Review Article

Adjuncts and multimodal analgesia: a narrative review

Victoria A. Bennett, Ben Morrison

Department of Anaesthetics, Royal Surrey NHS Foundation Trust, Guildford, UK

Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Ben Morrison. Department of Anaesthetics, Royal Surrey NHS Foundation Trust, Egerton Road, Guildford, GU2 7XX. UK. Email: benmorrison@nhs.net.

Background and Objective: Multimodal analgesia is recommended for pain management following major surgery. This method uses different analgesic agents, which may target different components of pain transmission, with the aim of improving post operative analgesia and decreasing reliance on opiate-based medications. This, in turn, aims to reduce the side-effects secondary to opiate use thus improving post operative recovery. It forms part of a successful enhanced recovery after surgery program and includes the combined use of neuraxial blockade, regional anaesthesia and systemic medications. This article aims to review the main adjuncts used as part of a multimodal analgesia strategy in an enhanced recovery after surgery program and evaluate their evidence base.

Methods: A literature search was performed using PubMed. The terms multimodal analgesia, adjuncts, surgery, and enhanced recovery were included. Only papers published in English after 2003 were reviewed.

Key Content and Findings: Our review covers contemporary evidence around the use of analgesic adjuncts including their associated risks and benefits in anaesthetic practice as part of an enhanced recovery after surgery programme.

Conclusions: A range of adjuncts have been studied to investigate whether their use as part of a multimodal analgesia plan improves post operative pain alongside other outcomes. It is recommended that all patients should receive paracetamol and a non-steroidal anti-inflammatory medication in the absence of contraindications. Ketamine and magnesium have evidence of benefit when used perioperatively. Clonidine and dexmedetomidine, both alpha-2-agonists, improve acute pain with opioid sparing properties. Glucocorticoids, which are commonly used for their antiemetic properties, may have additional analgesic benefits. The risks and benefits need to be carefully evaluated before considering using intravenous lidocaine due to its narrow therapeutic window. The evidence for benefit from perioperative use of gabapentinoids is inconclusive. Other medications which may have the potential to be used as adjuncts to multimodal analgesia show some promise. This will be an area for future research and includes the use of duloxetine, a selective-serotonin reuptake inhibitor.

Keywords: Adjuncts; multimodal analgesia; enhanced recovery; surgery

Received: 01 November 2021; Accepted: 27 December 2021; Published: 30 March 2022.
doi: 10.21037/dmr-21-80
View this article at: https://dx.doi.org/10.21037/dmr-21-80

Introduction

Perioperative pain management has evolved alongside the development of enhanced recovery after surgery (ERAS) programs with increased awareness of the risks of opioid dependance and development of opioid sparing techniques. As part of this, the role of an individualized, multimodal approach with input from a multidisciplinary team has been increasingly advocated. This aims to decrease opioid dependance, reduce the occurrence of side effects related to high opioid use whilst ensuring patients have good post

operative pain management and high patient satisfaction. ERAS programs aim to improve patient recovery through a combination of perioperative interventions. Effective pain management without high reliance on opiates may be important for a number of components of an ERAS program. For example, if fewer sedating analgesics are used and effective analgesia is achieved patients may be able to mobilise at an earlier stage postoperatively. Reduced dependance on opiate medications may be associated with a lower incidence of post operative nausea and vomiting and enteral nutrition may be successfully reestablished sooner (1).

Multimodal analgesia is the use of a number of different techniques or medications to simultaneously target different pain pathways or receptors. This aims to decrease the dependance on one analgesic modality and minimize the associated side effects. Simultaneously targeting multiple pain pathways can have either additive or synergistic effects (2). National guidelines by the American Society of Anaesthesiologists (ASA) advocate for the use of multimodal analgesia in perioperative pain management. A wide range of multimodal techniques are available. These may be two or more analgesic agents acting via different mechanisms but administered via a single route, for example local anaesthetic and an opiate via an epidural catheter. Alternatively, different agents may be administered via different routes, for example combining the use of regional anaesthesia with systemic opioids. Both are used to improve post operative analgesia and potentially improve the side effect profile by reducing the overall opioid dose required. The ASA guidelines highlight the need to individualise multimodal analgesia based on both patient and surgical factors (3).

