Healthcare and Rehabilitation 2 (2026) 100098

Contents lists available at ScienceDirect

Healthcare and Rehabilitation

journal homepage: www.keaipublishing.com/en/journals/hcr/

Central sensitization and opioid-sparing multimodal analgesia: An editorial perspective on restructuring perioperative pain management

ARTICLE INFO

Keywords:
Multimodal analgesia
Opioid-sparing anesthesia
Perioperative pain management
Enhanced recovery after surgery
Postoperative pain
Central sensitization

1. The imperative for structural change in perioperative care

Opioid-dominant regimens have long served as the default approach to perioperative pain control. Yet, reliance on opioids as the primary analgesic carries well-documented costs, including dose-dependent sedation and respiratory depression, nausea, and delayed return of bowel function. For opioid-naïve patients, persistent opioid use after surgery is an additional risk.[1] These risks have motivated a shift toward multimodal analgesia, defined here as the coordinated use of two or more analgesic classes or techniques, each acting through a distinct mechanism, so that adequate analgesia is achieved while reducing reliance on any single agent, particularly opioids. Perioperative pain guidelines have increasingly endorsed this approach to reduce reliance on opioid-dominant regimens and limit opioid-related adverse effects.[2,3]

Multimodal analgesia has its own implementation challenges. Opioid minimization alone does not guarantee high-quality analgesia. Inadequate postoperative pain control (oligoanalgesia) may occur when opioid-sparing initiatives are not accompanied by effective multimodal regimens and clearly defined rescue strategies. Inadequately treated acute postoperative pain affects more than patient comfort. Oligoanalgesia can trigger intense autonomic stress responses that induce systemic inflammation, hinder patient mobilization, and delay rehabilitation. Critically, unrelieved acute nociceptive input can further trigger central sensitization, an activity-dependent amplification of spinal pain processing (see Section 3), which links poorly controlled acute pain to persistent postsurgical pain that opioid-sparing strategies ultimately intend to prevent.[4,5]

Existing multimodal analgesia and enhanced recovery after surgery (ERAS) recommendations have already established which combination of non-opioid agents and techniques to use.[2,3,6,7] This review aims to organize the available choices around the key mechanistic principle of minimizing the nociceptive drive to central sensitization at each phase of care, and translate that principle into a phase-specific, procedure-aware decision framework rather than a fixed drug list.

Clinicians cannot simply revert to traditional opioid-dominant regimens to solve this problem. Resolving oligoanalgesia requires integrating opioids, when needed, within a patient-specific multimodal analgesic plan that minimizes unnecessary exposure while maintaining adequate analgesia during hospitalization and after discharge.[8] The solution therefore lies not in eliminating opioids entirely but in establishing well-coordinated, mechanism-aware pain management across the preoperative, intraoperative, and postoperative phases to address the patient-centered mobilization and functional recovery goals that define successful rehabilitation.

2. Implementation of the multimodal approach

Translating the mechanistic principle above into practice requires a framework organized by surgical phases, because the dominant nociceptive mechanism and therefore the most effective intervention differ before, during, and after surgery.

To address the fragmented perioperative pain management that is currently common, hospitals need to move away from rigid and generic use of specific analgesics toward a flexible, phase-specific, individualized pathway.[6] A framework integrating non-opioid analgesics, regional or local anesthetic techniques, and appropriately titrated opioids across the perioperative period, targeting nociceptive signaling through multiple complementary mechanisms rather than a single pharmacologic pathway may offer the desired solution (Fig. 1). This phase-specific approach is conceptually aligned with ERAS pathways,

Peer review under responsibility of Shandong University

https://doi.org/10.1016/j.hcr.2026.100098
Received 30 July 2026; Received in revised form 10 September 2026; Accepted 11 September 2026

