

## A SYSTEMATIC REVIEW ON THE EFFECTIVENESS OF OPIOID-SPARING STRATEGIES IN ICU PATIENTS

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### ABSTRACT

**Background:** Opioid administration in the intensive care unit (ICU) has been a longstanding adjunct for analgesia. However, safety concerns surrounding opioid-related adverse effects, such as respiratory depression/tolerance/dependence, have generated renewed interest in adopting opioid-sparing strategies. Multimodal analgesia strategies using regional anesthesia, non-opioid pharmacologic agents, and integrative medicine approaches have been examined to decrease opioid use in select patients. While there are potential benefits, issues with effectiveness, ease of implementation, and susceptibility to alternative therapies must still be addressed.

**Objective:** This study systematically reviews the effectiveness, benefits, and potential challenges of opioid-sparing strategies in ICU patients considering varying analgesic approaches. It aims to identify gaps in the existing research and to recommend future directions for maximizing pain management in critically ill patients.

**Methods:** A systematic review approach was adopted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched up to October 2023 using PubMed, Google Scholar, Scopus, ScienceDirect, and Web of Science. Both peer-reviewed articles and articles published during the previous five years (2019 through present day) were searched. Eligible studies were included based on pre-established criteria, with a focus on high-quality evidence of opioid-sparing strategies in the ICU. Quality assessment of the included studies was performed by the use of the AMSTAR, the Cochrane risk of bias tool, or the Newcastle-Ottawa scale.

**Conclusion:** The review results indicate that multimodal analgesia and opioid-sparing efficacy contribute to an enhanced pain management solution across surgical specialties that utilize regional anesthesia (45%), non-opioid pharmacologic agents (e.g. acetaminophen, ketamine) (50%) , and non-pharmacologic methods (e.g. cognitive-behavioral therapy, music therapy) (30%). The most commonly cited benefits are decreased opioid requirement (60%), fewer opioid-related side effects (50%), and improved patient outcomes in terms of early mobilization and reduced ICU length of stay (35%) Yet, barriers to adoption, including poor familiarity with alternative therapies (40%) among clinicians, inconsistent clinical guidelines (35%), and cost-related limitations (30%) stand in the way of widespread uptake. Other research priorities included the standardization of multimodal analgesia protocols (40%), improved education and training for healthcare providers (35%), and the incorporation of personalized pain management strategies (25%). This concludes that strategies that minimize the use of opioids in the ICU patient population provide greater risk management regarding the risk of long-term dependency and other complications related to opioid use. The conclusion of this review highlights the importance of future studies, the optimization of protocols, and further collaboration between different disciplines, to ensure optimal multimodal analgesia in critically ill patients. Implementation challenges, along with clinician training in newer opioid-sparing techniques, are critical for their adoption more broadly. This study reveals important information for researchers, clinicians, and policymakers who are seeking to improve pain management strategies and patient outcomes in ICUs.

**KEYWORDS:** Opioid-sparing strategies, multimodal analgesia, ICU pain management, regional anesthesia, non-opioid analgesics, opioid-related adverse effects, critical care analgesia, pain management, non-pharmacologic interventions.

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## INTRODUCTION AND BACKGROUND

Pain is an integral part of patient care in intensive care units (ICUs) as severely ill patients frequently suffer severe pain as a consequence of invasive procedures, the need for mechanical ventilation, and/or pre-existing illnesses. Opioids have traditionally been the mainstay of pain management in ICUs because of their powerful analgesic effects. However, due to increasing concerns regarding the adverse effects of opioids, such as respiratory depression and gastrointestinal dysfunction, tolerance, dependence, and opioid-induced hyperalgesia, opioid-sparing strategies are receiving increasing attention [1, 2]. The opioid epidemic, marked by increasing abuse and addiction, has amplified the need for the examination of safer, effective analgesics in the intensive care unit setting. The need to provide adequate pain control with limited adverse events has led investigators and providers to implement multimodal analgesia by using non-opioid pharmacologic agents, regional anesthesia techniques, and non-pharmacologic modalities to optimize patient outcomes [3, 4]. Opioid-sparing strategies use alternate methods of analgesia to either decrease or eliminate opioid reliance while still preserving adequate pain control. These strategies encompass regional anesthesia techniques (eg, epidurals and nerve blocks), non-opioid pharmacologic agents (eg, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], ketamine, gabapentinoids), and integrative therapy (eg, physical therapy, cognitive-behavioral therapy, music therapy) [5, 6]. These ICU strategies have been shown to improve recovery with less total opioid consumption and fewer opioid-related side effects. Although opioid-sparing strategies have the potential to improve health-related outcomes, their inclusion in clinical practice varies based on factors like clinician knowledge gaps, absence of standardized treatment protocols, cost considerations, and varying effectiveness in divergent populations [7-9]. In recent years, research has centered on determining which of these opioid-sparing techniques is the most effective and their contribution toward improving patient outcomes. As a result, multimodal analgesia, which uses an opioid-sparing combination of different analgesic

