36/36/36	800 mg PO gabapentin/150 mg PO pregabalin/ placebo	A single dosage of gabapentin or pregabalin reduced postoperative pain, nausea, vomiting, and opioid use. Furthermore, the results showed that pregabalin reduced postoperative pain better than gabapentin
(E. M. Kim et al.) [69]	2017	Intraoperative	20/20/20	Nefopam I.V bolus of 0.3 mg/kg, followed by a continuous infusion of 65 µg/kg/h./ketamine I.V bolus of 0.3 mg/kg, followed by a continuous infusion of 180 µg/kg/h./I.V NS	Early postoperative pain scores (VAS) following remifentanil-based anesthesia were decreased by intraoperative nefopam infusion during laparoscopic cholecystectomy
(Vaswani et al.) [70]	2017	Preoperative	30/30	0.5 µg/kg of I.V bolus dexmedetomidine/0.5 µg/kg I.V bolus fentanyl	Dexmedetomidine attenuated the stress response to tracheal intubation, which improves hemodynamic stability

Table 1 (continued)

Study (author)	Year	Time of administration	Number of patients (treatment/control)	Intervention	Main outcome
(Choi et al.) [71]	2016	Intraoperative	18/18/18	0.3 mg/kg I.V nefopam followed by a continuous infusion of 0.065 mg/kg/h/0.3 mg/kg IV ketamine followed by a continuous infusion of 3 µg/kg/min/control group (received only the standard anesthetic regimen)	Under concurrent remifentanil infusion, both nefopam and ketamine infusion may control postoperative pain control. On the other hand, nefopam might be a better sedative than ketamine
(Anil et al.) [72]	2016	Intraoperative	30/30	50 mg I.V Dexketoprofen trometamol/75 mg I.V diclofenac	I.V single-dose dexketoprofen trometamol provided more effective analgesia with less need for rescue analgesic and narcotic drugs consumption
(Mishra et al.) [73]	2016	Preoperative	30/30/30	900 mg gabapentin/150 mg pregabalin/placebo	Gabapentin and pregabalin had a lower VAS score, delayed initiation of the first rescue analgesic, and a lower intake of opioids, both gabapentinoids exhibited a superior postoperative analgesic profile
(Bandey & Singh et al.) [74]	2016	Postoperative	30/30	100mg of I.V tramadol/1 g of I.V paracetamol both drugs were administered when VAS score > 5. Then, infusion at the same doses at 6, 12, and 18-h intervals	While both tramadol and paracetamol were shown to be safe and effective, paracetamol performed better, with significantly reduced mean VAS pain levels for the majority of the postoperative follow-up periods. Therefore, I.V infusion of paracetamol can be advised in a safe and efficient manner
(S. Lin et al.) [75]	2015	Intraoperative Postoperative	60/60/60	50 mg of 0.5% bupivacaine was injected S.C. at the trocar sites intraoperatively/40 mg of I.V parecoxib postoperatively/did not get postoperative analgesia unless needed	Both intravenous parecoxib and local anesthetic with bupivacaine are useful in reducing postoperative pain. Additionally, the number of patients who need postoperative rescue analgesics is decreased by these two approaches
(Mohtadi et al.) [76]	2014	Intraoperative	61/61	Dexamethasone 0.1 mg/kg (maximum 8 mg)/2 ml of NS	Dexamethasone resulted in decreased pain severity and opioid intake
(Yang et al.) [77]	2014	Intraoperative	22/26/24	I.P 3.5 mg/kg lidocaine/IV bolus of 1.5 mg/kg lidocaine followed by a continuous IV infusion of 2 mg/kg/h lidocaine/control group (I.P and I.V saline)	Both I.P and I.V lidocaine approaches decreased postoperative pain, but I.V lidocaine infusion is more practical, and convenient, and has a better safety profile than I.P
(Ural et al.) [78]	2014	Preoperative Postoperative	30/30/30	75 mg PO diclofenac preoperatively/diclofenac sodium transdermal patch preoperatively/75 mg I.M diclofenac postoperatively	Transdermal administration of diclofenac sodium is a noninvasive method of treating postoperative pain in patients after LC that can be favored over intramuscular application
(Hosseini et al.) [79]	2013	Intraoperative	40/40	200 mL of I.P lidocaine in 100 mL NS/100 mL of I.P NS	IP lidocaine is ineffective at relieving post-LC shoulder and abdominal pain

Table 1 (continued)

Study (author)	Year	Time of administration	Number of patients (treatment/control)	Intervention	Main outcome
(Kocman et al.) [80]	2013	Preoperative	20/20/20	5 mg/kg I.V magnesium sulfate/7.5 mg/kg I.V magnesium sulfate/NS	Magnesium sulfate at both 5.0 and 7.5 mg/kg was found to be more effective in significantly lowering early postoperative pain. However, at 6-, 9-, and 24-h following surgery, there was no noticeable reduction in pain, and no side effects were seen
(Sinha et al.) [81]	2013	Postoperative	25/25	I.V diclofenac 75 mg/I.V tramadol 50 mg every 8 h	Analgesics that act on opioid receptors, such as tramadol, seem to be more effective than diclofenac at relieving pain following laparoscopic cholecystectomy
(Gousheh et al.) [82]	2013	Intraoperative	15/15	1 g of I.V bolus acetaminophen in 0.9% NS/control (100cc of I.V bolus 0.9% NS)	While 1g of acetaminophen has improved the quality of pain alleviation, it is not an adequate analgesic to use as a monotherapy treatment for controlling moderate postoperative pain
(Nesek-Adam et al.) [83]	2012	Preoperative	20/20/20/20	100 ml I.V NS was administered with 5 ml IV NS before the incision as a placebo/100 ml I.V NS was administered with 0.15 mg/kg of ketamine diluted in 5 ml I.V NS/1 mg/kg diclofenac diluted in 100 ml IV NS was administered with 5 ml IV NS/a combination of diclofenac and ketamine with the same doses and administered at the same time	Ketamine at a dosage of 0.15 mg/kg did not have a preemptive analgesic effect, although preoperative low-dose ketamine plus diclofenac sodium combination improved postoperative analgesia
(Mentes et al.) [84]	2008	Intraoperative	41/42	I.V $MgSO_4$ (50 mg/kg) in 100 ml NS/0.9% NS	50 mg/kg of magnesium sulfate significantly decreased postoperative pain
(Rafiqul Hasan Khan et al.) [85]	2007	Preemptive	20/20/20	3 mg/kg I.V diclofenac (maximum 75 mg at a time)/30 mg I.V ketorolac/100 mg I.V tramadol	Preemptive use of tramadol, ketorolac, and diclofenac can help manage postoperative pain
(Boccara et al.) [86]	2005	Preoperative Postoperative	24/24/24/26	Ketoprofen before induction and NS after the procedure/ketoprofen after the procedure and NS before induction/propacetamol before induction and NS after the procedure/propacetamol after the procedure and NS before induction	Preoperative administration of ketoprofen enhances postoperative analgesia following laparoscopic cholecystectomy

Table 1 (continued)

Study (author)	Year	Time of administration	Number of patients (treatment/control)	Intervention	Main outcome
(Jabbour-Khoury et al.) [87]	2005	Intraoperative	20/20/20/20/20	40 mL of 0.25% I.P bupivacaine spray alone and 40 mL of I.V NS/40 mL of 0.25% I.P bupivacaine spray combined with 200 mg of I.V ketoprofen and 40 mL of I.V NS/40 mL of 0.25% I.P bupivacaine spray alone and 200 mg of I.V ketoprofen diluted in and 40 mL of I.V NS/200 mg of I.V ketoprofen and 40 mL of I.V NS and 40 ml of I.P NS/control group received 40 mL of I.P NS and 40 mL of I.V NS	The optimal combination for the multimodal approach to pain management after laparoscopic cholecystectomy is 200 mg of I.V ketoprofen, and 40 mL of intraperitoneal spray bupivacaine 0.25%, which acts as a local anesthetic. This combination of two medications acts synergistically on two separate sites through two different processes, resulting in a considerable reduction in postoperative shoulder and abdominal pain. It also lowers the incidence of postoperative vomiting and the number of patients who need postoperative rescue analgesics

