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MULTIMODAL ANALGESIA: BEYOND PAIN CONTROL

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Abstract : Pain management represents a persistent clinical challenge due to its multifactorial nature and the limitations of traditional analgesic approaches based on a single mechanism of action, particularly the predominant use of opioids. In this context, multimodal analgesia has emerged as a comprehensive therapeutic strategy that combines pharmacological and non-pharmacological interventions targeting different pathophysiological targets of pain, with the aim of optimizing analgesic efficacy and improving patient safety.This narrative review analyzes multimodal analgesia from a global perspective, integrating pathophysiological fundamentals, mechanisms of action, and current clinical evidence. It examines the modulation of opioid receptors, the inhibition of peripheral inflammation, the attenuation of central sensitization, and the role of descending modulatory systems, as well as the contribution of non-pharmacological therapies to the pain experience. The available evidence suggests that the rational combination of these strategies reduces opioid exposure, decreases the incidence of adverse effects, and limits phenomena such as hyperalgesia and chronic pain. Beyond controlling pain intensity, multimodal analgesia has an impact on relevant clinical and functional outcomes, including the preservation of respiratory and neurocognitive function, improved mobility, and functional recovery. , multimodal analgesia should be understood as a personalized, mechanism-based strategy aimed at improving safety, functionality, and the overall patient experience, beyond simple pain relief.

Keywords: multimodal analgesia, quality of life, pain management, opioids.

INTRODUCTION

Pain is one of the most frequent and complex clinical problems in healthcare systems, with implications that transcend symptomatic relief and directly affect functionality, quality of life, patient safety, and healthcare costs(1) .

For decades, the management of acute and subacute pain has been based predominantly on a pharmacological approach centered on opioids, motivated by their analgesic efficacy and wide availability. However, accumulated evidence has shown that this paradigm has significant limitations and is associated with a high burden of adverse effects and unfavorable clinical outcomes(2) .

The extensive use of opioids has been linked to respiratory depression, gastrointestinal disturbances, neurocognitive impairment, drug dependence, and, in certain contexts, increased morbidity and mortality. Furthermore, analgesia based exclusively on opioids does not adequately address the pathophysiological complexity of pain, which involves peripheral, central, inflammatory, and psychosocial mechanisms.

This disconnect between the pathophysiology of pain and therapeutic strategies has driven the search for more comprehensive and saf(3) .

In this scenario, multimodal analgesia has emerged as a contemporary model for pain management, based on the rational combination of pharmacological and non-pharmacological interventions that act on different nociceptive pathways. Far from being a simple sum of analgesics, multimodal analgesia represents a strategy aimed at optimizing analgesic efficacy, reducing exposure to opioids, and minimizing associated adverse effects through the synergy of complementary mechanisms of action(4) .

However, the evaluation of multimodal analgesia continues to focus, in many studies and in clinical practice, on reducing pain intensity as measured by subjective scales. This limited approach does not adequately reflect its actual clinical impact.

Currently, there is growing recognition that the success of pain management should be assessed through broader outcomes, such as preservation of respiratory and gastrointestinal function, maintenance of neurocognitive status, mobility, quality of life, reduction of complications, and healthcare system efficiency(5) .

From a global perspective, multimodal analgesia aligns with the principles of patient-centered medicine and modern strategies for safety and quality of care. Its application extends to multiple clinical settings, including acute medical and traumatic pain, pain associated with invasive procedures, and pain management in complex patients, reinforcing its relevance as a cross-cutting tool in contemporary clinical practice(6) .

The objective of this narrative review is to analyze multimodal analgesia from a broad and integrative perspective, exploring its pathophysiological foundations, its main components, and, centrally, its clinical impact beyond pain control. It seeks to offer a critical synthesis that allows for an understanding of its true value as a global therapeutic strategy and to provide practical elements for its rational implementation in different healthcare contexts.

Pathophysiological basis of surgical pain and multimodal analgesia

Pain is a complex biological and experiential phenomenon resulting from the interaction between peripheral nociceptive mechanisms, central modulation processes, and inflammatory, neuroendocrine, and psychosocial factors(7) .