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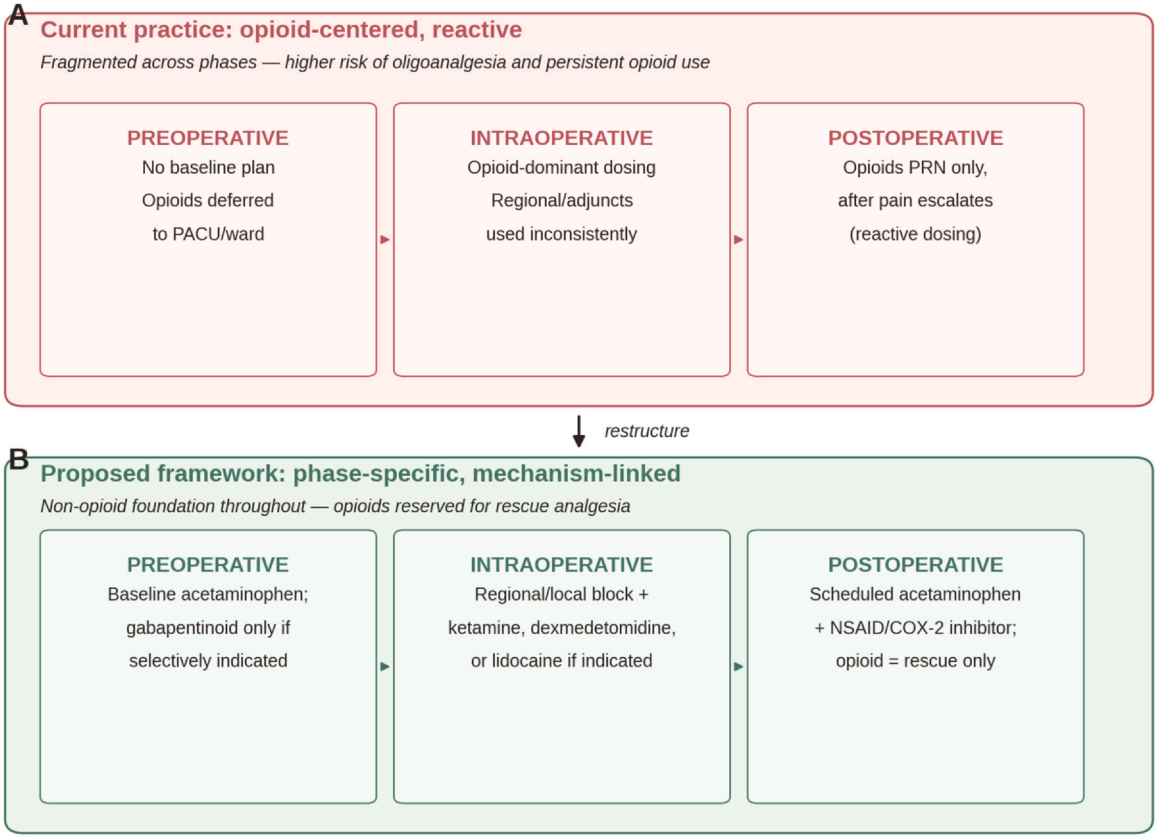


Fig. 1. Restructuring perioperative analgesia from a fragmented, opioid-centered default (panel A) to a structured, phase-specific multimodal framework (panel B). Specific agents and their role at each phase are shown directly in the figure. Opioids are reserved for rescue analgesia in the proposed framework rather than acting as the default postoperative agent. Abbreviations: PACU, postanaesthesia care unit;PRN, pro re nata; NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase.

which similarly position multimodal, opioid-sparing analgesia as a prerequisite for early mobilization and shortened hospital stay.[3,6]

Different procedures injure different tissues and generate different nociceptive input. Thus, the same three-phase structure yields different priorities depending on the operation. For major abdominal surgery, visceral and somatic incisional pain, combined with the risk of ileus, favor epidural or truncal regional techniques (e.g., transversus abdominis plane or erector spinae plane blocks) as the intraoperative priority, with scheduled non-opioid dosing and early return-of-bowel-function monitoring postoperatively. Moreover, systemic nonsteroidal anti-inflammatory drugs (NSAIDs) are used cautiously given anastomotic-healing and renal considerations.[7] For major joint replacement (e.g., total hip or knee arthroplasty), peripheral nerve or periarticular local infiltration blocks are the intraoperative priority, and postoperative emphasis shifts toward scheduled non-opioid dosing paired with same-day physical therapy, since early ambulation is both the therapeutic goal and, if delayed by unrelieved pain, a marker of inadequate analgesia.[7] A single generic multimodal protocol applied uniformly to both procedures would misallocate resources in either case.

