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Precision anesthesia and pharmacogenomics: a scoping review of personalized drug response

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Background: Anesthetic agent selection and dosing have historically relied on empirical models without taking into account inter-individual variability in drug response, leading to adverse drug reactions (ADRs). Precision medicine, specifically leveraging pharmacogenomics (PGx), offers a paradigm shift toward personalized anesthesia, enhancing efficacy and safety.

Methods: This scoping review synthesized literature from 2015 to 2025, using systematic database searches and Artificial Intelligence (AI)-powered tools, to identify the most extensively studied genetic variants impacting the pharmacokinetics and pharmacodynamics of common perioperative medications.

Results: Key genetic variants in metabolic enzymes, transporters, and receptors significantly influence anesthetic outcomes. Examples include Reduced Metabolism/Prolonged Effects: Variations in *CYP3A4/5* and *POR* alter midazolam metabolism, risking prolonged sedation. *CYP2B6*6* is associated with decreased clearance of propofol and ketamine. BChE deficiency causes significantly prolonged paralysis with succinylcholine. Altered Efficacy/Increased Dose Requirements: *OPRM1 118 A>G* (G-allele) carriers show a blunted response to morphine, requiring higher doses. *CYP2D6* ultra-rapid metabolizers (UMs) can have reduced efficacy of ondansetron and risk toxicity from pro-drugs like codeine and tramadol. Pathogenic mutations in *RYR1* and *CACNA1S* identify patients susceptible to Malignant Hyperthermia from volatile anesthetics. Drug-Drug Interactions (DDIs): PGx overlaps with chronic medications (e.g., antidepressants, beta-blockers) that inhibit *CYP2D6*, creating a phenoconversion risk that functionally mimics a Poor Metabolizer (PM) phenotype, drastically altering opioid efficacy.

Conclusions: PGx holds transformative potential for the field of anesthesiology by offering actionable insights for drug selection and dose adjustment to mitigate ADRs and optimize pain control.

KEYWORDS

clinical decision support, drug-drug interaction, pharmacogenomics, phenoconversion, precision anesthesia, precision medicine

1 Introduction

The practice of anesthesiology is intrinsically high-stakes, relying on the predictable performance of potent pharmacological agents across a heterogeneous patient population. For decades, the dosing and selection of anesthetic medication have been guided by empirical, “one-size-fits-all” models, often resulting in significant inter-individual variability in drug response and adverse outcomes. Contemporary perioperative medicine is undergoing a paradigm shift toward personalized anesthesia, driven by the need to enhance efficacy and reduce risks (1). This approach tailors anesthetic regimens to a patient’s genetic profile, comorbidities, and physiological parameters, aiming to minimize complications, optimize pain management, support Enhanced Recovery After Surgery (ERAS) protocols, ultimately improve patient safety and satisfaction (1–4). The concept of genetics influencing drug response emerged in the mid-20th century, but the practical development of precision medicine began with the Human Genome Project (HGP) in the 1990s (5). The HGP’s completion in 2003 provided a framework for identifying millions of single nucleotide variants (SNVs), leading to the rise of pharmacogenomics (PGx) (5, 6). PGx studies genetic variations affecting drug pharmacokinetics and pharmacodynamics, particularly in genes encoding metabolic enzymes like the cytochrome P450 family, drug transporters, and receptors, to predict drug efficacy and toxicity (1, 7). In anesthesia, this has profound implications: adverse drug reactions (ADRs) to crucial agents like opioids and intravenous anesthetics are frequently linked to molecular variants in genes such as *COMT*, *ABCBI*, *OPRM1*, *CYP2B6*, *CYP3A4*, and *CYP2D6* (8). These variants could affect drug metabolism, sensitivity, and duration of action, directly impacting the predictability and safety of clinical care. Currently, the U.S. Food and Drug Administration (FDA) recognizes the potential utility of pharmacogenomic information in prescribing certain medications and recommends its inclusion in drug labels (9).

The variability in individual drug response is further amplified by drug-drug interactions (DDIs). Anesthesiologists routinely administer multiple pharmacological agents simultaneously, often alongside a patient’s chronic non-anesthetic medications. These interactions may inhibit or induce shared metabolic enzymes, altering a patient’s metabolizer phenotype (10). Integrating PGx data is thus critical, as a known genetic poor metabolizer (PM) status may be drastically magnified or, conversely, offset by the patient’s concomitant medication profile. Precision medicine requires accounting for both genetic predispositions and environmental (drug) influence, along with the integration of PGx results with other clinical factors such as age, existing comorbidities, and current medications to avoid suboptimal patient outcomes (1). This scoping review aims to highlight the most extensively studied genes influencing the metabolism and effects of common anesthetic drugs, evaluate their impact on clinical practice, and pinpoint the primary barriers to effectively integrating pharmacogenomics into contemporary anesthesia care.