The activation of peripheral nociceptors by tissue, inflammatory, or traumatic stimuli initiates a cascade of afferent signals that are transmitted to the central nervous system, where they are modulated and ultimately interpreted as pain. This process is not static and can be amplified by peripheral and central sensitization phenomena.

Peripheral sensitization occurs as a result of the release of inflammatory mediators such as prostaglandins, bradykinin, and cytokines, which reduce the nociceptive activation threshold, increasing the intensity and duration of pain(8) .

Complementarily, central sensitization is characterized by increased neuronal excitability at the medullary and supraspinal levels, with alteration of descending inhibitory mechanisms. These changes explain why stimuli that are not usually painful can be perceived as painful and why pain can persist even when the initial tissue damage has been resolved(9) .

Sustained or poorly controlled pain also triggers a systemic neuroendocrine response mediated by activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. The release of catecholamines and cortisol generates a state of physiological stress that is associated with metabolic, immunological, and cardiovascular alterations, contributing to organ dysfunction, functional impairment, and worse clinical prognosis, especially in patients with comorbidities or in critical illness situations.

An analgesic approach focused on a single mechanism of action, particularly opioids, is insufficient to modulate this complex pathophysiological network(10) .

Although opioids act effectively on the transmission and central perception of pain, their limited action on peripheral and inflammatory mechanisms explains the need for increasing doses and the appearance of adverse effects, in addition to phenomena such as tolerance, opioid-induced hyperalgesia, and drug dependence(11) .

Multimodal analgesia is based on simultaneous intervention at different levels of the pathophysiology of pain. This approach combines drugs and strategies with complementary mechanisms of action, aimed at reducing peripheral sensitization, modulating central excitability, and attenuating the inflammatory and neuroendocrine response associated with pain. The concurrent use of non-opioid analgesics, interventional techniques, and adjuvant drugs allows for pharmacological synergy, achieving more effective analgesic control with lower individual doses and a better safety profile.

From a pathophysiological perspective, multimodal analgesia seeks not only to relieve pain, but also to prevent its amplification and chronicity, limit the systemic response to stress, and preserve the patient's organ function and functional capacity. These fundamentals explain why multimodal analgesia should be understood as a comprehensive therapeutic strategy and not merely as an alternative for reducing pain intensity as measured by subjective scales(12) .

Multimodal analgesia: concept, components, and clinical rationale

Multimodal analgesia is defined as a comprehensive therapeutic strategy based on the rational combination of pharmacological and non-pharmacological interventions that act on different pathophysiological mechanisms of pain. Unlike traditional analgesic approaches focused on a single drug or route of action, multimodality seeks to optimize analgesic efficacy through the synergy of complementary mechanisms, reducing dependence on a single agent and minimizing the adverse effects associated with high doses(13) .

The clinical basis for multimodal analgesia lies in the recognition that pain is a multifactorial and dynamic phenomenon. Non-opioid analgesics, such as paracetamol and non-steroidal anti-inflammatory drugs, play a central role in reducing peripheral sensitization and the inflammatory response(14) .

These interventions form the basis on which other therapeutic modalities are integrated, allowing for more stable control of baseline pain and a reduced need for opioid rescue.

Interventional and regional techniques, when indicated, provide effective blockade of nociceptive transmission, significantly reducing the afferent load on the central nervous system. Their integration into multimodal regimens not only improves analgesia but also helps preserve motor and sensory function when selective and well-dosed techniques are used, promoting functionality and early rehabilitation(14).

Adjuvant drugs play an important role in multimodal analgesia by acting on central pain modulation mechanisms. Agents such as ketamine, intravenous lidocaine, and magnesium exert antihyperalgesic and neuronal excitability-modulating effects, mainly through the inhibition of the N-methyl-D-aspartate receptor and the blockade of ion channels. These effects attenuate central sensitization and reduce the intensity of refractory pain, particularly in patients with severe pain or previous exposure to opioids.

Other adjuvants, such as alpha-2 adrenergic agonists and corticosteroids, contribute to analgesia by modulating the sympathetic response and inflammation, respectively. However, their use must be individualized, considering the patient's risk profile and the balance between benefits and adverse effects.

Similarly, gabapentinoids have shown analgesic effects in certain contexts, although their indiscriminate use has been associated with sedation, dizziness, and cognitive impairment, underscoring the need for careful selection(15) .