Patient-specific factors modify these priorities as much as the procedure does. Frail older adults are a particularly important vulnerable group. Perioperative gabapentinoid use in the older population has been associated with an increased risk of delirium, new antipsychotic use, and pneumonia in a large cohort study.[9] Similarly, subanesthetic ketamine, while mechanistically attractive (Section 3), should be used cautiously in patients at elevated risk of postoperative delirium pending more definitive evidence in this subgroup.[10] In frail older patients, the non-opioid foundation typically relies more heavily on scheduled acetaminophen and regional or local techniques, with gabapentinoids and ketamine reserved for cases in which the anticipated analgesic benefit clearly outweighs these risks rather than used routinely as in younger, non-frail patients.

This process begins in the preoperative phase, where the goal is to establish an analgesic and physiologic baseline before the operation (Table 1). Preoperative acetaminophen may form part of this baseline regimen. Gabapentinoids should be considered selectively rather than routinely, particularly given the risk of excessive sedation, respiratory depression, delirium, or impaired clearance in vulnerable patients, most notably frail older adults.[9] Clinical benefit from preoperative pharmacologic adjuncts varies across agents and procedures. Although some interventions may modestly reduce early postoperative pain or opioid consumption, the magnitude of benefit should be weighed against the risk of adverse effects on a case-by-case basis.[11]

During surgery, the analgesic plan should be adapted to the procedure performed, the feasibility of regional anesthesia, and the patient's comorbidities and prior analgesic exposure (Table 1). Even under general anesthesia, surgical incision and tissue injury generate ongoing nociceptive input that can contribute to central sensitization, postoperative pain, and neuroendocrine stress responses. Rather than relying predominantly on escalating opioid doses, clinicians may combine regional or local anesthetic techniques with selected systemic adjuncts, such as ketamine, dexmedetomidine, or intravenous lidocaine, when the anticipated benefits outweigh patient-specific risks. Subanesthetic ketamine, which acts through N-methyl-D-aspartate (NMDA) receptor antagonism, may reduce central sensitization and postoperative opioid requirements in general surgical populations.[12] A 2024 meta-analysis found that perioperative ketamine may reduce the incidence of chronic postsurgical neuropathic pain at 3 months, but the same study concluded that chronic postsurgical pain reduction at 6 months was not

Table 1
Agent selection criteria across the perioperative pathway.

Phase	Agent/technique	Typical indication/selection criteria	Key caution
Preoperative	Acetaminophen	Baseline for most patients without contraindication	Reduce dose in hepatic impairment
Preoperative	Gabapentinoid (selective)	Consider for high pain-catastrophizing or neuropathic-pain-prone procedures	Avoid/reduce in frail, older, renal-impaired, or high sedation-risk patients
Intraoperative	Regional or local anesthetic technique	Procedure allows access; no contraindication (infection, coagulopathy, refusal)	Block failure; local anesthetic systemic toxicity with high volume
Intraoperative	Subanesthetic ketamine	Anticipated high nociceptive burden, opioid tolerance, or chronic pain	Caution with delirium risk, psychiatric history, uncontrolled hypertension
Intraoperative	Dexmedetomidine	Sedation-analgesia adjunct with opioid-sparing goal	Bradycardia, hypotension
Intraoperative	Intravenous lidocaine	Abdominal surgery; ileus-prevention goal	Avoid in hepatic impairment, arrhythmia, local anesthetic allergy
Postoperative	Scheduled acetaminophen + NSAID/COX-2 inhibitor	Default non-opioid foundation unless contraindicated	GI, renal, cardiovascular, and anastomotic-healing caution
Postoperative	Opioid (rescue)	Breakthrough pain despite non-opioid foundation	Titrate to lowest effective dose; monitor sedation and respiration

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase; GI, Gastrointestinal.

significant, and that the evidence was of low certainty.[10] Ketamine's mechanistic rationale for limiting central sensitization is better established than its proven clinical effect on longer-term pain outcomes, and it may warrant particular consideration in patients with opioid tolerance or acute high-intensity pain rather than as a routine addition for all patients.[10,12] Alpha-2 adrenergic agonists such as dexmedetomidine may reduce perioperative opioid requirements and provide sedative-analgesic effects in selected settings, but their use should be balanced against the risk of bradycardia and hypotension.[13] Intravenous lidocaine may improve postoperative pain and selected recovery outcomes in some surgical populations, with the most consistent evidence in abdominal procedures.[14]

