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Opioid-Sparing and Pharmacogenomics Anesthesia Through Evidence-Based Multimodal Strategies to Address the Opioid Crisis

Ratri Dwi Indriani[1], Muhammad Ainur Rosyid Ridho[2]
[1]Department of Medicine, Faculty of Medicine and Health, Institut Teknologi Sepuluh Nopember, Indonesia
[2]Department of Biology, Faculty of Science and Data Analytics, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia

Corresponding Author: ratridwi80@gmail.com

Abstract —The opioid crisis is a significant public health emergency, with the perioperative period identified as a critical gateway to new persistent opioid use. Anesthesiologists and surgeons play a pivotal role in mitigating this crisis. This narrative review synthesizes the evidence for opioid-sparing anesthesia through multimodal strategies as a primary solution. A comprehensive literature search was conducted across major databases, including PubMed, Scopus, and Web of Science, to identify relevant clinical trials, meta-analyses, and review articles published between January 2000 and August 2025. The focus was on studies evaluating the efficacy and outcomes of multimodal, opioid-sparing analgesic techniques. The evidence strongly supports a paradigm shift away from opioid-centric pain management. Multimodal analgesia, founded on the principle of pharmacological synergy, combines non-opioid analgesics (e.g., NSAIDs, acetaminophen), adjuvant medications (e.g., ketamine, gabapentinoids), and regional anesthesia techniques. This approach consistently demonstrates superior pain control, reduced postoperative opioid consumption, a lower incidence of opioid-related adverse effects (e.g., nausea, respiratory depression), and facilitation of Enhanced Recovery After Surgery (ERAS) protocols. Critically, by minimizing initial opioid exposure, these strategies directly address the risk of iatrogenic dependence. The adoption of evidence-based, multimodal opioid-sparing anesthesia is a clinical and ethical imperative. By standardizing these protocols, perioperative clinicians can significantly improve patient outcomes, enhance recovery, and take a decisive role in combating the opioid crisis from within the operating room.

Keywords *— Opioid Crisis; Opioid-Sparing Anesthesia; Multimodal Analgesia; Postoperative Pain; Persistent Postoperative Opioid Use (PPOU); Pharmacogenomics.*

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INTRODUCTION

The opioid crisis constitutes a critical global public health threat in the 21st century, defined by a sharp surge in the abuse, dependency, and fatal overdoses linked to both legally prescribed and illegal opioids [1, 2]. The ramifications of this crisis are not confined to individual health outcomes but also levy a considerable socioeconomic toll on public health infrastructures and the wider community [3]. Furthermore, the widespread adoption of opioids as a primary treatment for pain, frequently implemented without well-defined plans for tapering, has unintentionally cultivated widespread dependence among patient populations [4].

From an epidemiological standpoint, the magnitude of the crisis is deeply concerning, with a pronounced impact in North America [5]. For instance, the United States recorded more than 75,000 deaths from overdose in the year leading up to April 2021, a figure largely driven by synthetic opioids like fentanyl [6]. Evidence suggests that initial exposure to opioids often occurs through medical prescriptions, which can act as a precursor to opioid use disorder (OUD) [7]. Research has quantified this risk, showing that approximately 8-12% of individuals receiving opioids for chronic pain subsequently develop OUD [8]. These findings highlight the critical responsibility of healthcare professionals to adopt safer prescribing and pain control methods to help alleviate the crisis [9].

The surgical setting, which includes the entire pre-, intra-, and postoperative timeline, is recognized as a key contributor to the opioid crisis [10]. Conventionally, pain control after surgery has been dominated by the use of high-dose opioids; this

practice, though potent for managing acute discomfort, carries the dual risk of significant side effects and the onset of long-term dependency [11]. Studies have revealed that for about 6% of patients with no prior opioid exposure (opioid-naïve), undergoing even a minor operation can lead to persistent opioid use [12]. Given the vast number of surgeries conducted worldwide each year, this positions surgical pain control as a critical entry point to the wider epidemic [13].

