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The anesthesiologist's role in preventing chronic post-surgical pain and opioid use through neurobiological programming: a mini review

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Background: Chronic Post-Surgical Pain (CPSP) and Postoperative Chronic Opioid Use (COU) pose significant public health challenges. Anesthesiologists play a vital role in modulating acute pain during surgery and influencing its chronic trajectory. CPSP is defined as pain persisting for ≥ 3 months, localized to the surgical field or relevant nerve territory, and with other causes excluded. COU, a surrogate marker for prolonged utilization, is defined as prolonged utilization (≥ 10 prescriptions or ≥ 120 days' supply) in the postsurgical year, excluding the initial 90 postoperative days. This mini-review synthesizes evidence on perioperative risk factors, mechanistic pathways, and anesthetic/analgesic interventions to influence the development of CPSP and COU.

Methods: We performed a narrative literature review (February 2000–December 2025) across PubMed and Google Scholar, focusing on risk factors and mitigation strategies for CPSP and COU. Key search terms included "CPSP," "COU," "multimodal analgesia," "neuroinflammation," "epigenetic changes," "TIVA," and "precision medicine." The search prioritized randomized controlled trials, systematic reviews, and key preclinical studies.

Results: Chronicity is highly predictable based on preoperative psychosocial factors (e.g., anxiety, catastrophizing) and phenotypic hyperalgesia. Key mechanisms include central sensitization, neuroinflammation, epigenetic molecular programming, and gut-brain axis disruption. Evidence supports regional anesthesia (e.g., neuroaxial/paravertebral blocks) for CPSP prevention in high-risk procedures and targeted systemic non-opioids to mitigate opioid consumption and chronicity.

Conclusions: CPSP and COU require a precision medicine approach that accounts for individual variability. This necessitates thorough preoperative risk stratification and the implementation of targeted, mechanism-based perioperative analgesia to intercept the neurobiological programming underlying chronic pain and opioid dependence.

KEYWORDS

chronic opioid use, chronic post-surgical pain, epigenetics, gut-brain axis, multimodal analgesia, neurophysiological biomarkers, opioid-sparing analgesia, precision medicine

1 Introduction

The trajectory from acute surgical trauma to the development of CPSP and postoperative COU is increasingly predictable and mechanistically understood. The development of chronic pain following a surgery is a widespread phenomenon, contributing significantly to patient suffering, functional limitations, and psychological trauma (1–3). While incidence varies considerably by the type of surgery, high-risk surgeries like thoracotomies and breast surgeries exhibit substantial rates of CPSP (3). This persistence of pain beyond the standard healing window represents a significant societal burden. The risk of developing COU following surgery is substantial; in opioid-naïve patients, COU incidence ranges from approximately 3.9%–14%, with some studies showing approximately 10% persistence in older populations (4). This significant iatrogenic burden, driven by the introduction of opioids during perioperative pain management, exacerbates the existing public health crisis.

To effectively prevent these long-term morbidities, a precise definition of each is required: CPSP: Defined as pain that persists for a minimum of three months following surgery, is localized to the surgical field or the nerve innervation territory within that field and cannot be attributed to pre-existing conditions or new causes (2, 3). COU: Defined in administrative claims data as prolonged utilization, specifically requiring the patient to have filled ten or more prescriptions or obtained more than 120 days' supply of an opioid during the postsurgical year, critically excluding the immediate first 90 postoperative days to differentiate expected acute pain management from pathological chronicity (5).

Preoperative psychosocial factors, including anxiety, depression, and pain catastrophizing, are validated and routinely utilized markers for risk stratification (2, 5, 6). The underlying biological mechanisms linking surgical insult to chronicity are multifactorial and involve both peripheral and central processes. Key pathways include sustained neuroinflammation driven by central cytokine release (7), enduring molecular programming via epigenetic changes (8, 9), and the perturbation of the gut-brain axis through anesthetic- or opioid-induced dysbiosis (10, 11). The perioperative period serves as a unique window of maximal vulnerability and therapeutic opportunity for prevention of CPSP and COU. This is the precise time when intense nociceptive input from surgical trauma intersects with widespread systemic and central neuroinflammatory signaling, coinciding with the administration of potent pharmacological agents, including anesthetics and opioids (7, 12). Anesthesiologists are uniquely positioned to leverage mitigation strategies focused on neural blockade and targeted pharmacology to potentially stop these pathways (13, 14). Systemic strategies also include the administration of non-opioid adjuncts, such as intravenous lidocaine, which reduces peripheral and central sensitization (CS) (15–17).

