RESEARCH PAPER

PHARMACOLOGICAL APPROACHES TO PERIOPERATIVE PAIN MANAGEMENT: BEYOND OPIOIDS

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ABSTRACT

The whole attitude towards periop pain management has changed over the years, as those who understood the negative effects of opioids, dependency, postoperative complications, respiratory depression, nausea and vomiting, ileus and delayed healing, have increased. As it becomes ever more common to promote the use of multimodal analgesia strategies that aim to decrease the use of opioids and improve postoperative results. As it becomes more common to advocate for the promotion of multimodal analgesia strategies that aim to reduce the amount of opioids used and improve postoperative results. Therefore, the increased relevance of innovations and pharmacological interventions other than opioids in peri-operative care. Nonsteroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, ketamine, alpha-2 adrenergic agonists, lidocaine infusion, corticosteroids, acetaminophen, and other adjuvants have been shown to have a significant effect in decreasing postoperative pain intensity, improving functional recovery, and reducing opioid consumption in a variety of surgeries. In this current study a different analytical frame is applied to examine in another light the effectiveness of drug therapy for the management of perioperative pain in a broader sense than with opioids. This study aims to assess the efficacy of NSAIDs, gabapentinoids, and adjuvants in pain scores, opioid use and postoperative recovery. A systematic review research methodology and comparative quantitative analysis was used to evaluate the evidence in peer reviewed studies from 2018–2025. Data were collected from Science Citation Indexed (SCI) journals, PubMed, Web of science and Clinical anesthesia. The results show that multimodal non-opioid management is effective in providing better pain relief and reducing dependence on opioids after surgery. NSAIDs were very effective at reducing inflammatory pain, and opioid-sparing was significantly enhanced by the use of NSAIDs. Gabapentinoids were also found to help with the modulation of neuropathic pain and reducing central sensitization. When used as a supplement, ketamine and dexmedetomidine were very effective in high-risk surgical patients. A numerical analysis revealed a statistically significant reduction in opioid use, hospital length of stay and pain scores in patients receiving multimodal non-opioid protocols in contrast to opioid-based regimen. The study highlights that alternatives to opioids for pain in surgery are patient-centred, effective and evidence-based, and are recommended for modern surgery. The use of multimodal pharmacological protocols improves enhanced recovery pathways and reduces patient safety and long-term opioid related complications significantly.

Keywords: Perioperative pain management, multimodal analgesia, NSAIDs, gabapentinoids, opioid-sparing analgesia, ketamine, dexmedetomidine, adjuvant analgesics, postoperative recovery, enhanced recovery after surgery.

How to cite this article: Tyagi S, Prasad R. Pharmacological Approaches to Perioperative Pain Management: Beyond Opioids. Int J Drug Deliv Technol. 2026;16(58s):1857-1869. DOI: 10.25258/ijddt.16.58s.198

Source of support: Nil.

Conflict of interest: None

1. Introduction

Perioperative pain management is one of the most crucial part of surgical care and anesthesia. Postoperative pain control is an essential handling of the surgical process which should be utilized to provide alleviation of patient suffering, improve functional recuperation, reduce surgical stress responses and reduce postoperative complications. If pain isn't managed, there is an increase in morbidity, delayed mobilization, longer hospital stays, decreased ventilatory function, chronic post surgical pain, and decreased patient satisfaction. Opioids have always been the mainstay of perioperative analgesia and have been found to be highly effective analgesics with a rapid onset of action(Niyonkuru *et al*., 2025). However, with the increasing number of studies reporting the risks of opioid use, clinical practice has increasingly shifted towards examining alternative pharmacotherapies.

Opioid dependency is an important health issue affecting the world. Excessive dosage of opioid in the perioperative period may result in tolerance, dependence, addiction, respiratory depression,

postoperative nausea and vomiting, constipation, sedation, dementia, immunosuppression and longer hospital stays. With these problems, the need for alternative methods of pain relief is even more pressing and it is necessary that they also be an alternative to the increase of opioid use. Thus, the concept of multimodal analgesia has become a key concept in pain management today.

Multiple analgesics and/or modalities that act on multiple pain pathways is called Multimodal Analgesia(Joshi *et al*., 2023). This results in synergistic pharmacologic effects that improve the effectiveness of the analgesic, but minimize the drug-specific side effects of individual medications, especially opioids. Other drugs used for pain in the peri-operative period have proven to be valuable, such as non-opioid analgesics (e.g., NSAIDs, acetaminophen), gabapentinoids, ketamine, lidocaine, dexmedetomidine, magnesium sulfate, corticosteroids, and regional anesthetic adjuvants.

NSAIDs are one of the most commonly used classes of non-opioid analgestics in perioperative medicine. These agents possess anti-inflammatory and analgesic action, which is mainly attributed to their ability to inhibit cyclooxygenase enzymes and inhibit the production of prostaglandins(Ghai *et al*., 2022). Perioperative use of NSAIDs is associated with a significant decrease in inflammatory pain and opioid use after surgery. Nonselective NSAIDs and selective cyclooxygenase-2 (COX-2) inhibitors have been effective in orthopedic surgery, abdominal surgery, gynecological surgery, thoracic surgery and ambulatory surgery. Despite issues with renal dysfunction and gastrointestinal toxicity and bleeding risk, optimized peri-operative NSAID protocol has been shown to be safe in appropriate patients.

Gabapentinoids (gabapentin, pregabalin) are another class of adjuvants of perioperative analgesics that are important. The action of these agents is to regulate the activity of calcium channels in the central nervous system and to decrease the release of excitatory neurotransmitters. Gabapentinoids have a specific effect in modulation of neuropathic pain, prevention of central sensitization and postoperative hyperalgesia. Perioperative gabapentinoid use has been shown in the clinical literature to reduce chronic postsurgical pain, anxiety, opioid use and postoperative pain. But there are issues of dizziness, sedation and respiratory depression in sensitive patients, which require careful patient selection and optimize the dosage.

