Am J Transl Res 2026;18(7):5854-5873
www.ajtr.org /ISSN:1943-8141/AJTR0172547

Review Article

Optimization of multimodal analgesic drug combinations under the concept of precision anesthesia

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Received March 10, 2026; Accepted May 15, 2026; Epub July 15, 2026; Published July 30, 2026

Abstract: Accumulating clinical and experimental evidence has highlighted multimodal analgesia as a pivotal strategy for improving perioperative outcomes, particularly within the emerging framework of precision anesthesia. In this paradigm, inadequately controlled postoperative pain and opioid-centric regimens are recognized not only as drivers of acute morbidity, but also as key contributors to persistent postsurgical pain, chronic opioid use, and impaired functional recovery. Multimodal analgesic combinations, integrating opioids with nonsteroidal anti-inflammatory drugs, acetaminophen, gabapentinoids, NMDA receptor antagonists, α_2-agonists, and systemic or regional local anesthetics, target distinct levels of the nociceptive pathway to achieve synergistic analgesia while limiting dose-dependent toxicity. However, the design of such regimens is profoundly influenced by patient-specific biology, psychological and contextual factors, procedure-related nociceptive patterns, temporal dynamics across the perioperative course, and institutional constraints. This review summarizes the pharmacological basis and synergistic mechanisms underlying multimodal analgesia, delineates key variables that shape the optimization of drug combinations, and traces the evolution from empiric, protocol-driven practice to model-informed and data-driven design. We further discuss current challenges - including heterogeneity, biomarker gaps, and implementation barriers - and outline future directions toward learning health system-based, decision-support-enabled strategies that can deliver individualized, context-aware multimodal analgesic regimens under the concept of precision anesthesia.

Keywords: Precision anesthesia, multimodal analgesia, drug combination optimization, perioperative pain management, individualized analgesia

Introduction

Perioperative analgesia optimization has become the centerpiece of modern anesthetic practice as the realization has developed that untreated or inadequately treated acute pain comes with both short- and long-term consequences with far-reaching implications. More than just high levels of sympathetic response, cardiopulmonary events, and slow postoperative recovery, severe postoperative pain is a definite contributor to the onset of persistent postsurgical pain, as well as chronic opioid use [1, 2]. Simultaneously, the opioid crisis in the world and the evident dose-dependent burden of adverse events associated with opioid use, such as respiratory depression, postoperative nausea and vomiting, ileus, and cognitive dysfunction [3-9], has questioned the traditional use of high-dose systemic opioids. These clinical realities make perioperative analgesia not only a question of pain relief, but also a question of safety, recovery quality, and long-term outcome. For this reason, the discussion of multimodal analgesia should be situated within the broader framework of precision anesthesia rather than being presented mainly as a pharmacologic strategy.

It is the combination of these convergent pressures, which have prompted the shift to precision anesthesia, an approach trying to customize anesthetic and analgesic approaches to the biology, procedure, and risk profile of individual patients by the incorporation of multimodal monitoring, quantitative phenotyping and information-driven decision making. This paradigm regards analgesia no longer as a solid intervention but as a dynamic and potentially personalized combination therapy, which is

https://doi.org/10.62347/NEVB6981

necessary to be rationally built and constantly optimized. Within this broader framework, precision analgesia may be understood as the perioperative design of analgesic strategies according to the individual patient's biologic profile, pain phenotype, procedural nociceptive burden, and risk of treatment-related harm, rather than the application of uniform analgesic bundles. In this sense, precision analgesia is not synonymous with simply giving more drugs or using multimodal analgesia routinely; rather, it refers to selecting the right combination, dose, route, and timing for the right patient and procedure. Its core elements include the identification of clinically relevant phenotypes, the incorporation of biomarkers or surrogate indicators of pain susceptibility and drug sensitivity when available, and the use of structured decision models that integrate patient-, procedure-, and system-level information. Thus, precision analgesia represents the individualized operational arm of precision anesthesia in the domain of perioperative pain management. From this perspective, the central issue is not how many agents can be combined, but how analgesic interventions can be matched to measurable patient needs and perioperative goals. Precision anesthesia therefore requires a shift from regimen-centered thinking to decision-centered thinking. The emphasis should be placed on who is likely to benefit, who is likely to be harmed, what outcome is being targeted at each perioperative stage, and how the regimen should be adjusted as physiologic and clinical conditions evolve. This also means that multimodal analgesia should be interpreted as one component of a broader precision pathway, rather than as the sole defining feature of individualized perioperative care.

The practice of multimodal analgesia in which analgesics and methods have synchronized actions through separate and complementary mechanisms is now seen as part of enhanced recovery pathways and is now advocated in an extensive range of surgical specialties [10]. Multimodal regimens can be designed in a prudent manner that is able to stimulate synergistic or at least additive analgesia by targeting various points in the pain signaling and modulation network (peripheral transduction, spinal transmission, supraspinal processing, and descending inhibition) without exposing the body to any particular drug and associated toxicities [11, 12]. Nevertheless, the existing application of multimodal analgesia to clinical practice is still more or less empiric in nature. Combination of opioids, nonsteroidal anti-inflammatory drugs, acetaminophen, gabapentinoids, NMDA receptor antagonists, alpha 2-agonist, local anesthetics, and regional anesthesia methods tend to be put together by broad institutional guidelines or physician bias, with little regard to interindividual differences in pharmacokinetics and pharmacodynamics, genetic factors determining drug responses, comorbidities, and pain patterns during a procedure [13]. Moreover, intricate cooperations and competition between several agents, including synergism, redundancy, antagonism, and cumulative toxicity, are hardly quantified or systematically utilized. Consequently, a large number of so-called multimodal regimens can be either maximally inefficient, or extravagantly complicated or poorly aligned to the objectives of actual precision anesthesia. What is lacking in conventional practice is not the availability of analgesic options, but a structured framework for selecting among them. Under the precision-anesthesia concept, analgesic design should begin with clinical stratification and end with pathway implementation. In other words, the key question is no longer whether multimodal analgesia is theoretically advantageous, but how to transform it into a reproducible and individualized perioperative strategy. This requires explicit links between phenotype assessment, risk prediction, treatment selection, monitoring feedback, and postoperative reassessment.

To move from conventional multimodal analgesia to precision analgesia, individualization must occur at several levels. First, patients need to be stratified according to relevant phenotypes, such as opioid-naive versus opioid-tolerant status, inflammatory versus neuropathic pain predominance, high versus low risk of respiratory depression, and vulnerability to adverse events related to age, frailty, obesity, obstructive sleep apnea, renal dysfunction, or hepatic impairment. Second, perioperative monitoring and data acquisition should extend beyond routine observation to include, where feasible, high-resolution clinical phenotyping, real-time nociception and sedation assessment, opioid exposure patterns, recovery trajectories, and patient-reported outcomes. Third, biomarkers and data-derived predictors - although not yet fully mature for routine use - rep-

resent a critical future component of precision analgesia, because they may enable earlier identification of patients at risk of exaggerated pain responses, central sensitization, opioid toxicity, or persistent postsurgical pain. Fourth, individualized decision-making increasingly depends on model-informed approaches, including risk prediction tools, PK-PD integration, clinical decision support systems, and, in the future, AI-assisted and closed-loop strategies capable of continuously adapting analgesic delivery to changing physiologic and clinical conditions. At the clinical level, these principles should be translated into an operational pathway. A precision-analgesia model should start before anesthesia induction, continue during surgery, and extend into postoperative recovery. Preoperatively, it should include phenotype identification, evaluation of prior opioid exposure, assessment of organ function and respiratory vulnerability, and definition of procedure-specific analgesic goals. Intraoperatively, it should support adjustment of analgesic intensity according to nociceptive burden, physiologic response, and the interaction between anesthetic depth, opioid exposure, and regional techniques. Postoperatively, it should guide reassessment based on pain trajectory, opioid requirement, recovery milestones, adverse effects, and risk of pain persistence. In this way, precision analgesia becomes a longitudinal management strategy rather than a static drug prescription.