2 Methods

This scoping review was prepared by conducting a comprehensive literature review across PubMed and Google Scholar to identify widely studied genes associated with common drugs used in perioperative care. Systematic searches were performed for articles published between 2015 and 2025. The search strategy included combinations of keywords such as “personalized anesthesia”, “pharmacogenomics”, and common anesthetic medications including “propofol”, “opioids”, “midazolam”, “rocuronium”, “local anesthetics”, “dexmedetomidine”, and “ketamine”. Artificial Intelligence (AI)-powered tools, such as Google Gemini and Research Rabbit, were employed to uncover interconnected and relevant publications. The search was restricted to human studies. Inclusion criteria prioritized randomized controlled trials, genome sequencing studies, meta-analyses, and systematic reviews investigating specific genetic variants affecting the pharmacokinetics and pharmacodynamics of anesthetic medications, with emphasis on actionable evidence supported by robust, replicated findings. The initial search was supplemented by citation tracking and snowballing techniques to uncover additional relevant studies, including those performed prior to 2015, ensuring a thorough analysis of the available research. Exclusion criteria included case reports, conference abstracts, and animal studies. Screening and data extraction were performed to identify the key genes and genetic variants, focusing on summarizing the mechanisms by which these variants affect drug response, including their impact on drug metabolism, receptor binding, and clinical outcomes in the perioperative setting. The flow diagram depicted in Figure 1 summarizes the study selection process.

3 Results

The literature search identified a comprehensive body of evidence detailing the impact of pharmacogenomic variants on perioperative drug response. The most extensively studied genes associated with common anesthetics, regional anesthetics, and analgesics are summarized and categorized in Table 1. These variants primarily affect drug pharmacokinetics (metabolism and transport) and pharmacodynamics (receptor affinity), leading to significant inter-individual variability in clinical outcomes. Specific genetic variants, such as the *CYP2B6**6 allele, the *OPRM1 118 A > G* SNV, and the butyrylcholinesterase (BChE) A variant, were consistently identified, underscoring their critical influence on drug action, which ranges from altered clearance and prolonged effects to increased dosing requirements and a heightened risk of adverse drug reactions (ADRs) such as prolonged paralysis, oversedation, or inadequate analgesia.

3.1 Pre-operative medication and pharmacogenomics

Pre-operative medication planning represents a critical window for pharmacogenomic intervention. Pre-operative