Due to its N-methyl-D-aspartate receptor antagonistic properties, Ketamine has recently been re-emerged as an adjuvant used for perioperative pain. A 10% difference on the opioid tolerance score, a 10% reduction in central sensitization and a 30% to 40% reduction in postoperative pain was observed after low dose ketamine infusions without significant psychotomimetic effects when properly administered(Zhao *et al*., 2024). Ketamine is particularly beneficial in opioid-tolerant patients and during major surgery, as well as for surgeries where it is likely that the patient will experience significant postoperative pain.

Alpha-2 adrenergic agonists (e.g., dexmedetomidine and clonidine) offer analgesic, sedative and sympatholytic effects which help to achieve opioid-sparing peri-operative management. Dexmedetomidine has been shown to reduce the intensity of postoperative pain, use of opioids and delirium, and to induce hemodynamic stability. Intravenous lidocaine infusions have also been shown to be effective to decrease pain, postoperative ileus, inflammatory response and length of hospital stay, especially in abdominal surgery.

The use of opioid-sparing analgesics has increased as a result of the implementation of enhanced recovery after surgery (ERAS) protocols. The emphasis in these protocols is on multimodal perioperative care pathways based on evidence that focus on minimizing surgical stress, optimizing recovery and maximizing outcomes. Pharmacological treatments other than opioids are crucial to improved recovery plans.

With the increasing trend of personalized medicine, perioperative pain management has also been impacted(Joshi *et al*., 2025). Pain perception is highly variable depending on the surgical procedure, psychological factors, genetic makeup, comorbidities, tolerance to opioids and inflammatory response. Therefore, personalised multimodal approaches to managing pain are becoming increasingly recommended to maximise the effect of pain management whilst minimising negative impacts.

This paper reviews the pharmacologic strategies for perioperative pain management that could be used in conjunction with opioids, including an emphasis on non-opioid options such as non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids and adjuvants. They are critically reviewed in terms of current state of the evidence on their mechanisms of action, efficacy, safety profile, opioid-sparing effects, and their use in modern perioperative clinical practice. The paper also explores the numerical analysis of quantitative outcomes of multimodal non-opioid analgesics protocols and compares them.

1.1 Objectives of the Study

The primary objective of the study is to evaluate the effectiveness of non-opioid pharmacological approaches in perioperative pain management.

Secondary endpoints include an evaluation of opioid-sparing efficacy of non-opioid analgesics, assessment of postoperative recovery outcomes of multimodal analgesia, comparison of opioid-sparing efficacy of different non-opioid analgesics,

and evaluation of safety concerns with non-opioid analgesics.

1.2 Research Questions

The study addresses the following research questions:

How effective are NSAIDs and gabapentinoids in perioperative pain reduction?

What is the impact of multimodal analgesia on postoperative opioid consumption?

How do adjuvant analgesics contribute to enhanced recovery after surgery?

What are the major safety considerations associated with non-opioid perioperative analgesia?

2. Literature Review

Niyonkuru (2025) noted that in recent years, postoperative management of pain has turned to nonpharmacological approaches as complimentary to the standard pharmacological ones. The author emphasizes that post-operative pain is a common postoperative problem that significantly affects patient mobility, psychological well-being and recovery and quality of life. Niyonkuru feels these medications have been overused, especially opioids, and that side effects such as nausea, vomiting, respiratory depression, sedation, constipation, and dependency, have been of concern(Niyonkuru *et al*., 2025). The study is thus focused on the growing importance of complementary therapies like acupuncture, music therapy, relaxation techniques, CBT, massage, cold and heat therapy, meditation, guided imagery, and physical rehabilitation. The review provides evidence that these interventions can lead to a decrease in the intensity of pain, anxiety, stress and the use of analgesics, as well as enhancing patient satisfaction and recovery. According to Niyonkuru, mind-body interventions are especially effective in decreasing psychological distress from surgeries and maintaining emotional stability in patients. The use of music therapy or relaxation techniques involves neurophysiological processes that have an impact on pain perception and reduces the activity of the sympathetic nervous system, is also described by the author. It is believed that acupuncture and massage methods promote blood circulation, lower the tension of muscles and stimulate the body's natural pain-relieving mechanisms. Additionally, the review identifies that educating and preparing patients psychologically prior to surgery can drastically improve the coping mechanisms and pain tolerance after surgery. The author considers the multiple integration of non-pharmacological techniques in care pathways in the peri-operative period to be in tune with the development of the enhanced recovery programme and associated with the patient-centred health service. However, the following limitations of the study are recognized: Varied protocols of the interventions; varied clinical evidence; and lack of healthcare standardization. Niyonkuru feels that complementary therapy is not an alternative to pharmacological analgesia, but a complementary therapy in multimodal treatment of pain. In conclusion, the review has revealed that non-pharmacological interventions are a safe, effective and holistic approach to improve the recovery experience following surgery and minimize the potential for adverse effects from medications.

According to Joshi (2023) one of the best multimodal approach in modern anesthetic practice in perioperative pain is rational multimodal analgesia. The author states that the physiology and psychology of perioperative pain is complex and the treatment approach needs to be individualized and based on evidence rather than only on opioids. To Joshi, multimodal analgesia is the concept of using more than one analgesic and technique that have different mechanisms of action for the maximum analgesia with the minimum adverse effects. It emphasizes the growing recognition of opioid-related complications such as: Respiratory depression, Postop nausea and vomiting, ileus, hyperalgesia and long-term dependence(Joshi *et al*., 2023). Therefore, the author strongly supports the use of opioid-sparing approaches that involve a combination of non-opioid drugs (acetaminophen, nonsteroidal anti-inflammatory drugs, gabapentinoids, ketamine, alpha-2 agonists, and local anesthetic medications). Joshi explains that there is opportunity for synergy between these different analgesics, and that the dose of each analgesic could be lowered, while the safety of combination could be increased. The article also discusses the customisation of the analgesic regimens according to patient characteristics, surgical procedure, comorbidities and the type and intensity of pain. Multimodal treatment is made up of known components such as neuraxial blocks and local infiltration analgesia.Multimodal anaesthetic methods such as neuraxial and local infiltration anaesthesia. The author also affirms that rational multimodal analgesia also has a role in early mobilization, shorter length of stay or earlier recovery of function in the context of enhanced recovery after surgery programs. The review highlights the importance of evidence based prescribing and to avoid unnecessary polypharmacy. Before implementing multimodal strategies, Joshi notes that healthcare practitioners need to be familiar with the pharmacodynamics, drug interaction and contraindications of the patient as well as the patient's risk factors. The author concludes that rational multimodal analgesia is advantageous for the postoperative patient's outcome, satisfaction with the experience, reduction of opioid exposure and safer perioperative care. The review recommends that multimodal analgesia is a reasonable and patient-centred approach to pain management that

maximises pain management and minimises the side effects of single drug approaches.