Taking optimization of multimodal analgesic drugs regimens as a part of the precision anesthesia concept, protocol-based techniques may no longer be the approach of choice: mechanisms and data need to be followed in their design. It will involve the combination of the understanding of systems pharmacology, quantitative model, and evidence of clinical trials with high-resolution clinical phenotyping, real-time nociception and sedation measurements and the emergence of pain susceptibility biomarkers and drug sensitivity. Instead of investigating the question of whether multimodal analgesia is beneficial (to which the answer is largely to be found), the research area needs to take into consideration the combination, dosage, route, and in which patients and in which surgical conditions provide the optimal balance between analgesia effects, postoperative performance, and safety. Importantly, the implementation of precision analgesia also requires translation into clinical pathways rather than remaining a purely conceptual construct. In practical terms, this means embedding individualized analgesic planning into the perioperative workflow: preoperative risk and phenotype assessment, intraoperative adaptation based on nociceptive monitoring and procedure-specific events, and postoperative reassessment according to pain trajectory, opioid requirements, recovery milestones, and adverse effects. Such a pathway-based approach is particularly relevant in enhanced recovery programs, where analgesia must be aligned not only with pain relief, but also with mobilization, bowel recovery, respiratory safety, discharge readiness, and prevention of chronic pain. Therefore, precision analgesia should be viewed as a longitudinal and adaptive pathway, rather than a single prescription decision made at one time point. In addition, a precision framework is particularly important for special populations, because the same multimodal regimen does not carry the same benefit-risk balance across all patients. Older adults, patients with obesity or obstructive sleep apnea, and those with renal or hepatic dysfunction often require tiered strategies with tighter control of sedative burden, opioid exposure, and drug accumulation risk. Therefore, individualized analgesia under precision anesthesia should not be understood only as pharmacologic diversification, but also as selective simplification when safety margins are narrow. This point is essential because the core of precision anesthesia is not maximal combination, but optimal matching.

This review summarizes the existing evidence on the key classes of analgesic agents and regional modalities employed in perioperative multimodal regimens, the pharmacologic and mechanistic rationale of particular combinations of analgesic agents and mechanisms and provides critical assessment of their application in divergent surgical patient groups. We also touch on principles of error and its ways of being translated into practice such as stratification of risks, personalized and tailor-made dosing and the application of sophisticated analytical techniques to eliminate therapy combinations. By putting multimodal analgesia in a precision anesthesia paradigm, we hope to give a conceptual and pragmatic map of how to transition to empiric, checklist-type combina-

tions to rationally-optimized, patient-centered multimodal analgesics.

Pharmacological basis and synergistic mechanisms of multimodal analgesia

The rationale for multimodal analgesia is rooted in the complex, multi-level organization of pain processing within the peripheral and central nervous system. Nociceptive input arises from peripheral transducers - most prominently voltage-gated sodium channels, TRP channels, and inflammatory mediators acting on prostaglandin, bradykinin, and cytokine receptors - before being conveyed via primary afferents to the dorsal horn, projected onward through ascending spinothalamic and spinoparabrachial pathways, and ultimately integrated within distributed cortical and subcortical networks [14, 15]. Superimposed on this ascending flow is a dynamic system of spinal and supraspinal modulation, including inhibitory GABAergic and glycinergic interneurons and descending noradrenergic and serotonergic pathways [16]. No single pharmacologic intervention can fully and selectively modulate all relevant nodes along this network without incurring substantial toxicity. Multimodal analgesia seeks to address this limitation by combining agents that act at distinct but complementary molecular and anatomical targets, thereby shaping nociceptive processing at multiple levels while avoiding excessive reliance on any one mechanism.

From a precision-anesthesia perspective, however, the value of multimodal analgesia lies not merely in combining different drugs, but in matching a given target to the dominant pathway, the relevant clinical pain phenotype, and the expected prognostic consequence. In practical terms, this means that a rational combination should be built according to the predominant drivers of pain in a specific patient and procedure - for example, peripheral inflammatory input, nerve injury-related hyperexcitability, spinal central sensitization, or deficient descending inhibition - rather than by adding agents indiscriminately. Thus, the mechanistic question is not simply which drugs are available, but which targets are biologically dominant in a given perioperative context and which combinations are most likely to improve clinically meaningful outcomes such as opioid exposure, early mobilization, respiratory safety, cognitive recovery, and the risk of persistent postsurgical pain. In such a scheme, it is possible to imagine the main groups of perioperative analgesic agents based on its location and mode of action. The μ-receptors-selective agonists of opioid receptors inhibit both pre- and postsynaptic transmission of nociceptive stimuli in the dorsal horn and the supraspinal circuits that are associated with pain, but their use is limited by dose-related respiratory depression, paralyses, hyperalgesia and abuse potential [17-20]. Clinically, opioids remain most relevant when the dominant phenotype is intense acute nociceptive pain requiring rapid suppression of ascending transmission, but prognosis deteriorates when escalating opioid exposure produces respiratory events, ileus, sedation, or opioid-related long-term dependence. COX-2 selective-block and nonsteroidal anti-inflammatory medications as well as the action of acetaminophen are all centrally biased (albeit this has not been fully understood) modulators of effects mainly acting at the periphery, by inhibiting the production of prostaglandin, which inhibit peripheral sensitization and inflammatory hyperalgesia [21, 22], and centrally biased respectively [23, 24]. These agents are therefore most relevant in procedures with a prominent inflammatory phenotype, where reducing peripheral transduction may translate into lower opioid consumption and better functional recovery, although this benefit must be balanced against renal, gastrointestinal, and bleeding risks in susceptible patients. Gabapentinoids inhibit excitatory release of neurotransmitters by modulating α2δ subunits of voltage-gated calcium channels, and are especially important in neuropathic aspects of postsurgical pain [25]. Their mechanistic role is strongest when the phenotype includes nerve injury, hyperalgesia, or central amplification, but the clinical trade-off is increased dizziness, delayed mobilization, and sedation in vulnerable patients. Antagonists of NMDA receptors like low-dose ketamine and adjunctive agents like magnesium interact more with central sensitization and wind-up effects in the dorsal horn [25]. These drugs are therefore conceptually best aligned with patients at risk of opioid tolerance, opioid-induced hyperalgesia, or marked central sensitization, in whom the prognostic goal is not only lower pain scores but also prevention of exaggerated postoperative opioid requirements. Systemic lidocaine and regional or neuraxial local anesthetics interrupt the conduction of impulses in the peripheral nerves and spinal roots directly inhibiting the afferent drive of central sensitization [26, 27]. These approa-