The choices made by the anesthesiologist regarding technique and adjuncts to mitigate pain during the perioperative period can influence the level of Central Sensitization (CS) and the processes that can chemically program the nervous system for long-term pain (8, 18). Therefore, the anesthetic goals should extend beyond surgical safety, anesthesia, and amnesia; they must also

consider how the technique serves as a primary determinant of long-term pain and opioid outcomes (6, 19).

2 Methods

A comprehensive narrative literature review was conducted across PubMed and Google Scholar to identify relevant articles on chronic post-surgical pain and chronic opioid use, focusing on risk factors and mitigation strategies studied over the last 25 years (February 2000 to December 2025). The search strategy combined keywords including “chronic post-surgical pain,” “CPSP,” “chronic opioid use,” “COU,” “risk factors,” “perioperative management,” “precision medicine,” “neuroinflammation,” “epigenetics,” “gut-brain axis”, “gut microbiome modulation”, “Anesthesia adjuvants” “biomarkers”, and “multimodal analgesia.” This review adheres to the principles of narrative synthesis, prioritizing key randomized controlled trials, systematic reviews, and mechanistic preclinical studies to synthesize current understanding.

3 Preoperative predictors and mechanistic pathways of chronicity

The synthesis of the included studies confirms that the risk for developing CPSP and COU is predictable, driven by converging patient-specific neurobiological and iatrogenic factors.

3.1 Preoperative risk predictors

The risk for CPSP and prolonged COU is strongly associated with pre-existing patient characteristics (2, 5, 6). This notion suggests that a structured approach to preoperative risk screening is needed, transforming the anesthetic consultation from a checklist review into a more comprehensive risk-mitigation approach (Table 1) (3, 19).

3.1.1 Psychosocial and pain phenotypic

Anxiety, depression, sleep disturbance, and pain catastrophizing (an exaggerated negative mindset toward pain that involves magnifying its severity) (2) are consistently identified as robust predictors of chronic pain (2, 4, 5). These preoperative psychological factors, often termed the “Negative Affect Phenotype,” are not merely symptoms but quantifiable markers reflecting underlying neurobiology (7, 8). The history of pre-existing chronic pain and preoperative opioid use are also major risk factors, significantly increasing the likelihood of persistent opioid consumption and difficulty in weaning postoperatively (4, 5).

3.1.2 Biological predictors: genomics, hyperalgesia, and biomarkers

Precision medicine is an emerging approach that takes into account individual variability in genes, environment, and lifestyle. In anesthesia, epigenetic heritable changes in gene

TABLE 1 Summarizes the key preoperative risk factors and stratification for CPSP and COU.

Domain	Risk factor	Outcome association (CPSP/COU)	Clinical relevance/actionable strategy
Psychosocial affective (5, 7)	Anxiety, Depression, Pain Catastrophizing, Sleep Disturbance	Strong predictors of prolonged opioid use (AUC = 0.97 for the combined model) and persistent pain severity	Mandates preoperative psychological screening and referral to specialized pain resources (e.g., Transitional Pain Service).
Pain sensitivity (8, 19)	Pre-existing chronic pain, Opioid tolerance, Hyperalgesia (to experimental stimuli)	Highly predictive of increased analgesic requirement, opioid difficulty, and CPSP incidence	Guides use of advanced regional techniques (CPNB in select cases) and mechanism-based adjuncts (e.g., IV Lidocaine).
Genomic (20)	Identified markers (e.g., DRD2, ATXN1)	Emerging association with CPSP risk and pain sensitivity	Current relevance: limited to research; Future relevance: personalized pharmacogenomic guided pain management.

expression not involving alterations to the underlying DNA sequence offer critical insight into how patients may differentially respond to anesthetic agents and pain management strategies by influencing the expression of genes encoding drug-metabolizing enzymes and opioid receptors (20). This shift towards personalization is heavily reliant on ‘omics’ data (genomics, epigenetics, etc.), which reveal inter-individual variability in drug response and perioperative risk (20). For instance, genetic polymorphisms in cytochrome P450 (CYP) enzymes, such as CYP2B6 and CYP3A4/3A5, significantly influence the metabolism of commonly used agents, including propofol, ketamine, and midazolam, leading to variable efficacy and duration of action.