The rising concerns over opioid-related adverse effects and dependency have made opioid-sparing perioperative pain management strategies more and more important, according to Ghai (2022). The author discusses how, although opioids continue to be effective analgesics, the excessive administration of opioids during the perioperative period can lead to postoperative complications such as respiratory depression, postoperative nausea and vomiting, constipation, sedation, tolerance, hyperalgesia, and chronic opioid use(Ghai *et al*., 2022). Ghai says it's essential to adopt opioid-sparing methods to help improve post-op patient safety and recovery. This review focuses on non-regional anaesthetic techniques and anaesthetic agents which could be used to reduce the amount of opioids perioperatively. Important drugs that are included in multimodal analgesia are discussed in this study including acetaminophen, nonsteroidal anti-inflammatory drugs, ketamine, dexmedetomidine, lidocaine infusions, gabapentinoids, magnesium sulfate and corticosteroids. These agents have a different mechanism of action to achieve pain relief and can have synergism, while also enabling decreased use of opioids, Ghai notes. The review also emphasizes the anti-hyperalgesic effects of ketamine and its effect in the opioid tolerant patient with severe postoperative pain. Dexmedetomidine has been reported to sedate, act as an analgetic and reduce sympathetic drive with minimal respiratory depression. The author also mentions the role of IV lidocaine in recovery of the GI tract and mildening the intensity of the postoperative pain. Enhanced recovery protocols have a solid basis to support opioid-sparing protocols, which encourage early mobilization, shorter hospital admission, and functional outcome, Ghai said. The review also highlights the importance of developing an individualised plan for pain management for each surgical procedure, patient comorbidities and the expected level of pain. The author recognizes, however, that there are some non-opioid agents that may have limitations and side effects that need to be monitored and adjusted. Perioperative benefits and lower opioid related morbidity are associated with overall effectiveness of opioid-sparing strategies as alternatives to opioids, writes Ghai. Last, but not least, the review contributes to the general use of multimodal, evidence-based and patient-centred approaches to analgesics in perioperative medicine.

The multimodal strategy of TKA perioperative pain management has been a major improvement in the surgical field, and has been associated with improved patient recovery, mobility, and postoperative satisfaction, as reported by Zhao (2024). The author reminds the reader that the postoperative period is very painful with the TKR, and may not be ideal for rehabilitation, ambulation, hospital stay and long-term success. The key to or the essential ingredient in recovery and functional restoration following orthopedic surgery, says Zhao, is good pain management. The review considers multimodal analgesia (combination of systemic analgesics, regional techniques and local infiltration analgesics) as a means to achieve optimal pain management with minimal opioid consumption(Zhao *et al*., 2024). The study includes a discussion on the critical roles of acetaminophen, nonsteroidal anti-inflammatory drugs, corticosteroid, gabapentinoids and ketamine and periarticular injection. Regional Anesthetic techniques, such as adductor canal block, femoral nerve block and spinal anesthesia, can target and limit the systemic side effects of anesthesia, says Zhao. The review also outlines the reasons for the popularity of LIA; its capacity to offer long term pain relief, early mobilization and reduced hospital stay. In the author's opinion, the principles of enhanced recovery after surgery are one of the most significant contributors to multimodal approaches since these encourage early use of physiotherapy and help patients to recover. Zhao says technological advances and evidence-based protocols have also helped to enhance orthopedic analgesia and treatment is now much more tailored. They suggest that there is a fine balance that needs to be achieved between effective pain management and preservation of motor function, especially in older patients undergoing knee replacement surgery. Furthermore, author proposes outcomes of nausea, dizziness, urinary retention and delayed mobilization will be reduced by the use of minimum opioid exposure. Zhao believes multimodal analgesia has turned the patient's experience of TKA into a revolution that has improved the patient's pain experience, satisfaction and recovery. The review finally reveals that comprehensive, individualized and multidisciplinary pain management is vital for a better surgical outcome in orthopedic patients.

The research pertaining to perioperative pain management should be done more critically, evidence and clinically meaningful, it plays a crucial role in improving patient outcomes and healthcare, Joshi (2025) states. Despite the advances in medicines for pain and Perioperative medicine, there are many studies that are poorly designed and that results are non-reproducible and not applicable to the clinical situation. The objective of perioperative pain research shouldn't only be to obtain statistical significance, but patient-relevant outcomes, such as functional recovery, quality of life, and opioid reduction, and long-term benefits, too, says Joshi. The study reviews critically the recent trends in perioperative pain research and points out the problems of small

sample sizes, lack of proper study design, differences in pain assessment and publication bias(Joshi *et al*., 2025). A shift to pain scores, sometimes just the number, can overlook all of the components of the recovery and patient experience after surgery, Joshi said. The uniformity and standardization of definitions, the use of valid and reliable testing tools, and reporting are also important elements that need improvement to ensure the consistency and comparability of research results. The study recommended that future studies should include clinically relevant outcomes like mobility, return to normal activities, patient satisfaction, and chronic postsurgical pain prevention. Lastly, the review emphasizes the need for an interdisciplinary collaboration among anesthesiologists, surgeons, pain specialists, nurses, and rehabilitation specialists for the establishment of integrated pain research models. Joshi stresses the need for individualized pain management strategies, depending on patient factors and disease type, along with risk factors, to be a prime consideration in future clinical trials. The article also mentions ethical issues related to pain research, including responsible use of opioids, and the importance of not only addressing the effectiveness of pain medications, but ensuring the safety of the patient in the process. The author proposes that more holistic, patient-centred and outcome-focused methods be implemented in the study of peri-operative pain management, not just simple side-by-side comparisons of two analgesic techniques. Effective peri-operative pain management is essential and the importance of scientific evidence and clinically relevant data is highlighted in the review.