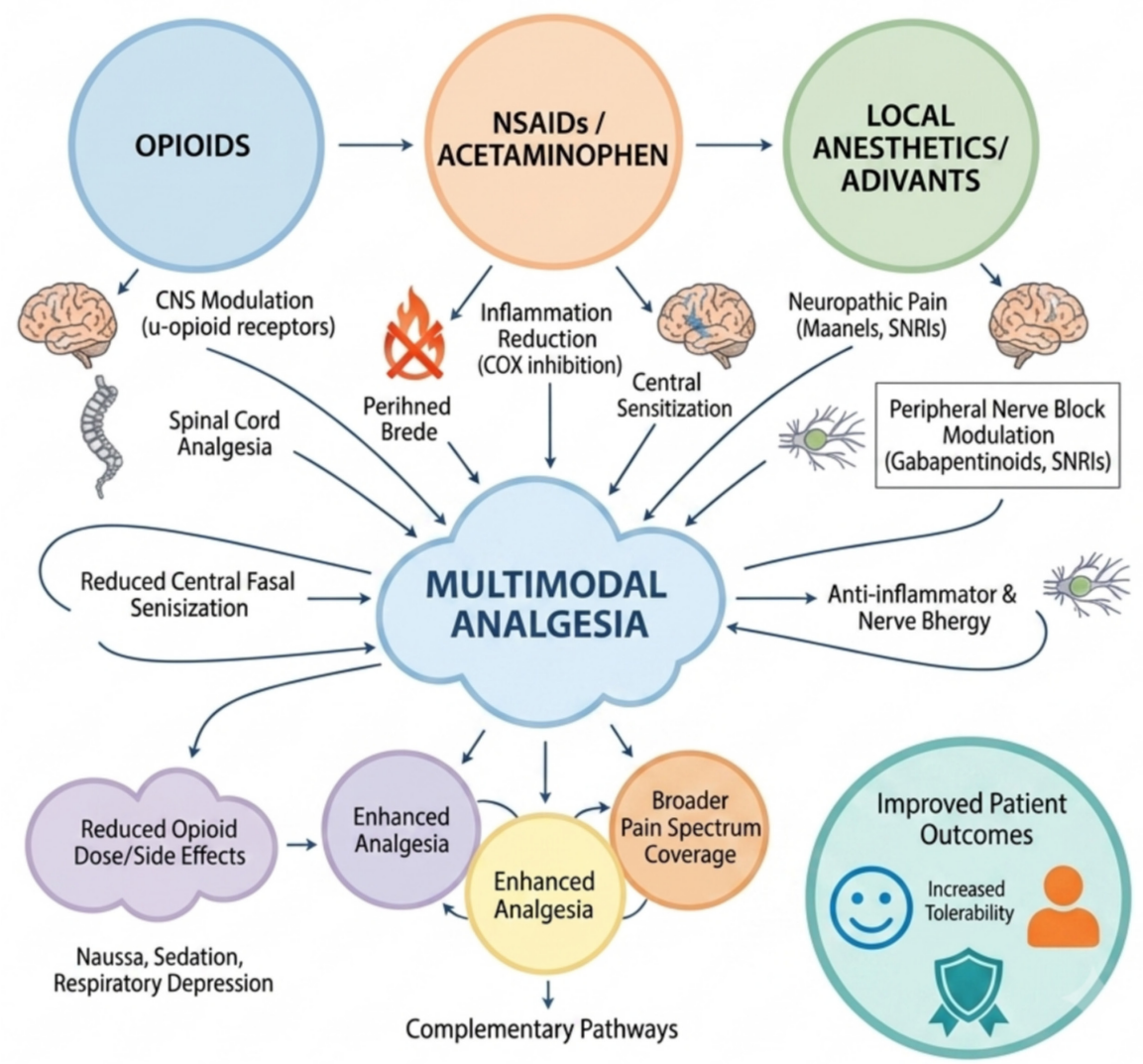

Figure 1. Pharmacological basis and synergistic mechanisms of multimodal analgesia. Schematic illustration of how combining distinct classes of perioperative analgesics - opioids, NSAIDs/acetaminophen, and local anesthetics/adjuvants - targets complementary nodes along the nociceptive pathway. Opioids primarily modulate central nervous system μ-opioid receptors and spinal cord transmission, while NSAIDs/acetaminophen reduce peripheral inflammation via cyclo-oxygenase inhibition and attenuate central sensitization. Local anesthetics and selected adjuvants provide peripheral nerve block, inhibit impulse conduction, and modulate neuropathic pain pathways. Acting in concert, these mechanisms dampen both peripheral and central sensitization, broaden coverage of diverse pain phenotypes, and permit substantial opioid dose reduction, thereby mitigating opioid-related adverse effects such as nausea, sedation, and respiratory depression. The net result is enhanced overall analgesia, wider pain-spectrum coverage, and improved patient outcomes with greater tolerability and safety within a precision anesthesia framework.

ches are particularly relevant when afferent barrage from the surgical field is the dominant driver of postoperative pain, and their clinical value often lies in reducing systemic opioid need, facilitating mobilization, and limiting central amplification. Lastly, α_2-adrenergic agonists (e.g., dexmedetomidine, clonidine) increase descending inhibition and reduce sympathetic outflow [28]. Their utility is greatest when analgesic goals overlap with anxiolysis, sympatholysis, and opioid-sparing, although hypotension, bradycardia, and excess sedation may narrow the therapeutic window. As these agents are rationally chosen, a layer-like approach of pharmacologic modulation is obtained which targets peripheral input, spinal gating, supraspinal perception and descending control in a coordinated manner (**Figure 1**).

This target-to-phenotype framework also clarifies that not all combinations should be regarded as equally "synergistic". The added value of multimodal regimens in the paradigm of the precision anesthesia is founded on the concept of synergy. Unlike simple additivity (when the combined effect is equal to the sum of the individual effects), pharmacodynamic synergy means that a convergent or serial node in the pain pathway will result in a supralinear increase in analgesia at each total drug exposure [29, 30]. In mechanistic terms, true synergy is most plausible when two agents act on different but biologically coupled levels of nociceptive processing - for example, peripheral inflammatory suppression plus central transmission control, or blockade of afferent input plus attenuation of spinal sensitization. By contrast, combinations that act on overlapping downstream effects without meaningfully expanding mechanistic coverage may be better understood as additive or even redundant. This distinction is important because "more drugs" does not automatically mean "better analgesia", and some combinations mainly increase adverse effects without producing a proportionate gain in analgesic benefit. Such synergistic interactions have been demonstrated in preclinical and clinical studies of a number of archetypal combinations: opioids with nonsteroidal anti-inflammatory drugs or acetaminophen, opioids with NMDA antagonists, local anesthetics with α_2-agonists, and regional techniques over systemic non-opioid analgesics [31-34]. Notably, synergy may be established not just in terms of the better scores on pain, but in terms of the clinically meaningful opioid-sparing, which in turn leads to the decrease in the number of adverse events related to opioid use [35]. Among these, the combination of opioids with NSAIDs or acetaminophen has the broadest and most mature clinical evidence base and is best viewed as a high-level, clinically validated opioid-sparing strategy, particularly in inflammatory postoperative pain. Opioid-ketamine combinations also have relatively strong mechanistic rationale and supportive evidence in selected high-risk settings, especially where opioid tolerance or central sensitization is suspected, although benefit appears more phenotype-dependent than universal. Regional techniques combined with systemic non-opioid analgesics likewise have a relatively high level of support in procedure-specific pathways, especially when the dominant pain generator is well localized anatomically. By comparison, some other combinations - such as the addition of gabapentinoids, magnesium, or α_2-agonists to otherwise established regimens - may be beneficial in selected contexts but more often remain conditional, procedure-specific, or empirically adopted rather than universally synergistic. In many cases, these regimens may represent useful additivity rather than robust, reproducible pharmacodynamic synergy, and their value depends heavily on whether the patient exhibits the phenotype they are biologically intended to target.

On a precision front, such interactions are mediated by patient- and context-dependent factors, such as the proportion between inflammatory and neuropathic control, the extent of central sensitization, genetic polymorphisms of the receptors and enzymes of interest, and the pharmacokinetic milieu due to age, organ function and comorbidity [35, 36]. Therefore, the same combination can behave very differently across patients: a regimen that is mechanistically synergistic in an opioid-tolerant patient undergoing major spine surgery may be only marginally additive - or unnecessarily toxic - in a low-risk ambulatory patient after minor soft-tissue surgery. This also means that the evidentiary status of multimodal combinations should be interpreted hierarchically. Some combinations are supported by relatively high-level clinical evidence across broad settings; some are supported mainly in selected subgroups or specific procedures; and others are still largely empirical combinations carried over from institutional practice or mechanistic plausibility rather than confirmed comparative effectiveness. The maximization of multimodal combinations clearly involves therefore not only leaving fixed recipe combinations behind in favor of mechanism-based, quantitatively informed choice and titration of agents most prone to act synergistically together to produce a given individual result.