Similarly, variants in the mu-opioid receptor gene OPRM1, such as A118G, are critical determinants of opioid analgesic requirements and the risk of postoperative nausea and vomiting (PONV) (9, 21).

Hyperalgesia, defined as increased sensitivity to experimental pain stimuli, is an independent risk factor for CPSP during procedures such as total knee arthroplasty and herniotomy (3, 7). Studies have shown that precision medicine can use molecular biomarkers (e.g., circulating cytokines, IL-1 β , TNF- α), Matrix Metalloproteases (MMPs), and genetic polymorphisms (e.g., the μ -opioid receptor gene OPRM1 and catechol-O-methyltransferase *COMT* gene variants) to predict pain response and guide opioid-sparing protocols (20).

The development of integrated biosignatures, more robust predictive models, integrates markers across genetic, molecular, and neurophysiological domains (22).

3.1.3 Biomarkers

Recent evidence has validated sensorimotor cortical biomarkers, such as Peak Alpha Frequency (PAF) and Corticomotor Excitability (CME), which objectively map CNS changes indicative of CS and predict prolonged pain sensitivity. Large-scale initiatives, such as the Acute to Chronic Pain Signatures (A2CPS) program, are working to validate these multimodal biosignatures to accurately identify high-risk individuals before surgery (22). These observations suggest that individuals who rate experimental pain stimuli as being of increased intensity possess an underlying altered pain sensitivity that predisposes them to chronic postoperative syndromes (7).

3.1.4 Clinical integration

Multivariable models incorporating both precision medicine with biomarkers, along with the psychosocial predictors of pain, show exceptionally high predictive accuracy for patients at risk for prolonged opioid use. This suggests that integration of validated psychological screening should be standardized into preoperative anesthetic consultation (5, 13). This stratification is the foundation for the targeted Transitional Pain Service (TPS) intervention, which has demonstrated efficacy in managing high-risk patients (Table 1) (2, 19).

3.2 Core mechanistic pathways of chronicity

Surgical trauma can initiate complex neurobiological and epigenetic reprogramming, stressing the rationale for mechanism-targeted interventions during the perioperative period to prevent CPSP and COU.

3.2.1 Central sensitization (CS) and neuroinflammation

Surgical injury can induce CS, a heightened pain state driven by sustained neuroinflammation characterized by increased central cytokines and chemokines (7, 12). This perpetual inflammatory state, mediated by glial cells (microglia and astrocytes), promotes hyperalgesia and allodynia (pain evoked by non-noxious stimuli), potentially promoting chronic widespread pain (7, 8).

3.2.2 Epigenetics reprogramming

Anesthetics and opioids themselves are capable of inducing prolonged epigenetic changes (9, 12). Preclinical data suggest that exposure to general anesthesia and surgery can lead to altered DNA methylation in genes regulating synaptic plasticity (e.g., Arc and JunB), with some changes persisting for over a year (9, 12). This suggests viewing the intraoperative period as a critical window of neuroplastic vulnerability requiring mechanism-based protective interventions to prevent altering the epigenetic status of the host’s tissue post-surgery (8, 9).

3.2.3 The gut-brain axis

General anesthetics and opioids are known to disrupt gut microbial homeostasis, leading to dysbiosis that has been implicated in the development of opioid tolerance and chronic neuropathic or visceral pain through the gut-brain axis (9, 11, 23). Preclinical studies demonstrate that microbial metabolites, particularly Short-Chain Fatty Acids (SCFAs), can modulate neuroinflammatory pathways, highlighting the gut microbiome as a promising therapeutic target for preventing CPSP and COU (10, 23). Proposed mechanisms include immunomodulation and microglia activation triggered by altered levels of circulating bacterial metabolites, such as lipopolysaccharide. Collectively, these findings underscore the pivotal role of the gut microbiota in shaping the central nervous system’s inflammatory status (Table 2) (10, 11).

4 Evidence-based perioperative interventions: a mechanism-targeted approach

Anesthesiologists can interrupt the trajectory to chronicity by implementing targeted analgesic strategies that directly address the identified neurobiological pathways (Table 3).

A comprehensive list of the literature used in this mini review can be found in Table 4.