From a clinical standpoint, multimodal analgesia should not be understood as a rigid protocol, but rather as a flexible and personalized strategy. The selection of components, doses, and duration of treatment should be based on the intensity and type of pain, patient characteristics, comorbidities, and therapeutic goals. This individualized approach maximizes the benefits of multimodality and avoids unnecessary exposure to interventions with low clinical performance.

(16)Overall, multimodal analgesia represents a therapeutic model focused on the pathophysiology of pain and patient safety,

aimed not only at analgesic relief but also at functional preservation and reduction of complications. Its rational implementation is a key element of modern pain management strategies in different clinical settings.

Beyond pain control: clinical and functional impact of multimodal analgesia

The effectiveness of pain management has traditionally been evaluated based on the reduction of pain intensity, measured using subjective scales. However, this approach is insufficient to capture the true clinical impact of an analgesic strategy. Currently, there is a growing consensus that the success of pain treatment should be assessed by its ability to improve clinical and functional outcomes relevant to the patient, beyond symptomatic relief(17) .

One of the most consistent benefits of multimodal analgesia is the reduction in opioid exposure and, with it, the adverse events associated with their use. The decrease in opioid requirements translates into a lower incidence of respiratory depression, nausea and vomiting, ileus, urinary retention, and excessive sedation, complications that directly affect patient safety and delay functional recovery(18) .

This opioid-sparing effect is particularly relevant in vulnerable populations, such as elderly patients, those with respiratory comorbidities, or those at risk of cognitive impairment.

The preservation of respiratory and neurological function is another key area in which multimodal analgesia shows clinical advantages. Adequate dynamic pain control promotes effective spontaneous ventilation, coughing, and early mobilization, reducing the risk of respiratory complications.

Likewise, limiting opioid use and the rational use of adjuvants contribute to reducing the incidence of delirium and other neurocognitive disorders, with a positive impact on autonomy and quality of life(19).

From a functional point of view, multimodal analgesia facilitates the recovery of mobility and daily activity by allowing better pain control during movement and rehabilitation. This aspect is particularly relevant in contexts of intense or prolonged pain, where fear of movement and immobility can perpetuate pain and promote disability.

By improving exercise tolerance and the patient's active participation in their recovery, multimodality contributes to restoring functionality more efficiently(8) .

Another aspect of growing interest is the role of multimodal analgesia in preventing pain from becoming chronic. Early modulation of central sensitization and reduced exposure to opioids could influence the transition from acute to chronic pain, an outcome with profound clinical, social, and economic implications. Although evidence in this area is still limited and heterogeneous, pathophysiological fundamentals support the potential benefit of well-designed multimodal strategies.

Finally, multimodal analgesia has implications for the healthcare system. By reducing complications, promoting functional recovery, and improving the patient experience, this strategy is associated with lower resource utilization, shorter hospital stays, and fewer readmissions, contributing to more efficient and patient-centered care.

Overall, multimodal analgesia should be understood as an intervention with a

cross-cutting clinical impact, whose value is expressed not only in pain reduction but also in improved safety, functionality, and overall health outcomes. This broad view is essential for its proper implementation and evaluation in contemporary clinical practice(6).

Therapeutic targets and mechanisms of action in multimodal analgesia

Multimodal analgesia is based on a mechanistic principle: pain does not depend on a single pathway, but rather on a network of processes (peripheral transduction, spinal transmission, descending modulation, cortical perception, and affective-cognitive components)(11) .

Therefore, combining interventions with complementary targets allows for: (i) better analgesia with lower doses of each component, (ii) reduction of adverse effects by avoiding the escalation of a single drug (especially opioids), and (iii) attenuation of peripheral and central sensitization, factors involved in refractory and chronic pain(3) .

➢ Opioid system: μ, κ, and δ receptors (central analgesia, but with physiological cost)

Opioids act primarily on receptors coupled to Gi/Go proteins:

μ receptor (MOR): main mediator of supraspinal and spinal analgesia. Its activation inhibits adenylate cyclase, reduces presynaptic Ca^{2+} influx, and increases postsynaptic K^{+} efflux, decreasing the release of excitatory neurotransmitters (e.g., substance P, glutamate). It is the receptor most closely linked to respiratory depression, sedation, constipation/ileus, pruritus, and potential for dependence.