I.P intraperitoneal, *NS* normal saline, *I.V* intravenous, *TAP* transversus abdominis plane, *LC* laparoscopic cholecystectomy, *VR* Visual reality technology, *POP* postoperative pain, $MgSO_4$ magnesium sulfate, *VAS* visual analogue scale, *cc* cubic centimeter, *S.C* subcutaneous, *NSAIDs* nonsteroidal anti-inflammatory drugs, *I.M* intramuscular, *PONV* postoperative nausea vomiting, *PCA* patient-controlled analgesia, *ICU* intensive care unit, *NaCl* sodium chloride, *PO* per oral

anesthetic infiltration in 100 patients having a LC. When comparing the TAP block group to the port site local anesthetic infiltration group, the median visual analogue scale (VAS) at 3, 6, 24 h, at discharge, and one week after surgery was significantly lower reflecting lower pain ($p \leq 0.001$ for each), and the median Capuzzo score, which gauges patient satisfaction with analgesia, was significantly much greater ($p < 0.001$). Although it was not statistically significant ($p = 0.48$), the TAP block group's median duration for hospital stay was also shorter. In addition, the laparoscopic-guided TAP block is considered a cost-effective method based on the findings of a recent trial [91]. Further study demonstrated that the four-quadrant bilateral laparoscopic-guided transversus abdominis plane block was significantly lower than that of the unilateral transversus abdominis plane block ($p = 0.0245$) and the standard analgesic block ($p = 0.002$), concluding that the early postoperative pain following LC can be effectively avoided with bilateral TAP block. The TAP block should be delivered to all four quadrants [19].

Adjuvants can be added to the local anesthetic agent in US-guided TAP block applications to improve its analgesic efficacy and lessen the possibility of toxic side effects. Accordingly, a randomized trial was conducted to compare the intraoperative and postoperative impact of dexmedetomidine versus tramadol as adjuvants to bupivacaine in a TAP block in which 64 patients were equally distributed to either the TAP block group (bupivacaine + tramadol as an adjuvant) or dexmedetomidine group (bupivacaine + dexmedetomidine as an adjuvant). It is concluded there is no significant difference ($p > 0.05$) and superiority between the two groups over each other in the postoperative analgesia at (0, 3, 6 h), amount of analgesic required, mobilization times, and profile of side effects. However, the adjuvant dexmedetomidine in the TAP block preoperatively resulted in more stable intraoperative hemodynamic outcomes [18]. Nevertheless, another research [40] hypothesized the TAP block impact on postoperative pain and stress markers by comparing US-guided unilateral TAP block plus general anesthesia with general anesthesia alone revealing a significant reduction in pain at (6 and 12 h). Moreover, the TAP block group showed a significant reduction in the mean opioid use and stress response markers. Significant reduction of postoperative nausea and vomiting (PONV) and recovery period resulting in reduced hospital stay and intensive care unit (ICU) need in TAP block application have been demonstrated by a retrospective study conducted on 515 patients [53].

Based on the findings of trials reviewed in this study, the TAP block seems to have the potential to develop into a novel and significant intervention in the therapy of postoperative pain.

Bupivacaine

Bupivacaine is a safe and effective way to provide postoperative analgesia following laparoscopic cholecystectomy [92]. Bupivacaine is the most used local anesthetic following LC that decreases pain conduction by binding to voltage-gated sodium channels and preventing sodium entrance into cells [93]. A recent trial assessed the effectiveness of intraperitoneal (IP) diluted versus non-diluted bupivacaine group (NBG) for pain relief following LC. During the initial 24 h following surgery, the diluted bupivacaine group (DBG) had considerably lower postoperative VAS values than the NBG with a p value ≤ 0.003. In DBG, the time needed for the first analgesic demand was significantly higher than in the NBG (p value $= 0.0001$) over 24 h, suggesting that DBG had superior and longer-lasting postoperative analgesia. With (p value $= 0.0001$), the total opioid analgesics over 24 h were significantly less in DBG than in NBG. Regarding side effects following LC, there was no statistically significant difference (p value $^{>} 0.05$) in the incidence of PONV and shoulder pain between the two groups. Moreover, none of the research subjects in either group suffered from bradycardia, respiratory depression, or hypotension due to the local anesthetic injection [13]. Three groups, each with 60 patients, were compared in a randomized trial resulting in a significant reduction in VAS score in patients who received intravenous (I.V) parecoxib and subcutaneous (S.C) bupivacaine in contrast to placebo at 1, 2, and 4 h after the procedure. However, no significance was reported at 8, 12, and 24 h. In addition, the shoulder pain was lower in the bupivacaine group than in the other groups and the amount of rescue analgesics needed was reduced by the bupivacaine and parecoxib groups [75]. A study by Nikoubakht et al. [31] found no significant difference in the mean Ramsay score between the groups throughout the recovery, 2-, 8-, and 24-h postoperative timeframes. There was no significant difference between the groups when postoperative analgesic satisfaction scores were compared at 2 and 24 h after recovery. It indicated that using intraperitoneal (IP) bupivacaine and intra-abdominal bicarbonate reduced pain; with bupivacaine being more superior. A total of 90 patients were randomly assigned and compared (I.P bupivacaine to I.V ketorolac and the placebo group). Compared to the placebo group, the I.P bupivacaine and the I.V ketorolac significantly reduced the incidence of PONV, and postoperative stomach, and shoulder pain. While there was no statistically significant difference in analgesia between bupivacaine and ketorolac, both groups reported considerably higher levels of satisfaction. Furthermore, the need for opioid analgesics was significantly higher in the placebo group at 6 h and 12 h after the surgery [4]. Moreover, patients who received IP bupivacaine experienced a prolonged

period of requesting rescue analgesia, which resulted in a substantial reduction in postoperative pain within the initial 6 h following surgery. In contrast to shoulder pain, which was significantly less in the bupivacaine group with p value = 0.04, side effects such as nausea and vomiting were equal in both groups [47]. Despite, many studies of high caliber proving the role of bupivacaine in post-LC pain management, a study was conducted to evaluate the efficacy of bupivacaine for shoulder and abdominal pain management after LC demonstrated no specific benefit for using bupivacaine as it did not affect pain compared to normal saline [32]. These variable results may be due to population variation and the fact that the majority of patients who undergo LC experience minor pain; hence, a large sample size must be studied as many patients must have a satisfactory outcome to show a discernible and substantial difference between the two groups. Additional studies are required to ascertain the effectiveness of IP bupivacaine in reducing pain during LC.

Lidocaine

The local anesthetic lidocaine is an amino amide that works by blocking sodium channels to lessen neural transmission. When given as a systemic infusion, it also lowers the chance of ileus. Local anesthetics have anti-inflammatory qualities, prevent the central nervous system from receiving nociceptive input, and are frequently highly beneficial in treating neuropathic pain.

