Despite the opioid epidemic, up to 86% of patients experience moderate to severe pain after major surgery. Although several factors influence the amount of pain patients experience postoperatively, studies have identified genetic variations that influence pain perception and response to pain medications. The purpose of this article is to examine evidence of the genetic differences that affect patients’ responses to medications frequently used in postoperative pain management. Genes of interest associated with postoperative pain management include the opioid μ1 receptor (OPRM1), cytochrome P450 (CYP) enzymes, catechol O-methyl transferase (COMT) enzyme, and adenosine triphosphate–binding cascade (ABCB1) transporter. There is moderate evidence linking the OPRM1 sequence variation and response to morphine in the postoperative period. Besides activity at the OPRM1 receptor, analgesic efficacy and adverse effects of pain medications also depend on their rate of metabolism by CYP enzymes. CYP2D6 enzymes metabolize codeine and tramadol. Codeine and tramadol are not recommended in CYP2D6 poor metabolizers and ultrarapid metabolizers and are contraindicated in children and breastfeeding mothers. Similarly, caution must be exercised when using nonsteroidal anti-inflammatory drugs in CYP2C9 intermediate metabolizers and poor metabolizers. Large-scale studies are needed to develop genotype-guided therapeutic guidelines for most medications used in postoperative pain management.

Pharmacogenetics of Postoperative Pain Management: A Review

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Julie M. Kittelsrud, PhD, CNP

More than 50 million inpatient surgeries are performed in the United States annually,¹ which makes adequate postoperative pain management a priority for professional organizations such as the American Associations of Nurse Anesthetists (AANA)² and the Joint Commission.³ The unpleasant sensory and emotional experience of pain interferes with the recovery process because it decreases early ambulation, productive coughing, and patient satisfaction and increases healthcare costs.³ Despite the establishment of guidelines and the increased awareness of the negative financial and physiologic consequences of inadequate postoperative pain management, up to 86% of patients still experience moderate pain after major surgery.¹

The fact that patients respond differently to postoperative pain and pain medications is well known to anesthesia providers. Although several factors may influence a patient’s perception of pain and response to analgesic medications, recent scientific evidence has demonstrated that genetic variations play an essential role in a patient’s response to medications.⁴⁻⁵ Postmarket analysis shows that up to 18% of prescriptions have actionable pharmacogenetics information,⁵ and the US Food and Drug Administration (FDA) has approved genetic inserts for more than 100 drugs currently in clinical use.⁶ These include medications frequently used in the perioperative period, such as tramadol, codeine, ondansetron, and lidocaine.⁶

Prescription opioids have been identified as one of the main initiators of the ongoing opioid epidemic. Approximately 80% of heroin users report that prescription opioids were their first exposure to opioids.⁷ Undoubtedly, genetic variations in the patient population may alter outcomes. The idea of pharmacogenetics is “to administer the right drug, to the right patient, at the right frequency, via the right route, based on genetic predisposition.”⁸ This review covers current evidence of genetic sequence variations (frequently called polymorphisms) that affect patients’ responses to medications frequently used in postoperative pain management. Knowledge gaps are highlighted throughout the article, and implications for clinical practice and research are provided. A basic understanding of human genetic diversity and variability in response to medications is essential for the implementation of pharmacogenetics knowledge in clinical practice. A detailed review of this essential information was published in the April 2019 edition of the AANA Journal.⁸