4.1 Pharmacological strategies to modulate central sensitization

The administration of intravenous adjuncts aims to inhibit receptor activation across distinct pain pathways:

- **Lidocaine** remains an important non-opioid analgesic, attenuating peripheral nociception and central sensitization through sodium channel inhibition, while also exerting anti-inflammatory effects (15–17). Clinical reports indicate that perioperative use can reduce postoperative neuropathic pain at three months (15).
- **Ketamine**, an N-methyl-D-aspartate (NMDA) receptor antagonist, prevents CS and reduces acute postoperative opioid consumption (18).
- **Magnesium sulfate**, a non-competitive NMDA receptor blocker, provides acute antinociception and reduces opioid use for up to 24 h (18)
- **Dexmedetomidine**, an alpha-2 agonist, highly effective opioid-sparing agent, reducing postoperative pain intensity and overall opioid requirements (24). Reduced time to extubation, decreased intensive care unit (ICU) length of stay, and indirectly diminished the cumulative window of high-dose opioid exposure and dependency risk (24).

TABLE 2 Outlines the proposed mechanisms and emerging interventions utilizing the gut microbiome and its role in pain.

Factor	Mechanism of influence on pain	Preclinical/clinical evidence	Future mitigation strategy
Anesthesia/Opioids (9)	Induce gut dysbiosis (alters bacterial composition); affects drug metabolism/tolerance	Preclinical studies show microbiome changes after general anesthesia and an association with opioid tolerance	Minimize unnecessary perioperative antibiotic/opioid use; develop active gut stewardship protocols.
Dysbiosis/Metabolites (9)	Altered bacterial metabolites (e.g., SCFA levels, lipopolysaccharide) lead to immunomodulation and microglia activation in the CNS	Linked to chronic pain (neuropathic, visceral, headache) in human and animal models	Targeted administration of specific bacterial strains (probiotics) or to restore microbial homeostasis.
Perioperative Probiotics (14, 20)	Reduce infection/gastrointestinal complications; specific strains may modulate visceral nociception via SCFA production	Proven efficacy in reducing short-term complications after major abdominal surgery; specific strains alleviate IBS pain symptoms	Targets chronic pain outcomes in high-risk abdominal surgery cohorts.

TABLE 3 Perioperative anesthetic modalities on long-term outcomes.

Modality/agent	Mechanistic influence on chronicity	Clinical evidence for CPSP/COU reduction	Mitigation strategy/recommendation
Regional anesthesia (Neuraxial/Para vertebral) (10)	Robust, prolonged neural blockade prevents central sensitization and nociceptive programming	Significantly decreases CPSP incidence post- thoracotomy and breast surgery	Technique of choice for high-risk truncal or neuraxial procedures where feasibility is high.
Total intravenous anesthesia (TIVA) (13, 26)	Avoids potential central neuroinflammation associated with volatiles; minimizes PONV	Reduces PONV (bariatric surgery); CPSP comparative studies ongoing	Consider for high-risk patients (e.g., bariatric, high inflammatory risk) based on emerging mechanistic concerns.
Volatile anesthetics (8)	May induce mild central neuroinflammation; associated with prolonged epigenetic changes (DNA methylation).	Evidence of non- inferiority to TIVA in immediate pain; potential for long-term adverse programming.	Requires careful consideration in vulnerable patients where neuroinflammation or epigenetic effects are concerns.
Perioperative gabapentinoids (11)	Modulate voltage-gated calcium channels.	No significant effect on CPSP prevention; increased adverse effects (dizziness, visual disturbance)	Strong recommendation against routine use for CPSP prophylaxis due to lack of benefit and increased adverse events.

TABLE 4 Results.