Equally important, the precision-anesthesia view requires explicit recognition that benefit and harm must be modeled together. Meanwhile, synergies of drug poisoning, including the possibility of renal risk caused by various nephrotoxins, cumulative sedation, or increased bleeding risk with some anti-inflamma-

gents, (notably) will have to be explicitly modelled and tracked, which is to observe that synergistic benefit and synergistic harm are two sides of one pharmacologic coin [37-39]. In other words, combinations should not be judged solely by lower pain scores or reduced opioid consumption, but by their net effect on prognosis: respiratory safety, hemodynamic stability, delirium risk, gastrointestinal recovery, mobilization, discharge readiness, and the prevention of persistent postsurgical pain. A mechanistically elegant combination that increases dizziness, oversedation, renal injury, or bleeding may be pharmacologically interesting but clinically suboptimal. For this reason, the core principle of precision multimodal analgesia is not maximal combination, but selective combination - linking the dominant target and pathway to the relevant pain phenotype, using the strongest available evidence where it exists, and avoiding empiric escalation when the expected interaction is merely additive, uncertain, or potentially harmful.

Key variables shaping the optimization of drug combinations

In order to optimize multimodal analgesic drug trends within the framework of a concept of precision anesthesia, it is of paramount importance that the definition of the optimal regimen cannot be a set of equations as there is a multifaceted interplay of patient-, procedure-, and system-level variables. At the patient level age, frailty, body composition and organ functioning are determinants of both pharmacokinetics and pharmacodynamics, which crucially affect the selection and dosage of each individual component drug [40, 41]. Renal and hepatic impairment only limit the safe use of nonsteroidal anti-inflammatory drugs, abused by gabapentinoids and some opioids [42]; OSA obstructs the safe use of sedating agents and requires higher limits of opioid exposure [43]; and cardiovascular comorbidities may affect 2-agonist tolerance and neuraxial methods. Additional complexity is presented by chronic pain, opioid therapy in place of primary care, and substance use disorders because opioid tolerance, opioid-induced hyperalgesia, and altered central pain information decrease the potency of traditional dose-response prediction [44]. Genetic variations in enzymes (e.g. CYP2D6, CYP3A4, UGTs), transporters and receptors and differences in sex related pain sensitivity and drug effect also contribute to further heterogeneousity only starting to be systematically integrated into perioperative analgesic decision making [45, 46].

Equally important are psychological and contextual determinants of pain and analgesic requirements, which modulate both the subjective experience of pain and the apparent efficacy of pharmacologic interventions. Anxiety, depression, catastrophizing, sleep disturbance, and prior traumatic medical experiences are robust predictors of heightened postoperative pain and prolonged opioid use [47-49]. These factors do not operate independently of pharmacology; rather, they influence the “effective dose-response” relationship by altering expectations, coping capacity, and central processing of nociceptive input. Precision-oriented multimodal regimens should therefore be embedded within a broader strategy that includes preoperative education, expectation management, and non-pharmacologic adjuncts such as cognitive and behavioral interventions. Failure to account for these variables risks misattributing inadequate analgesia to “drug failure” and escalating doses or adding agents in ways that increase toxicity without meaningfully improving pain control.

The second major axis according to which the multimodal combinations have to be individualized is the surgical and procedural context. The intensity and nature of nociceptive input, influenced by the type of surgery, surgery site, extent of tissue injury, presence or absence of the involvement of bone or nerve structures, and whether the surgery is performed with minimally invasive or open procedures define the predicted amount of pain and the relative relevance of individual mechanisms such as inflammatory, visceral, or neuropathic etiologies [50-52]. As an example, neuraxial blocks or truncal blocks as part of anti-inflammatory and opioid-sparing systemic regimens could especially be effective in extensive abdominal procedures or thoracic procedures with high levels of visceral manipulation [53, 54], whereas orthopedic surgery, related to the bone and joint, might require more aggressive local anesthesia and localized anti-inflammatory practices. The predicted length of the period of severe pain, the necessity of the early mobiliza-

tion, and the probability of averted bleeding or infections under the enhanced recovery procedures are all determinants of the relative appeal of the neuraxial techniques, constant peripheral nerve blocks, and definite systemic adjuncts [55, 56]. In addition, the intraoperative anesthetic selection such as the volatile or total intravenous anesthesia, depth of anesthesia control, and intraoperative opioid options have a relationship with postoperative analgesic needs and cannot be made in isolation but as a continuous pathway-based optimization process.

The third dimension that requires a personalized approach to the combination of drugs is the application of the concept of temporal dynamics across the perioperative continuum. The analgesic requirements and risk-benefit profile of respective drugs are less than during the preoperative (where prehabilitation, preemptive analgesia and mitigation of chronic pain amplification are pivotal), intraoperative (where attention is on narcotics blunting surgical nociception and preventing central sensitization), immediate and late (where the purpose increasingly shifts to functional recovery, minimum number of side effects, and avoidance of persistent postsurgical pain) [57, 58]. Agents with quick onset, and short times to context steady-state may be beneficial during surgery, but impossible to use over time, whereas those which require time to reach steady levels may have to be either pre- or intraoperatively initiated to reach their maximum useful effect. The presence of continuous infusions, patient-controlled modalities and long-acting regional techniques add another level of freedom that may be used to enhance the process of transition between care settings. Combinations of multimodes under a precision anesthesia paradigm hence need to be phase-specific and vary dynamically throughout the process instead of running regimes in the same way throughout the preoperative holding area and to discharge from the hospital.

Finally, system-level and logistical factors exert a substantial, often underappreciated influence on the optimization of multimodal analgesic regimens. Drug availability, formulary restrictions, staffing patterns, monitoring capacity, and institutional culture all constrain what is realistically implementable in a given environment (**Table 1**). The safety profile of more complex combinations - particularly those involving sedating agents, neuraxial or continuous regional techniques, and systemic lidocaine - depends critically on the ability to provide appropriate surveillance for hemodynamic instability, neurologic changes, and local anesthetic systemic toxicity [59]. Documentation systems, order sets, and clinical decision support tools determine whether individualized regimens can be implemented reliably at the bedside or are gradually eroded into simplified, protocol-driven “defaults”. In high-throughput or resource-limited settings, the marginal benefit of adding certain agents must be weighed against the complexity they introduce and the risk of administration errors [60, 61]. Precision anesthesia therefore demands not only mechanistic and patient-level insight but also an honest appraisal of institutional constraints and the intentional design of pathways that align mechanistically sound multimodal combinations with the realities of clinical practice.

Evolution of optimization methodology: from empiricism to data-driven design

Multimodal analgesic regimen evolution has been predominantly physiological, driven by clinical expertise, and experimental stages of clinical experience, and not by formal optimization models. Initial combinations were commonly built by merely combining some non-opioid agent (e.g., nonsteroidal anti-inflammatory drugs or acetaminophen) to an opioid backbone and the dose choice was selected by the labeled ranges and comfort of the clinician instead of using a quantitative analysis of their effect on each other. Randomized controlled trials (RCTs) are generally, but not necessarily or always, compared as standard care, versus standard care plus one adjunct, with 24-72 hours possibly identifying short-term outcomes, such as pain scores and opioid consumption. Although this method yielded significant evidence of proof-of-concept evidence on multimodal analgesia, it was likewise constrained in the ability to probe the high-dimensional space of possible combinations, doses, and timing in combination. On the basis of relatively small single-center trials or observational data, complex regimens were often embraced, and negative or neutral results were often

Table 1. Key variables shaping the optimization of multimodal analgesic drug combinations in precision anesthesia