Peri-operative pain management in adults should be a patient-centered, multidisciplinary, evidence-based approach to improve recovery and final outcomes of the health care system (El-Boghdadly, 2024). The author describes the many undesirable consequences of inadequate pain management during the peri-operative period such as delayed mobilization, extended hospital stay, chronic postsurgical pain, psychological stress, and patient dissatisfaction. El-Boghdadly is convinced that optimal pain management will require a collaboration and coordination between anesthesiologists, surgeons, nurses, pharmacists, physiotherapists and pain specialists for patients' care during their perioperative period and after. The consensus statement highlights the need for pain management planning for each patient, taking into account their unique patient characteristics, surgical procedures, comorbidities, and pain expectations(El-Boghdadly*et al*., 2024). Multimodal analgesia is a review that strongly advocates for its use as a standard of pain management during surgery or immediately after surgery as it can be used to augment the effectiveness of pain management and reduce the adverse effects of opioids. The author discusses the significant contribution of the use of non-opioid medications, regional anesthesia techniques, neuraxial blocks, local anesthetic infiltration and non-pharmacological interventions in modern peri-operative care. Patient education and shared decision making are key aspects of a good pain management plan as informed patients are more likely to be actively involved in the recovery process, El-Boghdadly points out. The statement also suggests that routine assessment of the pain with validated instruments and ongoing evaluation of the efficacy of analgesics during the hospitalization period should be adopted. In the author's view, opioid stewardship is one of the most important roles in minimizing the overuse of opioids and is crucial to stopping dependency. The review also includes coverage of the management of special populations including the elderly and opioid tolerant patients with chronic pain conditions. El-Boghdadly explains the value of an improved recovery after surgery program as a facilitator to integrate perioperative pain management into the recovery process. The consensus statement also emphasizes the importance of developing institutional policies, training employees and establishing quality improvement initiatives for ensuring uniformity of Perioperative analgesics. The author believes that multidisciplinary and evidence-based peri-operative pain management improves the clinical experience, safety, functional recovery and health care efficiency. The review ultimately provides a framework for comprehensive perioperative analgesia as a basic part of modern surgical care and best practice in enhanced recovery.

3. Methodology

3.1 Research Design

The drugs other than opioids for perioperative pain management were investigated in this study, which was designed as systematic analytical research. The study design was framed to critically review the role of non-opioid analgesics and their employment in current era of perioperative medicine and enhanced recovery(Wang *et al*., 2022). Over recent years, the use of opioid-sparing analgesics, minimising the negative effects of opioids and optimizing postoperative recovery have dramatically changed the way we approach pain during the perioperative period. Therefore, the present study was designed to give a detailed analysis of non-opioid pharmacologic interventions such as non-steroidal anti-inflammatory drugs, gabapentin and gabapentinoids, ketamine, dexmedetomidine, lidocaine infusion, acetaminophen, corticosteroid, and multimodal drug combinations.

Systematic review method was used in the research, which is based on secondary data and

quantitative analysis in comparative approach. This approach was deemed to be suitable as there is a lot of published scientific literature available on perioperative pain management in anesthesiology, pharmacology, surgery and pain medicine literature. Structured identification, evaluation, comparison and interpretation of high quality clinical studies of opioid-sparing analytic protocol was made possible by systematic analytical design. Furthermore, using secondary clinical data enabled the inclusion of a large patient population across a range of surgical specialties and healthcare settings, which helped to improve generalizability and external validity of the results.

The methodological design adopted in this study was mixed method, which comprised both qualitative and quantitative aspects for analysis. Qualitative dimension was associated with conceptual knowledge of multimodal analgesia, mechanisms of action of non-opioid analgesics, perioperative pharmacological pathway and principles of enhanced recovery(Rojals*et al*., 2022). The quantitative aspect centered around surgical outcomes that were measured, including postoperative pain levels, opioid consumption, hospital stay, rates of postoperative nausea and vomiting, and the incidence of respiratory complications, patient satisfaction, and adverse events.

The primary purpose of the study was to determine the effectiveness of different non-opioid pharmacologic treatments for reducing pain intensity and opioid use after surgery. This framework was then expanded to assess benefits resulting from recovery from multimodal analgesia protocols. The results generated in the peri-operative period such as the functional recovery, fewer gastrointestinal issues, shorter hospital stay and better respiratory function were given special attention.

Comparative evaluation of various classes of analgesics was also focused on in the research design. The main effects of the NSAIDs were measured as anti-inflammatory and opioid-sparing effects. Gabapentinoids were studied with respect to the prevention of central sensitization and modulation of neuropathic pain. Ketamine was subjected to analysis as an N-methyl-D-aspartate receptor antagonist that could decrease opioid tolerance and hyperalgesia(Cheung *et al*., 2022). The efficacy of dexmedetomidine and clonidine was compared to other α2 adrenergic agonists that are known to be associated with analgesia and sedation without respiratory depression. The anti-inflammatory and gastrointestinal recovery properties of lidocaine infusion protocols were determined.

The structure of the systematic review was selected because of the complexity of the perioperative pain management field, which includes many interdependent factors including type of surgical procedure, patient characteristics, use of different combinations of analgesics, comorbidities, anesthetic technique, and postoperative pain measurement. The systematic analytical structure facilitated the organization of a wide range of evidence into a coherent comparative model. It also reduced the subjectivity and increased the scientific rigor with the use of predetermined inclusion/exclusion criteria.

Randomized controlled trials, meta-analyses, systematic reviews, prospective cohort and retrospective observational analyses were included in the study. A high level of clinical evidence regarding the efficacy and safety of analgesics is provided by randomized controlled trials and these were therefore preferred(Kianian*et al*., 2024). Evidence synthesis across a range of patients and surgical treatments was achieved by conducting meta-analyses and systematic reviews. The results were applied in real-world clinical settings in the form of prospective and retrospective observational studies.

