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*Review*

# Emerging Non-Opioid Analgesics for Acute and Postoperative Pain Management

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**Abstract**

Effective pain control remains a central goal in acute and postoperative care, yet reliance on opioids continues to pose significant clinical and public health concerns. Opioids, while potent, carry well-documented risks including dependence, respiratory depression, and delayed recovery. In response, recent advances in pharmacology have introduced several non-opioid analgesics that offer alternative or complementary pathways to manage pain. These include classes such as cannabinoid receptor modulators, sodium and calcium channel blockers, NMDA receptor antagonists, monoclonal antibodies targeting nerve growth factor, and TRP channel modulators. Each class interacts with distinct biological targets involved in nociception, offering analgesic effects through both central and peripheral mechanisms. Non-opioid therapies are now being integrated into multimodal pain management protocols, where their combination with other agents helps reduce total opioid use while maintaining effective pain control. Applications span a variety of surgical procedures and acute care scenarios, with growing evidence supporting their role in lowering pain scores, improving recovery, and preventing transition to chronic pain. However, challenges remain, including variability in patient response, safety concerns, and limitations in translating preclinical success into clinical outcomes. Current research is exploring novel drug delivery systems, personalized pain management strategies, and improved trial methodologies to enhance efficacy and minimize adverse effects. As innovation in analgesic science continues, the role of non-opioid medications is expected to expand, shaping a future of pain management that is safer, more targeted, and responsive to individual patient needs.

**Keywords:** *non-opioid analgesics, acute pain, postoperative pain, multimodal analgesia, pain management*

## Introduction

Effective pain management remains a cornerstone of modern medical care, particularly in acute and postoperative settings. Despite significant advances in anesthesia and pharmacology, pain control continues to pose substantial clinical challenges. Opioids, long considered the gold standard for moderate to severe pain, are associated with a range of adverse effects including respiratory depression, constipation, sedation, tolerance, and dependence. In light of the opioid crisis and rising concerns over opioid-related morbidity and mortality, there is an urgent need to identify and develop non-opioid alternatives that provide effective analgesia with reduced risk profiles (1).

Acute pain, defined as pain lasting less than three months or directly related to tissue injury, often arises from surgery, trauma, or medical interventions. Postoperative pain, a subset of acute pain, affects millions of patients annually and, if inadequately treated, can delay recovery, prolong hospitalization, and increase the risk of chronic pain syndromes. Traditionally, opioid-based regimens have been used perioperatively, but their limitations have driven the pursuit of multimodal analgesia and non-opioid strategies. Recent research has explored a range of agents targeting different pathways involved in pain transmission and perception, including peripheral and central mechanisms (2).

Emerging non-opioid analgesics encompass a diverse array of pharmacological classes. These include agents that modulate ion channels, such as sodium and calcium channel blockers; drugs targeting the endocannabinoid system; selective NK-1 receptor antagonists; monoclonal antibodies against nerve growth factor (NGF); and novel formulations of existing drugs that enhance efficacy or reduce side effects. For instance, agents like ziconotide, a calcium channel blocker derived from marine snail venom, and EMA401, an angiotensin II type 2 receptor antagonist, have shown promising results in early trials (3). In addition, the use of peripherally acting agents that avoid central nervous system penetration holds potential in reducing systemic side effects commonly associated with opioids.

The development and clinical adoption of non-opioid analgesics are influenced by factors including mechanism of action, onset and duration of analgesia, side effect profile, and cost-effectiveness. While some agents have demonstrated efficacy in randomized clinical trials, many remain in early-phase research or face regulatory hurdles. Moreover, the variability in patient response and the complexity of pain pathways necessitate a personalized approach to pain management that integrates both pharmacological and non-pharmacological methods. The ongoing evolution of pain science continues to uncover novel targets, reinforcing the potential for safer and more effective non-opioid therapies (4).

## Review

Recent advances in pain pharmacology have led to the development of several non-opioid analgesics with promising clinical potential. Unlike opioids, which primarily act through mu-opioid receptors in the central nervous system, many emerging agents target peripheral pain pathways or modulate alternative receptors, offering effective analgesia with fewer central side effects. One notable area of innovation involves monoclonal antibodies against nerve growth factor (NGF), such as tanezumab, which have demonstrated efficacy in managing moderate to severe pain without the risks of dependence or respiratory depression (5). Although concerns regarding joint safety have delayed widespread adoption, these agents represent a significant shift in targeting chronic and postoperative pain.