Reference	Type of study	Description of study	Outcome	Quality of evidence
Chronic postsurgical pain and risk stratification				
Voscopoulos and Lema (1)	Narrative review	Reviews mechanisms underlying transition from acute to chronic postsurgical pain	Identifies central sensitization and neuroplasticity as key drivers of pain chronification	Low
Katz et al. (2)	Clinical program review	Describes multidisciplinary transitional pain service model	Demonstrates improved postoperative pain management and reduced opioid dependence	Low
Thapa and Euasobhon (3)	Narrative review	Reviews current prevention and treatment approaches for CPSP	Supports multimodal perioperative analgesic strategies	Low
Schug and Bruce (6)	Narrative review	Reviews CPSP risk stratification models	Identifies psychological, surgical, and genetic risk factors	Low
Sun et al. (4)	Retrospective cohort study	Evaluates incidence and predictors of chronic opioid use after surgery	Demonstrates association between perioperative opioid exposure and long-term opioid dependence	Moderate
Larach et al. (5)	Prospective cohort study	Evaluates predictors of prolonged opioid use following total knee arthroplasty	Identifies preoperative opioid use and pain severity as predictors	Moderate
Neuroinflammation and epigenetic regulation of chronic pain				
Ji et al. (7)	Translational review	Reviews neuroinflammatory contributions to chronic pain	Identifies microglial activation and cytokine release as key mechanisms	Low
Liang et al. (8)	Mechanistic review	Reviews epigenetic mechanisms regulating chronic pain pathways	Demonstrates role of DNA methylation and histone modification in pain regulation	Low
Mokini et al. (9)	Narrative review	Examines anesthetic-induced epigenetic changes influencing long-term outcomes	Suggests anesthetic techniques may affect chronic disease outcomes	Low
Blum and Zuo (12)	Narrative review	Reviews neuroinflammatory and anti-inflammatory effects of volatile anesthetics	Demonstrates anesthetics can modulate neuroinflammatory pathways influencing postoperative pain outcomes	Low
Microbiome and pain modulation				
Minerbi and Shen (10)	Narrative review	Reviews gut microbiome influence on pain modulation	Suggests microbiome alterations influence inflammatory pain pathways	Low
Guo et al. (11)	Mechanistic review	Examines molecular mechanisms linking microbiota to pain signaling	Identifies microbiota-driven cytokine modulation of nociception	Low
Fyntanidou et al. (23)	Narrative review	Reviews probiotic use in postoperative pain management	Suggests potential improvement in postoperative recovery and inflammation	Low
Liu et al. (27)	Randomized trial protocol	Investigates perioperative probiotic supplementation in surgical oncology patients	Ongoing evaluation of postoperative outcomes	Low
Potrykus et al. (28)	Randomized controlled trial	Evaluates probiotic supplementation in bariatric surgery	Demonstrates improvement in metabolic and inflammatory outcomes	High
Wu et al. (29)	Clinical narrative review	Reviews clinical significance of perioperative probiotics in intestinal surgery	Suggests improved short-term postoperative recovery	Low
Personalized medicine, genetics, and biomarkers				
Zeng et al. (21)	Comprehensive review	Reviews genetic and AI-driven personalized anesthesia approaches	Highlights patient-specific analgesic strategies	Low
Chowdhury et al. (22)	Prospective cohort study	Evaluates cortical biomarker signatures predicting individual pain sensitivity	Demonstrates objective neuroimaging predictors of pain risk	Moderate
Kong et al. (31)	Genetic association study	Evaluates OPRM1 polymorphism impact on postoperative outcomes	Demonstrates genetic variability influences opioid response	Low
Mohammadi-Yeganeh et al. (32)	OMICS review	Reviews genomic and metabolomic approaches in perioperative medicine	Supports development of precision anesthesia models	Low

(Continued)

TABLE 4 Continued

Reference	Type of study	Description of study	Outcome	Quality of evidence
Asimakopoulos et al. (20)	Narrative review	Reviews role of biomarkers in acute pain assessment	Suggests biomarkers assist with perioperative risk prediction	Low
Perioperative analgesia and anesthetic technique				
Hussain et al. (13)	Systematic review and meta-analysis	Compares single-shot versus continuous adductor canal block in knee arthroplasty	Continuous block improves postoperative analgesia	High
Albrecht et al. (14)	Systematic review and meta-analysis	Compares femoral nerve block techniques in total knee arthroplasty	Demonstrates improved postoperative pain control	High
Verret et al. (30)	Systematic review and meta-analysis	Evaluates perioperative gabapentinoid therapy	Demonstrates opioid-sparing effects but increased sedation risk	High
Ahmed et al. (26)	Systematic review and meta-analysis	Compares total intravenous anesthesia and inhalation anesthesia	TIVA associated with improved postoperative analgesia and reduced nausea	High
Yu et al. (25)	Randomized controlled trial protocol	Evaluates anesthetic technique influence on CPSP after cardiac surgery	Ongoing evaluation of chronic pain outcomes	Low
Pharmacologic adjuncts and multimodal analgesia				
Attal et al. (16)	Randomized controlled trial	Evaluates intravenous lidocaine for central neuropathic pain	Demonstrates significant analgesic effect	High
Onyeaka et al. (15)	Narrative review	Reviews clinical trials of intravenous lidocaine for chronic pain	Suggests effectiveness across neuropathic and inflammatory pain syndromes	Low
Striebel et al. (17)	Retrospective study	Evaluates combined lidocaine and ketamine infusion therapy	Suggests improvement in chronic pain symptom management	Low
Patch et al. (24)	Case report	Evaluates dexmedetomidine treatment for opioid-induced hyperalgesia	Demonstrates potential opioid-sparing analgesic effects	Very Low
Cazzaniga et al. (18)	Narrative review	Reviews multimodal analgesic strategies for preventing CPSP	Supports multimodal analgesia for perioperative pain prevention	Low
Moka et al. (19)	Narrative Review	Reviews implementation of transitional pain services in Europe	Suggests improved perioperative pain management pathways	Low