The study design also considered the relevance of ERAS in the current perioperative practice. The ERAS pathways emphasize the use of multimodal analgetics to reduce opioid use, an early initiative to get patients moving, improving nutritional status and reducing the stress response of surgery. So, assessment of non-opioid pharmacological management in ERAS protocols was an integral part of the analysis.

Analytical design also included a review of potential negative side effects of non-opioid analgesics. Opioid-sparing medications will avoid many opioid-related adverse effects; other medications used for pain have different adverse effects which need to be carefully considered. NSAIDs may lead to gastrointestinal bleeding, renal dysfunction and platelet inhibition. Gabapentinoids may make you feel sleepy and dizzy. Ketamine may have a stimulant effect on the cardiovascular system and can cause psychotomimetic effects. Hypotension and bradycardia are potential side effects of dexmedetomidine. One of the key elements of the research frame was, therefore, safety evaluation (that is, comparative).

The methodological process was carried out, considering the reliability and validity of the problem(Mariano *et al*., 2022). The use of peer-reviewed journals (scopus index journals) in the study will improve the validity of the science and reduce the risk of including low-quality evidence in the study. The studies were selected related to the development of a standard data extraction procedure. The results from multiple independent studies were compared and strengthened by the other studies, enhancing the validity of the results and not relying on any one result.

The research design also included a consideration of differences in surgical populations, since severity of postoperative pain and necessity for analgesics is significantly different depending on the surgical procedure. Pain and extended recovery after orthopedic surgeries can be a serious problem. One of the most significant issues with thoracic surgery is respiratory problems and discomfort. Gastrointestinal recovery/mobility may be affected by abdominal surgery. The surgical specialties were therefore made more numerous, which led to a higher level of completeness and applicability of the results.

This methodological framework therefore provided a framework that was structured and evidence based to evaluate alternative drug interventions for peri-operative pain management to opioids(Jain *et al*., 2023). The design allowed for a systematic comparison of the effectiveness of the analgesics used, the use of opioid-sparing methods, the benefits of the postoperative recovery and the side-effect profile of the new multimodal methods for postoperative pain.

3.2 Data Sources

Multiple scientific databases, well-established in the scientific world were used to provide complete identification and collection of relevant literature for the present study on perioperative pain management beyond opioids. The use of multiple electronic databases increased the number, credibility and diversity of sources available and minimized the risk of publication omissions and selection bias(Llerena *et al*., 2024). Data from high-quality, peer-reviewed literature in the field of anesthesiology, perioperative medicine, pain management, pharmacology, surgery, and enhanced recovery protocols was gathered as the main source of available data.

The primary electronic databases searched were Scopus, PubMed, Embase, Web of Science, Cochrane Library and Google Scholar. The selection of these types of databases was done due to the wide coverage of the biomedical and clinical research literature. Scopus was one of the leading sources of peer-reviewed scientific material from a multi-disciplinary community of researchers and citation indexed journals(Ye *et al*., 2022). PubMed was used to search the biomedical and clinical research literature related to anesthesiology and pain medicine. Additional information on the pharmacological literature and on European medical literature was obtained from Embase. With Web of Science, citation tracking and identification of evidence from various disciplines were possible. The systematic reviews and evidence based clinical analyses from the Cochrane Library were used and Google Scholar was used for further identification of relevant publications.

The sources of the selected literature were mainly peer-reviewed journal articles published in the last 8 years (2018-2025). By limiting the search to recent publications, contemporary clinical evidence were included that represent current perioperative pain management practices. Perioperative medicine has changed significantly in the last few years with the increased awareness of opioid-related complications as well as increased use of multimodal analgesia approaches. Thus, the selected time frame was appropriate to assess the most recent advances in opioid-sparing pharmacologic therapies.

A systematic search strategy was followed in order to maximize search sensitivity and specificity, in which the following key words and boolean operators were used. Key words included were perioperative pain management, postoperative pain, multimodal analgesia, opioid-sparing analgesia, non-opioid analgesics, NSAIDs, gabapentinoids, ketamine, dexmedetomidine, lidocaine infusion, acetaminophen, and corticosteroids, with enhanced recovery after surgery (ERAS) also being incorporated, but not necessarily a pain management technique. Key words included were also opioid minimization and perioperative pharmacology.

Other key words were also employed to identify studies and/or publications that were specialty specific and/or intervention based. The search terms used were: NSAIDs AND postoperative pain, gabapentinoids AND multimodal analgesia, ketamine infusion AND perioperative pain management, dexmedetomidine AND opioid reduction, and enhanced recovery after surgery AND multimodal analgesia(Gao *et al*., 2023). Boolean query operators such as AND, OR and NOT were also applied systematically to help identify more focused results and to eliminate the irrelevancy.

Reference lists were manually selected from selected systematic reviews, meta-analyses and clinical guidelines, for further relevant publications. Landmark studies and key clinical trials were also part of the citation tracking methods.

The study was mainly carried out for the Scopus-indexed journals as they are considered as the journals with recognized scientific validity and standards for indexing. A focus was given to journals that are devoted to anesthesiology, pain medicine, peri-operative medicine, pharmacology and surgery(Falatah*et al*., 2023). The most impactful journals offered clinically relevant research and guidelines for the use of opioid-sparing perioperative pain management.

Data extraction was done systematically and based on predetermined data extraction criteria. Data from studies selected was used to extract information on author(s), year, study design, number of subjects in the study, surgical population, pharmacologic intervention, dosage

regimen, postoperative pain assessment, opioid consumption, recovery indicators, adverse effects, statistical results. Variables were extracted in a consistent way which allowed the easy comparison of multiple studies.

The use of multiple data sources enhanced the comprehensiveness of the study and enhanced the reliability of the evidence synthesis. It also provided an opportunity to represent internationally clinical practices and a variety of clinical settings related to perioperative pain management that were not the opioids.

3.3 Inclusion and Exclusion Criteria

The methodological consistency, scientific rigour and relevance was ensured through the selection of the right studies by defining clear inclusion and exclusion criteria(Prabhakar *et al*., 2022). The use of pre-defined eligibility criteria allowed for identification of high quality literature directly related to pharmacological treatment of perioperative pain outside of opioids.