Another promising direction includes drugs that modulate voltage-gated sodium channels, especially Nav1.7, which plays a critical role in nociceptive transmission. Selective Nav1.7 inhibitors are being investigated as targeted analgesics that may avoid the systemic side effects of traditional pain medications. Preliminary studies suggest these inhibitors can reduce acute postoperative pain while preserving motor function and avoiding sedation


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(6). The ongoing development of these agents reflects a broader trend toward mechanism-specific analgesia, encouraging a move away from generalized central nervous system suppression and toward tailored therapies that align with individual pain mechanisms and clinical contexts.

### *Emerging Classes of Non-Opioid Analgesics*

The current trajectory in analgesic research is rapidly moving beyond opioid dependence, focusing instead on pharmacological classes that offer analgesia through distinct mechanisms. Among these, cannabinoid receptor modulators have gained traction. Unlike the psychotropic compounds associated with cannabis, selective modulators of the CB2 receptor display analgesic potential without inducing central nervous system effects. Preclinical studies support their anti-inflammatory and antinociceptive actions in models of acute and postoperative pain, positioning CB2 agonists as viable alternatives for clinical use (7). The peripheral localization of CB2 receptors helps avoid the sedation and cognitive disruption that limit the broader application of CB1-targeting agents.

In parallel, transient receptor potential (TRP) channel modulators are being refined for use in pain settings. TRPV1, commonly known as the capsaicin receptor, plays a role in thermal and inflammatory pain signaling. High-concentration topical capsaicin formulations have been shown to produce localized defunctionalization of nociceptors, leading to a prolonged reduction in pain sensitivity (8). This approach, already approved in some contexts, is undergoing renewed investigation as a non-systemic option for acute nociceptive states. TRP channels like TRPA1 and TRPM8 are also under scrutiny for their roles in nociceptive transmission, especially in surgical models of pain.

Beyond receptor modulation, epigenetic regulators have emerged as targets with therapeutic relevance. Histone deacetylase (HDAC) inhibitors, for example, influence gene expression patterns involved in pain sensitization. In experimental models, HDAC inhibitors have reduced mechanical hypersensitivity and modulated cytokine release, suggesting they affect both neural and immune contributors to pain (9). Their potential in postoperative contexts lies in the ability to dampen the transcriptional changes that sustain hyperalgesia after surgical injury. The complexity of their downstream effects, however, requires further characterization to ensure selectivity and safety in acute applications.

Gene-targeted therapies are also shaping the future of analgesia. Antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) are being engineered to suppress the expression of key pain mediators, such as sodium channels and inflammatory enzymes. For example, ASOs directed against Nav1.3 have attenuated neuropathic and postoperative pain behaviors in animal models by selectively silencing pain-associated isoforms (10). These nucleic acid-based agents offer a high degree of specificity, allowing for localized and time-controlled effects. Delivery methods and off-target risks remain areas of active development, but clinical progress is evident in early-phase trials.

### *Applications in Acute and Postoperative Pain*

Non-opioid analgesics have gained clinical ground in managing acute and postoperative pain, not only to reduce opioid exposure but also to address pain mechanisms opioids cannot fully control. NSAIDs, for instance, continue to be central in perioperative protocols due to their well-established inhibition of cyclooxygenase enzymes, which decreases prostaglandin synthesis and limits inflammation at the injury site. Selective COX-2 inhibitors such as parecoxib have been shown to be effective in postoperative settings, offering a reduced risk of gastrointestinal complications compared to traditional NSAIDs (11). These agents can be administered intravenously, making them especially suitable in the immediate postoperative period before oral intake is resumed.

Local anesthetics, including lidocaine and bupivacaine, remain widely used for intraoperative and postoperative pain relief. Continuous wound infiltration techniques and regional nerve blocks, enhanced by long-acting formulations such as liposomal bupivacaine, have demonstrated


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prolonged analgesia and decreased need for rescue opioids (12). In ambulatory surgeries, these strategies improve recovery profiles by minimizing systemic drug exposure while still targeting nociceptive input directly at the surgical site. Studies have also explored intravenous lidocaine infusions, which appear to provide analgesic and anti-inflammatory benefits extending beyond local effects, likely through modulation of central sensitization.