modalities to achieve a synergistic effect on pain relief, is frequently recommended. For example, multimodal approaches resulted in better pain control, shorter ICU length of stay, and facilitated early mobilization. Yet the safety, feasibility, and long-term effectiveness of such waking interventions warrant further exploration. The heterogeneity in ICU populations, pain perception, and institutional practice differences create further challenges in standardizing opioid-sparing protocols [10, 11]. The opioid-sparing approach is further affected by the increasing attention directed at personalized medicine, where targeted strategies are used to consider specific patient characteristics. Only recently have factors such as pre-existing comorbidities, pain thresholds, and genetic predispositions to opioid sensitivity been incorporated into pain management plans. Therefore, incorporating evidence-based, opioid-sparing approaches into standard ICU practice is necessary to prevent adverse effects while optimally managing pain, as the specialty of pain medicine evolves [12, 13]. The objective of this systematic review is to investigate the efficacy of opioid-sparing strategies among ICU patients, including specific analgesic approaches, advantages and difficulties, and their potential for large-scale clinical implementation. This review aims to analyze the current literature to give a holistic approach to optimizing opioid-sparing techniques to lead to better pain management in critical care. The results will inform ongoing initiatives to establish safer, more effective pain management protocols more in tune with contemporary critical care and to address important concerns about opioid use in ICUs [14, 15].

## LITERATURE REVIEW

There is increasing recognition of the risks of opioid use in the critically ill and significant investigation into alternative pain management methods that can reduce their use while maintaining adequate analgesia in ICU patients. Opioid-sparing techniques have become of interest in light of the well-recognized risks of opioid use such as respiratory depression, tolerance, dependency, and prolonged length of stay in intensive care units. A multitude of multimodal strategies have been proposed by combining pharmacological and non-pharmacological treatment options to improve pain control and decrease opioid adverse effects [16, 17]. Pharmacologic strategies include the use of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and gabapentinoids among non-opioid analgesics, which form the backbone of opioid-sparing pain management [18, 19]. It has been shown that intravenous acetaminophen and NSAIDs can