Anaesthetic techniques have changed with a move away from reliance on opioid-based techniques. Central neuraxial blocks, both intrathecal injections and epidurals, are used and increasingly the role of regional anaesthesia and field blocks is recognised. These areas form the basis of other review articles in this series so this article will focus on the use of adjuncts as part of multimodal analgesia.

Analgesic adjuncts have formed part of pain management plans for many years. The World Health Organization (WHO) analgesic ladder, initially published in 1985, was designed for the management of pain in patients with cancer and was then generalized to provide a stepwise approach to acute pain. This included the use of both paracetamol and cyclooxygenase (COX) inhibitors for mild pain and mentions the role of adjuncts in both mild, moderate and severe pain (4). Since then, their role has become more established and the evidence base for different adjuncts has grown considerably.

This review will cover paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, N-methyl-D-aspartate (NMDA) receptor antagonists, alpha-2-adrenergic antagonists, membrane stabilisers, glucocorticoids and review the novel agents being researched. They will be summarized in *Table 1*.

As part of this review a literature search was performed using PubMed. The terms multimodal analgesia, adjuncts, surgery, and enhanced recovery were included. Only papers published in English were reviewed.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dmr.amegroups.com/article/view/10.21037/dmr-21-80/rc).

Methods

As part of this review a literature search was performed using PubMed. The terms multimodal analgesia, adjuncts, surgery, and enhanced recovery were included. Only papers published since 2016 in English were reviewed. Further details of the literature search are listed in *Table 2*.

Paracetamol

Paracetamol has been used in pain management for more than a century. It is available in oral, intravenous and rectal preparations. Differences in bioavailability between oral and rectal administration can affect both the onset time and duration of action. When given intravenously, the onset of action is within five minutes, peak effect occurs between forty minutes and one hour after administration. The duration of action is between four and six hours. No significant analgesic benefit has been demonstrated when intravenous paracetamol is used over oral paracetamol in the perioperative setting (5). The dose is one gram four times a day for adults weighing more than fifty kilograms. There should be a minimum of four hours between doses with a maximum of four grams every 24 hours. Paracetamol is generally considered safe when used within the recommended dosing. It should therefore form part of the perioperative pain management plan (6).

The exact mechanism of action is still not fully understood. It is thought to act by COX inhibition and reduction in prostaglandin production. There is also some evidence of an effect upon descending serotonergic pathways. One of its active metabolites, N-arachidonoylphenolamine

Table 1 Summary of the main adjuncts available for use as part of a multimodal analgesic plan

Group	Examples	Reduces opioid requirements?	Contraindications
Paracetamol	–	Yes	Generally considered safe
COX inhibitors	Ibuprofen	Yes	Renal impairment, cardiac comorbidities, gastric ulceration
	Diclofenac		
	Ketorolac		
	Parecoxib		
Gabapentinoids	Gabapentin	Inconclusive data	Concern regarding side effects—drowsiness, dizziness, headache, respiratory depression
	Pregabalin		
NMDA receptor antagonists	Ketamine	Yes	Coronary artery disease, severe liver failure, raised intracranial or intraocular pressure
	Magnesium	Yes	Nil significant
Alpha-2-adrenergic agonists	Clonidine	Yes	Hypotension
	Dexmedetomidine	Yes	Bradycardia
Membrane stabilisers	Lidocaine	Possible reduction	Potential safety concerns regarding local anaesthetic toxicity
Glucocorticoids	Dexamethasone	Yes	Poorly controlled diabetes
SSRIs	Duloxetine	Potential reduction, more studies required	Seizure history, uncontrolled hypertension, raised intraocular pressure

COX, cyclooxygenase; NMDA, N-methyl-D-aspartate; SSRIs, selective serotonin reuptake inhibitors.