Once surgery is complete, the strategy enters its final stage in the postoperative phase (Table 1). Rather than waiting for pain to escalate postoperatively before prescribing opioids, a scheduled, fixed-interval baseline of non-opioid medications during recovery should be initiated immediately. Scheduled acetaminophen combined with an NSAID or cyclooxygenase-2 (COX-2)-selective inhibitor is an effective non-opioid foundation when not otherwise contraindicated. The combination of acetaminophen and NSAID acts through complementary central and peripheral analgesic mechanisms.[15] With this multimodal foundation in place, opioid exposure can often be reduced. However, appropriately titrated opioids should remain available as rescue analgesia if and when pain is inadequately controlled or functional recovery is limited by unrelieved pain. Ensuring that patients can participate in early physical therapy and ambulation is itself a meaningful outcome measure of adequate postoperative analgesia, and not merely a downstream benefit. As such, functional recovery tracked using validated instruments such as the 15-item Quality of Recovery score (QoR-15) alongside simple mobility milestones (e.g., time to first ambulation), is highly recommended.[16,17]

3. Neurobiological rationale for multimodal, opioid-sparing analgesia

Understanding why phase-specific, mechanism-matched analgesia outperforms a generic drug list requires understanding the neurobiological process such planning is designed to prevent: central sensitization, introduced briefly above and detailed mechanistically here (Fig. 2).

Surgical incision and tissue injury activate peripheral nociceptors, generating afferent signals that ascend through the dorsal horn of the spinal cord to the thalamus and cortex. When this nociceptive barrage is inadequately controlled, repetitive afferent input can drive activity-dependent synaptic changes in the dorsal horn neurons in a process referred to as central sensitization, which is mediated in part by NMDA receptor–dependent potentiation.[4] Central sensitization amplifies pain perception beyond the degree of tissue injury and represents a key mechanistic link between poorly controlled acute pain and the development of persistent postsurgical pain.[5]

At the molecular level, sustained glutamate release from primary afferent terminals removes the magnesium block from postsynaptic NMDA receptors, permitting calcium influx that triggers second-messenger cascades and increases the trafficking and phosphorylation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, thereby amplifying the postsynaptic response to subsequent afferent input. This process is distinct from and considerably longer lasting than ordinary synaptic transmission. In parallel, voltage-gated sodium channels on injured peripheral nociceptors become more excitable, lowering the threshold for ectopic firing, while local prostaglandin synthesis via cyclooxygenase-1 and cyclooxygenase-2 sensitizes peripheral nociceptor terminals to mechanical and thermal stimuli. Each analgesic class discussed can be mapped to one of these molecular targets (Fig. 2): intravenous lidocaine and regional anesthetic techniques act on peripheral sodium channels; subanesthetic ketamine acts postsynaptically at the NMDA receptor; NSAIDs, COX-2 inhibitors, and acetaminophen act on the prostaglandin pathway both peripherally and centrally; and dexmedetomidine acts on descending noradrenergic pathways originating in the locus coeruleus that normally inhibit dorsal horn transmission. In parallel, unrelieved surgical pain activates the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, producing the autonomic and neuroendocrine stress responses discussed above; these responses increase catecholamine and cortisol release and promote a catabolic state that can impair wound healing and immune function.[18]

These mechanisms directly inform the pharmacologic choices. Subanesthetic ketamine directly targets the synaptic mechanism of central sensitization by inhibiting the NMDA receptors. As noted above, this mechanistic rationale is more firmly established than its effect on established chronic-pain endpoints.[10,12] Dexmedetomidine, an alpha-2 adrenergic agonist, acts at the locus coeruleus and descending noradrenergic pathways that modulate dorsal horn nociceptive transmission, producing sedation and analgesia through a mechanism distinct from opioid receptor activation.[13] Notably, opioids themselves can paradoxically increase pain sensitivity through NMDA receptor–mediated mechanisms (opioid-induced hyperalgesia), providing additional mechanistic rationale for opioid-sparing strategies beyond simply avoiding the side effects.[19]

4. Overcoming barriers to implementation

A well-specified, mechanism-linked framework can fail if it is not reliably delivered. Therefore, organizational barriers are considered