The biomedical basis for opioid analgesia is mediated by their agonistic action on opioid receptors, most notably the mu (μ) receptor, located throughout the nervous system [14]. The binding of opioids to these receptors effectively dampens the propagation of nociceptive signals and modifies the emotional experience of pain [15]. However, this mechanism is prone to adverse neuroplastic changes with sustained use; chronic receptor stimulation initiates desensitization and internalization processes that underpin the development of pharmacological tolerance [16]. An even more problematic outcome is opioid-induced hyperalgesia (OIH), a paradoxical state where opioid exposure heightens pain sensitivity [17].

Relying solely on opioid-based anesthesia is associated with a range of clinical difficulties in the immediate perioperative period [18]. Postoperative nausea and vomiting (PONV), respiratory depression, sedation, pruritus, and delayed bowel function (postoperative ileus) are frequent complications that can hinder convalescence and extend hospitalization durations [19]. Among these, opioid-induced respiratory depression remains the most severe and life-threatening adverse event [20]. Consequently, this traditional unimodal strategy not only fuels a public health emergency but is also frequently associated with suboptimal patient outcomes after surgery [21].

To counter these issues, a paradigm shift towards opioid-sparing and opioid-free anesthetic techniques, grounded in evidence-based multimodal analgesia, is now recognized as a more favorable strategy [22]. This approach is founded on the concept of concurrently administering multiple non-opioid medications and regional anesthetic techniques, each targeting distinct mechanisms in the pain signaling pathway to achieve a synergistic effect [23]. By modulating different molecular targets such as cyclooxygenase enzymes with NSAIDs, NMDA receptors with ketamine, or voltage-gated sodium channels with local anesthetics effective analgesia can be achieved while minimizing or eliminating the need for opioids [24]. Such strategies are fundamental components of modern Enhanced Recovery After Surgery (ERAS) pathways [25].

The broad implementation of this multimodal approach is substantiated by a substantial and expanding volume of clinical research [26]. A consensus from meta-analyses and randomized controlled trials shows that opioid-sparing regimens lead to lower opioid requirements, improved pain scores, a reduced burden of opioid-related side effects, and more rapid functional recovery for patients [27]. Despite this robust evidence, the application of these techniques exhibits considerable heterogeneity in practice, hindered by a lack of institutional protocols, insufficient training, and resistance to modifying established clinical habits [28]. It is therefore imperative to conduct a thorough synthesis of the current evidence for multimodal strategies, in order to furnish clinicians with clear, actionable frameworks for reducing opioid reliance in the operating room and thereby actively combating the opioid crisis [29].

MATERIALS AND METHODS

Study Approach

This study was conducted as a narrative review, aiming to provide a comprehensive and integrative overview of evidence-based multimodal strategies for opioid-sparing anesthesia. The approach focuses on bridging the findings from fundamental pharmacology and pain physiology with their broader clinical implications in addressing the perioperative drivers of the opioid crisis [30]. The methodology combines a thorough synthesis of published literature, analysis of secondary data from clinical trials and meta-analyses, and a mechanistic interpretation of how different analgesic modalities can synergistically reduce opioid reliance.

Data Collection

A comprehensive literature search was performed to identify relevant scientific articles, original research papers, and authoritative reviews published between January 2000 and August 2025. The search was conducted across major scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar, to ensure a broad and inclusive retrieval of evidence [31]. Keywords used for the search, both individually and in combination, included: "opioid-sparing anesthesia", "opioid-free anesthesia", "multimodal analgesia", "Enhanced Recovery After Surgery (ERAS)", "persistent postoperative opioid use", "opioid crisis", "regional anesthesia", "nerve blocks", "NSAIDs", "acetaminophen", "ketamine", "gabapentinoids", "lidocaine infusion", "postoperative pain", and "opioid-related adverse effects". Additionally, clinical trial registries such as ClinicalTrials.gov were reviewed to identify ongoing or recently completed studies assessing clinical outcomes related to opioid-sparing protocols.