Table 2 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	13th October 2021
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters)	Multimodal analgesia; adjuncts; surgery; enhanced recovery
Timeframe	After 2003
Inclusion and exclusion criteria (study type, language restrictions etc.)	Inclusion: written or translated in to English
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Initial selection by V Bennett then review and amended by B Morrison
Any additional considerations, if applicable	NA

(AM404), acts on the cannabinoid pathway to increase receptor activation. The analgesic effect may also be due to this metabolite inhibiting the action of nitric oxide within the pain pathway (6).

NSAIDs and COX inhibitors

NSAIDs include a range of different analgesics, each with different preparation options. Some of the commonly used ones include ibuprofen available via the oral and intravenous route, diclofenac, available in oral, rectal and intravenous preparations, ketorolac which is available for intramuscular or intravenous administration and parecoxib which is available for either intramuscular or intravenous administration. They all act to inhibit COX, an enzyme which is required for the metabolism of arachidonic acid to prostaglandins. NSAIDs

can either be non-selective COX inhibitors acting on both COX-1 and COX-2 or COX-2 specific inhibitors. The analgesic effects are achieved through COX-2 inhibition. COX-1 enzymes predominately have a role in platelet function and the gastric and renal systems (7).

Post operative use of NSAIDs has been shown to decrease opioid requirements by 20% to 35% (7,8).Their use is routinely recommended where contraindications are not present (3). However, there are a number of patient and surgical factors which limit their use in the perioperative setting. Commonly described complications from the use of non-selective COX inhibitors include gastric ulceration, renal injury, increased cardiac morbidity and increased post operative bleeding. Their use is therefore avoided in the older population and in patients with a history of, or at risk of these complications. It was initially presumed that some of these potential complications could be avoided by use of selective COX-2 inhibitors. Initial studies demonstrated increased cardiotoxicity in patients treated with selective COX-2-inhibitors. Several of these studies had been performed in cardiac surgical patients. Further studies and meta-analyses have investigated whether the same risk profile exists in patients undergoing non-cardiac surgery and without significant cardiac risk factors. They did not demonstrate increased cardiac risk in this group of patients (9).

Gabapentinoids

Gabapentinoids include pregabalin and gabapentin which are both administered orally. Maximum plasma concentrations occur one hour post ingestion for pregabalin and four hours post ingestion for gabapentin. They have a similar half-life of around six hours. Dose adjustment is required in the setting of renal impairment. Their full mechanism of action is still not fully understood. They are calcium-channel blockers and act to reduce the release of excitatory neurotransmitters (7). Side effects include sedation, dizziness and headaches. More rarely respiratory depression has been reported (10). Their use in the management of non-neuropathic, perioperative pain is off label. Despite the fact their perioperative use has increased, the outcome of studies investigating their role in perioperative analgesia has been variable (7).

Perioperative doses of gabapentin between 300 and 1,200 mg have been studied in a range of surgical specialties. Studies have demonstrated both decreased opiate use and improved pain scores. Systematic reviews and meta-analyses have been performed and have also provided evidence of this. For perioperative pregabalin use the results are less consistent. A single pre-operative dose of 150 mg of pregabalin, in patients having an elective laparoscopic cholecystectomy, reduced post operative opiate use and improved pain scores (11). One study of the pre-operative administration of 300 mg pregabalin for elective hip arthroplasty showed reduced postoperative opiate use, increased sedation but overall pain scores were unchanged (12). Studies in patients undergoing major elective gynaecological surgery showed no benefit from preoperative pregabalin. There may be some evidence for the use of gabapentinoids in the prevention of chronic post-surgical pain (2). However, this was not supported by a recent large systematic review and meta-analysis which showed no benefit from either pregabalin or gabapentin for either acute or chronic post operative pain. It did demonstrate an increase in side effects associated with their use (13).