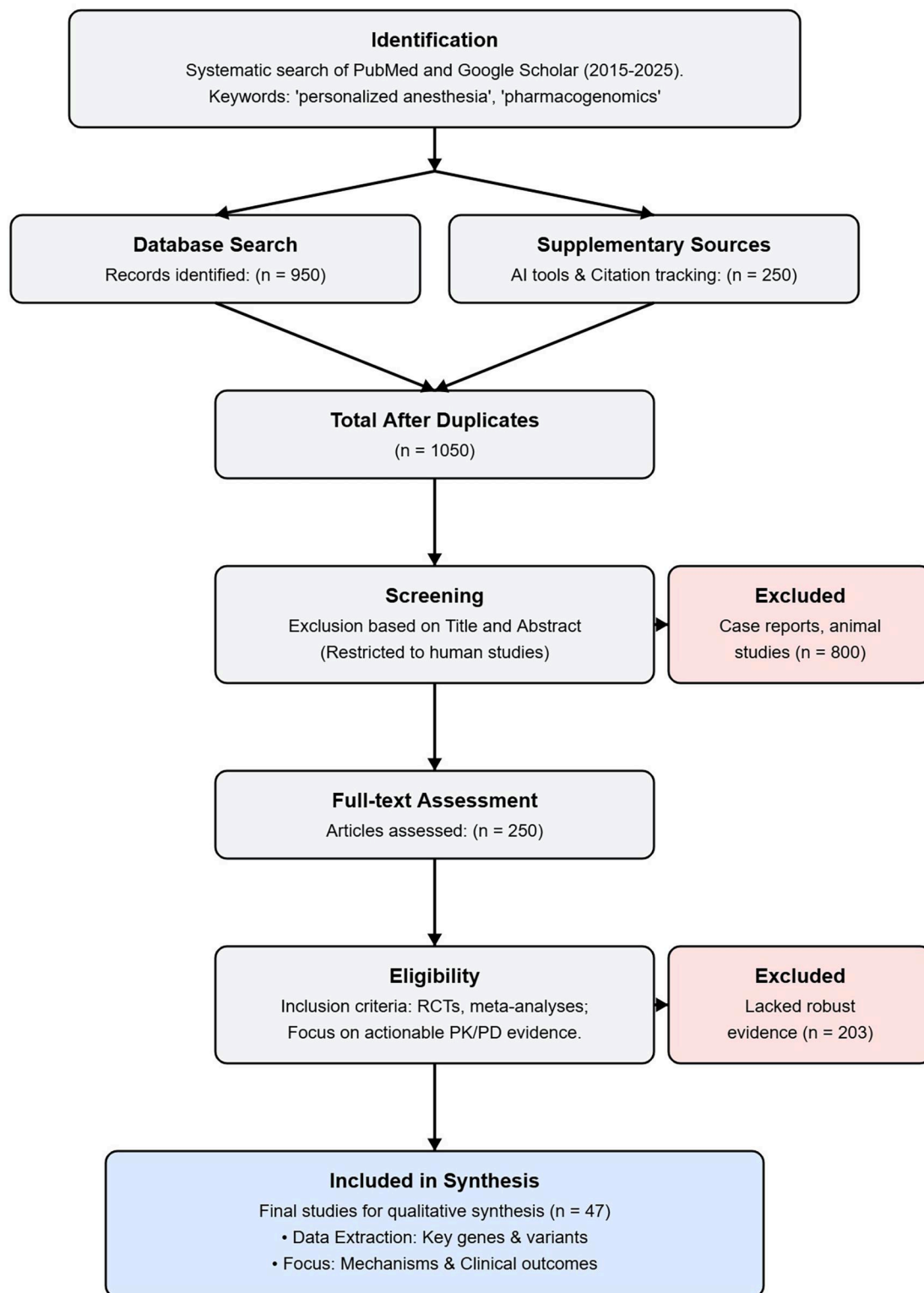


FIGURE 1
Flow diagram of the methodology. Created with Google Gemini.

pharmacogenomics focuses on optimizing sedation and anxiolysis, primarily through benzodiazepine. Variants in *CYP3A4* and *CYP3A5*, such as *CYP3A4*22* and *CYP3A5*3* significantly alter midazolam metabolism, leading to prolonged sedation in

patients with reduced enzyme activity. For example, patients with the *POR*28* variant exhibit a 45% reduction in midazolam metabolism among *CYP3A5* expressors, necessitating dose adjustments to prevent oversedation (1, 11, 12). Recent studies

TABLE 1 Pharmacogenomic targets of common perioperative anesthetic agents.