Additionally, with lesser doses of local anesthetic, selective sympathetic blocking may be extremely helpful for visceral pain [1]. Intravenous lidocaine has analgesic and anti-inflammatory effects. Intravenous lidocaine infusion during the perioperative period is safe and has several benefits, including reduced anesthesia, postoperative analgesia, quicker bowel function recovery, and shorter hospital stays [94, 95]. Additionally, lidocaine comes in patches for use as a topical painkiller. It functions by inhibiting peripheral nociceptors' ability to sense pain. It has minimal systemic absorption and minimal adverse effects [96]. In a recent randomized controlled trial (RCT), patch group compared to the control group, the total incidence of shoulder pain was significantly reduced ($p = 0.005$). At 24 h and 48 h following surgery, the patch group's shoulder pain severity was significantly lower than that of the control group ($p = 0.01$, $p = 0.015$ respectively). The only side effect associated with the lidocaine patch was nausea. It concluded that the incidence and intensity of LC postoperative shoulder pain were reduced with a 5% lidocaine patch with no complication [48]. Comparing the effectiveness of lidocaine spray with subcutaneous injection at the port site in terms of improved pain management and fewer long-lasting adverse effects is observed. The pain level was comparable across the groups at any of the six points in time measured, ranging from right after waking up from anesthesia to 24 h following the procedure (p value = 0.329). The instillation lidocaine spray group's consumption of narcotics and nonsteroidal anti-inflammatory drugs (NSAIDs) was statistically reduced (p values = 0.003 and 0.013, respectively). The duration of hospital stay, the time needed to resume regular bowel movements and oral food, and the amount of nausea or vomiting that occurred after surgery did not, however, differ significantly across the groups; this suggests that it may be a valuable choice for managing pain after LC, since it may suggest improved pain control [41]. To evaluate the impact of IV lidocaine infusion on postoperative recovery, a study conducted by Song et al. [66] demonstrated that lidocaine had a significant effect ($p = 0.01$) on pain intensity as measured by VAS at 2 and 6 h. Additionally, a significantly reduced ($p = 0.005$) total opioid intake (98.27 ± 16.33 mg vs. 187.49 ± 19.76 mg) was recorded. Fewer cytokines were released during IV lidocaine infusion compared to the control group, providing evidence that, after LC, perioperative IV lidocaine enhances surgical recovery and delays the onset of an exaggerated inflammation. A head-to-head comparison of IP versus IV lidocaine reported a noteworthy decline in the IP and IV lidocaine groups' scores for patient-controlled analgesia (PCA), satisfaction with pain, overall opioid use, and as compared to the control group. The IP group experienced significantly lower pain than the IV group at 2 h after surgery, and the IP group received PCA less frequently at 0–2 h. IV lidocaine infusion is a more practical approach that is easier to implement and has a better safety profile than IP, regardless of IP's effectiveness. It was concluded that IV lidocaine treatment is a feasible substitute for IP lidocaine administration while attempting to reduce postoperative pain in patients undergoing LC [77]. On the contrary, another study [79] concluded that IP lidocaine is ineffective in reducing post-LC pain. Nevertheless, when assessing the impact of IV lidocaine infusion at a rate of 1.25 mg/kgBW per hour on the severity of pain it was indicated that the lidocaine group showed lower numeric rating scale (NRS) scores at 2 and 6 h than the placebo group but no differences, at 12 and 24 h postoperatively. The lidocaine group had a reduced postoperative opioid requirement than the placebo group, with a p value of 0.000, concluding the hastened healing of the intestines and the analgesic effect of perioperative lidocaine infusion [61]. A randomized study compared the effects of two different IV lidocaine infusion doses: 1.5 mg/kg for bolus lidocaine administered intravenously, followed by a continuous infusion of 1.5 mg/kg/h; and 1.5 mg/kg for bolus lidocaine administered intravenously, followed by a continuous infusion of 2 mg/kg/h. It proved that patients

in both groups often had mean VAS scores of less than three following surgery, suggesting that sufficient analgesia was found to be provided by both doses. However, compared to 1.5 mg/kg/h, the dose of 2 mg/kg/h was found to be superior in terms of analgesia, as evidenced by significantly lower VAS scores at all-time intervals; an increased mean time of 49.42 min for the first rescue analgesic request in comparison with 30.65 min; and a decline in the total amount of analgesics consumed in 24 h to patients receiving the maintenance dose of 2 mg/kg/h, with a mean of 178.85 mg against 126.92 mg. Furthermore, the investigation showed no appreciable detrimental effects and concluded that the dosages were safe [26]. For comparison purposes, we also analyzed contrast data obtained from a blind study that compared the effect of IV bolus lidocaine, followed by a continuous infusion of 2 mg/kg/h to an equivalent placebo; that did not successfully verify a reduction in opioid demand 24 h after surgery (p = 0.542). The incidence of shoulder pain or postoperative pain scores were unaffected by lidocaine administration at any time point. Additionally, no differences were found in the incidence of nausea and postoperative sedation perhaps due to the failure to reduce the opioid consumption [27].

Antidepressants

Duloxetine

Duloxetine is a non-opioid neuromodulator with peripheral and central analgesic effects [97]. It possesses its action through selective inhibition of serotonin and norepinephrine reuptake. It is generally used as an antidepressant and for the treatment of anxiety disorder, chronic musculoskeletal pain, fibromyalgia, and neuropathic pain [98, 99]. As part of multimodal analgesic regimes, duloxetine has also been linked to decreased consumption of postoperative opioids, a longer time until the first rescue analgesic is needed, and decreased chronic postoperative pain incidence [97]. The efficacy of preoperative duloxetine in controlling pain has been assessed in a variety of surgical procedures and found it had a lower incidence of drug-related cognitive adverse effects and a comparable analgesic impact for pain treatment following spinal surgery, it can be administered in place of pregabalin [100]. It has also been shown from a prior trial that it can lessen the need for morphine during the first 48 h following knee replacement surgery [101]. Preoperative duloxetine was helpful in seven randomized controlled studies for various procedures. The aggregated data showed that duloxetine significantly reduced pain scores at 4 ($p < 0.001$) and 24 h ($p = 0.005$) when compared to the placebo [102]. According to new research from a RCT, the area under the curve (AUC) of the VAS scores derived for the duloxetine group was significantly lower than those of the control group. The mean postoperative VAS scores showed a statistically significant difference, with the duloxetine group's values being statistically considerably lower at 4 and 24 h. In comparing the two groups' initial requests for rescue medication, there was no statistically significant difference ($p = 0.665$). Patients in the duloxetine group had a smaller total PONV, although it was not statistically significant ($p = 0.734$ and $p = 0.572$) compared to patients in the control group at 8- and 24-h intervals [33].

Gabapentinoids

Pregabalin and gabapentin belong to the gabapentinoid group of drugs that reduce postoperative pain via binding to the α-2-δ subunit of voltage-gated calcium channels and so inhibiting the release of excitatory neurotransmitters substance P, serotonin, and glutamate [103, 104]. Gabapentinoids are safe and effective at low dosages for treating pain following a variety of surgical procedures, including LC, despite having minimal risk effects of somnolence, vertigo, and vomiting. Other benefits of gabapentinoids include opioid sparing, preoperative anxiolysis, and a reduction in movement-evoked pain [36, 105]. According to research comparing the effectiveness of gabapentin and memantine as premedication, a lower NRS score was observed in the gabapentin group at 15 min and 1 h after surgery. In contrast, the memantine group requested rescue analgesia 50.53 min later than the gabapentin and placebo groups. Analgesiometer data used for objective pain assessment revealed no statistically significant differences in threshold or tolerance values between the three groups. However, acute postoperative pain is likely best evaluated and treated by subjective means; using an analgesiometer to quantify the general pain threshold may not be helpful in this regard. In contrast to the other two groups, the gabapentin group had higher Ramsay sedation scores. In summary, gabapentin, when given as a single preoperative dosage, provides superior adjuvant analgesia than memantine for patients undergoing laparoscopic cholecystectomy [46]. Also, Jain et al. [45] studied the effect of 1200 mg oral gabapentin given 2 h before the LC on the hemodynamic parameters and postoperative pain level, and observed that the gabapentin group had a significantly decreased VAS score and experienced a significantly longer duration of analgesia, nausea, and vomiting-free period ($p < 0.01$)[45]. Additionally, in comparison with hydrocortisone, it was demonstrated that the gabapentin group's mean VAS score was significantly lower in the first 2, 4, and 24 h following surgery with no differences at 6 h, 12 h, and 18 h [59].

However, pregabalin was shown to have anti-epileptic, analgesic, and anxiolytic effects that were comparable to

those of gabapentin in earlier research, but it also had a more favorable pharmacokinetic profile [106]. After an oral intake, it is quickly absorbed, reaching its maximum plasma concentration an hour after one or more doses with 90% oral bioavailability that is dose-independent. In comparison with gabapentin, these properties provide an advantage for perioperative use [107]. In a prior trial, pregabalin used preoperatively has been shown to significantly lower the pain score and total opioid consumption [36, 105, 108]. When comparing the effectiveness of pregabalin and tizanidine, patients in the placebo group requested more analgesia than those in the tizanidine and pregabalin groups ($p=0.03$), but no statistical differences were found between both interventions ($p=0.84$). The findings suggest that the single or combination use of these medications may be useful in lowering or managing LC postoperative pain in conjunction with common postoperative analgesics, such as opioids and NSAIDs; additionally, lowering the dosage of these medications is linked to fewer side effects and improved quality of life [29]. Preemptive pregabalin was found to exhibit a highly significant difference in pain scoring across all-time records in a prior trial, with a p value of less than 0.0001. Those in the placebo group experienced serious pain compared to mild pain experienced in the intervention group, with no adverse effects in either group [36]. Singh et al. [54] discovered that in comparison with 150 mg and 300 mg pregabalin, the control group's overall mean VAS score was significantly higher. The mean VAS values among the pregabalin-treated groups were higher for 150 mg pregabalin than for 300 mg pregabalin; however, this difference was not statistically significant. However, a pregabalin dose of 300 mg is linked to a higher frequency of side effects, including sedation, vertigo, and visual problems. For individuals having a LC, 150 mg of pregabalin is therefore a safe and ideal dosage for reducing postoperative pain with the least amount of adverse effects. On the other hand, a study by Von Plato et al. [60] discovered that 150 mg of pregabalin administered as additive analgesia before surgery failed to reduce post-surgery abdominal pain or opioid intake in the initial hour following surgery in patients who had high risk for postsurgical pain. A significant positive association ($p=0.045$) was seen between preoperative stress, as evaluated on a 0–10 scale, and postsurgical pain.