Clinically there is considerable variation in practice. This includes the dose used, timing of initiation and duration of use. Recent guidance published by National Institute of Health and Care Excellence (NICE) highlighted this. It stated the need for further research in the perioperative use of gabapentin (14). The guidance from national societies on the role of gabapentinoids is conflicting, with some recommending their use and others not (13,15).

NMDA receptor antagonists

NMDA receptor antagonists include both ketamine and magnesium. Activation of the NMDA receptor has been demonstrated to contribute to central sensitization which may predispose to chronic pain. Additionally, opioid use activates mu-receptors which may increase activity at the NMDA receptor resulting in hyperalgesia.

Perioperatively ketamine can be given as an intravenous bolus, as an infusion, intramuscularly or as a sublingual or intranasal medication. It may be used intra operatively as part of the analgesic strategy for post operative pain relief or as part of a “rescue analgesia” strategy. It has both analgesic and dissociative effects that may be useful. Analgesic dosing requires titrating to the individual’s response, in an appropriately monitored environment. The American Society of Regional Anesthesia and Pain Medicine recommends that a bolus dose should not exceed 0.35 mg/kg. The infusion dose ranges from 0.5 to 1 mg/kg/hr, with max of 1 mg/kg/hr for acute pain management (16).

Ketamine use as part of multimodal analgesia has been demonstrated to improve pain scores and reduce opioid requirements. It has been shown to be more effective

in some surgical groups than others, with the biggest benefits seen in patients undergoing abdominal, thoracic or orthopaedic surgery (17). It may have particular benefit for patients with chronic pain who require preoperative opiate-based medications. Complications, or serious side effects appear to be infrequently reported in clinical studies (18).

Ketamine administration can cause distressing hallucinations. In addition to the analgesic affects it causes multisystemic changes, some of which may be disadvantageous. These include an increase in cerebral oxygen consumption and intracranial pressure, increase in heart rate and cardiac output with an increase in myocardial work, bronchodilatation and hypersalivation. Its use is therefore relatively contraindicated in the presence of coronary artery disease, severe liver disease, and in patients with raised intracranial or intraocular pressure (19). The potential effect of ketamine administration on depth of anaesthesia monitoring has been studied. Bispectral index (BIS), is one commonly used monitor. When ketamine is administered at a dose of 0.5 mg/kg an increase in BIS values has been demonstrated, this is despite a greater degree of sedation. There should be an awareness of this effect when interpretating the BIS values, if administering ketamine. At lower doses, of ketamine, 0.2 mg/kg, no increase in BIS values has been demonstrated (20,21).

Although magnesium also acts as an NMDA receptor antagonist, it poorly crosses the blood brain barrier so it is unclear if this is the mechanism of action for its analgesic effects (2). Perioperatively it is given intravenously. The first randomized control trial to study its role as an analgesic adjunct was in 1996 and a number of further studies have followed since. They have produced conflicting results. However, a meta-analysis of these studies shows a decrease in opioid requirement with perioperative magnesium use. The method of administration, including bolus dosing versus prolonged infusion of magnesium, as well as the optimal dose have both been studied. A suggested dose of 40–50 mg/kg has been proposed but authors state more research would be required to confirm if this is the optimal dose. Despite potential side effects from the use of high dose magnesium, including bradycardia, hypotension and prolonged neuromuscular blockade, studies have not reported any significant side effects or complications. Its use as part of multimodal analgesia is therefore recommended (22).

Alpha-2-adrenergic agonists

Alpha-2-adrenergic agonists include clonidine and dexmedetomidine. Alpha-2-adrenergic receptors are present in both the peripheral and central nervous system, pre and post-synaptically. The main mechanism of action for clonidine and dexmedetomidine is via blockade of the presynapatic receptors, reducing noradrenaline release with decreased sympathetic activation. Additionally, they are thought to inhibit pain pathways via their action on receptors in the substantia gelatinosa of the dorsal horn (2,23).