Example drug	Gene/protein	Role of protein	Effect of variation	Specific variant	Clinical implications
Midazolam (11, 12, 36)	<i>CYP3A4, CYP3A5</i>	Metabolism (Phase I Hydroxylation)	Reduced enzyme function leads to decreased metabolism, resulting in prolonged sedation and potential for re-sedation.	<i>CYP3A4*22, CYP3A5*3, POR*28</i>	Requires significant dose reduction (25%–50%) or substitution with an agent not metabolized by <i>CYP3A4/5</i> (e.g., Lorazepam)
Diazepam (13)	<i>CYP2C19</i>	Metabolism	PM ^a exhibit increased plasma levels and prolonged half-life, increasing risk of over-sedation.	Various <i>CYP2C19</i> PM alleles	Risk of prolonged or excessive sedation (over-sedation). Consider using an alternative benzodiazepine (e.g., Lorazepam).
Local Anesthetics (14)	<i>SCN5A</i>	Target voltage-gated Na ⁺ channel	<i>SCN5A</i> variants (e.g., associated with Brugada syndrome) can increase susceptibility LAST	<i>SCN5A*D1790G</i>	Requires reduced dose and slow, fractionated injection.
Lidocaine, Ropivacaine, Mepivacaine (15)	<i>CYP1A2, CYP3A4</i>	Metabolism (oxidative)	Reduced enzyme function in PMs ^a leads to decreased clearance and accumulation of parent drug/toxic metabolites.	<i>CYP1A2*1F, CYP3A4*22</i>	Risk of prolonged effect and systemic toxicity (CNS and cardiac). Requires dose reduction or substitution with a different amide local anesthetic.
Ropivacaine, Bupivacaine (16)	<i>ABCB1</i>	Afflux transporter (P-glycoprotein)	Reduced transporter function leads to higher intracellular concentrations in target tissues (e.g., CNS), increasing toxicity risk (e.g., seizure)	<i>ABCB1*C3435T</i>	Dose reduction is indicated.
Propofol (17, 18)	<i>CYP2B6, UGT1A9</i>	Metabolism (Hydroxylation & Glucuronidation)	<i>CYP2B6*6</i> allele associated with decreased clearance, leading to higher drug concentrations and increased ADRs.	<i>CYP2B6*6</i>	Increased risk of delayed emergence/recovery and Propofol Infusion Syndrome (PRIS) at standard doses. Requires dose reduction.
Etomidate (20)	<i>GABAA receptor (GABRB2)</i> GABAA receptor polymorphisms in variability to propofol and benzodiazepines would provide a more complete pharmacodynamic picture	Mediates sedation and amnesia	Variations profoundly alter etomidate sensitivity and efficacy.	<i>Beta2N265</i> variants	Variability in hypnotic effect (higher or lower required dose). High risk of adrenocortical suppression remains.
Ketamine (19)	<i>CYP2B6, CYP3A4</i>	Metabolism	<i>CYP2B6*6</i> allele associated with reduced steady-state plasma clearance, requiring dose reduction.	<i>CYP2B6*6</i>	Higher plasma concentrations increase risk of psychomimetic side effects and prolonged emergence. Dose reduction may be necessary for PMs ^a .
Fentanyl, Remifentanyl, Alfentanil, Sufentanil (32, 37–40)	<i>CYP3A4, CYP3A5</i>	Metabolism	Polymorphisms in <i>CYP3A5</i> associated with altered metabolism and risk of ADRs.	<i>CYP3A5*14T > C</i>	Risk of prolonged or profound respiratory depression in PMs ^a . Requires careful titration and increased respiratory monitoring.
All Opioids (10, 36)	<i>COMT</i>	Pain modulation/ Central processing	Decreased enzymatic activity is associated with higher pain sensitivity, requiring higher opioid doses.	<i>COMT p.Val158Met (rs4680)</i>	High pain sensitivity requires significantly higher opioid doses. Multimodal pain management helps reduce opioid requirements.
Succinylcholine, Mivacurium (21, 27)	<i>BChE</i>	Hydrolysis (metabolism)	BChE deficiency slows drug metabolism, causing significantly prolonged paralysis (apnea) post-administration.	Atypical <i>rs1799807 (209A > G)</i> , <i>K variant (1615G > A)</i>	High risk of prolonged neuromuscular blockade. Requires confirmation with nerve stimulator and mechanical ventilatory support.
Rocuronium (21–24)	<i>SLCO1A2, ABCB1, SLCO1B1</i>	Transport/Uptake (OATP1A2, P-glycoprotein)	Variants in <i>SLCO1A2</i> associated with differences in dose requirements; <i>ABCB1</i> variants prolong clinical duration.	<i>SLCO1A2</i> locus, <i>ABCB1 rs1128503 (C > T)</i>	Variability in onset and duration of blockade. UM ^a status may require a higher initial dose; PM ^a status may prolong duration.

(Continued)