Selection Criteria

Studies were selected based on their relevance to a set of predefined inclusion and exclusion criteria to maintain the focus and quality of this review [32]. Inclusion criteria were: (1) studies investigating the efficacy of non-opioid analgesics or regional anesthesia techniques in reducing perioperative opioid consumption; (2) studies examining the impact of multimodal analgesic strategies on clinical outcomes such as postoperative pain scores, opioid-related side effects (e.g., PONV, respiratory depression), and length of hospital stay; (3) research linking perioperative opioid management to the risk of developing new persistent postoperative opioid use; and (4) articles describing the implementation and outcomes of institutional protocols like ERAS. Studies were excluded if they focused exclusively on chronic pain management outside the surgical context, did not measure opioid consumption or pain as an outcome, or were articles such as case reports, letters to the editor, or editorials lacking primary data.

Data Analysis

The collected literature was analyzed qualitatively using a thematic synthesis approach, which facilitates the identification, categorization, and integration of key findings across a diverse body of research [33]. The findings were organized into four primary thematic domains: (1) the pharmacological basis and mechanisms of action for key non-opioid analgesic agents and regional techniques; (2) clinical evidence and efficacy of specific multimodal combinations across different surgical specialties; (3) the impact on patient-centered outcomes, including pain control, functional recovery, and the prevention of long-term opioid dependence; and (4) implementation strategies and the role of standardized institutional protocols in successfully adopting opioid-sparing practices. Evidence from randomized controlled trials (RCTs), meta-analyses, and large observational studies was comparatively analyzed to identify consistent patterns and highlight existing gaps in knowledge.

Limitations

This study acknowledges the limitations inherent to a narrative review methodology. In contrast to a systematic review, this format may be susceptible to selection bias in the literature chosen, and it does not involve a quantitative meta-analysis, which could limit the statistical power and generalizability of the conclusions [34]. The significant heterogeneity across the included studies in terms of surgical procedures, patient populations (e.g., opioid-naïve vs. opioid-tolerant), specific analgesic dosages and timing, and definitions of clinical outcomes also presents a challenge for direct comparison and definitive recommendations. Nevertheless, a rigorous effort was made to incorporate recent, high-impact studies to ensure the review is comprehensive, balanced, and clinically relevant.

RESULTS AND DISCUSSION

Opioid-sparing anesthesia, achieved through evidence-based multimodal analgesic strategies, has emerged as a crucial perioperative standard of care in response to the opioid crisis (Fig.1) [35]. This paradigm shifts away from a unimodal, opioid-centric model toward a holistic approach that targets multiple pain pathways simultaneously to achieve superior pain control with minimal opioid exposure [36]. The analysis of existing literature consistently demonstrates that this approach is not only effective in managing acute postoperative pain but also significantly mitigates the risk of opioid-related adverse effects and the potential for long-term dependence [37]. The following discussion will synthesize the pharmacological evidence, clinical outcome data, and implementation strategies that support the widespread adoption of this practice [38].



Figure 1. Contribution to the Opioid Crisis [84].

Furthermore, the evolution of opioid-sparing anesthesia is moving towards a highly personalized approach through the integration of pharmacogenomics [84]. From a biomedical science perspective, it is now understood that an individual's genetic makeup significantly influences both their perception of pain and their response to analgesic medications [85]. Key genetic polymorphisms, such as those in the CYP2D6 enzyme which metabolizes codeine to morphine, the COMT gene which modulates pain sensitivity, and the OPRM1 gene encoding the mu-opioid receptor, can predict a patient's analgesic requirements and their susceptibility to opioid-related adverse effects [86]. For the anesthesiologist, this translates into the potential to move beyond standardized protocols and tailor a multimodal regimen to a patient's unique genetic profile, thereby selecting the most effective non-opioid agents and optimizing dosing strategies to maximize efficacy while minimizing risk [87].