Kappa receptor (KOR): contributes to analgesia (more spinal), but may be associated with dysphoria , and psychomimetic effects.

δ receptor (DOR): involved in analgesic and affective modulation; its direct clinical relevance is less in routine practice.

Strategic limitation: although effective in reducing nociceptive transmission, opioids do not sufficiently block peripheral inflammation or central plasticity induced by sustained stimuli. In addition, with repeated use, acute tolerance and opioid-induced hyperalgesia may occur, phenomena that justify the "opioid-sparing" logic of multimodality. This reasoning is consistent with the motivation for multimodal studies and protocols that seek to reduce rescue requirements and opioid burden(17) .

➢ Prostaglandin–COX pathway and peripheral transduction: NSAIDs/COX-2 and paracetamol

Tissue injury and inflammation increase prostaglandins, which reduce the nociceptive threshold (peripheral sensitization). At this level:

NSAIDs (COX-1/COX-2) and selective COX-2 inhibitors: decrease prostaglandin synthesis; they particularly impact the inflammatory component, somatic pain, and dynamic pain.

Risks: bleeding (more COX-1), renal/hemodynamic injury in vulnerable patients, gastrointestinal risk (more COX-1). COX-2 reduces some GI/platelet effects, but cardiovascular caution is required depending on the patient's profile.

Pathophysiological target	*Receptor/pathway involved*	*Therapeutic strategies*	*Main mechanism*	*Expected clinical impact*
Central nociceptive transmission	μ, κ, δ receptors (opioids)	Opioids	Inhibition of excitatory neurotransmitters	Effective analgesia, but with risk of adverse effects
Peripheral sensitization	COX-1 / COX-2	NSAIDs, COX-2 inhibitors	Decrease in prostaglandins	Reduction of inflammatory and dynamic pain
Central modulation of basal pain	Non-COX central pathways	Paracetamol	Central pain modulation	Enhancement of multimodal approaches
Central synaptic plasticity	NMDA receptor	Ketamine, magnesium	Inhibition of central sensitization	↓ hyperalgesia and tolerance
Nerve conduction	Sodium channels (Na^+)	Local anesthesia, IV lidocaine	Nerve conduction block	↓ nociceptive afferents
Downward modulation	α2-adrenergic receptors	Clonidine, dexmedetomidine	Sympathetic inhibition	Analgesia and anxiolysis
Affective-cognitive component	Cortical and limbic pathways	Non-pharmacological therapies	Modulation of perception	Functional improvement and patient experience

Table 1. Pathophysiological targets of pain and multimodal analgesia strategies

Clinical domain	*Observed impact*	*Clinical relevance*
Opioid consumption	Significant reduction	↓ adverse events
Respiratory function	Preservation of effective ventilation	↓ complications
Neurocognitive function	Less delirium and sedation	↑ Patient safety
Mobility and rehabilitation	Early mobilization	↓ disability
Prevention of chronicity	Attenuation of central sensitization	↓ persistent pain
Use of resources	↓ hospital stays and readmissions	↑ healthcare efficiency
Patient experience	Overall improvement	Patient-centered care

Table 2. Clinical impact of multimodal analgesia beyond pain control

Paracetamol: acts predominantly at the central level (mechanisms not fully unified: modulation of serotonergic pathways, endogenous cannabinoids, and/or central COX). In multimodality, it functions as a "basal analgesic" that enhances other classes with a favorable safety profile at therapeutic doses(19) .

Multimodal rationale: by decreasing peripheral sensitization, afferent input to the spinal cord is reduced, which mitigates central amplification and reduces the need for opioids.

➢ Sodium channels and conduction block: local anesthesia and systemic lidocaine

Local anesthetics block voltage-gated sodium channels (Nav), interrupting nerve conduction. In multimodal anesthesia, this is exploited in two ways:

Regional/locoregional techniques: these reduce the primary afferent signal with high efficacy, allowing robust analgesia with minimal systemic opioid load.

Intravenous (IV) lidocaine: in addition to its action on Nav, it is attributed with antihyperalgesic and anti-inflammatory properties (y modulation of neuronal activation and, in some models, reduction of inflammatory mediators).