TABLE 1 Continued

Example drug	Gene/protein	Role of protein	Effect of variation	Specific variant	Clinical implications
Morphine, Fentanyl (all) (32, 34)	<i>OPRM1</i> (μ -opioid receptor) ^b	Receptor binding, Pain modulation	G-allele carriers show blunted response to morphine, requiring higher doses; linked to post-op side effects (e.g., vomiting).	<i>OPRM1 rs1799971</i> (c.118A > G; p.N40D) G allele	Due to the reduced receptor efficiency, patients may require significantly higher cumulative opioid doses. Titrate dose carefully: monitor for respiratory depression (safety) while aiming for effective multimodal pain relief.
Volatile Agents (Sevoflurane, Desflurane, Halothane) (18, 25–27)	<i>RYR1, CACNA1S</i>	Ryanodine Receptor Sarcoplasmic Reticulum Calcium Release Channel/L-type Calcium Channel (Excitation-Contraction Coupling)	Pathogenic mutations result in susceptibility to Malignant Hyperthermia (MH) upon exposure to triggering agents.	<i>RYR1</i> (highest mutational heterogeneity)	AVOID all volatile anesthetics (and succinylcholine) if MH susceptibility is known or strongly suspected (Pre-test probability). Follow MHAUS protocol.
Dexmedetomidine (29–31)	<i>GABRA2, CYP2A6, UGT</i>	Neuronal Signaling/ Receptor function (GABARA2) Metabolism (Phase I/II) (<i>CYPE2A6, UGT</i>)	Polymorphism in <i>GABARA2</i> is associated with a more pronounced decrease in heart rate. Variants of <i>CYP</i> and <i>UGT</i> lead to reduced enzyme function, resulting in lower metabolic efficiency.	<i>GABRA2 rs279847, CYP2A6 rs28399433</i>	Careful dose titration is necessary to avoid ADRs and prolonged sedation.
Ondansetron (42)	<i>CYP2D6</i>	Metabolism	UM ^a convert drug to inactive metabolite too quickly, reducing antiemetic efficacy and increasing risk of Postoperative Nausea/ Vomiting (PONV)	<i>CYP2D6</i> UM phenotype	Consider an alternative antiemetic agent.
Codeine, Tramadol (38)	<i>CYP2D6</i>	Metabolism (Pro-drug activation)	UM ^a convert drug too quickly leading to toxicity; PM ^a get insufficient pain relief.	Various <i>CYP2D6</i> alleles	Codeine/Tramadol is contraindicated in both UM and PM phenotypes. Consider multimodal pain management.

^aMetabolizer Phenotypes (PM/UM): Poor Metabolizers (PM) possess little to no functional enzyme activity, leading to drug accumulation and toxicity. Ultra-rapid Metabolizers (UM) have significantly increased enzyme function (often due to gene duplication), resulting in rapid drug clearance or excessive active metabolite production.

^b*OPRM1* 118 A > G: A common single nucleotide polymorphism resulting in reduced μ -opioid receptor expression. Carriers of the G allele typically exhibit a blunted analgesic response and require higher opioid doses.

emphasize the role of *CYP2C19* in diazepam metabolism, where PM may require dose reductions to avoid excessive sedation, requiring preemptive dose reductions (13).

Pharmacogenomics is also essential in regional anesthesia, as genetic variations modulate both the effectiveness and the risk side effects, including Local Anesthetic Systemic Toxicity (LAST). The most critical safety determinant is the *SCN5A* gene, which encodes the cardiac Nav1.5 sodium channel, the primary off-target site for local anesthetics. Pathogenic variants in *SCN5A*, also associated with Brugada syndrome, can impair cardiac conduction and are associated with a heightened susceptibility to LAST due to exaggerated cardiac effects (14). The duration and systemic toxicity of local anesthetics are further divided by their chemical class and underlying metabolic pathways. Amide-type local anesthetics (e.g., lidocaine, bupivacaine) rely on hepatic metabolism by *CYP1A2* and *CYP3A4*. PM patients have reduced clearance of medication, which increases the risk systemic toxicity, particularly during continuous regional infusions (15). Furthermore, variants in the efflux transporter *ABCB1* can alter the transport of local anesthetics across the blood-brain barrier, influencing the

severity of central nervous system (CNS) neurotoxicity by modulating the drug's access to the central nervous system (16).

3.2 Intra-operative medication and pharmacogenomics

Intra-operative pharmacogenomics influences the choice and dosing of induction agents, neuromuscular blockers, and maintenance anesthetics. Propofol, a cornerstone of induction, exhibits variable metabolism due to *CYP2B6* (e.g., *rs3745274, rs2279343, rs3211371*) and *UGT1A9* polymorphisms, affecting induction doses and recovery times (17, 18). Similarly, ketamine, used for induction and maintenance, shows reduced clearance with the *CYP2B6*6* allele, prolonging its effects, particularly in chronic pain patients (19). For etomidate, mutations in GABAA receptor subunits, such as *GABRB2 rs121909230* (c.794A > G), can modify efficacy, requiring vigilant monitoring (20). Neuromuscular blockers (NMBs) like succinylcholine and rocuronium are highly sensitive to genetic variations. *BChE* variants (e.g., *Atypical rs1799807*) cause pseudocholinesterase

deficiency, leading to prolonged paralysis with succinylcholine, while *SLCO1A2* variants (e.g., *rs2306283*) increase rocuronium dose requirements (21–23). Other known variants related to rocuronium are *ABCB1* and *SLCO1B1*, which have been shown to prolong the clinical duration of the drug (24).