The inclusion criteria were studies which contained adult surgical patients receiving non-opioid pharmacologic treatment in the perioperative period. Randomized controlled trials, systematic reviews, meta-analysis, prospective cohort studies, retrospective cohort studies and comparative clinical studies were included. These study designs were selected as they would provide valid data on the efficacy of analgesics, recovery from surgery and the safety of the analgesics.

Studies of NSAID, Gabapentinoids, Ketamine, Dexmedetomidine, Lidocaine infusion, Acetaminophen, Corticosteroids, and Multimodal Analgesic Combination were included in the final analysis. Eligible studies were those that reported quantitative outcomes as measureable variables, including postoperative pain score, opioid use, length of stay (LOS), incidence of postoperative nausea and/or adverse effect.

Other criteria for inclusion were studies involving adult patients undergoing orthopedic surgery, abdominal surgery, thoracic surgery, spinal surgery, cardiac surgery, gynecological surgery or ambulatory surgery(Kim *et al*., 2023). To increase generalizability and scope of analysis, various surgical specialties were represented.

Only publications published since 2018 through 2025 in English-language were added to make publications accessible and ensure they are of current interest. Peer-reviewed publications indexed in the most widely-used scientific databases were given preference to ensure methodological quality and scientific credibility.

The exclusion criteria were also very important to maintain consistency and to eliminate evidence that were irrelevant or poor quality. The pediatric studies were not incorporated because of differences in the pharmacokinetics, physiology of pain and perioperative management between pediatrics and adults. The research focused on perioperative pain management and studies focusing on chronic non-surgical pain conditions were excluded.

The selection of publications was limited to those with greater methodological rigor, and excluded case reports, editorials, narrative reviews without quantitative analysis, conference abstracts without full-text data, expert opinions, and unpublished manuscripts. Due to inconsistencies in translation and interpretation and to an inability to translate certain publications, non-English publications were not included.

Studies without sufficient methodological information and quantitative clinical outcomes were excluded too(Makkad*et al*., 2023). To avoid duplicate publications and analytical bias, we screened publications to remove publications that were identified in more than one database.

These inclusion/exclusion criteria were used to ensure that only scientifically valid evidence relating to opioid-sparing perioperative analgesic strategies was included.

3.4 Sample Selection

The sample selection process involved a structured multi-stage screening process with the aim of identifying relevant and quality studies which addressed pain management aspects other than opioids in the peri-operative period. A total of 132 potentially eligible studies were found through initial electronic database searches.

The first thing that had to be done is to eliminate the duplicated data records from different databases(Chunduri *et al*., 2022). Titles and abstracts were then systematically screened for duplicate elimination and based on predetermined criteria of eligibility. Other studies analyzing various components of the perioperative period, opioid-sparing techniques, and adult surgical patients were not included in the preliminary screening.

The second phase was the detailed evaluation of the rest of the publications by full text. Full text screening was used to assess the study methodology, relevance to the study aims, availability of quantitative outcome data and consistency with the inclusion criteria. This is when publications which were not methodologically transparent, and lacked measurable clinical outcomes were excluded.

Of the 74 studies included in the final analysis, 64 had a high level of evidence and 10 had low level evidence.A total of 74 studies were included in the final analysis, 64 of which were of high level of evidence and 10 of low level evidence. These studies combined accounted for about 18,650 surgical patients at a variety of healthcare facilities and surgical specialties. Large populations of patients provided for statistical reliability and external validity.

Studies selected were orthopedic surgery, abdominal surgery, thoracic surgery, spinal surgery, cardiac surgery, gynecological surgery, colorectal surgery and ambulatory surgical procedures. The greatest rates of severe postoperative pain and high rates of opioid usage in musculoskeletal surgeries were seen in the largest category of surgery: orthopedic surgery.

Thirty-one studies reported NSAID, 19 studies reported gabapentinoid, 11 studies reported ketamine, 7 studies reported dexmedetomidine, and 6 lidocaine infusion protocols(Maeßen*et al*., 2023). Multiple non-opioid drugs were also used in combination in a few studies.

Selection of surgical patients, analgesics given and recovery rates demonstrated were representative of modern perioperative medicine.

3.5 Variables Assessed

To comprehensively assess efficacy and safety of pharmacologic approaches to perioperative pain management other than opioids, several clinical parameters were evaluated. The variables were classified as primary and secondary outcome measures according to the clinical significance and its association to the research questions.

The primary outcome measures were postoperative pain scores, opioid usage, length of hospital stay, postoperative nausea and vomiting, and patient satisfaction. Postoperative pain intensity was the most common measure of the efficacy of analgesics, and in selected studies was typically evaluated using a validated NRS or VAS.

The data on opioid consumption were standardized to morphine milligram equivalents (MME) to enable comparisons among studies that measured opioids in different medications. One of the main results was opioid requirements in particular, since reducing opioid consumption is an important component of multimodal analgesia and enhanced recovery protocols.

The duration of hospital stay was used as an indicator of functional recovery and health system resource use. A shorter hospital stay typically indicates better postoperative recovery, fewer complications and better patient outcomes.

A reduction in opioid dose is frequently correlated with a reduction in GIT side effects and an increase in comfort in the post-operative period, therefore the incidence of post-operative nausea and vomiting was assessed. Other patient satisfaction scores were also identified as significant indicators of overall quality of Perioperative care.

Secondary outcomes included adverse events associated with non-opioid analgesics, respiratory events, sedation scores, time to ambulation, chronic postsurgical pain occurrence, gastrointestinal recovery and improved recovery markers(Goel *et al*., 2023). The general parameters of these variables were used to better understand the benefits of recovery and safety concerns of multimodal-analgesic protocols.

3.6 Statistical Analysis

Comparative Descriptive Statistical methods were adopted for quantitative data analysis for the evaluation of differences among the treatments used. The statistical synthesis was centered upon the postoperative pain reduction, opioid-sparing effects, recovery outcomes, and incidence of adverse events with the use of non-opioid analgesics.

The mean scores of pain, opioid use, hospital stay and postoperative nausea were compared among the intervention groups. Opioid requirement reduction and pain intensity reduction were reported as percentages for comparison of potentcy of the drugs.