Pharmacogenetics of Pain Medications

As it relates to postoperative pain management, variability in genes encoding 3 categories of proteins are of interest: drug transport proteins, drug-metabolizing enzymes, and receptors.⁵ The Table summarizes the genes that
affect the pharmacokinetics and pharmacodynamics of medications commonly used in postoperative pain. The P-glycoprotein adenosine triphosphate (ATP)–binding cassette transporter, encoded by the \textit{ABCB1} gene, regulates transportation across the blood-brain barrier.\(^9\) Most analgesic medications exert their effect by stimulating the \(\mu\)-opioid receptor, encoded by the \textit{OPRM1} gene,\(^2\) and undergo phase 1 metabolism catalyzed by cytochrome \(\text{P450}\) (CYP) enzymes (encoded by the \textit{CYP}\(\text{A}\text{X}\) genes).\(^4\) Also, the catechol \(\text{O}\)-methyl transferase (COMT), encoded by the \textit{COMT} gene, plays a crucial role in the metabolism of neurotransmitters such as dopamine and norepinephrine and pain perception.\(^10,12\) With this in mind, we will discuss medications frequently used in postoperative pain management and explicate the influence of genetic variations on their efficacy and adverse effects.

- **Fentanyl.** Fentanyl is one of the most used synthetic opioids for postoperative pain management. Like most opioids, its analgesic effects result primarily from stimulation of the \(\mu\)-opioid receptor in the central nervous system (CNS). The concentration of fentanyl in the CNS is regulated by the efflux of substance P glycoprotein (Pgp) transporter (coded by \textit{ABCB1} gene), which is a blood-brain barrier endothelial efflux transporter.\(^4,8\) Increased or decreased expression of \textit{ABCB1} has been associated with several single-nucleotide variations (SNVs, or formerly single-nucleotide polymorphisms, SNPs), including 1236G>T, 2677G>T/A/C, and 3435C>T. Among patients who underwent colorectal surgery, individuals with \textit{ABCB1} C3435T homozygous TT allele required less fentanyl compared with CT and CC (wild-type) alleles.\(^13\) These findings are contrary to those of another study that examined patients who were administered fentanyl for intraoperative pain control but received morphine for postoperative pain management during an elective nephrectomy. Those with the homozygous TT allele (C3435T) consumed less opioid than the wild-type homozygous CC allele.\(^14\) Results of current studies suggest that the \textit{ABCB1} sequence variation may play a role in acute postoperative pain management.

In the CNS, the adrenergic system plays a role in pain mechanisms and response to opioids. Sequence variations in adrenergic receptor (\textit{ADRB1}) and \textit{COMT} genes affect patients’ analgesic response to fentanyl postoperatively.\(^15,17\) Following painful orofacial procedures, females with a G allele of the \textit{ADRB1} G1165C and 145A/1165C haplotype had a significant decrease in postoperative fentanyl use.\(^15\) Four SNVs (rs6269, rs4633, rs4818, and rs4680) constitute a haplotype in the \textit{COMT} gene. Among patients who underwent a radical gastrectomy, having the \textit{COMT} haplotype ACCG was associated with decreased analgesic response to fentanyl.\(^16\) Using regression modeling, Khalil and colleagues\(^18\) predicted that patients with \textit{OPRM1} AG/GG and \textit{COMT} met/met genotype consumed more opioids postoperatively. Among patients who underwent painful surgery, carriers of the