Level/domain	Key variables (examples)	Effect on pain biology/PK-PD	Impact on multimodal regimen design	Typical optimization strategies/examples
Patient - organ function & comorbidities	Age, frailty, body composition (obesity, sarcopenia), renal and hepatic impairment, cardiovascular disease, obstructive sleep apnea	Modify drug distribution and clearance; narrow therapeutic window for sedatives and opioids; increase risk of hemodynamic and respiratory complications	Constrain use and dose of NSAIDs, gabapentinoids and certain opioids; influence tolerance of α_2-agonists and neuraxial techniques	Avoid/reduce NSAIDs in renal dysfunction; limit sedatives and opioids in OSA and frailty; cautious α_2-agonist and neuraxial use in cardiovascular disease
Patient - pain & analgesic history	Chronic pain, pre-existing opioid therapy, opioid use disorder, other substance use	Opioid tolerance, opioid-induced hyperalgesia, altered central pain processing; higher baseline pain burden	Necessitate higher non-opioid and regional analgesia; simple opioid up-titration often ineffective and toxic	Emphasize ketamine, lidocaine, regional blocks and non-opioid adjuncts; structured perioperative opioid taper plans
Patient - genetic and sex-related factors	CYP2D6, CYP3A4, UGT polymorphisms; transporter and receptor variants; sex differences in pain sensitivity and drug response	Interindividual variability in efficacy and toxicity of opioids and adjuvants	Limit generalizability of "standard doses"; support movement toward genotype-/sex-informed dosing where feasible	Adjust pro-drug opioids in CYP2D6 poor/ultra-rapid metabolizers; consider sex-specific differences in side-effect profiles
Patient - psychological and contextual factors	Anxiety, depression, catastrophizing, sleep disturbance, prior traumatic medical experiences, social support	Amplify perceived pain and analgesic requirements; alter expectation and coping; modulate apparent dose-response	Pharmacologic regimens alone may be insufficient; risk of mislabeling as "drug failure" and toxic dose escalation	Integrate preoperative education, expectation management, and cognitive-behavioral interventions alongside drug combinations
Procedure - magnitude and type of nociception	Type of surgery, incision site, degree of tissue trauma, bone/joint involvement, nerve manipulation	Determine intensity and quality of nociceptive input (inflammatory, visceral, neuropathic components) and pain trajectory	Drive selection of regional techniques and systemic agents matched to dominant mechanisms	Use neuraxial/truncal blocks plus anti-inflammatory regimens for major abdominal/thoracic surgery; aggressive regional and NSAID-based strategies for orthopedic procedures
Procedure - surgical approach & recovery goals	Open vs. minimally invasive; expected duration of severe pain; need for early mobilization; bleeding and infection risk under ERAS protocols	Influence required depth/duration of analgesia and tolerance of NSAIDs and neuraxial techniques	Balance block density and duration against hemostatic and mobilization goals	Short-acting techniques for ambulatory minimally invasive surgery; long-acting blocks or catheters when early mobilization is critical but pain is intense
Intraoperative anesthetic strategy	Volatile vs. TIVA; depth of anesthesia targets; intraoperative opioid exposure; use of ketamine, lidocaine, dexmedetomidine	Modulate central sensitization, hemodynamics and immediate postoperative opioid need	Intraoperative choices should be integrated with postoperative combination planning rather than treated as isolated decisions	Opioid-sparing intraoperative strategies paired with robust non-opioid and regional postoperative regimens; adjust PACU dosing to intraoperative exposure
Temporal - perioperative phase	Preoperative, intraoperative, early postoperative, late postoperative/transition to chronic pain	Phase-specific shifts in priorities: sensitization prevention vs. acute pain control vs. functional recovery and chronic pain prevention	Regimens should be dynamically adapted over time; static "one-regimen" approaches are suboptimal	Prehabilitation and pre-emptive analgesia pre-op; titratable agents intra-op; long-acting blocks/PCA early post-op; step-down and simplification in later phases
Temporal - drug kinetics & delivery mode	Onset, context-sensitive half-life, time to steady state; continuous infusions; patient-controlled analgesia; long-acting regional techniques	Determine feasibility of sustained exposure versus rapid titration; affect transitions across care settings	Matching drug properties and delivery mode to phase-specific goals and monitoring capacity	Use short-acting agents intra-op; consider pre-/intra-operative start of agents needing time to steady state; deploy long-acting blocks or catheters across high-pain windows
System - resources and monitoring capacity	Drug availability, formulary restrictions, staffing patterns, hemodynamic and neurologic monitoring capabilities, institutional culture	Define what can be safely implemented; limit use of complex or high-risk combinations	Require alignment of "optimal" theoretical regimens with local feasibility and safety	Avoid complex lidocaine infusions or dense neuraxial techniques where monitoring or expertise is limited; prefer simpler but robust combinations
System - informatics, pathways and workflow	Electronic order sets, documentation systems, clinical decision support, case throughput, training level	Influence fidelity of individualized regimens and risk of protocol drift or medication error	Determine whether precision regimens can be reliably delivered or collapse into simplified defaults	Build pathway-based, risk-stratified order sets with embedded decision support; ensure education and workflow integration before increasing regimen complexity

called due to either an error such as wrong patient, wrong dose, or wrong timing.

Throughout the last ten years, there has been a gradual transformation towards more rigorous and structured methodology in an attempt to define and optimize the multidrug, multi-time-point perception of perioperative analgesia. The factorial and adaptive trial designs have also allowed multiple agents and dosing strategies to be simultaneously assessed, permitting study investigators to estimate, not only, the main effects but also, the interaction terms, which are vital in determining, whether drugs interact in a positive, negative, or neutral manner. Pharmacodynamic/pharmacokinetic PKPD modeling and response-surface methods which have been long utilized in the development of anesthetic drugs have been used to characterize isoboles of equal effect, regions of favorable benefits-to-harm ratio, and the identification of dose pairs to achieve predetermined opioid-sparing goals with tolerable side-effects [62]. These model-based approaches recognize multimodal analgesia as a continuous optimization problem rather than a binary "use versus do not use" question, and they provide a conceptual bridge between mechanistic pharmacology and bedside dosing decisions. At the same time, network meta-analyses and large-scale comparative effectiveness studies using pragmatic designs have begun to synthesize evidence across heterogeneous trials and practice settings, offering a broader view of how different combinations perform in real-world populations and across diverse surgical procedures.

With the advent of precision anesthesia, there has been a rapid migration away from the population-average assessment model to data-driven and individualized planning of multimodal programs. The extension of electronic health records and anesthesia information management systems and the perioperative registries has produced large amounts of high-dimensional information related to the characteristics of patients, intra-operative monitoring, drug administration trends, and postoperative outcomes. Causal inference algorithms, propensity-score models, and Bayesian hierarchical models are becoming popularly used in order to gain actionable information about these datasets using machine learning and advanced statistical techniques [63-66]. Instead of answering the question of which regimen is best on average, these tools have the capability to determine patient subgroups that benefit or harm disproportionately in response to a specific agent or regimen, or to discover a nonlinear relationship between cumulative exposure and adverse events, and generate the individual risk-benefit profiles which can be used to inform the choice of regimen. Simultaneously, real-time physiologic evaluation of nociception and analgesia with indices and indicators of nociception, pupillometry, and autonomic markers allows the introduction of adaptive intraoperative dose algorithms regulating the relative relationship between anesthetic and analgesic drugs according to the changing response of a patient instead of using fixed scheduling [67, 68].

In the future, the multimodal analgesic combination of drugs will be optimally computed on a continually learning and closed-loop basis in effective cooperation with the overall objectives of precision perioperative care. The products of early-stage model-based experiments and adaptive designs of platforms can be expeditiously utilized to explore and optimize candidate regimens, establishing a list of optimized defaults depending on the particular procedure and intensity. In turn, these defaults could be implemented in the clinical decision support systems, which consider patient-specific data such as demographics, comorbidities, chronic pain and opioid history, genetic markers (where available), and psychological risk factors in conjunction with procedure-specific features and institutional restrictions to provide individualized regimen advice. Clinical implementation feedback of pain dynamism, opioid use, functional recovery indicators, and adverse events can be continually consumed into learning health system structures to revise and re-calibrate models as time passes. Finally, the understanding of empiricism to data-driven design is not intended to displace clinical judgment, but to provide the expert decision making process with quantitative tools, which are able to cope with the complexity of multidrug analgesic therapy. In this changing ecosystem, the organizing principle will be precision anesthesia, and optimized multimodal analgesia will become a dynamic, evidence- and data-driven intervention, which evolves depending on the

patient and the procedure, as well as the healthcare environment in which it is administered.