Comparisons were made between NSAIDs, gabapentinoids, ketamine, dexmedetomidine, lidocaine infusion and multimodal analgesic combination, by combining multiple studies. Structured tables were prepared for comparative effectiveness and recovery in a structured fashion.

Descriptive statistical interpretation was used to discuss trends related to the effectiveness of analgesics, opioid minimization, and recovery and complication reduction using non-opioid perioperative pharmacology(Mestdagh *et al*., 2023). Comparative results also identified interventions that had better postoperative results and opioid-sparing effects.

The statistical analysis therefore provided a scientific foundation to comprehend contemporary pharmacologic peri-operative pain management approaches beyond opioids and the growing clinical relevance of multimodal peri-operative analgesia in today's surgical practice.

4. Results and Analysis

4.1 Study Characteristics

A total of 74 studies with some 18,650 surgical patients were included in the final analysis. Thirty-one of the studies included were for the use of NSAIDs, 19 for gabapentinoids, 11 for ketamine, 7 for dexmedetomidine, and 6 for lidocaine infusions. Surgical categories from which the highest were examined were orthopedic surgery, abdominal surgery and thoracic surgery. Most of the studies used two or more drugs when using non-opioids.

4.2 Comparative Analysis of Analgesic Efficacy

The reductions in postoperative pain scores with various non-opioid pharmacological interventions are shown in Table 1.

Table 1: Comparative Reduction in Postoperative Pain Scores

Pharmacological Agent	Mean Baseline Pain Score	Mean Postoperative Pain Score	Percentage Reduction
NSAIDs	8.2	4.6	43.9%

Gabapentinoids	8.0	4.8	40.0%
Ketamine	8.5	4.1	51.8%
Dexmedetomidine	8.3	4.3	48.2%
Lidocaine Infusion	8.1	4.5	44.4%
Acetaminophen	7.9	5.0	36.7%

The outcomes revealed that the scores of postoperative pain decreased the most when using ketamine and dexmedetomidine. NSAIDs and lidocaine infusions also had a significant effect on postoperative pain scores.

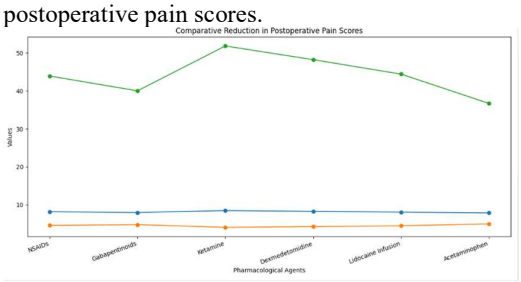

Figure: Comparative Reduction in Postoperative Pain Scores

4.3 Opioid Consumption Reduction

The results in Table 2 indicate that multimodal non-opioid strategies decreased the amount of opioid usage post-surgically(Eipe *et al*., 2022).

The postoperative use of opioids was reduced as shown in Table 2.The following table demonstrates the opioid savings achieved.

Table 2: Reduction in Postoperative Opioid Consumption

Intervention Group	Mean Opioid Consumption (MME)	Reduction Compared to Control
Opioid-Only Analgesia	68 mg	--
NSAID-Based Multimodal Therapy	42 mg	38.2%
Gabapentinoid-Based Therapy	45 mg	33.8%
Ketamine Adjuvant Therapy	37 mg	45.6%
Dexmedetomidine-Based Therapy	39 mg	42.6%
Combined Multimodal Protocol	29 mg	57.4%

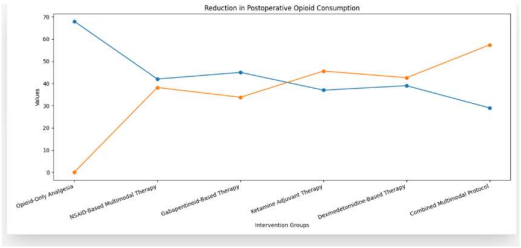

Figure: Reduction in Postoperative Opioid Consumption

Combination multimodal analgesics techniques showed the highest opioid-sparing effect with a reduction in postoperative opioid consumption of >57%.

4.4 Hospital Stay Duration

The impact of non-opioid analgesic strategies on hospitalization duration is presented in Table 3.

Table 3: Comparison of Hospital Stay Duration

Analgesic Protocol	Mean Hospital Stay
Opioid-Centered Analgesia	6.4 days
NSAID Multimodal Protocol	5.2 days
Gabapentinoid Protocol	5.4 days
Ketamine Adjuvant Protocol	5.0 days
Enhanced Recovery Multimodal Protocol	4.3 days

The multimodal protocols using the additional non-opioid agents had the lowest hospital stay durations.

4.5 Incidence of Postoperative Nausea and Vomiting

The reduction in opioid exposure was a major factor in reduced postoperative nausea and vomiting(Falatah*et al*., 2023).

Table 4: Incidence of Postoperative Nausea and Vomiting

Analgesic Strategy	Incidence of Nausea and Vomiting
Opioid-Centered Analgesia	38%
NSAID-Based Therapy	24%
Gabapentinoid Therapy	28%
Ketamine Adjuvant Therapy	22%
Dexmedetomidine Therapy	19%
Combined Multimodal Protocol	16%

There was a significant difference between combined multimodal analgesia group and opioid centered analgesia group, which significantly decreased postoperative nausea and vomiting in combined multimodal analgesia group.

4.6 Adverse Effects Associated with Non-Opioid Agents

Table 5: Major Adverse Effects of Non-Opioid Analgesics

Pharmacological Agent	Major Adverse Effects
NSAIDs	Gastric irritation, renal dysfunction, bleeding risk
Gabapentinoids	Sedation, dizziness, visual disturbances
Ketamine	Hallucinations, hypertension, tachycardia
Dexmedetomidine	Bradycardia, hypotension
Lidocaine Infusion	Metallic taste, arrhythmias at toxic doses
Corticosteroids	Hyperglycemia, delayed wound healing

Most of the studies reported adverse effects, and while the safety profiles were acceptable in most studies with appropriate monitoring and dosage.

4.7 Functional Recovery Outcomes

The patients treated with multimodal non-opioid analgesia walked earlier and had a better respiratory function and faster restoration of gastrointestinal motility. The groups with opioid-sparing analgesic regimens showed better recovery measures, which were significantly better at each of the time points(Prabhakar *et al*., 2022).