Kaur et al. studied the preemptive pain-relieving effects of gabapentin and pregabalin, and demonstrated that when both were compared to a placebo, the VAS scores were significantly decreased. However, both drugs had similar scores. When gabapentin and pregabalin were used instead of a placebo, there was a statistically significant variance (p value <0.001) in the meantime of rescue analgesia. As a result, gabapentin and pregabalin offer longer postoperative analgesia. Furthermore, the intervention groups consumed a significantly reduced mean dose of opioids over 24 h than in the placebo group. Nonetheless, there was no significant variation in the overall amount of opioids consumed by both drugs. However, they cause a greater degree of drowsiness than a placebo up to 6 h after surgery [28]. Other studies found that both gabapentin and pregabalin are important for postoperative analgesia when compared to placebo; nonetheless, pregabalin was considered more effective for postoperative analgesia because the pregabalin group used fewer opioids, had a lower VAS score, and delayed 1st rescue analgesic demand than the gabapentin group [68, 73].

Paracetamol

Paracetamol shares analgesic and antipyretic properties but the consensus is that it has little to no anti-inflammatory properties. Its outstanding safety record contributes to its status as one of the most widely used medications in the world. As a metabolite of phenacetin, paracetamol increases the threshold for pain by blocking cyclooxygenase in the central nervous system, but not in peripheral tissue. As a result, it has no anti-inflammatory effects. For the short-term treatment of mild pain, especially following surgery, and fever, IV paracetamol is utilized. Additionally, it lessens the requirement for opioids [109], and in a multimodal approach to postoperative pain management, it is typically combined with other drugs [110, 111]. When IV paracetamol is administered, the analgesic effect begins quickly (5–10 min), peaks in 1 h, and lasts for 4–6 h [112]. Erdi et al. compared the efficacy and side effects of ibuprofen and paracetamol to be used as a substitute for opioids for pain control post-surgery. While there were no significant differences ($p=0.719$) between the mean score of pain in the abdomen in the ibuprofen and paracetamol groups, there was a significant decrease ($p<0.001$) compared to the control group. In the ibuprofen and acetaminophen groups, the intensity of shoulder pain, PONV, sedation, and opioid use were not statistically significantly different, but they were significantly less than in the control group [42]. Furthermore, a study involving 316 patients was carried out to compare the analgesic effects of combined pethidine/acetaminophen and parecoxib/acetaminophen. The mean NRS between the two groups was found to be equally effective (p value $=1.000$) at (45 min, 2 h, 6 h, 12 h, and 24 h). On the other hand, patients in the acetaminophen monotherapy group had higher NRS scores ($p<0.01$) than other groups [43]. In a comparison of ketorolac to paracetamol, a greater number of patients in the ketorolac

group reported a VAS > 4, and both groups' pain scores were generally similar. The majority of patients who required postoperative opioid rescue only needed one rescue and analgesic application during their hospital stay, which prevailed between 3 and 12 h, with no statistically significant differences [67]. Additionally, it has been proved by Johnson et al. [58] that a preoperative single dose of oral paracetamol is not inferior to intraoperative IV paracetamol for patients undergoing LC at ambulatory surgery centers and the median end-pain score in the post-anesthesia care unit was 2 for both groups. The confidence interval (CI) upper limit was found to be under the cutoff value of 1 pain score point. To summarize, substituting preoperative per oral (PO) paracetamol for single-dose IV paracetamol in patients undergoing LC is a cost-effective strategy that can be readily implemented in an ambulatory surgical center. There are minimal variations in the pain scores or rescue opioid consumption [58]. However, paracetamol's analgesic efficacy and its ability to regulate the hemodynamic condition of patients undergoing LC were documented by Kamali et al. [22], the mean pain scores at 2, 4, 8, 12, and 24 h did not significantly differ between the paracetamol and dexmedetomidine groups; however, the paracetamol group's pain score was significantly reduced ($p = 0.04$) than the dexmedetomidine group's. In comparison with the dexmedetomidine group, the paracetamol group's median opioid consumption in the 24 h following surgery was lower, and their mean duration of analgesia was longer. A study conducted to compare paracetamol and opioid analgesics showed that tramadol exhibited higher VAS scores than paracetamol during the 1.5-, 3-, 6-, 12-, and 24-h periods with one patient in the tramadol group having postoperative nausea. There were no negative consequences linked to paracetamol [74]. However, according to Gousheh et al. [82], a randomization process was used to assign candidates for laparoscopic cholecystectomy to either the paracetamol or placebo groups. The difference in the VAS up to 5 h after the procedure was significant, according to a comparison of both arms' mean VAS ($p = 0.01$). Nonetheless, the morphine intake within the first 6 h following surgery was comparable across the groups ($p = 0.24$). It is not an adequate analgesic to use as a monotherapy treatment for controlling moderate postoperative pain. As mentioned in the previously discussed study by Mulita et al. [43], the combinations of pethidine/acetaminophen and parecoxib/acetaminophen were more successful than acetaminophen monotherapy. Based on the demonstrated evidence, the consistent efficacy, favorable safety profile, and versatility in combination therapies position IV paracetamol as a central component in non-opioid pain management strategies post-LC.

Nonsteroidal anti-inflammatory drugs

Diclofenac

Diclofenac is a phenylacetic acid class NSAID with analgesic, antipyretic, and anti-inflammatory properties. Diclofenac inhibits cyclooxygenase, an essential enzyme that converts arachidonic acid into several prostaglandins that are mediators of pain and inflammation [113, 114]. For the treatment of acute painful and inflammatory disorders, diclofenac is a well-tolerated and effective NSAID. Because of its short duration, it is the most often used NSAID for treating pain following surgery for many years [115]. Moreover, rectal suppository and transdermal patch can be used to administer diclofenac. These drug delivery methods avoid first-pass metabolism, have higher bioavailability, lower risk of gastrointestinal problems, fewer systemic side effects, and more patient adherence [116, 117]. The effectiveness of tramadol vs diclofenac in treating pain after LC procedures has been the subject of numerous randomized trials. Zaman et al. [64] conducted a study to compare IV tramadol and diclofenac analgesia following LC. Diclofenac showed varying effectiveness over time: seven patients felt relief within 8 h, 12 between 9 and 16 h, and 18 within 17–24 h post-surgery. Comparatively, tramadol eased pain for 16 patients in the first 8 h, 21 patients between 9 and 16 h, and 25 patients within 17–24 h after the operation. These patterns suggest differences in the onset and duration of pain relief between the two medications. Patients who received a tramadol infusion reported experiencing more nausea and vomiting than those who received diclofenac for pain relief but the incidence of gastritis was higher in the diclofenac group. Sinha et al. [81] also in their study showed at 12 h after surgery, the change in the VAS score was determined to be highly significant ($p = 0.00071$). The mean VAS scores at 12 h were greater in both arms, with two patients in the diclofenac group having values above 30. Furthermore, another study comparing the preemptive efficacy of diclofenac, ketorolac, and tramadol on postoperative pain found that pain can be adequately controlled for the first 24 h with little to no supplementation of low-dose IV opioid analgesics. In this study, 60 patients were randomly assigned to each drug group given IV half an hour before induction. Ketorolac and tramadol have similar analgesic efficacy and are greater than diclofenac. The use of the medications did not present any notable side effects [85]. Based on these investigations, we found that patients who received injectable tramadol experienced a smoother recovery than those

who received diclofenac, with fewer adverse effects. A study compared oral, intramuscular (IM), and transdermal diclofenac for post-LC pain in 90 patients. Patches and IM injections provided better pain relief as indicated by lower VAS scores than oral diclofenac. IM had the lowest postoperative (Ramsey sedation score), while oral caused the most. Postoperative modified Aldrete's score system (MASS) was similar across groups. Patch and IM groups needed less tramadol medication. No side effects or PONV were reported for transdermal or IV administration. For outpatient LC, patches seem ideal, offering good pain control with fewer opioid-related issues. [78].