Clonidine can be given orally, intravenously or neuraxially. Suggested starting doses post operatively for oral clonidine are 50 µg up to three times a day which can be increased to 75 µg. When used intraoperatively it is given intravenously, generally in small aliquots and the response assessed and dose titrated. For intrathecal injection 1–2 µg/kg has been proposed or 2–4 µg/kg as a single administration via the epidural route (24). Dexmedetomidine is given as an intravenous infusion, its use is limited to the theatre or critical care environment.

Both clonidine and dexmedetomidine have been demonstrated to reduce postoperative pain and decrease opioid requirements. Clonidine has been shown to reduce opiate requirements in the first 24 hours after surgery by up to 25 percent and dexmedetomidine by up to 30 percent (25). There is insufficient data currently available on whether the use of clonidine affects the development of chronic pain syndromes.

The alpha-2-agonists have a number of reported side effects which include sedation and cardiovascular effects. The increased sedation reported was not however demonstrated to slow recovery times. Intraoperative clonidine administration increases the incidence of both intra and post operative hypotension which may limit its use. Intraoperative dexmedetomidine use does not appear to be associated with hypotension but does increase the incidence of post operative bradycardia (25).

Membrane stabilisers

Lidocaine is an amide local anaesthetic that acts through blockade of sodium channels. When given intravenously lidocaine has both analgesic and anti-inflammatory effects. When used perioperatively an initial bolus dose may be given, which can be followed by an infusion. A loading dose of up to 1.5 mg/kg, then an infusion of up to 1.5 mg/kg/hr is described in consensus documents. The total dose in an hour should not exceed 120 mg. The use of intravenous lidocaine for perioperative analgesia is off label (26).

Intravenous lidocaine has been extensively studied with

differing conclusions found. A number of systematic reviews and meta-analyses reported considerable potential benefit associated with its use. This included improved post-operative pain, decreased opioid use and decreased hospital length of stay (27-29). A Cochrane review of the evidence published fewer positive conclusions on the benefits of intravenous lidocaine. It concluded there was no definite, good quality evidence of benefit from either improved pain scores or reduced opioid use (30). This has been further explored and a recent consensus statement published in *Anaesthesia* on the efficacy and safety of perioperative use of intravenous lidocaine. It commented on considerable variability in the doses studied, duration of infusion used and outcome measures recorded in the various studies performed. The statement concluded that intravenous lidocaine may offer some possible benefits but highlighted the potential safety concerns associated with its use. The need for assessment of risk benefit in specific patients, considering their individual factors and the surgical operation performed was stated (26).

Lidocaine, given intravenously, has a narrow therapeutic window with therapeutic plasma levels of 2.5–3.5 µg/mL. Toxicity occurs with plasma levels above 5 µg/mL when neurological symptoms can develop. Initial symptoms include tongue numbness, light headedness and these can then progress to generalised seizures. Respiratory or cardiorespiratory arrest can occur if untreated. Cardiotoxicity is rarely seen below plasma levels of 10 µg/mL. The plasma level is influenced by both how the lidocaine is administered and individual patient factors. These include the total dose given and the infusion rate used, the patient's acid-base status, plasma protein levels and presence of renal or hepatic dysfunction. This can make an individual's response difficult to predict (31).

Given the potential toxicity, narrow therapeutic window, and uncertainty about the clinical benefits of its use, the consensus document states a number of measures should be taken before deciding to administer intravenous lidocaine. These include specific patient consent for its administration, limiting duration of use to 24 hours and provision of adequate monitoring in a minimum of a level 2 bed. 20% lipid emulsion should be readily available in areas where it is used in case of the occurrence of toxicity (26).