Challenges and future directions

Although the concept is appealing to theory and the evidence base is growing, there are some formidable challenges when it comes to translating optimized multimodal analgesia combinations into day-to-day precision anesthesia. Among them, biologic and clinical heterogeneity is the most important: even within one type of procedure, patients have radically different degrees of pain sensitivity, inflammatory and neuropathic relationships, pharmacogenomic phenotype, and susceptibility to adverse drug events [69-71]. Existing clinical preoperative risk stratification instruments - which are predominantly dependent on demographics, comorbidities, and roughly inquired pain history - solely define the portion of this variation [1, 72]. Powerful biomarkers to forecast predictably acute pain patterns, vulnerability to central sensitization, or opioid toxicity are yet to be found and are not consistently available in clinical practice. Lacking sufficient granularization of phenotyping, even the state-of-the-art optimization models threaten to degenerate again to stratified empiricism, whereby regimens are customized to wide groups, and no longer in fact individualized. Determining this divide will need joint actions in the area of biomarker identification, multimodal pain phenotyping, and incorporating genomics, transcriptomics, and digital behavioral information in perioperative evaluation.

Lack of methodological and data-related limitations also limits the speed of the development. Although traditional randomized trials are necessary to prove causality, in the case of multidrug interactions or offering action-oriented advice to many patient-procedure combinations, these trials are frequently underpowered. On the other hand, observational data based on electronic health records and registries is only scale abundant with indication bias, confounding, and inconsistent documentation. Such data requires stringent methodology of causal inference, reporting and cross institutional-health system validation of building models of trust and clinical utility. Besides, the vast majority of existing databases in terms of pain intensity, functional recovery, and patient-reported outcomes that fall outside of discharge lack standardized and high-resolution measures, preventing the association of particular drug regimens with long-term outcomes such as persistent postsurgical pain or chronic opioid use. Infrastructure for future research should thus put emphasis on systematic gathering of granular, longitudinal result information and embrace common information models that can be used to aggregate across centers and comparative efficacy study.

The application to real-world clinical environments is another area where it becomes even more complicated and cannot be addressed using analytics. The resource constrained developing world may not be served with over complex regimens, high reliance on continuous infusions, or dependent on medications with a restricted therapeutic index that may become impractical in ambulatory or community-based environments. Perioperative care specialists and anesthesiologists have to operate between conflicting goals: standardization versus individualization, simplicity versus nuance, and efficiency versus comprehensiveness. Clinical decision support systems integrated into electronic ordering systems represent a hopeful avenue of operationalizing precision multimodal analgesia, but will need to be crafted to supplement, not to flood clinicians with visible recommendations in clear formats with interpretable recommendations and with explicit rationale, and with power to deviate on technological judgment. It is also important to educate anesthesia providers, surgeons, nurses and pharmacists to make sure that they understand the mechanistic explanation, anticipated advantages, and necessary monitoring of more complex multimodal regimens. The bridging of the gap between improved methods and sustainable change in practice will require implementation science systems and pragmatic trials specifically addressing feasibility, adherence and impact on workflow.

Finally, there are ethical, equity, and regulatory factors that will influence the course of future developments. The use of advanced optimization techniques based on genomics, continuous physiologic surveillance or custom machine learning models all provoke the concerns of data privacy, the transparency of the

algorithm, and fair access. The fact is that there is a tangible possibility of the selectivity of precision multimodal analgesia in the centers with advanced digital facilities that provide high-quality care, and patients in under-resourced facilities still receive care that is not the most optimal, i.e. based on opioids. The regulatory pathways have also not yet readily accommodated the assessment of regimens as interventions, especially where algorithmically designed combinations based on off-label use of dynamically tailored combinations of off-patent drugs are being done in a manner which the individual labels did not design to offer. The future directions should thus comprise the establishment of regulatory frameworks that can safely embrace adaptive, data-guided combination therapy; along with the development of interpretable, validated across different populations model designs and intentional attempts to make sure that optimal multimodal plans are scalable and cheap. Simultaneously, studies need to shift to closed-loop or semi-closed-loop analgesic systems with the combination of nociception monitoring, pharmacologic modeling, and real-time optimization must be maintained, without losing control of the part of the clinician or side effects on the part of the patient. Should these scientific, practical and ethical challenges be overcome, the area will be set to achieve the full potential of precision anesthesia: multimodal analgesic regimens that are not only effective and opioid-sparing, but also dynamically personalized, context-adaptive and equitably executed over the global perioperative environment (**Figure 2**).

Development of tiered analgesic regimens for special populations and risk stratification

The optimization of multimodal analgesia within the paradigm of precision anesthesia requires not only recognition of patient heterogeneity, but also the establishment of structured decision pathways that translate risk stratification into concrete perioperative analgesic plans. Special populations, including older adults, obese patients, those with obstructive sleep apnea (OSA), and patients with renal or hepatic impairment, do not merely require "more careful" analgesia; they require targeted, tiered, and dynamically adjusted regimens. Therefore, the core of this section is not simply the description of vulnerable groups, but the development of an individualized decision-making model that links patient phenotype, procedural characteristics, expected pain trajectory, and safety constraints to analgesic selection. A practical precision-analgesia model for special populations should be organized around three sequential steps. First, the patient should undergo preoperative stratification according to baseline vulnerability, including age-related frailty, body habitus, respiratory risk, organ dysfunction, chronic opioid exposure, prior pain phenotype, and major comorbidities. Second, the patient should be assigned to a perioperative analgesic tier, ranging from standard opioid-sparing multimodal therapy to high-risk restricted regimens in which sedatives, systemic opioids, or renally cleared drugs are deliberately minimized. Third, analgesic planning should be continuously updated across the perioperative course according to intraoperative nociceptive burden, recovery trajectory, opioid requirement, and adverse-event signals. In this framework, individualized analgesia becomes an operational pathway rather than a descriptive principle.

For elderly patients, pharmacokinetic and pharmacodynamic changes, including alterations in drug metabolism and clearance, require the adjustment of drug choices and dosages. The aging process often results in diminished organ function, including renal and hepatic capacity, which can significantly alter the drug's half-life, metabolism, and clearance. Furthermore, polypharmacy, common in elderly patients, increases the risk of drug-drug interactions. Therefore, analgesic regimens for this group should prioritize non-opioid agents, minimize the use of sedatives, and consider the incorporation of regional anesthesia techniques to reduce systemic drug exposure. In addition, the targeted pain-relief plan for older adults should emphasize simplicity, slow titration, early reassessment, and avoidance of cumulative toxicity. In many elderly patients, the main goal is not only lower pain scores, but preservation of cognition, mobilization, bowel function, and respiratory safety. For this reason, the decision model should favor regimens with lower delirium risk, fewer centrally depressant combinations, and stronger alignment with postoperative functional recovery.