significantly reduce opioid requirements while ensuring adequate analgesia in post-surgical and critically ill patients. Gabapentinoids (gabapentin and pregabalin) have been studied as adjuncts for use in surgical patients, due to their ability to inhibit neuropathic pain pathways and decrease acute postoperative opioid consumption (Shraddha Baldania, 2024). Nonetheless, terbutaline-induced sedation and feared adverse effects warrant further studies to define ideal dosing and safety parameters [20, 21]. Opioid-sparing strategies have included increasing use of regional anesthesia techniques such as epidural and peripheral nerve blocks despite their poor applicability in the ICU. Continuous epidural analgesia is an effective means of post-operative and trauma-associated pain relief, especially following thoracic and abdominal surgery. In a similar fashion, peripheral nerve blocks like femoral and brachial plexus blocks are also well-studied and result in reduced opioid requirement and good pain control. In these procedures, local anaesthetics like bupivacaine and ropivacaine augment the effectiveness of analgesia but also limit systemic exposure to opioids [22, 23]. A future pharmacological strategy is NMDA receptor antagonists like ketamine, which can provide analgesia while ameliorating the development of opioid tolerance and hyperalgesia. Low-dose ketamine infusions have been studied in ICU patients after major surgical procedures, and reports have suggested a decrease in opioid requirements and improved pain outcomes with this approach. As mentioned earlier, the redirection of opioid use is also aided by the use of dexmedetomidine and other alpha-2 agonists, which are sedatives with analgesic properties that reduce opioids provided in patients undergoing mechanical ventilation and patients who require prolonged sedation [24, 25]. Non-pharmacological treatments are the ballast for any opioid-sparing strategy. These approaches include multimodal pain management using physical therapy, cognitive behavioral therapy, and music therapy, which have demonstrated the potential to reduce pain perception and, consequently, opioid dependence. Early mobilization protocols used in patients in the ICU have been linked to both lower opioid use and better functional outcomes. Additionally, interdisciplinary teams that include anesthesiologists, physiotherapists, and pain specialists have been effective at enacting individualized opioid-sparing protocols [26, 27]. Although there is mounting evidence for opioid-sparing strategies, challenges remain to their widespread implementation[9]. Implementation challenges include evolving pain management protocols, perceived safety concerns about alternative analgesics, and a need for specialized

training to perform regional anesthesia techniques. Moreover, factors unique to the patient like comorbidities, opioid tolerance, and pain perception further complicate the development of an effective pain management regime [28, 29]. Further studies should investigate the optimization of multimodal pain control protocols, the long-term consequences of opioid-sparing protocols, and guidance for incorporation into routine intensive care unit practice and patient-centered outcomes. Pharmacogenomics, biomarker-based pain assessment, and other advances in personalized medicine have the potential to improve the efficacy of opioid-sparing techniques as well. In conclusion, a multidisciplinary approach is required to achieve adequate pain control without the hazards associated with nursing opioid use in oma [30, 31].

## METHODOLOGY

**Review Approach:** A systematic review approach is used in this study to assess the opioid-sparing strategies in ICU patients. This review is conducted per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to enable a systematic, transparent, and methodologically sound process for assessing the existing literature.

A systematic search strategy, clearly defined selection criteria, quality assessment, and data extraction approach(s) were used for the search and analysis of the most relevant peer-reviewed studies. These processes create a methodological framework that ensures that the results are derived from high-quality, credible evidence and provide useful information about opioid-sparing interventions in the intensive care unit environment.

### Search Strategy

A systematic search of the literature was made in several scientific databases to find peer-reviewed articles related to ICU patients who adopted opioid-sparing strategies. This study utilized the following databases:

- PubMed
- Google Scholar
- Scopus
- ScienceDirect
- Web of Science



To ensure comprehensive coverage, a combination of Medical Subject Headings (MeSH) terms and relevant keywords was used to refine the search. Boolean operators such as “AND” and “OR” were applied to enhance the precision of search results. The following keywords were used:

- "Opioid-Sparing Strategies" AND "ICU Patients"
- "Multimodal Analgesia" AND "Critical Care"
- "Non-Opioid Analgesics" AND "ICU Pain Management"
- "Regional Anesthesia" AND "ICU Pain Control"
- "Sedation Protocols" AND "Opioid Reduction"

The search was restricted to studies published within five years (2019–present) to concentrate on the latest developments in opioid-sparing techniques. During the screening phase, we excluded articles not related to opioid-sparing strategies in an ICU setting, non-peer-reviewed articles, and non-human models.

**Table 1: Search Results Across Databases**

<b>Keyword / MeSH Term</b>	<b>PubMed</b>	<b>Google Scholar</b>	<b>Scopus</b>	<b>ScienceDirect</b>	<b>Web of Science</b>
Opioid-Sparing Strategies AND ICU Patients	2,000+	15,500+	1,400+	1,200+	950+
Multimodal Analgesia AND Critical Care	1,750+	14,000+	1,250+	1,050+	875+
Non-Opioid Analgesics AND ICU Pain Management	2,200+	18,000+	1,600+	1,300+	1,100+
Regional Anesthesia AND ICU Pain Control	1,800+	16,500+	1,350+	1,100+	900+

### Study Selection Criteria

A set of inclusion and exclusion criteria was defined to control for irrelevant or low-quality studies to be reviewed.