The foundation of opioid-sparing anesthetic strategies fundamentally lies in the principle of pharmacological synergy, a concept wherein various medications with unique mechanisms of action are concurrently utilized to target the nociceptive cascade at multiple levels [39]. From a biomedical science perspective, postoperative pain is not a monolithic signal but rather a complex, multi-step biological process. This process begins with transduction, where surgical tissue injury releases a "soup" of inflammatory mediators (such as prostaglandins, bradykinin, and hydrogen ions) that activate and sensitize peripheral nerve endings known as nociceptors [40]. The resulting electrical signal then undergoes transmission along A-delta and C nerve fibers to the dorsal horn of the spinal cord, a process dependent on voltage-gated sodium channels. Within the spinal cord, this signal

undergoes modulation, where it can be either amplified by excitatory neurotransmitters (like glutamate and substance P) or dampened by descending inhibitory pathways from the brainstem (utilizing serotonin and norepinephrine). Finally, the modulated signal ascends to the brain for perception, where it is interpreted as the conscious experience of pain across various regions, including the somatosensory cortex and the limbic system [40]. From an anesthesiology standpoint, the multimodal approach strategically places "blockades" all along this pathway. For instance, NSAIDs act at transduction by inhibiting prostaglandin synthesis at the wound site. Local anesthetics work at transmission by blocking sodium channels. Opioids, ketamine, and alpha-2 agonists act at modulation within the central nervous system. By attacking the pain process from multiple angles simultaneously, an anesthesiologist can achieve more effective and complete pain control compared to relying solely on a single mechanism like high-dose opioids. This synergy allows for the use of lower doses of each drug, which directly reduces the body's toxic load and minimizes the risk of adverse side effects from any single agent [41, 42].

A fundamental component in the multimodal analgesia armamentarium is the scheduled administration of systemic non-opioid analgesics, primarily acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) [43]. Although often grouped together, biomedical science reveals that they operate via distinct yet remarkably complementary mechanisms. NSAIDs, such as ketorolac or ibuprofen, exert their effects predominantly in peripheral tissues. There, they inhibit the cyclooxygenase (COX) enzymes, which are responsible for converting arachidonic acid from damaged cell membranes into pro-inflammatory prostaglandins (like PGE_2) [44]. By blocking PGE_2 production, NSAIDs effectively prevent the sensitization of peripheral nociceptors, thereby reducing the pain signal at its source. In contrast, the mechanism of acetaminophen (paracetamol) is primarily central. While it is a weak COX inhibitor peripherally (where the peroxide-rich environment inactivates it), it is far more effective in the low-peroxide environment of the central nervous system. Leading theories suggest that acetaminophen modulates the endogenous cannabinoid system and may inhibit a brain-specific COX variant (COX-3), ultimately suppressing pain signal processing at the level of the spinal cord and brain [44]. From an anesthesiology perspective, this mechanistic distinction is critically important for clinical practice. By administering both drugs concurrently and on a scheduled ("around-the-clock") basis, the anesthesiologist creates a dual blockade: one peripheral (NSAID) and one central (acetaminophen). This establishes a stable and constant analgesic "baseline," which significantly reduces pain fluctuations and lowers the patient's baseline requirement for opioids. Robust clinical data from numerous meta-analyses confirm that this combined strategy consistently reduces postoperative morphine consumption by 20-40%, making it the cornerstone of nearly all modern opioid-sparing anesthetic protocols [45, 46].