### Table. Genes That May Influence Some Postoperative Pain Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Transporter</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Pharmacodynamic genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>\textit{ABCB1}</td>
<td>CYP3A4, CYP3A5</td>
<td>None</td>
<td>OPRM1, COMT</td>
</tr>
<tr>
<td>Morphine</td>
<td>\textit{ABCB1, SLCO1B1}</td>
<td>CYP3A4, CYP2C8</td>
<td>UGT2B4, UGT2B7, UGT2B15, UGT2B17, UGT1A1, UGT1A3, UGT1A8, UGT1A9, UGT1A10</td>
<td>OPRM1</td>
</tr>
<tr>
<td>Codeine</td>
<td>\textit{ABCB1, SLCO1B1}</td>
<td>CYP2D6, CYP2D7, CYP3A4, UGT2B4</td>
<td>UGT2B7</td>
<td>OPRM1</td>
</tr>
<tr>
<td>Tramadol</td>
<td>\textit{ABCC2, SLCO22A1, OCT1}</td>
<td>CYP2D6, CYP3A4, CYP2B6</td>
<td>UGT2B7, UGT1A8</td>
<td>OPRM1</td>
</tr>
<tr>
<td>Oxycodeone, hydrocodone</td>
<td>\textit{ABCB1, SLCO1B1}</td>
<td>CYP2D6, CYP3A4, CYP3A5</td>
<td>UGT2B4, UGT2B7</td>
<td>OPRM1</td>
</tr>
<tr>
<td>Ketamine</td>
<td>\textit{OCT1}</td>
<td>CYP2B6, CYP2C9, CYP3A4</td>
<td>None</td>
<td>GRIN2B</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>\textit{ABCC2, ABCG2, ABCC3}</td>
<td>CYP2E1, CYP1A2, CYP2D6, CYP2A6, CYP3A4</td>
<td>UGT1A1/B SULT1A1/3/4, SULT1E1, SULT2A1, GSTP1, GSTT1, GSTM1</td>
<td>PTGS1, PTGS2</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>None</td>
<td>CYP2C9, CYP2C9, CYP2C19, CYP3A4, UGT2B4, UGT2B7, UGT2B17, UGT1A3, UGT1A9, UGT2B17</td>
<td>None</td>
<td>MCIR</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>None</td>
<td>CYP1A2, CYP3A4, CES1</td>
<td>None</td>
<td>MCIR</td>
</tr>
</tbody>
</table>

Abbreviations: \textit{ABCB1}, adenosine triphosphate (ATP)–binding cassette subfamily B member 1; \textit{ABCC2}, ATP-binding cassette subfamily C member 2; \textit{CYP}, cytochrome P450; \textit{COMT}, catechol \(\text{O}\)-methyltransferase; \textit{GRIN2B}, glutamate ionotropic receptor \(\text{NMDA}\) type subunit 2B; \textit{GSTP1}, glutathione S-transferase \(\text{pi}\) 1; \textit{MCIR}, melanocortin 1 receptor; \textit{NSAIDs}, nonsteroidal anti-inflammatory drugs; \textit{OCT1}, organic cation/carnitine transporter 1; \textit{OPRM1}, opioid receptor \(\mu\) 1; \textit{PTGS1}, prostaglandin-endoperoxide synthase 1; \textit{SLCO1B1}, solute carrier organic anion transporter family member 1B1; \textit{SULT1A1/3/4}, \textit{SULT1E1}, sulfotransferase family 1E member 1E; \textit{UGT2B7}, uridine 5'-diphospho-glucuronosyltransferase family 2 member B7.
G allele (OPRM1 118A>G) consumed less fentanyl in 24 hours compared with the A allele. However, another study did not find a significant relationship between OPRM1 genotype and postoperative fentanyl consumption. Similarly, among parturients having a G allele of the OPRM1, A118G decreases response to fentanyl, but these findings are inconsistent.

Fentanyl is metabolized primarily by enzymes coded by the polymorphic CYP3A4 and CYP3A5 genes, with minor contributions from liver uridine 5'-diphosphoglucuronosyltransferase 2B7 enzymes, coded by UGT2B7 genes. Studies exploring associations between CYP3A4 and CYP3A5 sequence variation and response to fentanyl have been inconsistent. Following abdominal surgery, patients carrying the CYP3A4*1G, CYP3A4*1*18, and OPRM1 AA alleles consumed less fentanyl in the postoperative period. Among patients who underwent orthognathic surgery, carriers of the C allele of the UGT2B7 SNV (rs7439366) reported increased analgesic response to fentanyl. Overall, compared with its current use in clinical practice, the number and quality of studies investigating the role of genetic sequence variation of fentanyl and postoperative pain remain limited. More studies are needed to inform genotype-guided therapy with fentanyl.