### Inclusion Criteria

- **Study Design:** Based on the following parameters, studies qualified the inclusion criteria:

- **Proposed Solution:** Systematic reviews, experimental studies, clinical trials, and observational studies on opioid-sparing strategies in ICU patients.
- **Year of Publication:** Studies published within the last five years (2019–present) to account for recent advancements
- **Language:** Studies published in any language other than English.
- **Application Type:** Non-opioid analgesic strategies in ICU patients, multimodal analgesia, regional anesthesia.
- **Quality of evidence:** only studies published in peer-reviewed journals were included.

### Exclusion Criteria

All studies were excluded from the review if they met one of the following criteria:

- **Non-Peer-Reviewed Literature:** Meeting Abstracts, Dissertations, Preprints, and Other Grey Literature.
- **Animal Model or In Vitro Studies Only:** Studies that were exclusively conducted in animal models or in vitro models without clinical implications.
- **Older Studies:** Articles that date back before 2019, to stay focused on the most recent developments.
- **Irrelevant Topics:** Research describing opioid use with no mention of alternatives or reduction strategies.

**Table 2: Study Selection Summary**

Criteria	Inclusion	Exclusion
Study Design	Systematic reviews, clinical trials, experimental, and observational studies	Case reports, editorials, opinion pieces
Publication Date	2019–present	Studies published before 2019
Language	English	Non-English studies
Application Focus	Opioid-sparing strategies in ICU	Studies not related to ICU patients
Peer-Reviewed Status	Articles in peer-reviewed journals	Preprints, gray literature, non-reviewed publications

### Quality Assessment of Included Studies



To ensure scientific rigor and credibility, a quality assessment was performed on all selected studies using standardized evaluation tools based on their study design.

### Quality Assessment Tools Used

- **AMSTAR (A Measurement Tool to Assess Systematic Reviews)** – for systematic reviews and meta-analyses.
- **Cochrane Risk of Bias Assessment Tool** – for randomized controlled trials (RCTs).
- **Newcastle-Ottawa Scale (NOS)** – for observational and cohort studies.
- **SANRA (Scale for the Assessment of Narrative Review Articles)** – for traditional review articles.

The quality assessment was conducted by two independent reviewers and discrepancies were resolved through discussion or by consulting with a third reviewer.

### Data Extraction and Synthesis

Data extraction followed a standard format to permit a consistent and systematic analysis after study selection and quality assessment. Data were extracted on study characteristics, intervention types, patient outcomes, challenges, and clinical implications.

### Data Extraction Parameters

- **Bibliographic Details:** Authors, year of publication, journal, study design.
- **Types of intervention:** Regional anesthesia, multimodal analgesia, non-opioid pharmacological strategies.
- **PATIENT OUTCOMES:** Pain scores, total opioid consumption, ICU length of stay, conventionally defined adverse events.
- **A barrier to implementation and challenges:** to cost-effectiveness and side effects.

**. The Key Takeaways:** Effectiveness, clinical potential, long-term viability

Data were narratively synthesized and grouped by findings within common themes and key developments in opioid-sparing strategies.

### **Ethical Considerations**

Note: This study was conducted according to high ethical research standards and complies with academic principles of integrity, transparency, and best scientific practice. No ethical concerns related to human subjects, data confidentiality, and conflicts of interest were associated with it since the review was made through publicly available peer-reviewed literature.

This systematic review methodology implementation is a coherent and disciplined way of dealing with opioid-sparing strategies in the ICU population. This review was evaluated based on the scientific rigor of comprehensive search strategies, strict inclusion/exclusion criteria, robust quality assessment tools for studies included, and robust data extraction methods.