However, the evidence is not universally positive: a randomized clinical trial in adolescents undergoing major orthopedic surgery, with a prolonged IV lidocaine regimen added to a standardized multimodal regimen, did not reduce morphine consumption at 48 h and reported events consistent with mild symptoms of local anesthetic systemic toxicity (LAST), underscoring that the incremental benefit may be modest when multimodality is already effective and that safety must be monitored with appropriate protocols and monitoring(18) .

➢ NMDA receptor and central plasticity: ketamine and magnesium

Central sensitization (wind-up and synaptic potentiation) is linked to the N-methyl-D-aspartate (NMDA) receptor. Two classic adjuvants are relevant here:

Ketamine (subanesthetic doses): NMDA antagonism that reduces opioid-induced hyperalgesia and tolerance; useful in severe, refractory pain or pain with prior opioid tolerance.

Magnesium: acts as a physiological blocker of the voltage-dependent NMDA channel; its analgesic effect is usually more moderate, but it can help reduce central excitability.

NMDA-targeted logic is central to multimodality: it not only "removes pain," but also reduces the amplification of the nociceptive system. In practice, comparative studies have explored ketamine, lidocaine, and magnesium as non-opioid components within multimodal regimens, observing variability in pain and rescues, which supports the principle of selection by phenotype rather than indiscriminate application(10) .

➢ Calcium channels (α2δ subunit) and neurotransmission: gabapentinoids (selective benefit, real risk)

Gabapentinoids bind to the α2δ subunit of presynaptic Ca^{2+} channels, reducing the release of excitatory neurotransmitters. Their rationale is stronger in neuropathic

components and in the prevention of hyperalgesia; however, in real clinical settings, they are associated with sedation, dizziness, and cognitive impairment, especially in older people, those with respiratory comorbidity, or those on polypharmacy. Therefore, in a high-impact article, it is appropriate to present them as: adjuvants with restricted indications, not as a routine component(12) .

➢ Downward modulation, sympathetic tone, and analgesia with cooperation: α2-adrenergic agonists

α2 agonists (e.g., clonidine, dexmedetomidine) reduce norepinephrine release (locus coeruleus) and decrease sympathetic activity, facilitating analgesia and anxiolysis. Their value in multimodal therapy lies in:

- Decreased opioid requirements.
- Potentiation of descending inhibitory mechanisms.
- A more cooperative sedation profile in some contexts.

Risk: bradycardia and hypotension, so their usefulness depends on the clinical context and monitoring.

➢ Additional receptors and pathways: serotonin/noradrenaline, GABA, and anti-inflammation

In multimodal therapy, other targets may play a complementary role:

Serotonergic/noradrenergic modulation (e.g., some antidepressants in chronic neuropathic pain).

GABA (clinical use should be cautious due to sedation/respiratory depression when combined with opioids).

Corticosteroids: reduce inflammation and may improve related outcomes (e.g., nausea, hyperalgesia), but require risk-benefit assessment (glycemia, infection, etc.).

➢ Non-pharmacological and alternative therapies: targets on the pain experience

Contemporary multimodal approaches incorporate interventions that act on the affective-cognitive and behavioral components of pain:

- Patient education and expectations (reduces catastrophizing, improves adherence).
- Physical therapy/rehabilitation, progressive mobilization, breathing techniques.
- Brief psychological interventions (e.g., cognitive-behavioral strategies).
- Neuromodulation

These strategies do not replace pharmacological treatment when pain is moderate- r severe, but they improve functionality, self-efficacy, and quality of life, which are precisely the outcomes beyond pain(4) .

Practical integration: from evidence to clinical decision-making

The effective application of multimodal analgesia in clinical practice requires moving beyond the adoption of standardized regimens and advancing toward decision-making based on a comprehensive assessment of the patient. Given that pain is a dynamic and multifactorial phenomenon, the selection of analgesic interventions must

respond to the individual characteristics of the patient, the type and intensity of pain, as well as the therapeutic objectives defined in each clinical context(15) .

A fundamental principle of the practical integration of multimodal analgesia is the prioritization of strategies with high clinical benefit and an adequate safety profile. Non-opioid analgesics constitute, in most cases, the basis of treatment, to which other modalities are added in a stepwise manner according to the clinical response. This approach allows for the optimization of baseline analgesia and limits exposure to opioids, reserving them for situations of refractory or high-intensity pain.