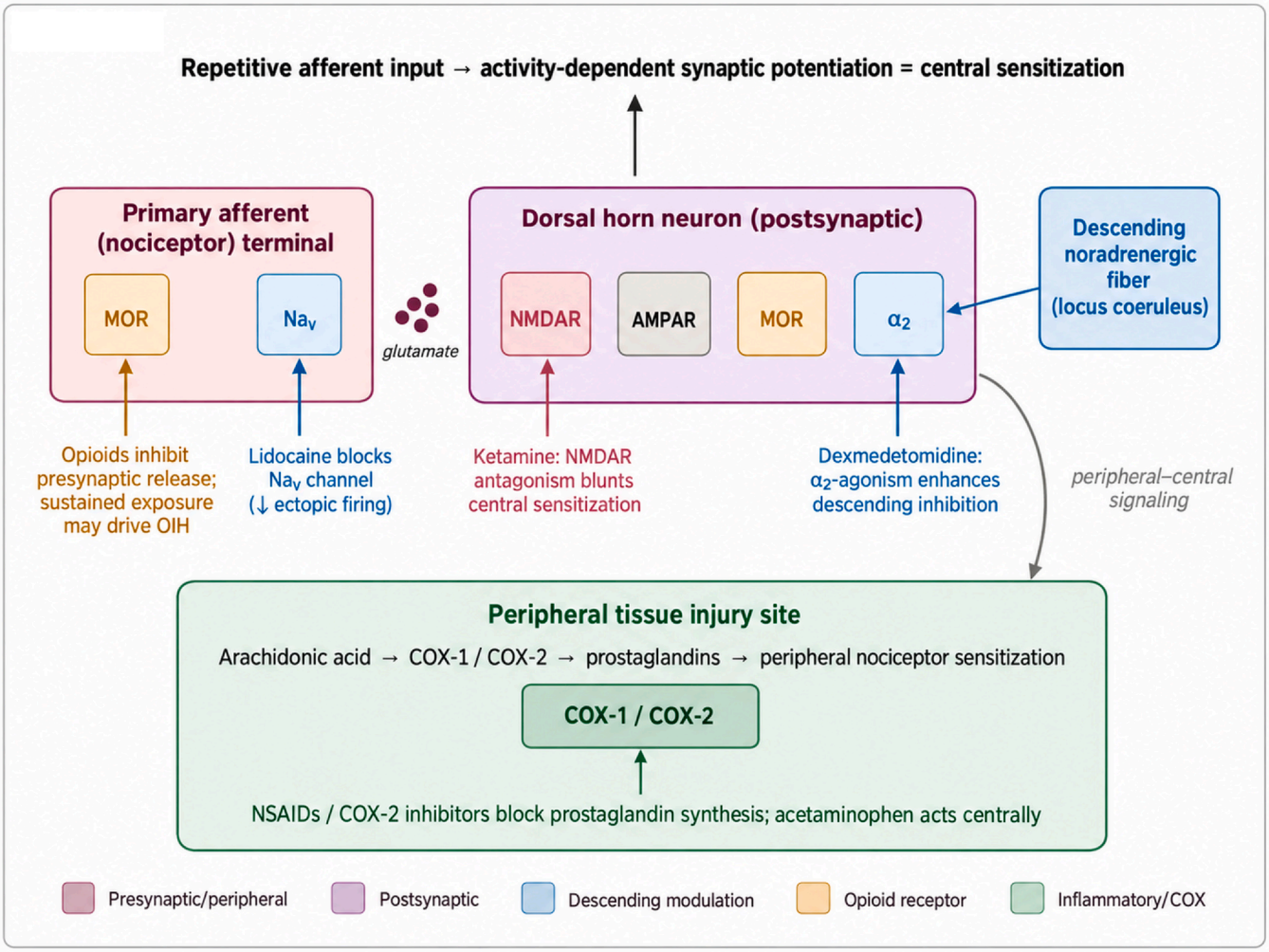


Fig. 2. Molecular targets of multimodal analgesic agents at the primary afferent synapse, the dorsal horn postsynaptic neuron, descending modulatory pathways, and the peripheral inflammatory (cyclooxygenase) pathway. Each analgesic class discussed in this editorial perspective maps to a distinct site in this schematic, illustrating the mechanistic complementarity of a multimodal regimen. Abbreviations: MOR, mu-opioid receptor; Na_V, voltage-gated sodium channel; NMDAR, N-methyl-D-aspartate receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; α2, alpha-2 adrenergic receptor; COX, cyclooxygenase; OIH, opioid-induced hyperalgesia.