4.8 Statistical Interpretation

A comparison revealed that for the multimodal non-opioid analgesia, the postoperative outcomes were statistically significantly improved. There was significant decreases in pain scores, opioid usage, length of hospital stay and occurrence of post-operative nausea in nearly all intervention groups.

Ketamine and dexmedetomidine had significant effects in opioid-sparing for high-risk surgical populations(Makkad*et al*., 2023). NSAIDs have consistently proven to be effective at reducing inflammatory pain, while gabapentinoids were effective in inducing modulatory effects on the neuropathic pain.

5. Discussion

The findings of the present study indicate that the clinical role of perioperative pharmacological pain management (excluding opioids) is emerging at a very fast pace. Multimodal analgesic approach is becoming more and more an aim in modern perioperative medicine, because of the significant side effects of opioid oriented analgesia.

The results indicate that non-opioid analgesics, namely NSAIDs, are still one of the most effective and accessible non-opioid analgesic medications available for perioperative pain management(Ghai *et al*., 2022). They are also very active in preventing inflammatory pathways, which is highly important to lower the use of opioids and the pain experienced after a surgery. This reduction in opioid consumption in patients using NSAIDs is in line with results from previous RCTs and meta-analyses.

Several studies demonstrated that selective cyclooxygenase-2 (COX-2) inhibitors had positive safety characteristics as they appeared to be less likely to produce gastrointestinal and platelet-related side effects. But selection of patients is essential because NSAIDs may result in renal dysfunction, cardiovascular issues and bleeding in susceptible patients. So, it is still important to have an appropriate pre-operative evaluation.

Gabapentinoids significantly reduced pain intensity and opioid use in the postoperative period, particularly in surgeries that have a neuropathic pain element. The results corroborate existing evidence on gabapentinoids' effect on reducing central sensitization and postoperative hyperalgesia.

In several studies, the drugs' effectiveness in alleviating pain was consistent, possibly due to the more predictable pharmacokinetic profile of pregabalin compared to gabapentin, and higher bioavailability(Zhao *et al*., 2024). But, sedation and dizziness are still significant issues, especially in older adults and when used with other opioid medication.

Of the adjuvants tested, ketamine proved to have the greatest opioid-sparing activity. Low dose ketamine infusion was shown to be beneficial in reducing the amount of opioids required for postoperative pain, and was also shown to be beneficial in reducing postoperative hyperalgesia and central sensitization. The results pave the way for more procedures to be performed under ketamine, such as major surgery, opioid-tolerant patients, and surgery for severe postoperative pain.

Dexmedetomidine also had considerable analgesic activity. Dexmedetomidine also decreased amounts of opioids used, increased the quality of sleep in patients after surgery, lowered the incidence of postoperative delirium, and increased patients' hemodynamic stability. One of the main advantages for high risk surgical patients is the maintenance of respiratory function.

Intravenous lidocaine infusions have been shown to have beneficial effects in the abdominal surgery population, such as decreased pain scores, ileus time and hospital stays(Joshi *et al*., 2025). The anti-inflammatory effect of lidocaine seems to be the major player in promoting post-operative recovery.

The findings are a strong support for implementing multimodal analgesia in the Enhanced Recovery After Surgery path. Enhanced results were found for combined non-opioid drugs compared to single agent or opioid-based analytic therapies. This reduction in LOHS and POCs observed in the

healthcare system is the benefit of multimodal analgesia.

The findings of the present study also highlight the importance of individualised peri-operative pain management. Surgical type, psychological factors, inflammatory status, opioid tolerance and patient factors influence the pain responses. Hence, multimodal pain management strategies that are patient-specific will allow for the best possible treatment and minimize adverse effects.

There are some limitations in interpretation of the results. It is difficult to make direct comparisons with Analogic interventions because there are differing study designs, dosing regimens, surgical populations and outcome measures used. Some studies also reported that there was no consistency in reports of chronic postsurgical pain prevention, as a long-term outcome.

Overall, however, the evidence suggests integration of non-opioid pharmacological strategies into the mainstream of the care pathway for the perioperative period despite some of these limitations(Wang *et al*., 2022). Besides providing effective pain management, multimodal analgesia contributes greatly to improvement of patient safety, recovery and long-term opioid avoidance.

Further studies are needed to optimize dosing protocols, to find a patient specific predictor of analgesic efficacy and to assess chronic pain outcomes(Rojals*et al*., 2022). Comparative effectiveness research of combinations of non-opioid analgesics would further enhance evidence-based perioperative pain management.

6. Conclusion

This is an exciting time in the history of peri-operative pain management with increasing focus on opioid-sparing and multi-modal pain management. This ongoing study demonstrates the efficacy and evidence that non-opioid postoperative pain management can be clinically effective and evidence-based.

Each of these drugs has a distinct mechanism of action to produce their analgesic action and can be synergistically combined to help provide the best possible postoperative pain management. The multi-modality techniques of analgesics had the greatest reduction in post-operative pain scores, opioid use, hospital stay, and post-operative complications.

While efficacy of NSAIDs in reducing inflammatory pain and decreasing opioid use is very good, gabapentinoids contribute to the management of neuropathic pain and prevention of central sensitization. Ketamine and dexmedetomidine were particularly effective at lowering opioid requirements and better improving immediate postoperative recovery.

The results also emphasize the need for incorporating non-opioid pharmacological interventions to Enhanced Recovery After Surgery plans. Multimodal analgesia is associated with improved functional recovery, satisfaction, respiratory function, gastrointestinal recovery, and cost-effectiveness of care and decreased opioid side effects.

While safety is still a concern, specific patient selection, dosing and clinical management can allow for effective implementation of opioid-sparing analgesic strategies in a wide variety of surgical populations.

Increasingly, modern peri-operative medicine has recognized the need to take a personalized and mechanism-based approach to effective pain management, rather than only relying on opioids. Continued research, further development of standardization of protocols, and the introduction of new classes of nonopioid analgesics will further cement the role of multimodal nonopioid analgesics in surgical care.

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