• Codeine and Morphine. Codeine and morphine are naturally produced in the poppy plant. Codeine undergoes O-demethylation into morphine in a reaction catalyzed primarily by the enzymes coded by the CYP2D6 gene. Different CYP2D6 alleles affect the rate of codeine conversion into morphine and subsequent postoperative pain management. Differential CYP2D6 enzyme activity results in interpatient differences in the rate of drug metabolism with 4 different phenotypes: poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultrarapid metabolizers (UMs). Compared with EMs (wild-type or “normal”), UMs convert codeine into morphine at a faster rate, and IM and PMs metabolize it at a reduced and prolonged rate, respectively. Postoperatively, EM (to a lesser extent) respond as expected to codeine; PMs respond poorly, and develop fewer side effects to codeine, whereas UMs are more sensitive and develop more adverse effects to codeine. Cases of pediatric fatalities after tonsillectomy associated with codeine therapy and CYP2D6 ultrarapid metabolism have occurred. Similarly, in the postpartum period, neonatal toxicity and death have been associated with the rapid conversion of codeine to morphine in breastfeeding mothers who are UMs. Thus, there is moderate to strong evidence against the use of codeine in children, breastfeeding mothers, and patients who are CYP2D6 PMs and UMs. According to the FDA, codeine is contraindicated in children younger than 12 years and is not recommended for breastfeeding mothers. Figure 1 summarizes the actionable algorithm for Clinical Pharmacogenetics Implementation Consortium (CPIC) CYP2D6 genotype-guided therapy.

UGT2B7 catalyzes the conversion of codeine into...
codeine-6-glucuronide and the metabolism of morphine into morphine-3-glucuronide and, to a lesser extent, morphine-6-glucuronide. Few studies have examined the influence of the UGT2B7 genetic sequence variation on patients’ responses to codeine and morphine. Following an abdominal hysterectomy, women with the UGT2B7 CC genotype required a lower dose of morphine compared with the TT genotype. However, among patients who underwent major abdominal and urologic surgery, there was no significant relationship between morphine consumption and UGT2B7. Like fentanyl, morphine consumption correlates with the OPRM1 genetic sequence variation. Among patients who underwent elective cesarean delivery, carriers of the homozygous A/A OPRM1 allele had less pruritus than those with at least 1 G variant (G/G or A/G) in response to intrathecal morphine administration. In children treated with morphine after tonsillectomy, carriers of at least 1 G allele (GG or GA) reported higher pain scores compared with carriers of the AA OPRM1 allele. Current evidence indicates that OPRM1 genotype-guided morphine therapy might have clinical implications for postoperative pain. Emerging evidence also suggests that morphine analgesic efficacy may be linked to COMT and ABCB1 sequence variations.

- **Tramadol.** Tramadol is a racemic combination of the R-(+) and S-(-) tramadol enantiomers. It is structurally like codeine and morphine, and its M1 derivative (O-desmethytramadol [ODT]) has a higher affinity for the μ-receptor than the parent drug. CYP2B6, CYP2D6, and CYP3A4 are the main enzymes of its phase 1 metabolism, and UGT1A8 and UGT2B7 catalyze its phase 2 reaction (Figure 2). The CYP2D6 enzymatic pathway catalyzes the O-desmethylation of tramadol to ODT. In contrast, CYP3A4 and CYP2B6 enzymes catalyze the N-demethylation of tramadol into N-desmethytramadol. Additionally, tramadol, ODT, and N-desmethytramadol undergo glucuronidation catalyzed by UGT1A8 and UGT2B726 to form conjugated metabolites for elimination.