- **Dexamethasone**, an anti-inflammatory glucocorticoid and sympatholytic that prevents chronicity. It also reduces acute opioid consumption (e.g., a 34% relative decrease on Postoperative Day 1) and pain reduction (18).
- Non-steroidal anti-inflammatory drugs (NSAIDs), strong evidence supports optimizing anti-inflammatory combinations plus dexamethasone to provide a reduction in postoperative opioid consumption (mean reduction ≈ -29.5 OMEs) (18).
- **Esmolol**, a short-acting β_1 -adrenergic antagonist, is utilized for its sympatholytic and peripheral analgesic properties, reducing intraoperative opioid use and immediate postoperative pain scores (18). Its ability to dampen the sympathetic nervous system and modulate systemic inflammation provides a compelling mechanistic rationale for its potential role in mitigating central neuroinflammation and preventing CPSP (7, 18).

4.2 Regional anesthesia and neural blockade

Regional techniques that block nociceptive transmission are highly effective in reducing postoperative pain. Literature reports

that epidural anesthesia and paravertebral blocks significantly reduced the incidence of CPSP at six months following high-risk procedures such as thoracotomy and breast surgery (2, 3). This benefit is attributed to suppression of high-intensity nociceptive signaling before it reaches the central nervous system (7). Evidence also indicates that routine use of continuous catheter-based peripheral nerve blocks (CPNBs) offers no clear advantage over single-shot blocks for general postoperative analgesia and is associated with higher complication rates. Accordingly, CPNBs should be reserved for individualized use in high-risk or opioid-tolerant patients (13, 14, 24).

4.3 Anesthetic choice and epigenetic modulation

The intraoperative choice of anesthetic technique remains a key debate for preventing long-term sequelae.

4.3.1 Total intravenous anesthesia (TIVA)

TIVA, typically using propofol, has been explored as a potentially safer option for high-risk patients. The hypothesis is that volatile agents may trigger neuroinflammation, leading to

greater epigenetic changes, while propofol-based TIVA may offer a neuroprotective or anti-inflammatory advantage (8, 12, 25, 26). Further high-quality evidence is needed, but this mechanism provides a strong rationale for TIVA use in highly stratified patients.

4.3.2 Targeting the gut-brain axis

Emerging preclinical data exploring the comparative effects of volatile agents vs. TIVA on inflammatory signaling also suggest a role for modulating chronicity via the gut microbiome using targeted probiotics (23, 27–29). This remains a speculative area for human application but highlights future avenues for intervention.

4.3.3 Transitional pain service (TPS)

The TPS model represents the optimal multidisciplinary care strategy for high-risk patients identified through preoperative screening (2, 19). These services provide coordinated care from the preoperative period through the acute postoperative phase and into the recovery window, managing high-risk factors like preoperative opioid use and severe anxiety, and ensuring a safe opioid taper plan.

4.4 Gabapentinoid dilemma

Gabapentinoids (gabapentin, pregabalin) modulate voltage-gated calcium channels, reducing excitatory neurotransmitter release and attenuating central sensitization (30). It has been reported that their perioperative use decreases acute postoperative pain and opioid consumption; however, evidence for preventing CPSP remains inconsistent (30). Systematic reviews demonstrate limited long-term analgesic efficacy, with no consistent prevention of chronic pain (30). Current recommendations therefore advise restricting gabapentinoid use to carefully selected patients, particularly those at high risk for opioid tolerance or neuropathic pain, rather than broad prophylactic administration.