Beyond the foundational analgesics, adjuvant agents such as ketamine and the gabapentinoids play a crucial role in targeting more complex pain mechanisms, particularly the phenomenon of central sensitization [47]. Biomedically, central sensitization is a form of pain "memory" or synaptic plasticity in the dorsal horn of the spinal cord. An intense and prolonged surgical stimulus causes a massive release of the neurotransmitter glutamate. This activates the N-methyl-D-aspartate (NMDA) receptor, which is normally quiescent, leading to a major influx of calcium ions into the post-synaptic neuron. This wave of calcium triggers intracellular signaling cascades that render the neuron hyperexcitable and more responsive to subsequent stimuli, clinically manifesting as hyperalgesia (an exaggerated response to pain) and allodynia (pain from a normally non-painful stimulus) [48]. Ketamine, as a non-competitive NMDA receptor antagonist, directly blocks this ion channel, preventing the calcium influx and effectively halting this pain amplification process. Meanwhile, gabapentinoids work presynaptically; they bind to the alpha-2-delta subunit of voltage-gated calcium channels, which reduces calcium entry into the presynaptic nerve terminal and thereby decreases the release of glutamate and other excitatory neurotransmitters into the synapse [49]. From an anesthesiology perspective, the use of these agents is a prime example of preventive or pre-emptive analgesia. An anesthesiologist will administer a sub-anesthetic dose infusion of ketamine during surgery, not for unconsciousness, but specifically to shield the

central nervous system from the nociceptive barrage as it is happening. Similarly, gabapentinoids are often given orally before surgery to "quiet down" the nervous system in advance. The clinical decision to use these agents depends on a careful evaluation of the patient and surgery type; they are particularly valuable in opioid-tolerant patients or those undergoing procedures known to be intensely painful (e.g., major spine surgery), where the risk of central sensitization is exceptionally high [48, 49].

The role of regional anesthesia cannot be overstated in modern opioid-sparing practice [50]. Techniques such as neuraxial blockade (epidural and spinal) and peripheral nerve blocks provide highly effective analgesia by blocking the transmission of nociceptive signals directly from the surgical site [51]. The use of single-injection or continuous peripheral nerve blocks under ultrasound guidance has revolutionized pain management for orthopedic and extremity surgery, often allowing patients to recover with little to no need for systemic opioids [52]. The available evidence strongly supports the integration of regional anesthesia as a core component of nearly all major surgical protocols [53].

The clinical efficacy of opioid-sparing protocols has been extensively validated across a wide range of surgical disciplines [54]. In colorectal surgery, the application of Enhanced Recovery After Surgery (ERAS) protocols emphasizing thoracic epidural analgesia or fascial plane blocks (e.g., transversus abdominis plane/TAP block) has been shown to accelerate the return of bowel function, reduce complications, and drastically decrease opioid requirements [55]. Data indicate that patients within ERAS programs not only consume fewer opioids but also report higher satisfaction scores [56].

In orthopedic surgery, particularly total joint arthroplasty, aggressive multimodal strategies are essential given the high intensity of postoperative pain [57]. The combination of peripheral nerve blocks (e.g., adductor canal block for total knee arthroplasty), spinal anesthesia, and a scheduled regimen of acetaminophen and NSAIDs has become the gold standard [58]. Randomized controlled trials consistently demonstrate that this approach results in superior pain control, earlier mobilization, and a significant reduction in opioid consumption compared to opioid-centric management [59].

Other specialties such as thoracic and gynecologic surgery have also demonstrated clear benefits from opioid-sparing techniques [60]. Thoracic epidural analgesia or paravertebral blocks for thoracotomy provide excellent segmental analgesia that facilitates postoperative respiratory function by reducing incision-related pain [61]. In laparoscopic gynecologic surgery, a multimodal approach including TAP blocks and non-opioid analgesics is often sufficient to render the entire perioperative episode opioid-free [62]. Even in ambulatory surgery, where rapid recovery is paramount, opioid-sparing strategies are highly beneficial [63]. By minimizing intraoperative and postoperative opioid use, the incidence of side effects that can delay discharge, such as postoperative nausea and vomiting (PONV) and excessive sedation, is significantly reduced [64]. This not only improves the patient experience but also enhances the efficiency and throughput of ambulatory surgery centers [65].