Unlike many intravenous agents, inhalational anesthetics are almost exclusively eliminated by the lungs, meaning their effects generally do not depend on common polymorphisms in genes encoding metabolic enzymes or drug transporter proteins; however, they are still influenced by ion channel variants (*KCNK9/TASK-1*, *KCNK2/TREK*), which can alter their hypnotic effects (18, 25, 26). Genotyping surgical candidates can identify patients at risk for malignant hyperthermia (MH) due to *RYR1* or *CACNA1S* variants, allowing providers to avoid triggering agents like volatile anesthetics or succinylcholine (27). While preemptive *RYR1* screening is not currently endorsed by the Malignant Hyperthermia Association of the U.S. (MHAUS) for the general population, it is strongly advised if there is a pre-test probability for MH-susceptibility (28).

Dexmedetomidine, a widely used α_2 -adrenergic agonist for perioperative sedation and analgesia, exhibits both pharmacokinetic and pharmacodynamic variability driven by genetic factors. Its metabolism, handled primarily by *CYP2A6* and *UGT* enzymes, is impacted by polymorphisms such as the *CYP2A6 rs28399433* variant, which results in lower metabolic efficiency (29, 30). Furthermore, genetic influence extends to its cardiovascular effects: the *GABRA2 rs279847* polymorphism has been significantly associated with the pronounced degree of heart rate decrease observed in some patients (29, 31).

3.3 Post-operative medication and chronic pain management

Inadequate Postoperative Pain (POP) management and postoperative nausea and vomiting (PONV) can lead to increased healthcare costs, prolonged length of stay, higher morbidity, and the development of chronic pain Syndromes (32, 33). PGx holds the promise of enhancing pain management by preemptively predicting an individual's reaction to a particular analgesic before treatment begins (32). Post-operative pain management relies heavily on opioids, where pharmacodynamic genes, particularly *OPRM1* polymorphisms, play a critical role. The μ -opioid receptor, encoded by *OPRM1*, is highly studied, and the *OPRM1 rs1799971 (c.118A > G; p.N40D)* variant has been shown to result in a blunted response to morphine, consequently requiring higher doses to reach analgesia (32, 34). Notably, this variation is also linked to a lower incidence of nausea (33, 35). Conversely, *OPRM1 304G* variant has been found to enhance intrathecal fentanyl analgesia in women (1). Catechol-O-methyltransferase (*COMT*) gene modulates central pain signals; patients homozygous for the Val/Val genotype exhibit higher pain sensitivity whereas Met/Met patients are more opioid-sensitive.

Patients with the *COMT rs4680 (p.Val158Met)* are less opioid-responsive, consequently require higher opioid doses and are thus

paradoxically at a higher risk of toxicity when escalated doses are used (10, 36). Pharmacokinetic variability mediated by *CYP2D6* variants further complicate opioid therapy. This gene is highly polymorphic, translating to enzymatic activities ranging from poor PMs to ultra-rapid metabolizers (UMs) (37, 38). This greatly affects pro-drugs like codeine and tramadol, with UMs at risk of fatal toxicity and PMs at risk of inadequate pain relief (10, 32). The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend avoiding codeine in *CYP2D6* UMs to prevent overdose (38). Since analgesic effect is a result of the cumulative impact of multiple genes, a multifactorial model integrating genetic data with biological, physical, and social factors is necessary. Given the costs, initially targeting high-risk patients with poor pain control or those at risk of chronicity represents the best practice for minimizing costs and complications (32, 39–41). For instance, for chronic pain, *CYP2D6*-guided therapy has shown improved pain scores in intermediate metabolizers and PM (39, 40). This also highlights the importance of employing multimodal pain management strategies to achieve effective pain control while minimizing the risks associated with opioids.

Additionally, ondansetron, used for antiemetic prophylaxis, shows reduced efficacy in *CYP2D6* UM, increasing the risk of PONV. Genetic testing for *CYP2D6* can guide the selection of alternative antiemetics, such as tropisetron, for these patients (42).