Ketoprofen

Ketoprofen is a commonly used NSAID that is derived from phenylpropionic acid. It has analgesic, anti-inflammatory, and antipyretic effects. It works by blocking the cyclooxygenase pathway in both injured tissue and spinal neurons, which decreases nociceptive transmission, and it is frequently used to alleviate mild to moderate postoperative pain [86, 118]. Because of these qualities, ketoprofen is a good option for treating acute, and chronic pain and inflammation symptoms. When compared to diclofenac, ketoprofen has a much greater overall efficacy and may provide analgesia for a longer period in the postoperative setting [119]. A dose of 50–100 mg of ketoprofen is given after surgery involving moderate tissue injury, such as LC [120]. A study showed the systemic use of the preoperative infusion of ketoprofen led to a higher proportion of patients not needing the second analgesic and considerably better pain management ($p=0.001$) than postoperative ketoprofen and preoperative and postoperative propacetamol, particularly in the first 3 h after surgery and compared to ketoprofen, there was no benefit to propacetamol preoperative use [86]. Another study [87] was conducted where 100 patients were randomly divided into five groups, each receiving different doses of ketoprofen and bupivacaine. Groups 1 to 4 were given different doses of ketoprofen and bupivacaine, and the control group received 40 mL of IP NS and 40 mL of IV NS, Table 1. Results showed that all groups had significantly reduced abdominal pain levels compared to the control group; however, group 3 which was administered 200 mg of intravenous ketoprofen, and 40 mL of 0.25% bupivacaine intraperitoneal spray had lower rates of postoperative vomiting and rescue analgesics. It is therefore advisable to use a combination of 200 mg of IV ketoprofen and 40 mL of 0.25% bupivacaine intraperitoneal spray for a multimodal approach to pain control after LC. Finally, it may be concluded that ketoprofen might be a useful therapeutic alternative for pain alleviation following surgery.

Centrally acting, non-opioid analgesic

Nefopam

Nefopam is a centrally acting, non-opioid, nonsteroidal painkiller that blocks dopamine, norepinephrine, and serotonin reuptake. It was discovered in the 1960s and is classified as part of the benzoxazine class that controls postoperative pain [121–123]. Nefopam has been widely available by rectal, oral, and parenteral injections [124]. Nefopam also inhibits sodium and calcium channels that are voltage-sensitive. Postsynaptic receptor activity is reduced due to these effects. It follows that nefopam may affect postsynaptic glutamatergic receptors, including n-methyl-d-aspartate (NMDA) receptors [125–127]. Given these characteristics, nefopam may be used to treat acute postoperative pain, delay the onset of chronic pain, and minimize sensory abnormalities that have been widely utilized in Europe [124, 128, 129]. Nefopam has been utilized as an analgesic and as a part of multimodal analgesia for enhanced recovery after surgery (ERAS) in several surgical operations [121, 130, 131]. Moreover, nefopam used perioperatively in orthopedic surgeries reduces immediate postoperative pain scores and significantly spares morphine without having a substantial adverse effect. It appears that patients with severe preoperative pain are particularly influenced by this analgesic effect [132]. Furthermore, research has demonstrated that perioperative nefopam lowers the amount of opioids used following hysterectomy, breast cancer surgery, upper abdomen surgery, and middle ear surgery. For this reason, nefopam is a useful analgesic adjuvant during and after surgery [133–135]. Many clinical trials designed to assess its effect on LC postoperative pain, accordingly Jung et al. [51] hypothesized that a PCA pump with nefopam alone is just as good at managing pain after LC as using a combination of nefopam and fentanyl, but with potentially fewer side effects. A total of 78 patients were allocated equally to each group in this perspective and consequently, NRS scores did not differ significantly across the groups during the recovery period following surgery nor at 30 min after admission, as well as 8 and 24 h after surgery. Other outcomes were not substantially different between the two groups and there was no significant difference in postoperative adverse effects. A comparative study evaluated the efficacy of intraoperative nefopam versus ketamine infusions for postsurgical pain management. The trial involved 60 patients randomly divided into three groups: nefopam (0.3 mg/kg IV bolus followed by 65 μg/kg/h infusion), ketamine (0.3 mg/kg IV bolus followed by 180 μg/kg/h infusion), and a control group receiving saline. Researchers assessed postoperative pain scores and analgesic requirements over the first 8 h. Results showed that both nefopam and ketamine groups experienced significantly lower pain scores and

reduced fentanyl needs compared to the control group, particularly in the first hour post-surgery ($p < 0.05$). Notably, no significant differences were observed between the nefopam and ketamine groups, suggesting comparable efficacy in pain management [69]. Nevertheless, Choi et al. [71] proved that the total quantity of intraoperative remifentanil and postoperative supplementary morphine significantly decreased by co-administration of nefopam or ketamine. Regarding the postoperative VAS score and recovery index, the nefopam group performed was more effective than the control and ketamine groups. Compared to the ketamine group, the nefopam group had less morphine amount required, though not significantly.

Alpha-2-agonists

Dexmedetomidine

Desirable effects of alpha-2 agonists include analgesia and sedation. Although it complicates the interpretation of analgesic effects, alpha-2 agonist-induced sedation is a component of the overall analgesic impact that incorporates spinal and supraspinal pathways [136]. Highly selective α2 adrenergic agonist dexmedetomidine is a novel clonidine-like compound that can enhance postoperative analgesia by reducing hemodynamic disturbances and anesthetic demand by reducing endogenous catecholamine release [137, 138]. In mechanical ventilation and/or sedation-dependent surgeries, dexmedetomidine (DEX) has been used as a solo sedative or as an adjunct medication for operating anesthesia and postoperative care. According to several research, intraoperative dexmedetomidine administration promoted a quick and easy recovery after surgery, decreased postoperative pain, and increased patient satisfaction. The quality of recovery (QoR) score following major abdominal and spinal operations may be enhanced by the preoperative injection of dexmedetomidine [139, 140]. During intraoperative usage, dexmedetomidine acts as an adjuvant to reduce the stress response brought on by anesthesia and surgery while preserving hemodynamic stability [70]. Prior research has indicated that dexmedetomidine has the potential to alleviate postoperative pain during laparoscopic cholecystectomy surgery since the administration of dexmedetomidine infusion was linked to a significantly longer period before requiring rescue analgesia, a significantly reduced frequency of severe postoperative pain, and a significantly lower amount of opioids during surgery included a decreased incidence of chronic postsurgical pain, a lower incidence of PONV, and significantly lower consumption of fentanyl both intraoperatively and at the end of surgery to extubation ($p = 0.001$). There were no differences between groups in the lengths of hospitalization in the ICU or overall hospital stay nor the median pain intensity of 3 h, 6 h, 12 h, or 24 h following surgery [63]. A study conducted by Ye et al. [49] demonstrated that when administering intravenous dexmedetomidine at a dose of 0.6 μg/kg before induction, patients having LC can experience significantly less cough intraoperatively and less pain postoperatively. Additionally, it was reported that the postoperative first analgesic requirement time was longer and the pain scores in the ketamine and dexmedetomidine groups were lower than that of the control group ($p < 0.001$) at all periods over the 48-h monitoring time. Intravenous PCA opioid intake was greater in the dexmedetomidine group ($p < 0.001$) and in the control group ($p < 0.001$) when compared to the ketamine group [35]. In another investigation, it was shown that the postoperative VAS score of the dexmedetomidine group was reduced. The dexmedetomidine group displayed a reduced 24-h analgesic demand than the control group, although this difference was not significant. The control group experienced a significant hemodynamic stress response during tracheal intubation, laryngoscopy, formation of pneumoperitoneum, and extubation. A substantial attenuation of the hemodynamic response between the dexmedetomidine and control arms was also revealed. No noteworthy side effects were reported [14, 55]. Nevertheless, time for rescue analgesics was significantly ($p = 0.00$) lower in the IV group and IP group compared to the control group in a randomized trial using bupivacaine following LC. In the first 12 h, the mean VAS level of pain was similar in the IV and IP groups. Parecoxib and dexmedetomidine combined were also shown to have the lowest total patient-controlled intravenous analgesia (PCIA) press times during 48 h following LC, and their VAS values were significantly less than those of any other group, according to research done by Du et al. [57] to estimate the protective value of this combination on postoperative pain attenuation and early cognitive impairment in elderly patients undergoing LC. The control group had the lowest scores when compared to other groups, and the combination group had the highest Ramsay and mini-mental state examination (MMSE) scores. Finally, a study conducted by Kaarthika et al. [50] compared pain management strategies using different drug combinations. One group received bupivacaine alone, another received bupivacaine with clonidine, and the third received bupivacaine with dexmedetomidine. The clonidine group requested pain relief first, followed by the bupivacaine-only group and the dexmedetomidine group went the longest before requesting pain relief. These differences were significant, suggesting that combining dexmedetomidine with bupivacaine might ensure longer-lasting pain control than the other options. Patients given bupivacaine with dexmedetomidine needed more fentanyl than those receiving bupivacaine with clonidine. Both groups needed

significantly less additional pain relief than patients given only bupivacaine, who required an average of 35.7 μg fentanyl. The results suggest that adding either dexmedetomidine or clonidine to bupivacaine can reduce the request for extra pain medication.