Glucocorticoids

Dexamethasone is a glucocorticoid that is commonly used intraoperatively for its antiemetic properties. Reduced postoperative nausea and vomiting may help to decrease post operative pain as part of a multimodal perioperative analgesia plan. It also acts as an anti-inflammatory medication through inhibition of pro-inflammatory pathways. Intraoperatively it is given intravenously, in doses of 4–8 mg. The optimal dose for analgesic effects remains an area of research and higher doses have been used as part of research studies (7).

Single studies and meta-analyses have shown that a single dose of intraoperative dexamethasone improves pain scores both initially and at 24 hours. They also showed decreased opiate requirements and earlier discharge from the recovery unit to the ward (32,33). A single of dose of intraoperative glucocorticoid is safe for the majority of patients. It has been shown to cause an increase in blood sugar level (7), but no increase in postoperative infection or delayed wound healing has been demonstrated.

Novel agents

A selective serotonin reuptake inhibitor (SSRI) duloxetine has been used in the management of chronic and neuropathic pain for a number of years. Its potential role in perioperative pain management has also been explored. Studies in gynaecology and orthopaedic surgery showed that administration of a single dose preoperatively and then a second dose 24 hours later improved pain scores and reduced opiate requirements. This has been highlighted as a medication that would warrant further investigation of its potential role as a multimodal analgesic agent (7,34,35).

Conclusions

The use of multimodal analgesia for perioperative pain management is vital to deliver effective analgesia and potentially improve patient recovery. With the risks associated with post-operative opioid use becoming more apparent the importance of opioid-sparing methods is increasingly recognised. The pain management plan should be individualized to the patient and the procedure they are having. Where possible regional or neuraxial anaesthetic techniques form a key part of this plan. Patients should receive paracetamol and a NSAID if not contraindicated. The use of NMDA-receptor antagonists, including both magnesium and ketamine is recommended. Alpha-2 agonists can also be used for acute postoperative pain management. The role for gabapentinoids and membrane stabilisers is less clear. The potential risks associated with

intravenous lidocaine must always be considered before it is given. Novel adjuncts continue to be an area of interest in perioperative medicine and more research is likely to provide further clarity in this area.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Chris Jones and Leigh Kelliher) for the series "Current Issues in Analgesia for Major Surgery" published in *Digestive Medicine Research*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://dmr.amegroups.com/article/view/10.21037/dmr-21-80/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://dmr.amegroups.com/article/view/10.21037/dmr-21-80/coif). The series "Current Issues in Analgesia for Major Surgery" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Beverly A, Kaye AD, Ljungqvist O, et al. Essential Elements of Multimodal Analgesia in Enhanced Recovery After Surgery (ERAS) Guidelines. Anesthesiol Clin 2017;35:e115-43.
2. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol 2009;22:588-93.
3. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice Guidelines for Acute Pain Management in the Perioperative Setting. Anesthesiology 2004;100:1573-81.
4. Ventafridda V, Saita L, Ripamonti C, et al. WHO guidelines for the use of analgesics in cancer pain. Int J Tissue React 1985;7:93-6.
5. Fenlon S, Collyer J, Giles J, et al. Oral vs intravenous paracetamol for lower third molar extractions under general anaesthesia: is oral administration inferior? Br J Anaesth 2013;110:432-7.
6. Sharma CV, Mehta V. Paracetamol: mechanisms and updates. Contin Educ Anaesth Crit Care Pain 2014;14:153-8.
7. Helander EM, Menard BL, Harmon CM, et al. Multimodal Analgesia, Current Concepts, and Acute Pain Considerations. Curr Pain Headache Rep 2017;21:3.
8. Maund E, McDaid C, Rice S, et al. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. Br J Anaesth 2011;106:292-7.
9. Schug SA, Joshi GP, Camu F, et al. Cardiovascular safety of the cyclooxygenase-2 selective inhibitors parecoxib and valdecoxib in the postoperative setting: an analysis of integrated data. Anesth Analg 2009;108:299-307.
10. Schmidt PC, Ruchelli G, Mackey SC, et al. Perioperative gabapentinoids: choice of agent, dose, timing, and effects on chronic postsurgical pain. Anesthesiology 2013;119:1215-21.
11. Agarwal A, Gautam S, Gupta D, et al. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. Br J Anaesth 2008;101:700-4.
12. Mathiesen O, Jacobsen LS, Holm HE, et al. Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. Br J Anaesth 2008;101:535-41.
13. Verret M, Lauzier F, Zarychanski R, et al. Perioperative Use of Gabapentinoids for the Management of Postoperative Acute Pain: A Systematic Review and Meta-analysis. Anesthesiology 2020;133:265-79.
14. National Institute of Health and Care Excellence.