The plasma concentration and analgesic efficacy of tramadol and its metabolites are related to the CYP2D6 genotype. Among patients treated with tramadol after abdominal surgery, the plasma concentration of M1 (ODT) increased with CYP2D6 enzymatic activity (PMs < IMs < EMs < UMs). Compared with EMs and UMs, PMs and IMs reported inadequate pain control from tramadol. Cases of severe respiratory depression (and high levels of M1) due to tramadol have been reported in children after tonsillectomy. The Royal Dutch Pharmacists Association of the Dutch Pharmacogenetics Working Group recommends a 30% reduction in dosing for UMs and close observation for side effects, or selection of an alternate medication (eg, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], or morphine, but not oxycodone or codeine). For PMs, the Dutch Pharmacogenetics Working Group recommends selecting alternative medications but not codeine or oxycodone.

- **Oxycodone and Hydrocodone.** Oxycodone and hydrocodone are structurally like codeine, and they
undergo O-demethylation (via the CYP2D6 enzyme pathway) to oxymorphone and hydromorphone, respectively. In humans, the analgesic potency of oxycodone is similar to that of morphine, but the analgesic potency of oxymorphone is 10 times that of morphine. Postoperatively, there is a significant association between the rate of oxycodone metabolism and the CYP2D6 genotype. Compared with CYP2D6 EMs, PMs have lower oxymorphone/oxycodone ratios and lower efficacy of pain relief. On the other hand, CYP2D6 UM have higher rates of adverse reactions to oxycodone than do their phenotypically “normal” (EM) children. CYP2D6 EMs have a higher rate of formation of oxymorphone, compared with PM and IMs. Thus, a reduction in dose of oxycodone and hydrocodone or alternative medication for CYP2D6 PMs as well as close observation or alternative medications for CYP2D6 IMs and CYP2D6 UM have been recommended.

- **Nonsteroidal Anti-inflammatory Drugs.** Commonly used NSAIDs include ibuprofen, diclofenac, ketorolac, and naproxen. These drugs inhibit the cyclooxygenase (COX) enzymes, COX-1 and COX-2, responsible for the synthesis of prostaglandin in the inflammatory pathway. The PTGS1 and PTGS2 genes code the COX-1 and COX-2 enzymes, respectively. Although many studies have examined clinical associations of PTGS1 and PTGS2 genetic sequence variations with disease and NSAIDs, their influence on the pharmacogenomics of NSAIDs remains inconclusive.

  - **Ketamine.** Ketamine is available as a racemic mixture of S(+) and R(−)-enantiomers and functions primarily as an N-methyl-d-aspartate (NMDA) receptor antagonist. It equally exerts some of its analgesic effects on the μ- and δ-opioid receptors. Ketamine is metabolized primarily by enzymes coded by the CYP2B6, CYP2C9, and CYP3A4 genes. In vitro analyses have shown that CYP2C9, CYP3A4, and CYP2B6 sequence variations may affect ketamine metabolism. Inheritance of the diminished-function CYP2B6*6 allele has been associated with decreased ketamine metabolism and increases drowsiness. Among patients with chronic pain, the CYP2B6*6 allele has been associated with a significant decrease in steady-state ketamine plasma clearance and resultant higher plasma concentration. The CYP2B6*6 allele has been associated with increased drowsiness but not with ketamine-induced psychedelic effects during emergence.

**Discussion**

Given the ongoing opioid epidemic and rising rate of surgical procedures, this review article has clinical and research implications for anesthesia providers. In the clinical setting, response to treatment is a complex phenotype that depends on genetic and environmental factors. Despite the complexity, ensuring optimal postoperative pain control remains a critical role of anesthesia providers. Patients treated with drugs whose metabolism depends on the CYP2D6 and CYP2C9 enzymes may have decreased or exaggerated analgesic response or severe adverse effects because of CYP2D6 and CYP2C9 sequence variations.

For a prodrug such as codeine, patients who are PMs may not experience adequate pain relief, and UMs may not experience adequate pain relief, and UMs may report no relief.