alongside pharmacological rationales. The central challenge facing modern perioperative medicine lies not in discovering new non-opioid compounds, but in building systems that reliably translate individualized analgesic plans into coordinated care across different settings and clinical teams. Concrete, actionable steps are needed to narrow this gap. For example, embedding phase-specific order sets directly into electronic medical record software so that scheduled non-opioid dosing is the default rather than an opt-in order; establishing explicit triggers for Acute Pain Service consultation (e.g., opioid tolerance, anticipated high-intensity pain procedures, or frailty) rather than leaving referral to individual clinician's discretion; using structured handoff checklists that carry the analgesic plan and its rationale across shift changes and between anesthesia, surgery, and nursing teams; granting nursing staff standing protocol authority to initiate scheduled non-opioid dosing without a new physician order; and tracking unit-level dashboards of pain scores, opioid consumption, and time-to-first-ambulation to make performance visible and actionable rather than anecdotal.

Perioperative analgesic pathways should be standardized where evidence supports routine care, while retaining sufficient flexibility to accommodate patient-specific and procedure-specific needs. For example, different approaches are needed for abdominal versus joint-replacement surgery and for frail older adults. As clinical guidelines continue to evolve, there is a pressing need to move away from generic, one-size-fits-all multimodal protocols and toward pain management plans that vary according to surgical and patient-specific factors.[7,20] Given that different surgical procedures injure distinct tissues and engage different neural pathways, analgesic plans should be procedure-specific rather than drug-centered. A phase-specific anesthesia process tailored to the procedure performed may help hospitals minimize oligoanalgesia, avoidable opioid exposure, and opioid-related adverse events, thereby supporting the reliable pain control needed for optimal recovery and rehabilitation.

5. Future directions and research gaps

The current framework also identifies where evidence is still needed. Three gaps are particularly consequential. First, studies that directly compare a phase-specific, mechanism-linked pathway against standard opioid-dominant care using patient-centered functional outcomes, such as QoR-15 scores or time to independent mobilization rather than opioid consumption or pain scores alone, are scarce.[16,17] Prospective trials designed around these endpoints, rather than extracted post hoc from opioid-focused studies, are needed. Second, evidence for the vulnerable subgroups most likely to benefit from individualized planning, including frail older adults, patients with opioid

tolerance or chronic pain, and patients with high psychological pain catastrophizing, remains disproportionately drawn from general surgical cohorts rather than from these subgroups specifically.[9,10,12] This limits the reliability and validity of subgroup-specific recommendations. Third, emerging approaches in perioperative precision medicine, including machine learning-based quantitative pain assessment, may eventually allow the proposed phase-specific framework to be individualized further in real time, but this potential remains to be tested prospectively against standard multimodal care.[21] Addressing these gaps will determine whether mechanism-linked, phase-specific analgesia becomes standard practice or remains a conceptually appealing but empirically under-tested framework.

6. Conclusions

The practical implication of the mechanistic and organizational arguments above is straightforward to state, but not always easy to implement. Effective perioperative pain management framed as a binary choice between opioids and non-opioids is not ideal. A coordinated, patient-specific, and procedure-specific multimodal strategy that establishes a safe non-opioid foundation, incorporates regional and local analgesic techniques when appropriate, and preserves timely opioid rescue for clinically significant pain offers a superior alternative. The success of such pathways should ultimately be judged by analgesic efficacy, safety, and functional recovery and not by opioid reduction as an end in itself. Outcome measures should consider how reliably the pain management plan allows patients to sit up, walk, and resume the activities of daily living after surgery.

In practice, this means tracking validated, patient-centered instruments, such as the QoR-15 and simple mobility milestones (e.g., time to first ambulation, timed walking distance) alongside pain scores and opioid consumption. Defining success by what patients can do, and not by how they rate their pain, is critical.[16,17]

CRediT authorship contribution statement

Ziqian Xu: Conceptualization, Investigation, Writing – original draft, Visualization. **Jerry Gao:** Investigation, Writing – review & editing. **Yuewen He:** Investigation, Writing – original draft, Writing – review & editing. **Jingping Wang:** Conceptualization, Supervision, Project administration, Writing – review & editing. All authors have read and approved the final version of this manuscript.

Ethics approval

Not applicable. This editorial perspective does not report new studies involving human participants or animals.

Funding

None.

Data availability

Not applicable. No new data were generated or analyzed in connection with this editorial perspective.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Claude (Anthropic) to assist with language editing, figure drafting. The authors critically reviewed, verified, and revised all AI-assisted content and take full responsibility for the accuracy, integrity, and originality of the published article.

Acknowledgments

None.

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