Perioperative care in adults (NICE guideline 180). cited 2021 Oct 10. Available online: https://www.nice.org.uk/guidance/ng180
15. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 2016;17:131-57. Erratum in: J Pain 2016;17:508-10.
16. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med 2018;43:456-66.
17. Jouguelet-Lacoste J, La Colla L, Schilling D, et al. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. Pain Med 2015;16:383-403.
18. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology 2010;113:639-46.
19. Barrett W, Buxhoeveden M, Dhillon S. Ketamine: a versatile tool for anesthesia and analgesia. Curr Opin Anaesthesiol 2020;33:633-8.
20. Hans P, Dewandre PY, Brichant JF, et al. Comparative effects of ketamine on Bispectral Index and spectral entropy of the electroencephalogram under sevoflurane anaesthesia. Br J Anaesth 2005;94:336-40.
21. Faraoni D, Salengros JC, Engelman E, et al. Ketamine has no effect on bispectral index during stable propofol-remifentanil anaesthesia. Br J Anaesth 2009;102:336-9.
22. Albrecht E, Kirkham KR, Liu SS, et al. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. Anaesthesia 2013;68:79-90.
23. Ramaswamy S, Wilson JA, Colvin L. Non-opioid-based adjuvant analgesia in perioperative care. Contin Educ Anaesth Crit Care Pain 2013;13:152-7.
24. Fernandes HS. Clonidine in Anesthesiology: A Brief Review. Biomed J Sci Tech Res 2018;7:5815-8.
25. Blaudszun G, Lysakowski C, Elia N, et al. Effect of perioperative systemic α2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. Anesthesiology 2012;116:1312-22.
26. Foo I, Macfarlane AJR, Srivastava D, et al. The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety. Anaesthesia 2021;76:238-50.
27. Marret E, Rolin M, Beaussier M, et al. Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. Br J Surg 2008;95:1331-8.
28. McCarthy GC, Megalla SA, Habib AS. Impact of Intravenous Lidocaine Infusion on Postoperative Analgesia and Recovery from Surgery. Drugs 2010;70:1149-63.
29. Vigneault L, Turgeon AF, Côté D, et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. Can J Anaesth 2011;58:22-37.
30. Weibel S, Jelting Y, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. Cochrane Database Syst Rev 2018;6:CD009642.
31. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain: an evidence-based clinical update. BJA Educ 2016;16:292-8.
32. Waldron NH, Jones CA, Gan TJ, et al. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth 2013;110:191-200.
33. Kim SY, Koo BN, Shin CS, et al. The effects of single-dose dexamethasone on inflammatory response and pain after uterine artery embolisation for symptomatic fibroids or adenomyosis: a randomised controlled study. BJOG 2016;123:580-7.
34. Ho KY, Tay W, Yeo MC, et al. Duloxetine reduces morphine requirements after knee replacement surgery. Br J Anaesth 2010;105:371-6.
35. Castro-Alves LJ, Oliveira de Medeiros AC, Neves SP, et al. Perioperative Duloxetine to Improve Postoperative Recovery After Abdominal Hysterectomy. Anesth Analg 2016;122:98-104.

doi: 10.21037/dmr-21-80
Cite this article as: Bennett VA, Morrison B. Adjuncts and multimodal analgesia: a narrative review. Dig Med Res 2022;5:17.