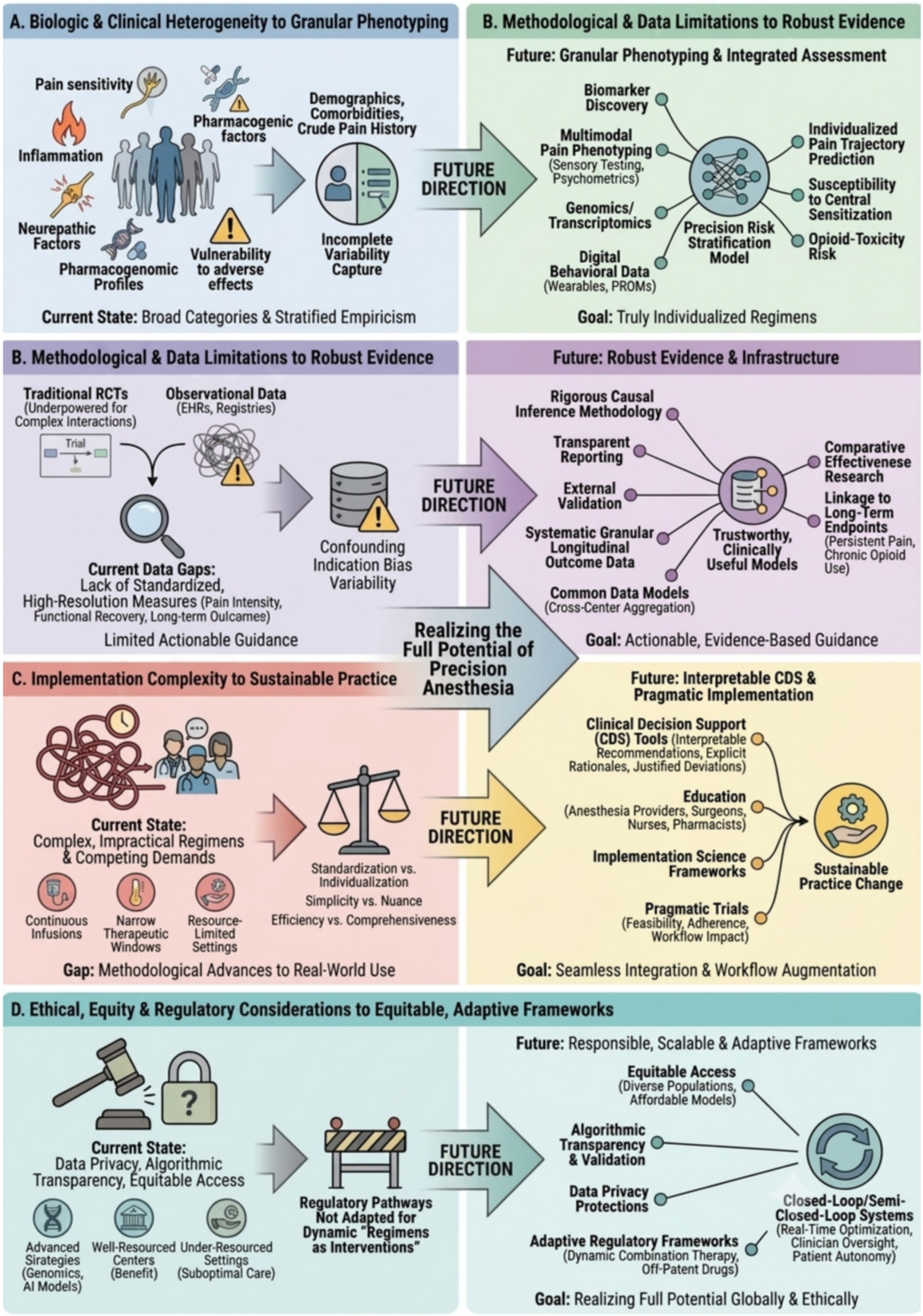

Figure 2. Conceptual framework summarizing key challenges and future directions for implementing optimized multimodal analgesia within precision anesthesia. Biological & clinical heterogeneity (A), methodological and data

limitations that constrain robust, generalizable evidence (B), the complexity of translating intricate regimens into sustainable real-world practice (C), and ethical, equity, and regulatory concerns surrounding data-intensive, algorithm-driven care (D) - must be addressed through coordinated advances in granular phenotyping and biomarker discovery, rigorous causal and comparative-effectiveness analytics, implementation-focused decision support and team education, and interpretable, scalable, and fair regulatory frameworks.

Obesity further complicates analgesic management. Excess body fat affects the distribution, metabolism, and elimination of many analgesic drugs, particularly opioids. Opioid dosing often needs to be individualized, and caution is necessary, especially with lipophilic drugs, which may have prolonged effects in obese patients. In addition, obesity is frequently associated with comorbidities such as OSA, which complicates opioid use due to an increased risk of respiratory depression. Therefore, for obese individuals, a balanced multimodal approach that integrates non-opioid agents, regional anesthesia, and close monitoring of respiratory function is essential. These patients may benefit from opioid-sparing strategies such as nerve blocks or long-acting local anesthetics that can effectively manage pain while minimizing opioid consumption. Under a precision-anesthesia framework, however, the plan for obese patients should also be procedure-specific and surveillance-linked. For example, regimens should be designed with explicit consideration of postoperative airway vulnerability, anticipated mobility limitations, and the need for monitoring in the post-anesthesia care unit or ward. Thus, analgesic selection in obesity should not only aim to reduce opioid consumption, but also to reduce residual sedation, hypoventilation risk, and delayed recovery caused by prolonged drug effect.

Patients with OSA present another layer of complexity in the design of analgesic regimens. OSA patients have an increased risk of opioid-induced respiratory depression, and the traditional reliance on opioids for postoperative pain management can exacerbate this risk. For these patients, non-opioid analgesia, particularly regional anesthesia and alternative pharmacologic agents such as gabapentinoids or ketamine, should be prioritized. Close monitoring of respiratory function, along with multimodal strategies that reduce the need for systemic opioids, is paramount in ensuring patient safety. In this population, individualized decision-making should be especially strict, because the therapeutic window may be narrow. A clinically useful pathway would include preoperative identification of known or suspected OSA, restriction of opioid-heavy regimens, prioritization of block-based or local anesthetic-centered strategies when feasible, and postoperative respiratory surveillance that is matched to the expected duration of sedative and opioid effect. In other words, the targeted pain-relief plan for OSA should be based not only on analgesic efficacy, but on the combined objective of pain relief and respiratory risk containment.

In patients with renal or hepatic impairment, drug elimination and metabolism can be severely compromised. Renal dysfunction, in particular, can prolong the half-life of many analgesic medications, such as NSAIDs and opioids, thus increasing the risk of adverse effects like renal toxicity or sedation. Careful selection of drugs and adjusted dosing regimens are crucial, often favoring agents with minimal renal clearance or those that are predominantly metabolized by the liver. For example, avoiding NSAIDs in patients with renal impairment is recommended due to the risk of further renal damage. Similarly, opioid use should be minimized, with particular attention given to dosage adjustments to avoid complications like respiratory depression. For these patients, the tiered approach should explicitly separate agents that are relatively contraindicated, agents that may be used with dose reduction and monitoring, and agents that are preferred because of more predictable elimination profiles. This is where precision anesthesia adds practical value: it converts a general warning about organ dysfunction into a structured regimen design principle. In high-risk patients, analgesic pathways should also include more frequent reassessment and earlier de-escalation if toxicity signals emerge.

Risk stratification in these special populations not only involves clinical evaluations but also the consideration of underlying pain phenotypes. For instance, inflammatory pain may pre-

dominate in patients undergoing major abdominal surgery, while neuropathic pain may be more relevant in those undergoing procedures related to nerve manipulation. The tiered approach to analgesia should reflect these differences, with agents chosen based on the specific pain mechanisms present in the patient. For example, NMDA receptor antagonists like ketamine are particularly beneficial in patients at risk of central sensitization, while anti-inflammatory drugs may be prioritized for those with inflammatory pain. To make this clinically actionable, phenotype assessment should be integrated with a model-informed decision structure. One practical way is to combine three domains: patient vulnerability, dominant pain mechanism, and procedure-specific nociceptive intensity. A low-risk patient with predominantly inflammatory pain after routine abdominal surgery may be appropriately managed with a standard opioid-sparing multimodal regimen, whereas a frail patient with OSA and central sensitization risk may require a restricted-opioid, monitoring-enhanced pathway with stronger emphasis on regional analgesia and serial reassessment. This type of decision structure better reflects the concept of precision anesthesia than a simple list of drug options.