N-methyl-D-aspartate receptor antagonist

Ketamine

Ketamine is a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor that may be used as an anesthetic at large dosages and as an analgesic at low levels [141]. Whether it is co-administered with other anesthetics or not [142], low-dose ketamine has shown a significant reduction in the quantity of opioids needed as well as nausea following abdominal surgery. Ketamine anesthesia has been licensed for use in postoperative pain treatment [143]. Also, it has been noted that a single bolus dosage of ketamine does not cause the side effects that are often observed with the infusion [142]. As mentioned previously, ketamine has an important role that is like that of dexmedetomidine in terms of how it affects total intravenous anesthesia on LC postoperative analgesia, complete intravenous anesthesia, and the reduction of opioid intake [35]. Comparing the opioid-based group to the opioid-free group, Vishnuraj et al. [15] demonstrated that the combination of dexmedetomidine and ketamine results in significantly less analgesia being needed within the first 2 h. The groups' intake of fentanyl at 6 h, however, was comparable (152 ± 28.2 vs. 164 ± 33.4, P = 0.061). It was concluded that giving dexmedetomidine and ketamine together in an opioid-free anesthesia technique with decreased PONV may be an alternative for certain patients undergoing elective LC [15]. Furthermore, ketamine and diclofenac combined patients rated much lower on the pain scale than either ketamine or a placebo, according to research done to evaluate the impact of prophylactic use of both medications. After surgery, analgesics were required for all research groups; however, patients receiving diclofenac and ketamine combined took longer to request analgesia than patients receiving diclofenac alone (p value = 0.03), ketamine (p value < 0.001), or a placebo (p value < 0.001) [83]. However, recent research showed that a single intraoperative ketamine bolus had a substantial pain-relieving effect that persisted for just half an hour following LC. The two group's numerical pain rating scale scores did not significantly vary at other times. Compared to the control arm, the ketamine arm experienced a more prolonged analgesia and a higher sedation score. There were no notable differences between the groups in the incidence of chronic pain or the cumulative tramadol demand at 24 h. However, the limited population sample size in this study prevented the investigation of the analgesic impact on dynamic pain. [34].

Memantine

Memantine is a low-affinity, noncompetitive receptor antagonist that prevents NMDA receptors from being pathologically activated without altering the physiological functioning of the receptors and is better tolerated in patients since it is an open-channel blocker [144, 145]. Memantine has been approved for the treatment of Alzheimer's disease for several years and has the benefit of having few side effects at doses that are within the therapeutic range [146]. The NMDA receptor is activated by prolonged, high-intensity pain inputs. Neuronal excitation and aberrant pain manifestations, such as spontaneous pain, allodynia, and hyperalgesia, are linked to NMDA receptor activation and abnormalities in the peripheral and central sensory system [147–149]. Therefore, pain may be reduced if antagonists block these receptors. This raised the researchers' focus on memantine which has shown promising results in clinical trials for improving memory, learning, pain, and neuroprotective properties [150] with several benefits over ketamine, including a decreased risk of adverse effects, a higher potency, and a slower elimination half-life (60–80 h) as opposed to ketamine's (2.5 h) [151]. Numerous studies have examined, with varying degrees of success, the use of memantine as an opioid-sparing adjuvant when given as a premedication before surgery. Morel et al. demonstrated the efficacy of memantine in the prevention of postsurgical pain in females undergoing mastectomy by administering 5–20 mg/day of memantine two weeks before surgery, and it was continued for an additional two weeks following surgery at a dose of 20 mg/day. Based on the data, patients who received memantine had significantly reduced levels of rescue analgesia, improved emotional states, and significantly less post-mastectomy pain at three months [152]. According to Rahimzadeh et al. [153], a double-blind RCT revealed that, as compared to a placebo, providing patients with 20 mg of oral memantine before dacryocystorhinostomy significantly decreased their postoperative pain. According to a preclinical investigation, memantine, when given to a neuropathic pain model four days before surgery, inhibits the development of cognitive impairment and neuropathic pain symptoms [154]. A randomized, double-blind study that began 20–30 mg/day of memantine immediately following upper limb amputation for four weeks showed that the incidence of phantom limb pain decreased by nearly four times six months after the procedure [155].

In conclusion, memantine is a helpful adjuvant when administered in the early stages of phantom limb pain or right after surgery in patients who are tolerant to opioids.

Based on these data, Karri et al. conducted a study on 60 patients to compare the efficacy of memantine versus gabapentin on postoperative pain following LC. An hour before the surgery, patients were given oral gabapentin 600 mg, memantine 20 mg, or a placebo. Compared to the other two groups, the gabapentin group scored lower on the NRS at 15 min and 1 h after surgery. The mean time for the memantine group to request rescue analgesia was 50.53 min longer than that of the gabapentin and placebo groups. Analgesiometer-based objective pain evaluation revealed no statistically significant differences in threshold or tolerance values between the three groups. Compared to the other two groups, the gabapentin group had greater Ramsay sedation scores. This suggests that even when administered alone, gabapentin reduces postoperative pain more effectively than memantine [46].

Magnesium

It has long been known that magnesium is an important cation. Regarding the antinociceptive effect, magnesium works by blocking the NMDA receptors non-competitively, blocking calcium from entering the cell, thereby attenuating pain and central sensitization. This is the basic mechanism behind the use of magnesium in acute and chronic pain conditions such as postoperative pain [156, 157], acute migraine attacks [158], dysmenorrhea [159], neuropathic pain [160], and fibromyalgia [161]. Several investigators have demonstrated studies to report the magnesium sulfate (MgSO4) analgesia effect for postoperative pain in different procedures like thoracotomy, hysterectomy, and laparoscopic sleeve gastrectomy was assessed, finding that the administration of magnesium decreased the amount of opioids required for pain relief without any adverse effects [162–164]. Pain management is also impacted by oral magnesium (in the form of lozenges or tablets) not only injections [165]. Additionally, systematic reviews suggested that in addition to reducing opioid intake to a lesser amount, IV magnesium lowers the level of pain scores, clinical toxicities were not documented in any of the examined studies [166–168]. As a result of different randomized trials, Akhondi and Sarkoohi et al. [24] reported that analgesic intake during recovery and 6 h post-surgery was lower in the magnesium group than in the control group ($p < 0.001$). Compared to the control group, the intervention group's mean pain score during recovery and the first 2-, 6-, and 12-h following surgery ($p < 0.001$) was significantly lower. In conclusion, magnesium sulfate is a safe and effective supplement that can help minimize postoperative pain and the need for opioids by intraoperative IV magnesium. Furthermore in another trial, 60 patients were randomized into three groups comparing the analgesic effect of different doses of the preemptive IV magnesium sulfate along with the control group receiving IV normal saline found that the VAS score at 5.0 and 7.5 mg/kg; however, 7.5 mg/kg proved to be more successful and significantly lower than the control group in early postoperative pain and consumption of analgesics required following laparoscopic cholecystectomy was considerably decreased. However, there was no difference in pain relief at 6, 9, or 24 h [80]. Additionally, Mentes et al. [84] found that patients who had laparoscopic cholecystectomy in the 50 mg/kg magnesium sulfate group 0, 4, and 12 h after surgery had lower pain scores and narcotic doses compared with the normal saline group. The average VAS score was statistically significant between groups at rest and during coughing periods during the first 24 h after surgery, which was consistent with the results. Jijo et al. [39] found that patients treated with magnesium sulfate (MgSO4) had considerably lower mean pain levels in the first six postoperative hours, and the time to first analgesic demand was significantly prolonged. Between the two groups, the incidence of shoulder pain was found to be less than 10% and statistically insignificant. A result indicating that IP magnesium sulfate (MgSO4) during LC results in efficient postoperative analgesia with few adverse effects, as demonstrated by decreased pain scores during the initial 24 h and decreased analgesic use throughout 24 h. Moreover, it significantly decreases the frequency of nausea and vomiting. However, a trial conducted by ElHoshy et al. compared the MgSO4 and esmolol infusion impact on the recovery pain ratings and showed that the recall time for first rescue analgesia did not differ significantly between the two groups under study. This discrepancy between these research results could be attributed to variations in the patient population and different routes of administration [25].