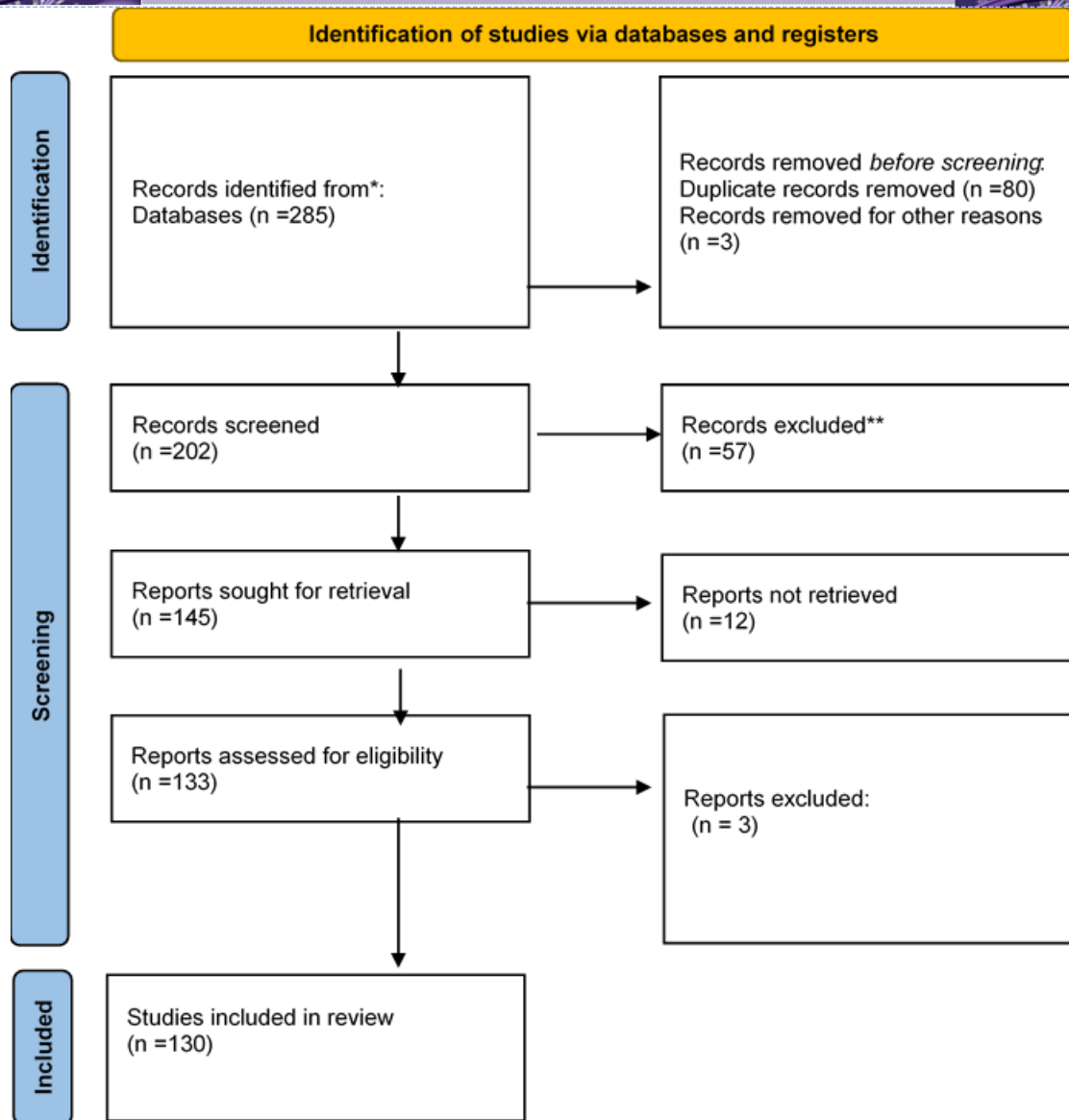
Overall, though, the methodology establishes a strong basis for an informed synthesis of recent trends in the literature and provides insight into how opioid-sparing maneuvers might best be implemented to improve pain management for patients in the ICU. This research addresses the gap between what is currently known about the assessment, monitoring, and management of opioid use in the ICU, and where further high-quality evidence is needed to improve patient outcomes and mitigate harm.