3.4 Drug-drug interactions

DDIs in anesthesia are exacerbated by genetic variations in shared metabolic pathways and thus, are a potential risk in the perioperative setting (Table 2). Propofol, for example, demonstrates a concentration-dependent inhibition of *CYP2B1* and *CYP1A1* enzymes, posing risks when co-administered with certain cardiac drugs that are also metabolized by these *CYP450* enzymes. Examples of affected medications are quinidine, amiodarone, and nifedipine, potentially leading to prolonged effects or cardiovascular instability in polymedicated patients (43). Similarly, beta-blockers, which *CYP2D6* metabolizes, can cause hypotension and bradycardia in presence of propofol (44). Carbamazepine, a common anticonvulsant, upregulates *SLCO1A2*, reducing rocuronium's duration of action (45). DDIs can also alter a patient's metabolizer phenotype, a phenomenon known as phenoconversion (46). For instance, *CYP2D6*-mediated interactions are crucial for drugs like codeine and tramadol, which are converted into active metabolites. When co-administered with *CYP2D6* inhibitors such as fluoxetine and paroxetine, patients can mimic PM phenotypes, reducing efficacy (47). Furthermore, genetic factors can intersect with non-genetic ones: individuals with lower levels of HDL, often associated with Apolipoprotein-A1 (APO-A1) deficiency, also have a higher risk of having low levels of BChE, significantly increasing their risk of prolonged paralysis from NMBs (48–50). The integration of pharmacogenomics with other clinical factors, such as age, existing comorbidities, and current medications, is imperative to provide optimal patient

TABLE 2 Pharmacogenomic overlap and drug-drug interactions (DDIs) between common chronic medications and anesthetic agents, highlighting the importance of preemptive dose adjustment in the polymedicated surgical patient.

Patient's non-anesthetic drug class (comorbidity)	Example drug/factor	Gene/protein in common	Anesthetic drug affected	Mechanism/impact of DDI
Antihypertensive (Beta-Blockers) (44)	Metoprolol, Propranolol	<i>CYP2D6</i>	Opioids (Codeine, Tramadol), Ondansetron	Both drug classes rely on <i>CYP2D6</i> . <i>CYP2D6</i> PM status increases Metoprolol concentration (risk of hypotension/bradycardia) and concurrently renders Codeine/Tramadol ineffective (ineffective pain relief).
Antidepressants (SSRIs/SNRIs) (47)	Fluoxetine, Paroxetine	<i>CYP2D6</i> (Strong Inhibitor*)	Opioids (Codeine, Tramadol), Ondansetron	Potent <i>CYP2D6</i> inhibition prevents pro-drug activation of Codeine/Tramadol, leading to treatment failure for pain management. Also alters Ondansetron metabolism.
Type II Diabetes (51)	Metformin	<i>SLC22A1</i> (OCT1)	Opioids (Morphine, Tramadol), Local Anesthetics	<i>SLC22A1</i> is a major transporter for Metformin and also influences the distribution and pain signaling pathways for certain opioids and local anesthetics.
Anticoagulants (52)	Warfarin	<i>CYP2C9</i> , <i>VKORC1</i>	Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) (e.g., Celecoxib)	Warfarin metabolism is heavily dependent on <i>CYP2C9</i> . Co-administration of NSAIDs (which are also <i>CYP2C9</i> substrates) can increase Warfarin concentration, raising the risk of perioperative bleeding.
Anticonvulsants (45)	Carbamazepine	<i>SLCO1A2</i> (OATP1A2)	Rocuronium	Carbamazepine acts as an Inducer of <i>SLCO1A2</i> expression, increasing rocuronium uptake and requiring a significantly higher rocuronium dosage.
Cardiovascular (43)	Antiarrhythmics, CCBs (Quinidine, Nifedipine)	<i>CYP450</i> Enzymes (<i>CYP2B1</i> , <i>CYP1A1</i>)	Propofol	Propofol can cause concentration-dependent inhibition of these CYP enzymes, increasing plasma concentration and toxicity risk of coadministered cardiac drugs.
Lipid-Lowering/Metabolic (48–50)	Apolipoprotein-A1 (APO-A1) Deficiency (Low HDL)	BChE	Succinylcholine, Ester Local Anesthetics	Low BChE levels associated with low HDL led to prolonged paralysis from succinylcholine or extended effect of ester-based local anesthetics.
Chronic Pain/Antiepileptic (53)	Phenytoin	<i>CYP2C9</i>	NSAIDs (Celecoxib, Diclofenac)	Phenytoin acts as an inducer of <i>CYP2C9</i> . Chronic use can decrease the efficacy of preemptively administered NSAIDs by increasing their metabolism.
Immunosuppressants (54, 55)	Cyclosporine, Tacrolimus	<i>CYP3A4/5</i> , P-glycoproteins (<i>ABCB1</i>)	Fentanyl, Midazolam	Potent Inhibition: These calcineurin inhibitors are strong inhibitors of <i>CYP3A4/5</i> and the efflux transporter P-gp. Co-administration severely decreases the clearance of Fentanyl (risk of respiratory depression) and Midazolam (prolonged sedation).
Statins (56)	Simvastatin, Atorvastatin	<i>CYP3A4</i>	Midazolam	Competition/Inhibition: These statins are <i>CYP3A4</i> substrates. Co-administration can competitively inhibit Midazolam metabolism, potentially leading to prolonged sedative or hypnotic effects.

outcomes. Since DDI can functionally alter a patient's metabolizer phenotype, accounting for both inherited genetic variability and drug-induced enzymatic change is essential for precision medicine and minimizing potential complications (46).