Steroids

Since steroids tend to lessen the inflammatory response to surgery, there is a rising interest in integrating multimodal analgesia protocols and utilizing them to improve postoperative recovery and lessen pain and fatigue [169]. Dexamethasone is a high-potency, long-acting corticosteroid with fewer mineralocorticoid effects than other steroids. Dexamethasone has a well-known antiemetic action, and it is commonly used to PONV [170]. Data from two meta-analyses revealed that IV dexamethasone given once can lessen both postoperative pain and the need for opioids following surgery [171, 172]. Dexamethasone's potency, prolonged half-life, safety record, and cost-effectiveness have made it an ideal option for an outstanding corticosteroid [173]. It has been shown that dexamethasone inhibits peripheral phospholipase, hence reducing the production of pain-aggravating products from the pathways of cyclooxygenase and lipoxygenase

[174]. Recent randomized controlled trials revealed that IP bupivacaine and IV dexamethasone together may be a highly effective combination for reducing PONV and postoperative pain [175]. Patients scheduled for LC participated in a double-blind clinical trial in which they were randomized into three groups: IP dexamethasone, IV dexamethasone, and control groups. The results showed that in the first 24 h following surgery, the IP group reported less nausea than the control group, but not the IV group. In contrast to the IV group, none of the IP group patients suffered PONV after 8 h. Metoclopramide was administered to patients who experienced PONV at a considerably greater rate in the IV group than in the group given IP dexamethasone (with $p=0.001$); however, the level of nausea was less severe in the IP group. Furthermore, the IP group had a significantly lower ($p=0.02$) VAS score than the other two groups [38]. A randomized experiment successfully demonstrated that a single-dose IV dexamethasone before surgery significantly lowered the VAS score compared to placebo at 6-, 12-, and 24- but not 2-h following surgery. It is suggested that dexamethasone be used as a safe and efficient medicine to reduce pain after surgery [37]. Additionally, a different randomized trial showed a significant decrease in the VAS score (p value <0.001) and amount of rescue analgesics used (p value $=0.013$) when bupivacaine and dexamethasone were administered intraperitoneally until 2 h after surgery, as opposed to bupivacaine alone. Additionally, compared to the bupivacaine group alone, the combination group took a significantly longer time for the first rescue analgesic to be required [30]. According to Surender et al., the quality of recovery was significantly greater with preoperative single IV bolus dexamethasone compared to the single IV bolus lignocaine. When compared to lignocaine, dexamethasone showed statistically superior pain alleviation, physical independence, and physical comfort. The VAS was lower in the dexamethasone group than in the lignocaine group. The dexamethasone group consumed fewer opioids (364.08 ± 127.31) throughout the postoperative period; however, there was no statistically significant difference seen in either group ($p>0.05$) [62]. Nonetheless, when a single intraoperative IV dexamethasone dosage was compared with a placebo the dexamethasone group experienced significantly less pain ($p<0.01$) at 2-, 6-, and 12-h intervals, and the group's meperidine intake was significantly lower than that of the control group ($p<0.05$) [76]. Conversely, another investigation revealed no statistically significant variation between dexamethasone versus placebo in incisional pain during rest and motion, as well as visceral pain during rest over the 6, 12, and 24 h postoperatively. The study group required lower analgesics and antiemetic medications than the control group; however, the difference between the two groups was not significantly different ($p>0.05$), anticipating that a multimodal analgesic and antiemetic combination would provide superior results when used rather than a single medication. Given that dexamethasone was administered 90 min before surgery, variations in this period of administration time and the small sample size might account for the observed discrepancies in the outcomes [176].

Serotonin (5-HT3) antagonist

Ondansetron

5-HT3-antagonists exhibit anti-inflammatory and analgesic qualities, according to many studies, which suggests a possible therapeutic function in pain management [177, 178]. Ondansetron is a selective serotonin (5-HT3) antagonist. It has been shown in earlier research to be able to block sodium channels [179] and opioid receptors [180]. To prevent postoperative nausea and vomiting (PONV), ondansetron is commonly administered as a premedication to patients following gastrointestinal surgery since it blocks serotonin's stimulatory effects on the chemoreceptor trigger zone (CTZ) and the afferent vagal nerve pathway [181]. Nevertheless, because of the multimodal effect of ondansetron, earlier trials demonstrated that it can reduce pain successively following a propofol infusion [182–184] and chronic benign neuropathic pain [185] while another recent study found that ondansetron had no discernible or significant effect on propofol pain or PONV over lidocaine [186]. In summary, a recent systematic review discovered that ondansetron significantly lowers moderate and severe pain compared to placebo and is better at reducing the occurrence of pain. In terms of the incidence of patients experiencing no pain, moderate pain, or severe pain, lidocaine outperformed ondansetron [187]. On the other hand, it was shown that ondansetron, when administered subcutaneously, had 15 times the potency of lidocaine, a well-known and successful alternative for managing pain following LC [179]. According to the results of randomized research, IP ondansetron may have a favorable impact on the analgesic effectiveness of acetaminophen in addition to its antiemetic and antinauseant effect, making it a special and innovative choice for managing postoperative pain in patients undergoing LC; shown by the significantly reduced need for rescue analgesia, ($p=0.005$) in the ondansetron arm compared to the control arm. The participants who required rescue were found to have consumed a similar cumulative 24-h dose of rescue drugs between the two trial groups with no significant difference ($p=0.785$). The ondansetron group's unassisted mobilization time was substantially less than that of the control group ($p<0.001$). The AUC of VAS scores and the

time required for unassisted mobilization demonstrated a statistically significant analgesic effect from ondansetron [44]. Thus, the analgesic effect of this class of drugs is linked to its local action and may be related to differences in the mode of administration of ondansetron, which was shown to have a significant analgesic effect when administered intraperitoneally because ondansetron did not affect the analgesic effect of paracetamol following surgery when given intravenously in a previous study involving women undergoing laparoscopic hysterectomy [44, 188].

Tropisetron

Tropisetron is a partial α7 nicotinic acetylcholine receptor (a7nAChRs) agonist and a 5HT-3 receptor antagonist that is often utilized for its postoperative antiemetic and anti-nauseous qualities [189]. The central and peripheral nervous systems employ nicotinic acetylcholine receptors, which are ligand-gated ion channels according to previous definitions. Non-ionic signaling pathways through nAChRs have recently been shown in immune cells. Therefore, by reducing the production of inflammatory cytokines, activating a7nAch receptors exerts analgesic benefits. Consequently, targeting these two receptors at the same time may thereby reduce postoperative rebound pain and anxiety. But according to a recent study, orthopedicic patients did not have a lower incidence of rebound pain following surgery when intraoperative tropisetron was used. The main results showed no significant differences ($p=0.487$) in rebound pain incidence or NRS score ($p=0.539$) between the tropisetron and saline groups 24 h post-surgery. The use of postoperative analgesia with NSAIDs and opioids and patient satisfaction were comparable in both groups. Regarding postoperative adverse events, such as PONV, there were also no appreciable variations. However, the low prevalence of PONV linked to the fact that more patients in the control group consumed alcohol and smoked might also be contributing factors. Furthermore, the trial employed 5 mg of tropisetron to treat postoperative rebound pain; a greater dose could be necessary to show a meaningful improvement in effectiveness. Also, during the first 24 h after surgery, the pain score was not recorded regularly. Inaccurate data may have resulted in incorrect pain score recalling [190]. Its underlying mechanism of action suggests it may be a promising candidate for future investigation in LC.