5 Linical translation

Effective prevention of CPSP and COU requires a multidisciplinary perioperative pain management approach rather than reliance on a single anesthetic technique. Four key pillars support this paradigm:

- (I) **Pre-habilitation & Screening:** Early identification and management of psychosocial risk factors and hyperalgesia through TPS (2, 19).
- (II) **Surgical Optimization:** Minimizing tissue trauma, shortening operative time, and preventing iatrogenic nerve injury (2, 3).
- (III) **Mechanism-Based Anesthesia:** Strategic use of regional techniques and careful selection between TIVA and

volatile agents, guided by concerns about neuroinflammation and epigenetic effects (9, 12–14).

- (IV) **Targeted Pharmacological Intervention:** Using evidence-based non-opioid adjuncts (lidocaine, ketamine, dexmedetomidine, NSAIDs, esmolol) while avoiding routine prophylactic gabapentinoid use due to limited efficacy (15, 30).

6 Limitations and controversies

Although mechanistic evidence on neuroinflammation and epigenetics is compelling, the clinical impact of anesthetic choice on long-term outcomes remains uncertain. Confounding factors such as heterogeneous surgical models, patient variability, and difficulty separating anesthetic effects from surgical influences limit definitive conclusions. Additionally, promising preclinical findings on epigenetics and the gut microbiome require rigorous clinical validation before translation into routine practice.

7 Conclusions and future directions

The prevention of CPSP and COU in surgical patients is achievable through the application of personalized medicine that accounts for individual variability in genes, environment, and lifestyle. This necessitates thorough preoperative risk stratification by anesthesiologists and the implementation of targeted, mechanism-based perioperative analgesia to intercept the neurobiological programming that underlies chronic pain and opioid dependence. Clinical translation includes increased rigor in pre-habilitation screening for psychosocial risk factors, outlines in Table 1 and mechanism-based anesthesia guided by targeted epigenetic knowledge outlines in Table 3. Future research must focus on validating integrated multimodal biosignatures to accurately identify high-risk individuals before surgery and on confirming the long-term clinical effectiveness of mechanism-targeted interventions, such as TIVA and adjunct non-opioids, in large-scale clinical trials.

Author contributions

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Glossary

Hyperalgesia as increased sensitivity to experimental pain stimuli. Studies have shown that hyperalgesia is an independent risk factor for CPSP during procedures such as total knee arthroplasty and herniotomy.

Pain catastrophizing an exaggerated negative mindset toward pain that involves magnifying its severity.

Precision medicine an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle. With respect to anesthesia, epigenetics, the study of heritable changes in gene expression that do not involve alterations to the underlying DNA sequence, offers critical insight into how individual patients may differentially respond to anesthetic agents and pain management strategies by influencing the expression of genes encoding drug-metabolizing enzymes and opioid receptors.

Epigenetics the study of heritable changes in gene expression that occur without an alteration to the underlying DNA sequence. These changes, such as DNA methylation and histone modifications, influence how genes are read and expressed and are highly sensitive to environmental factors, such as surgical trauma, inflammation, and pharmacological agents.

Chronic post-surgical pain a persistent pain for ≥ 3 months, localized to the surgical field or relevant nerve territory, and with other causes excluded.

Chronic opioid use as prolonged utilization (≥ 10 prescriptions or ≥ 120 days' supply) in the postsurgical year, excluding the initial 90 postoperative days.

Multimodal analgesia an approach to pain management that utilizes a combination of two or more analgesic agents or techniques that act on different mechanisms of the pain pathway (e.g., peripheral nerve block, anti-inflammatory drugs, non-opioid central agents). The goal is to achieve superior analgesia with fewer side effects by reducing the required dose of any single agent, particularly opioids.

Central Sensitization a phenomenon of increased responsiveness of neurons in the central nervous system to normal or subthreshold afferent input. It is a key mechanism of chronic pain, driving hyperalgesia and allodynia and often sustained by neuroinflammation and glial cell activation.

Dysbiosis an imbalance in the gut's microbial community, characterized by a loss of beneficial bacteria, an overgrowth of harmful microbes (pathobionts), and/or a significant reduction in overall microbial diversity, disrupting normal gut function