The selection of adjuvant drugs should be done rationally, considering both their mechanisms of action and potential risks. Available evidence suggests that not all patients benefit equally from the same multimodal components, reinforcing the need for a personalized strategy. In this regard, continuous assessment of analgesic response and adverse effects is essential for timely treatment adjustment(2) .

Another key aspect is the integration of multimodal analgesia into a comprehensive patient-centered care plan. Pain management should be coordinated with other therapeutic interventions, such as rehabilitation, nutritional support, and prevention of complications, in order to promote functional recovery and quality of life. This integrated approach helps to avoid fragmentation of care and improve the efficiency of healthcare(16) .

Monitoring the impact of multimodal analgesia should go beyond pain intensity and include functional and safety indicators. Mobility, cognitive status, respiratory function, and treatment tolerance provide relevant information for assessing the actual effectiveness of the analgesic strategy and guiding therapeutic adjustments(14)40 adult patients were randomised (1:1, stratified by type of surgery .

In summary, multimodal analgesia should be understood as a dynamic and adaptive process, guided by scientific evidence and clinical judgment. Its effective integration into clinical decision-making allows for the optimization of pain management, improved functional outcomes, and the reinforcement of safer, patient-centered care.(11) .

Limitations of evidence and knowledge gaps

Despite the growing adoption of multimodal analgesia in various clinical settings, the available evidence has limitations that hinder uniform implementation and accurate assessment of its impact. One of the main weaknesses lies in the methodological heterogeneity of the studies, which include diverse populations, variable therapeutic regimens, differences in dose and duration of interventions, and non-standardized clinical outcomes(15) .

Most studies continue to use pain intensity measured by subjective scales as the primary outcome, which limits understanding of the actual effect of multimodal analgesia on functional, safety, and quality of life aspects. The lack of patient-centered outcomes, such as functional capacity, cognitive status, or overall treatment experience, reduces the clinical relevance of many reported results(16) .

Another important limitation is the inconsistency of findings related to certain components of multimodal analgesia. Some adjuvant drugs have shown clear benefits in certain scenarios, while in other contexts the results have been neutral or even unfavorable. These discrepancies reflect, in part, the absence of adequate patient stratification and rational selection of interventions based on pathophysiological mechanisms and risk profiles(17) .

There is also a shortage of studies evaluating the medium- and long-term effects of multimodal analgesia, particularly in relation to the prevention of chronic pain and the impact on functionality and quality of life. Most research focuses on short-term outcomes, which limits the ability to draw solid conclusions about sustained benefits(18) .

Finally, the implementation of multimodal analgesia in clinical practice is conditioned by organizational, educational, and resource availability factors, aspects that are rarely considered in clinical studies. These gaps between evidence and actual practice underscore the need for more pragmatic research, oriented toward diverse clinical contexts and focused on outcomes relevant to patients and health systems(19).

Taken together, these limitations highlight the need for critical interpretation of the available evidence and reinforce the importance of continuing to develop research that will optimize and personalize multimodal analgesia strategies in different clinical settings.

Conclusions

Multimodal analgesia is a modern and pathophysiologically coherent approach to pain management, as it simultaneously intervenes on multiple peripheral and central nociceptive mechanisms. This model overcomes the limitations of monomodal treatment, particularly the exclusive use of opioids, by allowing effective analgesia with a lower pharmacological burden and a better safety profile.

The available evidence indicates that multimodality not only reduces pain intensity but also impacts relevant clinical outcomes, such as reducing opioid-related adverse effects, preserving respiratory and neurocognitive function, and improving patient functionality and recovery. These benefits reinforce the need to evaluate analgesic success using broader, patient-centered indicators.

However, multimodal analgesia should not be applied indiscriminately. Its effectiveness depends on a rational selection of interventions, tailored to the clinical context and the individual patient profile. Inappropriate or excessive combination of components may limit the expected benefits and increase risks.

In conclusion, multimodal analgesia should be understood as a personalized therapeutic strategy, aimed not only at pain control, but also at the comprehensive improvement of the patient's safety, and functionality. Its implementation based on mechanisms and clinical evidence is an essential pillar of contemporary pain management beyond its intensity.

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