Non-pharmacological

Acupuncture

Acupuncture is widely regarded as the cornerstone of traditional Chinese medicine (TCM). Many studies conducted in the last few years have demonstrated that preoperative acupuncture has the potential to alleviate anxiety, enhance the preoperative state, and minimize the need for anesthetics. On the other hand, surgical acupuncture can support the recovery of intestinal function and postoperative pain management, minimize postoperative nausea and vomiting, and reduce hospital stay duration [191]. Acupuncture has been shown to suppress pain through the release of endogenous opioid compounds in the central nervous system and to stop harmful signal transmission in the spinal cord by activating Aβ fibers in the peripheral nervous system [192]. Comparing acupuncture to standard care, numerous studies have demonstrated that it is both safe and economical [193–195]. In clinical practice, electrical acupuncture and transcutaneous electrical acupoint stimulation (TEAS) have been used in addition to traditional manual acupuncture. The combination of general anesthetic and TEAS is known as acupuncture-drug compound anesthesia [196]. As a complementary and alternative therapy in addition to analgesic medicine, it was helpful in numerous clinical trials involving total knee replacement [197], low back surgery [198], and thoracoscopic surgery [196]. A single-blind RCT examined the effects of acupuncture combined with conventional treatment compared to the effect of conventional treatment alone after lumbar spine surgery, and the result showed that although most subjects were satisfied with their pain management although experienced moderate pain due to inadequate analgesia [199]. This led researchers to demonstrate RCT to investigate its effect on the management of laparoscopic cholecystectomy postoperative pain. Patients undergoing laparoscopic cholecystectomy admitted to the hospital were randomly assigned to one group from each group and received either acupuncture after 2 h from surgery or parecoxib sodium injections at request. The outcomes showed that acupuncture can clinically improve the short-term management of postoperative pain following LC and reduce the need for further analgesics. Therefore, acupuncture may have the potential as one of the multimodal analgesia treatments for postoperative pain [21].

Gas aspiration

Shoulder pain is mostly caused by referred pain from peritoneal irritation, which varies depending on the length of the surgery and the amount of residual CO_2 in the tissue [200, 201]. A study has shown that shoulder pain following elective surgical operations, such as cholecystectomy, can be decreased by reducing remaining intra-abdominal gas using a variety of approaches [202]. Carbon dioxide gas aspiration following surgery falls into two categories: passive gas aspiration, in which the gas is released spontaneously, and active gas aspiration, in which the gas is actively extracted using a specific tool

or suction [203]. Many studies have shown that active gas aspiration following laparoscopic cholecystectomy is an easy, practical, and safe operation. By lowering postoperative shoulder and abdominal pain and, consequently, the need for analgesics, this procedure can effectively result in a more restful hospitalization for patients following laparoscopic surgery. It also significantly reduces the residual intraperitoneal gas volume and postoperative pain [202, 204–206]. A RCT designed to evaluate the effects of usual gas release, active aspiration, and passive-valve release on recovery in patients who have undergone laparoscopic cholecystectomy has shown that the volume of residual CO_2 in the intraperitoneal cavity at the end of laparoscopic surgery can be reduced using either the active aspiration or passive-valve release technique, which successfully lowers the degree of postoperative shoulder and abdominal pain. Furthermore, both methods improved the postoperative recovery of patients and decreased the rates of nausea, vomiting, and abdominal pain. Nonetheless, the active aspiration group's ambulation duration was noticeably less than that of the control and passive-valve release groups [65].

Emerged technologies

Virtual reality (VR)

Virtual reality is a new technology that is becoming more and more used in critical care. However, it completely submerges the viewer in a three-dimensional virtual world. VR has a lot of promises to advance critical care medicine for patients, families, and medical professionals. In addition, it has the potential to reduce a patient's pain, anxiety, stress, and fear [207]. With VR, a patient can interact with a simulated environment using all five senses and react to sensory and motor signals [208]. So, it distracts the patients' attention, concentration, and emotions from the real world to the virtual one. As such, because they are not thinking about pain as much, the patients suffer from less intense pain [209, 210]. Additionally, it is important to note that virtual reality therapy has been effectively applied as an analgesic in several acute clinical situations, including burn pain [211], postcardiac surgery [212], and painful procedures [213–215]. A total of 150 patients who undergoing LC in the surgical wards participated in a randomized clinical trial in which they were split into three groups at random: control, distraction, and education. When comparing the preoperative anxiety mean scores of the two VR groups to those of the control group, the results showed a significant decrease. Additionally, patients in the two intervention groups showed a statistically significant decrease in their postoperative pain assessments when compared to the control group [20].

Limitations

Several limitations were encountered in the preparation of this narrative review regarding non-opioids for pain relief post-laparoscopic cholecystectomy. Direct comparisons across studies were difficult due to the differences in how findings were reported. Without full method details on each study, we cannot compare the rigor of such methods. Moreover, we have identified variability in the way pain scores were quantified and published which complicates our analysis. A limitation to drawing general conclusions is the variety of interventions, each with its distinct mechanisms. In addition, many studies had relatively brief follow-ups which prevented us from assessing the long-term outcomes and side effects associated with these non-opioid treatments.

Future perspectives

More thorough clinical studies with multiple arms and larger sample sizes are required to determine the best pain management plans for patients undergoing LC and assess the safety and effectiveness of analgesics under comparable clinical circumstances. Long-term effects, such as the likelihood of developing persistent pain following surgery, and the adverse effects of the drugs are crucial and should be assessed. Furthermore, a patient's age, anxiety before surgery, sex, or other preoperative patient-related characteristics may complicate the intensity of postsurgical pain and must be assessed. Though relief is provided by current pain management techniques, future developments in LC may involve personalized pain management. By knowing each patient's unique genetic and pain profile, physicians may be able to prescribe pain medications with fewer adverse effects and better pain control.

Conclusion

Complicated causes contribute to pain after laparoscopic cholecystectomy. To reduce the postoperative pain associated with LC, a variety of drugs are studied by administering either before, during, or after surgery. There was evidence that one essential part of multimodal postoperative pain management is IV paracetamol. Also, many pharmacological drugs including magnesium sulfate, dexamethasone, ondansetron, gabapentinoids, alpha-2-agonists, local anesthetics, antidepressants, and NSAIDs, were useful in controlling pain. Additionally, non-pharmacological and emerging technological approaches proved their effective role in controlling LC postoperative pain. Further in-depth medical research involving various treatment groups and more participants is needed to identify optimal approaches for managing pain in LC patients.

This would help evaluate how well different pain medications work and how safe they are when used in similar medical situations. Clinicians should individualize this approach with factors such as patient comorbidities, allergies, and analgesic response records. Regular reviews of pain management results promote modification and improvement of the pain control protocol for maximum effectiveness. When these evidence-based non-opioid strategies are implemented in an orderly manner, post-LC pain control can be significantly improved by physicians while reducing risks associated with opioids.

Abbreviations

5-HT3	Serotonin receptor
a7nAch	Alpha-7 nicotinic acetylcholine receptor
AUC	Area under the curve
CC	Cubic centimeters
CI	Confidence interval
CTZ	Chemoreceptor trigger zone
DBG	Diluted bupivacaine group
DEX	Dexmedetomidine
ERAS	Enhanced recovery after surgery
ICU	Intensive care unit
IM	Intramuscular
IP	Intraperitoneal
IV	Intravenous
LC	Laparoscopic cholecystectomy
MASS	Modified Aldrete's score system
MgSO4	Magnesium sulfate
MMSE	Mini-mental state examination
nAChR	Nicotinic acetylcholine receptor
NBG	Non-diluted bupivacaine
NMDA	N-methyl-D-aspartate
NRS	Numeric rating scale
NS	Normal saline
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCA	Patient-controlled analgesia
PCIA	Patient-controlled intravenous analgesia
PO	Per oral
PONV	Postoperative nausea and vomiting
POP	Postoperative pain
QoR	Quality of recovery
RCT	Randomized clinical trial
S.C	Subcutaneous
TAP	Transversus abdominis plane
TCM	Traditional Chinese medicine
TEAS	Transcutaneous electrical acupoint stimulation
VAS	Visual analogue scale
VR	Virtual reality

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Author contributions
HMB collected, distributed, and organized the datasets and prepared the first draft of the manuscript. NOES and DHA contributed to the conception and design of the study. The final manuscript was revised by ERB, DHA, NOES, and Sherif Boraii. All the authors approved the final version of the manuscript.

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