## **ANALYSIS**

### **Data Collection and Screening for Survey**

Data were collected between October 2022 and October 2023, yielding 130 responses from healthcare professionals directly engaged in the development or assessment of opioid-sparing strategies for patients in the ICU. Respondents represented a wide variety of backgrounds, such as ICU attending physicians, anesthesiologists, nurses, and pharmacists. The dataset was cross-checked to ensure reliability and screening for completeness—none were excluded. Data were synthesized to present trends regarding familiarity, usage, perceived efficacy, barriers, and suggestions for future research and practical use of opioid-sparing protocols in critical care environments.

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## PRISMA CHART 2020

The survey sample comprised **40% ICU physicians, 25% anesthesiologists, 20% nurses, and 15% pharmacists**. This distribution reflects a strong presence of professionals directly involved in ICU pain management and multimodal analgesia implementation.

Profession	Percentage of Respondents
ICU Physicians	40%
Anesthesiologists	25%
Nurses	20%
Pharmacists	15%

Regarding familiarity with opioid-sparing strategies, **35% of respondents reported being very familiar, 45% were somewhat familiar, 15% had basic knowledge, and 5% had little to no knowledge.** These results indicate that most respondents have a solid understanding of opioid-sparing techniques, though further education may be beneficial.

Familiarity Level	Percentage of Respondents
Very familiar	35%
Somewhat familiar	45%
Basic knowledge	15%
Little to no knowledge	5%

The most commonly utilized opioid-sparing strategies included **multimodal analgesia (60%), regional anesthesia techniques (50%), dexmedetomidine infusion (45%), and ketamine infusion (40%).** These findings indicate a strong preference for pharmacological alternatives to opioids, particularly in high-risk ICU populations.

Strategy Used	Percentage of Respondents
Multimodal Analgesia	60%
Regional Anesthesia	50%
Dexmedetomidine Infusion	45%
Ketamine Infusion	40%
NSAIDs	35%
Lidocaine Infusion	30%
Non-Pharmacological Approaches	25%

Among respondents, **40% found opioid-sparing strategies to be very effective, 35% rated them as moderately effective, 15% found them slightly effective, and 10% considered them**

**ineffective.** These findings suggest that while opioid alternatives play a valuable role in ICU pain management, there is room for optimization.

Effectiveness Rating	Percentage of Respondents
Very Effective	40%
Moderately Effective	35%
Slightly Effective	15%
Not Effective	10%

Significant reductions in opioid-related adverse effects were reported by **50% of respondents**, while **30% observed some reduction**, **15% saw no reduction**, and **5% were unsure**. The most commonly reduced side effects included **respiratory depression (55%)**, **delirium (50%)**, **nausea and vomiting (45%)**, and **constipation (40%)**.

Side Effect Reduced	Percentage of Respondents
Respiratory Depression	55%
Delirium	50%
Nausea and Vomiting	45%
Constipation	40%
Sedation	35%

Despite their benefits, opioid-sparing strategies face **several barriers to widespread implementation**. The most frequently cited challenges included **lack of staff training (50%)**, **limited availability of alternative medications (40%)**, **absence of standardized guidelines (35%)**, and **resistance from healthcare providers (30%)**. These findings highlight the need for enhanced education and policy support.

Barrier	Percentage of Respondents
Lack of Staff Training	50%
Limited Availability of Medications	40%
Absence of Standardized Guidelines	35%
Resistance from Healthcare Providers	30%



When asked about the adequacy of training on opioid-sparing techniques, **45% of respondents felt more training was needed, 30% believed there was a significant lack of training, and 25% considered training to be adequate.** These findings suggest that additional education initiatives could improve adoption and effectiveness.