The most immediate benefit of opioid-sparing anesthesia is the reduction in the incidence and severity of opioid-related adverse effects (ORADEs) [66]. Respiratory depression, the most feared complication, is virtually eliminated by avoiding high-dose systemic opioids [67]. Furthermore, significant decreases in PONV, sedation, pruritus, and postoperative ileus directly contribute to a faster functional recovery and a more comfortable patient experience [68]. Crucially, reducing perioperative opioid exposure directly addresses one of the primary drivers of the opioid crisis: persistent postoperative opioid use (PPOU) [69]. Large-scale observational data have established a clear link between the quantity of opioids prescribed at hospital discharge and a patient's risk of becoming a chronic user [70]. By minimizing or eliminating the need for postoperative opioids, multimodal strategies effectively interrupt the pathway from acute pain management to long-term dependence [71].

The application of these protocols is consistently associated with improved overall recovery outcomes [72]. Patients managed with opioid-sparing regimens tend to mobilize earlier, have shorter lengths of hospital stay, and are less likely to be readmitted [73]. This enhancement in functional recovery, combined with effective pain control, cumulatively results in a significant increase in patient satisfaction [74]. The successful implementation of opioid-sparing anesthesia relies heavily on the

adoption of standardized institutional protocols and a multidisciplinary team approach [75]. Programs like ERAS provide an ideal framework, integrating evidence-based practices across the entire continuum of perioperative care, from preoperative patient education to discharge planning [76]. The success of these programs depends on close collaboration among surgeons, anesthesiologists, nurses, and pharmacists [77].

Despite the robust evidence, several barriers still impede the universal adoption of opioid-sparing practices [78]. These obstacles include institutional inertia and a reluctance to change long-standing practices, a lack of ongoing education and training, and the logistical and cost challenges associated with implementing new techniques like regional nerve blocks [79]. Overcoming these barriers requires leadership commitment, data-driven advocacy, and investment in educational resources [80]. In conclusion, the shift toward opioid-sparing anesthesia via multimodal strategies is no longer an option, but a clinical and ethical imperative [81]. The abundant evidence supports its approach in providing superior pain control, reducing side effects, and meaningfully combating the opioid crisis by preventing new cases of iatrogenic dependence [82]. Future directions should focus on personalizing multimodal regimens for specific patient populations (e.g., the opioid-tolerant), developing novel non-opioid analgesics, and conducting further long-term research to confirm the reduction in PPOU through these interventions [83].

CONCLUSION

The opioid crisis remains one of the most formidable public health challenges of our time, with the perioperative period identified as a critical and often unintentional gateway to iatrogenic dependence. This review has synthesized the extensive evidence demonstrating that a paradigm shift from traditional, opioid-centric pain management to evidence-based, opioid-sparing multimodal anesthesia is an effective and necessary strategy to mitigate this risk. Our analysis confirms that the foundation of this approach pharmacological synergy achieved by combining non-opioid analgesics, adjuvants, and regional anesthesia techniques provides superior analgesia while minimizing opioid exposure. The clinical data are compelling, showing consistent benefits across diverse surgical specialties in reducing opioid consumption, lowering the incidence of opioid-related adverse effects, and facilitating enhanced recovery pathways. Critically, these strategies directly address a root cause of the epidemic by lowering the risk of new persistent postoperative opioid use, thereby helping to break the cycle of acute medical treatment leading to chronic dependence. Therefore, the implementation of standardized opioid-sparing protocols is not merely a clinical option but an ethical imperative for all perioperative clinicians and healthcare institutions. It represents a fundamental evolution in the role of the anesthesiologist towards one of long-term patient advocacy and public health stewardship. Looking forward, the continued refinement of these strategies through personalized approaches, such as the integration of pharmacogenomics, promises to further optimize patient outcomes. By universally adopting these evidence-based multimodal strategies, the medical community can take a decisive and impactful step in resolving the opioid crisis from within the operating room.

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