Gabapentinoids, primarily gabapentin and pregabalin, are now routinely evaluated for use in multimodal analgesic plans, especially in surgeries known for neuropathic components like spine or orthopedic procedures. Their mechanism, involving inhibition of alpha-2-delta subunits of voltage-gated calcium channels, reduces excitatory neurotransmitter release and dampens central sensitization. Though originally developed for epilepsy, these agents show efficacy in decreasing both the intensity of acute pain and the incidence of chronic postsurgical pain (13). Careful dosing remains essential, however, as sedation and dizziness may occur postoperatively, particularly in elderly populations or those receiving multiple CNS depressants.

Ketamine, at sub-anesthetic doses, has gained renewed attention in acute pain management through its antagonism of NMDA receptors. This mechanism is particularly effective in preventing central sensitization and opioid-induced hyperalgesia. Low-dose ketamine infusions have shown benefit in high-pain surgeries such as abdominal or thoracic operations, reducing both postoperative pain scores and cumulative opioid consumption (14). Unlike traditional sedatives, ketamine preserves respiratory function, making it suitable in opioid-sparing protocols when managed in controlled settings. Its psychomimetic effects, once a limiting factor, are less concerning at analgesic doses and can often be mitigated with adjunct medications.

### *Current Limitations and Research Opportunities*

Despite the rapid expansion of non-opioid analgesic development, several challenges continue to limit clinical impact. One of the most persistent issues lies in the variability of analgesic response. Patient-specific factors such as genetic polymorphisms, comorbidities, and prior opioid exposure significantly influence outcomes. For instance, the efficacy of sodium channel blockers or cannabinoid-based therapies may differ depending on the expression levels or structural variations of their molecular targets (15). This variability complicates dosing strategies and often leads to inconsistent pain relief in real-world settings, especially outside tightly controlled clinical trials.

Safety concerns also shape the trajectory of non-opioid innovation. While these drugs aim to sidestep the respiratory depression and addiction risk seen with opioids, they are not without adverse effects. Gabapentinoids, for example, may cause excessive sedation and dizziness, particularly in older adults or those on polypharmacy regimens. Similarly, anti-NGF monoclonal antibodies have raised joint-related safety alarms, which led to temporary clinical holds during early trials (16). The challenge lies in striking a balance between meaningful analgesia and a tolerable safety profile, especially when patients are exposed to these drugs in combination as part of multimodal protocols.

Another area that complicates progress is the translational gap between preclinical findings and human application. Many compounds with robust analgesic effects in animal models fail to produce similar results in clinical populations. Rodent models of postoperative pain, while helpful for early screening, often fail to capture the complexity of human pain perception and recovery. Differences in immune system responses, pain pathways, and behavioral endpoints limit the predictive power of these models (17). Addressing this gap requires the development of more advanced translational frameworks, potentially including humanized models, organ-on-a-chip platforms, or improved in silico simulations.

Funding patterns and market dynamics also influence the pace of discovery. While public health agencies support pain research due to its societal burden, pharmaceutical companies may be less


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inclined to invest heavily in non-opioid projects with uncertain return on investment. Many promising compounds are abandoned in early-phase development due to regulatory uncertainty, patent challenges, or insufficient efficacy in preliminary trials. Open-label extensions and adaptive trial designs could improve early decision-making while preserving resources. Collaborative frameworks that bring together academic centers, industry sponsors, and regulatory bodies are beginning to address this issue but remain underutilized.

Emerging technologies offer new directions that could accelerate progress. Techniques like CRISPR-based gene editing, mRNA delivery systems, and nanoparticle-mediated targeting are being explored for their ability to direct analgesic action to specific tissues or neural populations. Biomarker-driven patient selection is another active area, allowing clinicians to predict treatment response based on neurochemical, genetic, or imaging data (18). These tools may eventually bridge the gap between broad-spectrum analgesia and personalized pain control, but their integration into routine clinical practice will require further validation and cost-effective deployment strategies.

## Conclusion

Non-opioid analgesics represent a promising shift in the management of acute and postoperative pain. Their diverse mechanisms offer targeted relief while minimizing opioid-related risks. Continued research is essential to overcome current limitations and optimize clinical applications. A future built on precision pain management is increasingly within reach.

## Disclosure

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There is no conflict of interest.

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Non applicable.

### *Data availability*

All data are available within the manuscript.

### *Author contribution*

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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