3.5 Clinical practice, anesthesiologist perspective, and barriers to implementation of pharmacogenomics

Even though the benefits of PGx and precision medicine are clear, their integration into clinical anesthesia faces several clinical and logistical barriers, including the limited availability of rapid, high-quality genotyping tests, high costs, and a lack of reimbursement. In the U.S., clinical laboratories are required to be accredited, and concerns about false positives/negatives persist due to test design limitations (57). Anesthesiologists

often cite an insufficient understanding of PGx, a lack of integration into electronic medical records (EMR), and inadequate clinical decision support as major hurdles (9). Additionally, providers have reported that the most common reason for not considering PGx results, even when available, was forgetting to access the information, indicating that the information was not yet part of their usual clinical workflow (2). Other barriers cited by providers include: "testing is not worth the financial costs" (17%), "my awareness about the existence of pharmacogenomics information is lacking" (13%), and "there is insufficient pharmacogenomics information for most drugs" (13%) (9).

Another hurdle in the implementation of PGx is that certain ethnic and racial groups are underrepresented in genetic studies, which can limit the generalizability of current PGx findings and lead to disparities in care (10). To overcome these barriers and successfully implement PGx into routine clinical and

perioperative practice, a robust clinical decision support (CDS) infrastructure is necessary (58). This system must act as a bridge, translating accurate and comprehensive raw genetic data into meaningful clinical actions. It must seamlessly integrate standardized resources, such as the CPIC guidelines, to provide anesthesiologists with immediate, actionable recommendations for drug selection and dosing (41, 58). Initiatives like the “All of Us Research Program” are vital for providing the large-scale, diverse genetic datasets to standardize protocols and address disparities in genetic data representation (59). Lastly, training healthcare professionals to recognize DDI and inter-individual variability, while simultaneously developing AI-driven predictive models, remains critical for the successful and widespread implementation of personalized medicine (57, 59).

3.6 Limitations

While this review provides a comprehensive synthesis of pharmacogenomic targets in anesthesia, several limitations inherent to the current manuscript and the nature of a scoping review must be acknowledged. First, because a scoping review methodology was employed rather than a formal systematic review or meta-analysis, this paper does not provide a quantitative assessment of the effect size or the level of evidence for each genetic association described. Furthermore, the reliance on existing literature introduces a significant geographic and ancestral bias; the majority of the data synthesized herein originates from Caucasian populations, which limits the applicability of our conclusions to more diverse global populations who may harbor unique, uncharacterized alleles in genes.

The manuscript is also constrained by the lack of robust, large-scale prospective clinical trials specifically investigating the impact of preemptive genotyping on hard surgical outcomes, meaning that many of the clinical recommendations discussed are extrapolated from pharmacokinetic models or smaller observational cohorts. Additionally, this review focuses primarily on single-gene-drug interactions, potentially oversimplifying the highly polygenic nature of anesthetic response, which is governed by complex gene-gene and gene-environment interactions that are not yet fully elucidated in the literature.

Finally, while we address the critical role of phenoconversion and drug-drug interactions, the current manuscript cannot provide a dynamic tool for real-time clinical application, as static genetic data often fails to capture the fluctuating physiological and pharmacological state of the perioperative patient.

4 Conclusion

Pharmacogenomics holds transformative potential for the field of anesthesiology by enabling tailored anesthetic regimens that enhance safety and efficacy while reducing ADRs and costs. This scoping review highlights key genetic variants, such as those in

CYP2B6, CYP3A4, OPRM1, and BChE, that could influence the metabolism and action of common anesthetic drugs, offering actionable insights for personalized care. However, barriers such as limited access to rapid genotyping, high costs, and insufficient provider training hinder robust implementation. By addressing these challenges through standardized protocols, EMR integration, and AI-driven decision support, the implementation of pharmacogenomics can potentially revolutionize anesthesia practice and ensure precision medicine benefits all patients.

Author contributions

OE-L: Conceptualization, Investigation, Supervision, Visualization, Writing – original draft, Writing – review & editing. SN: Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. RW: Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing.

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