The implementation of precision analgesia in these populations involves leveraging available biomarkers, phenotypic assessments, and model-informed decision-making tools to guide drug selection and dosing. Although biomarkers are not yet widely used in clinical practice, they hold promise in identifying patients at risk of exaggerated pain responses, opioid toxicity, or persistent postsurgical pain. Future advancements in biomarker discovery, along with the continued refinement of clinical decision support systems, will enable more precise stratification and optimization of multimodal analgesic regimens for these vulnerable groups. At present, however, clinical translation depends less on isolated biomarker use and more on embedding decision support into the perioperative workflow. In practical terms, this means that preoperative assessment tools, intraoperative monitoring information, and postoperative reassessment protocols should all inform the same analgesic pathway. The strength of a precision model lies not only in prediction, but in its ability to guide bedside action. Accordingly, a complete clinical translation pathway for special populations should include at least four linked components: preoperative screening and tier assignment, intraoperative execution of a phenotype-matched regimen, postoperative monitoring and rescue adjustment, and outcome review for future pathway refinement. This pathway-based approach is essential because targeted analgesia cannot succeed if individualized planning is lost during transitions between the ward, operating room, post-anesthesia care unit, and surgical recovery unit. Precision anesthesia therefore requires continuity of decision logic across settings, not just isolated moments of individualized drug prescription.

The development of tiered analgesic regimens for special populations requires a nuanced understanding of patient-specific risks and the interplay of pharmacologic factors. Precision analgesia, by integrating individualized assessment and data-driven decision-making, offers the potential to improve outcomes and minimize the risk of adverse events. As research into biomarkers and pharmacogenomics advances, the ability to tailor pain management to the unique needs of each patient will continue to evolve, ensuring that multimodal analgesia is not only effective but also safe across diverse patient groups. More importantly, future progress should focus on making individualized decision models clinically executable, so that the concept of precision anesthesia is reflected not only in theory, but also in reproducible perioperative pathways for high-risk and heterogeneous patient populations.

Balancing analgesic benefit against treatment-related harm in multimodal analgesia

A more balanced interpretation of multimodal analgesia is essential within the framework of precision anesthesia. Although multimodal strategies are often promoted for their opioid-sparing and analgesia-enhancing effects, their value should not be judged solely by reductions in pain scores or opioid consumption. In clinical practice, the addition of multiple agents or techniques may also increase cumulative sedation, dizziness, hemodynamic instability, postoperative delirium, respiratory compromise, renal or gastrointestinal toxicity, bleeding risk, and drug-drug interactions. Moreover,

greater regimen complexity may itself introduce implementation burden and reduce reproducibility, particularly in high-risk or resource-constrained settings. Therefore, the true merit of multimodal analgesia lies not in the number of components used, but in whether the regimen provides a favorable net clinical benefit across analgesia, safety, recovery, and functional outcomes.

This issue is especially important when balancing regional blockade against systemic medication. Regional techniques can offer substantial opioid-sparing benefit and may be highly effective when the dominant pain generator is anatomically localized. However, they are not universally superior in every perioperative context. Their potential benefits must be weighed against procedural invasiveness, block-related complications, monitoring demands, delayed mobilization in selected settings, and institutional limitations in expertise or workflow. Conversely, systemic pharmacologic strategies may avoid procedural risk, yet may expose susceptible patients to excessive sedation, respiratory depression, or organ-specific toxicity. From a precision-anesthesia perspective, the relevant question is not whether regional or systemic analgesia is intrinsically preferable, but which approach, or which combination of approaches, yields the most favorable benefit-risk profile for a given patient, procedure, and perioperative phase.

It is equally important to recognize that not all multimodal combinations are truly synergistic. Some combinations are additive rather than synergistic, some are mechanistically redundant, and some may provide little incremental benefit while amplifying toxicity. In particular, combinations that appear pharmacologically attractive may prove clinically suboptimal when applied outside the patient populations or procedural settings in which they are biologically justified. For example, adding sedating adjuvants to opioid-based regimens in older adults, frail patients, or individuals with obstructive sleep apnea may increase harm more than benefit. Likewise, escalating multimodal therapy in response to uncontrolled pain may sometimes reflect inadequate phenotypic matching rather than insufficient treatment intensity. Accordingly, an objective discussion of multimodal analgesia must consider both therapeutic gain and treatment-related harm. The goal of precision analgesia is therefore not maximal combination, but selective and individualized combination, with explicit attention to who is likely to benefit, who is likely to be harmed, and when simplification may be safer than escalation.

Conclusion

Multimodal analgesia, once conceived primarily as an empiric “opioid-sparing add-on”, is increasingly recognized as a complex, high-leverage intervention that sits at the heart of precision anesthesia. By strategically combining agents and techniques that act at distinct points along the nociceptive axis, multimodal regimens can attenuate acute pain, prevent central sensitization, and reduce opioid exposure and its attendant harms. Yet, as this review underscores, the true potential of multimodal analgesia will not be realized through simple checklists or fixed institutional bundles. Optimal combinations emerge from the interplay of patient biology, psychological context, procedural characteristics, temporal dynamics, and system constraints. In this setting, an undifferentiated “one-size-fits-all” approach is not merely suboptimal - it risks both undertreatment and avoidable toxicity. Importantly, multimodal analgesia should not be understood as an unlimited accumulation of drugs and techniques. Excessive combination may increase cumulative sedation, hemodynamic instability, renal or gastrointestinal toxicity, bleeding risk, and drug-drug interactions, while adding complexity that may not translate into clinically meaningful benefit. Likewise, the balance between regional techniques and systemic medication must be assessed carefully, because a more invasive regional strategy is not always preferable if its incremental analgesic gain is offset by procedural risk, monitoring burden, delayed mobilization, or resource limitations. Moreover, some multimodal combinations may be primarily additive or even redundant rather than truly synergistic, and certain combinations may offer no clear benefit - or may even cause harm - when applied outside the patient populations or procedural settings in which they are biologically and clinically justified.

The concept of precision anesthesia provides a unifying framework for transforming multimodal analgesia from a largely protocol-driven

practice into a quantitatively informed, adaptively individualized therapy. Advances in systems pharmacology, PK-PD and response-surface modeling, and innovative trial designs offer powerful tools for rigorously characterizing synergistic and antagonistic drug interactions and defining benefit-risk frontiers. At the same time, the proliferation of rich perioperative data - from electronic health records, registries, and high-resolution physiologic monitoring - creates unprecedented opportunities for data-driven design, machine learning-assisted personalization, and continuous learning at scale. Realizing these opportunities will require parallel progress in pain phenotyping, biomarker development, and integration of patient-reported and long-term outcomes, as well as the deployment of decision support systems that can translate complex models into actionable, interpretable recommendations at the bedside. Just as importantly, future optimization must explicitly model both benefit and harm, so that multimodal regimens are judged not only by analgesic efficacy or opioid sparing, but also by respiratory safety, delirium risk, gastrointestinal recovery, mobilization, and overall functional outcome.

Looking forward, the central challenge is not merely to identify the “best” multimodal regimen in the abstract, but to engineer pathways and infrastructures that can deliver the right combination, at the right dose, at the right time, for the right patient, in a way that is safe, feasible, and equitable. This will demand close collaboration among anesthesiologists, surgeons, pain specialists, pharmacologists, data scientists, and implementation experts, alongside thoughtful regulatory and ethical stewardship. If these scientific and practical challenges can be met, multimodal analgesia - embedded within a precision anesthesia paradigm - has the potential to substantially improve perioperative outcomes, reduce the burden of persistent postsurgical pain and chronic opioid use, and redefine perioperative analgesic care as a dynamic, learning system rather than a static set of protocols. At the same time, a mature precision-analgesia framework must remain selective rather than maximalist: its goal is not to use more agents, but to use better-matched combinations whose expected benefits clearly outweigh their procedural, pharmacologic, and systems-level risks.

Disclosure of conflict of interest

None.

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