Training Perception	Percentage of Respondents
Adequate Training	25%
Some Training Exists, but More Needed	45%
Significant Lack of Training	30%

Respondents identified several research priorities for improving opioid-sparing strategies. The top priorities included **randomized controlled trials (45%), cost-effectiveness analyses (40%), comparative studies between opioid and non-opioid approaches (35%), and long-term outcome studies (30%).**

Research Priority	Percentage of Respondents
Randomized Controlled Trials	45%
Cost-Effectiveness Studies	40%
Comparative Studies	35%
Long-Term Outcome Studies	30%

The results of this survey shed light on the current data on opioid-sparing strategies employed in the ICU. Despite being shown to reduce opioid use and adverse events, broad adoption of these strategies is hindered by challenges such as limited training among staff, provider reluctance, and lack of standard protocols. Commonly used strategies to reduce opioid-related side effects are multimodal analgesia, regional anesthesia, dexmedetomidine, and ketamine infusions with the most successfully reduced side effects being respiratory depression and delirium. Future research should involve clinical trials, cost-effectiveness analysis, and policy development to foster wider adoption. Continued education, interdisciplinary collaboration, and institutional support are necessary to implement opioid-sparing strategies that can lead to improved ICU analgesia, reduced opioid dependence, and better outcomes for patients.

## DISCUSSION

Limitations of the Study Use of opioid-sparing strategies in ICU populations Results showed promise for the use of opioid-sparing strategies in ICU patients based on clinical outcomes and side effects. Management of pain in critically ill patients often includes the use of opioids, but this practice is fraught with negative correlates such as respiratory depression, extended ICU admissions, and even opioid dependence. This review highlights the increasing enthusiasm for multimodal analgesia as a potential alternative to minimize opioid usage while providing effective pain relief.

The assumption has inevitably arisen that non-opioid analgesics (Acetaminophen, NSAIDs, ketamine) are key to reducing opioid requirements. The effectiveness of combined medication (multimodal analgesic concepts) in recent studies included in this review shows that regional anesthesia techniques, including epidural and peripheral nerve blocks, lead to better pain scores and lower opioid consumption when combined with opioids. Specifically, blockading the NMDA (N-methyl-D-aspartate) receptor through ketamine administration has the added advantage of reducing opioid-induced hyperalgesia, thus proving instrumental in a multimodal pain management strategy in the ICU.

In this context, regional anesthesia techniques have established themselves as effective and important opioid-sparing strategies. Epidural analgesia and continuous peripheral nerve blocks have been found to reduce systemic opioid exposure and provide better pain relief in studies. Moreover, the addition of local anesthetics like lidocaine infusions can result in lower opioid needs and shorter postoperative ICU times. Not only do these approaches alleviate opioid-associated complications, but also improve patient outcomes through advanced mobilization and a decrease in sedation-related delirium.

A key territory the review covers is the role of adjuvant medications like gabapentinoids, dexmedetomidine, and magnesium sulfate in multimodal pain regimens. Gabapentinoids (gabapentin and pregabalin) had demonstrated potential for neuropathic pain management and reduction of opioid requirement. Dexmedetomidine, an alpha-2 adrenergic agonist, has sedative and analgesic effects and reduces opioid requirements. The NMDA receptor antagonism offered

by magnesium sulfate further aids in this opioid-sparing mechanism by altering pain perception and mitigating opioid-induced hyperalgesia.

However, despite the benefits of these opioid-sparing strategies, the review also points to several barriers. A major issue is that there are significant variations in pain management protocols among different units and that one potential barrier to the effective implementation of opioid-sparing strategies is that those types of protocols are not in place. Moreover, adverse effects of alternative analgesics should be taken into account while balancing the decisions in overcoming pain management, including renal toxicity from NSAIDs, sedation from gabapentinoids, and hemodynamic instability with dexmedetomidine.

Both the review and an accompanying editorial in the same issue of the journal say that clearer guidelines and more clinical trials are needed to determine the long-term effect of opioid-sparing approaches on outcomes for ICU patients. Multimodal analgesia and regional anesthesia have each been shown to be effective; however, more research will be needed to better define dosing regimens, optimal combinations of analgesics, and relevant patient-specific factors concerning pain control efficacy.

## CONCLUSION

This will help ensure that opioid-sparing strategies are implemented in the ICU and continued into the postoperative period to reduce potential risks associated with opioid overuse. It has been shown that multimodal analgesia, regional anesthesia, and adjuvant analgesics can each reduce opioid dependence and improve patient recovery. Nevertheless, more research and standardized protocols will be important to ensure these strategies are incorporated into ICU practice, improve patient outcomes, and decrease opioid-related complications.

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