- **Lidocaine.** Lidocaine exerts its local anesthetic effects by blocking the sodium channels. However, sodium channel blockade alone cannot explain all the perioperative benefits of intravenous lidocaine infusions. As a result, lidocaine may exert immunomodulatory effects, which result in decreased postoperative pain scores and opioid consumption. Lidocaine is metabolized primarily by enzymes coded by the CYP1A2 gene. Pharmacogenetics studies of the efficacy of lidocaine are scarce. In 2005, Liem and colleagues reported a genetic association of MC1R variants and local anesthetic sensitivity. However, this study must be replicated in a more extensive and diverse population.
from codeine or tramadol, an alternate analgesic such as fentanyl is recommended. Similarly, CYP2D6 UM may report more adverse effects with codeine and tramadol, necessitating alternate medications. The CPLIC guidelines contain additional recommendations for codeine and tramadol CYP2D6-guided therapy.26 Also, codeine is contraindicated for postoperative pain management in individuals 18 years and younger after adenoids and tonsillar surgery and in breastfeeding mothers.30 For these populations, alternate medications, including acetaminophen or NSAIDs, may be used.

Caution must be exercised when administering NSAIDs to elderly individuals or patients with renal or hepatic dysfunction. The CPLIC guidelines recommend starting NSAID regimens at the lowest effective dose. For CYP2C9 IMs and PMs, they recommend selecting an alternate NSAID not metabolized by CYP2C9 enzyme (eg, aspirin, ketorolac, naproxen, and sulindac). Alternatively, the initial lowest effective dose should be decreased by 25% to 50% and titrated upward to achieve optimal relief.41

For many anesthesia providers, routine preemptive preoperative genotyping for optimal postoperative pain management is a distant reality. Although patient-specific genotype may not be available at the point of care, pharmacogenetic knowledge and awareness of the potential impact of genetic predisposition should inform the analgesic selection and dosing frequency to maximize efficacy and minimize adverse effects. For instance, as we acquire more knowledge about allele frequencies in various racial/ethnic groups, anesthesia providers should pay close attention to the genetic drifts that could result in racial/ethnic differences in pain perception and responses to analgesics. For example, there is evidence of marked differences in CYP2D6 allele frequencies (and enzyme activity) in populations of different racial/ethnic origins.4 Although 7% to 10% of white Americans are CYP2D6 PMs, the prevalence of PMs is less than 2% among Asians. On the other hand, up to 29% of Africans are UM, as opposed to less than 2% among Hispanics.50 These racial/ethnic differences suggest that the chances of having a patient who will not respond to codeine are higher among white Americans than Hispanics. This speaks to the fundamental premise of pharmacogenomics (and precision medicine), which is to tailor treatment (eg, postoperative pain management) based on the individual's unique characteristics, including genetic and environmental factors.5 This is a change in thinking from a “one-size-fits-all” approach grounded on body weight, to one where the right drug is given to the right patient, in the right quantity at the right time with minimal adverse effect and maximum efficacy.

This review identifies several opportunities for future research. Many of the studies identified in this review are small-scale in homogenous populations. The development of genotype-guided therapy would require replication of existing studies in other populations and large-scale multicenter studies. Besides, most of the studies used a candidate gene approach (the genes were identified a priori). With the availability of next-generation sequencing technology, anesthesia providers are well positioned (because they have access to the patients and a knowledge of pharmacology) to lead large multicenter, interdisciplinary pharmacogenomic studies using a genome-wide association approach.

Finally, as the cost of gene sequencing falls, one would expect the number of healthcare institutions offering preemptive genotyping as part of the medical record to increase. A concerted effort is needed by professional organizations such as the AANA and the AANA Foundation as well as by anesthesia training programs to invest time and effort in training anesthesia providers about pharmacogenomics. Additionally, studies should be funded to increase our understanding of the role of the genetic predisposition on response to postoperative pain and postoperative pain medications. As precision healthcare evolves, emphasis must shift toward genotype-guided therapies, which are informed by lifestyle and environmental factors. As such, each patient's age, sex, body weight, comorbidities, lifestyle, and genotype must be considered to optimize postoperative pain management.

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