

Pharmacogenetics of Postoperative Nausea and Vomiting

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Postoperative nausea and vomiting (PONV) remains one of the most common adverse effects of anesthesia, affecting up to 80% of high-risk patients within 24 hours after surgery. Patient-related factors, surgical procedure, and perioperative medications such as opioids determine a patient's risk for PONV. To prevent and manage PONV, ondansetron, a 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonist, is frequently administered. Ondansetron is metabolized predominantly by hepatic cytochrome P450 (CYP2D6) enzymes, encoded by the CYP2D6 gene, whereas most of the effects of opioids are exerted at the opioid mu-1 receptor, encoded by the OPRM1 gene. Genetic polymorphisms of the CYP2D6 and OPRM1 genes may have a role in interindividual variation in the occurrence of PONV. Specifically, the occurrence of the G-allele produced by the OPRM1 A118G appears to be protective against PONV, whereas CYP2D6 ultrarapid metabolism increases the risk for PONV. The Clinical Pharmacogenetics Implementation Consortium guidelines provide CYP2D6-guided therapeutic recommendations for ondansetron. However, further studies are needed to investigate the role of genetic polymorphism in the occurrence of PONV and response to antiemetics.

Keywords: *postoperative nausea and vomiting, antiemetic, pharmacogenetics, pharmacogenomics, postanesthesia care.*

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OBJECTIVES—1. Discuss the genetic basis of inter-patient response to medication. 2. Explain the potential influence of genetic variations on PONV. 3. State the Clinical Pharmacogenetic Implementation Consortium (CPIC) CYP2D6 guidelines for the management of PONV with ondansetron.

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Postoperative nausea and vomiting (PONV) remains one of the most common adverse effects of anesthesia, affecting up to 30% of the general population and 80% of high-risk patients within 24 hours after surgery.¹⁻³ These adverse effects are significant because they cause fluid and electrolyte imbalances, esophageal tears, and wound dehiscence; increase intracranial pressure, hospital length of stay, unplanned hospital admissions, and health care costs; and decrease patient satisfaction with care.^{4,5} Prevention is the gold standard for the management of PONV.^{3,6} Antiemetic medications such as ondansetron, dexamethasone, droperidol, prochlorperazine, and haloperidol are frequently administered during the perioperative periods to prevent and manage PONV. Recent consensus guidelines recommend a multidrug therapy approach to prevent and manage PONV.⁶ Unfortunately, even with the multidrug therapy, some patients still develop PONV. The

risk of PONV runs higher in some families,^{7,8} and an individual's genotype (genetic makeup) has a significant role in his or her response to medications.⁹ As a result, patients' genetic information is increasingly being incorporated into clinical decision making.¹⁰ The field of pharmacogenomics seeks to predict a patient's response to medication based on genetic makeup.^{9,10}

The purpose of this review is to discuss the pharmacogenetics of the medications most frequently used in the management of PONV. To achieve this goal, we present an overview of the fundamental concept of pharmacogenomics, summarize findings of pharmacogenomic studies on classes of antiemetic medications, and provide implications for clinical practice.

Overview of Pharmacogenetics

Basic knowledge of pharmacology and genetic variables is essential to the understanding of pharmacogenetics. Numerous excellent reviews have been published on the genetic basis of responses to medications, and we do not seek to replicate what has been done. In their review, Dorman et al¹¹ provide a historical overview of genomics and define the processes by which genetic information is expressed. Furthermore, Roden et al¹² provide a comprehensive discussion of the genetic basis of variable response to medications. We encourage readers to consult standard genetic textbooks such as *Concepts of Genetics*¹³ and *Thompson & Thompson Genetics in Medicine*¹⁴ for additional information.

The terms pharmacogenetics and pharmacogenomics are often used interchangeably and arbitrarily. Pharmacogenetics refers to the influence of a specific genetic variation (candidate gene) on the response to medication(s), whereas pharmacogenomics is a broader term that encompasses the influence of the entire genome (all the genes or genetic material in an organism) on the response to medication(s).¹⁰ The field of pharmacogenetics seeks to predict a patient's response to medications based on genetic predisposition. As a branch of precision medicine, pharmacogenetics seeks to give the right drug to the right patient at the right time, in the right concentration and via the right route.¹¹ To achieve this goal, pharmacogenetics

research studies genetic variabilities that affect drug transporters, drug metabolizing enzymes, and drug receptors.

At the molecular level, most of the genetic information in humans is stored in the nucleus of cells as chromosomes. Most individuals inherit 23 pairs of chromosomes (22 pairs of autosomes and 1 pair of sex chromosomes) from their parents (one set from each parent). These chromosomes are made of densely coiled DNA, genetic information in the form of genes. The specific location of a gene on the chromosome is referred to as the locus of that gene. Given that humans inherit one set of chromosomes from each parent, each individual has two copies, or alleles, of each gene. For some genes, multiple alleles have been identified in the general population, and the difference in sequences among these alleles forms the basis of genetic variation.¹¹ The term homozygous describes the condition in which both alleles of a gene are identical in sequence; the term heterozygous describes the condition in which the two alleles differ in sequence.

The central dogma of molecular biology holds that genetic information is transcribed into messenger RNA, which is translated into proteins.¹⁵ In simpler terms, the DNA sequence (genetic information or genotype) determines the structure and functions of proteins. Therefore, genetic variation may result in the synthesis of proteins that differ in structure and function. The genetic variability that affects the function of drug transporters, drug receptors, and drug metabolizing enzymes is of great interest in pharmacogenetics. Examples of genetic variations that may affect these important molecules include single-nucleotide polymorphisms (SNPs), copy number variations, and insertions and deletions (indels), among others.^{11,15} A detailed description of human genetic variation is beyond the scope of this review; however, it must be mentioned that a genetic variation (mutations and polymorphisms) refers to a difference in the DNA sequence between species or individuals within a population.⁹ Historically, a genetic variation (variant) that causes or is associated with a disease and occurs in less than 1% of the population is referred to as a mutation. A genetic variation that occurs in more than 1% of the population is referred to as a polymorphism.¹⁵

Genetic variations in various neurotransmitter systems, receptors, and metabolic enzymes may affect the efficacy of antiemetic drugs and the occurrence of PONV. In particular, genetic variations in the 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonists, cytochrome 450 (CYP) enzymes, dopamine receptor type 2 (DRD2), neurokinin type 1 (NK-1), and opioid-related genes have been found to influence the occurrence of PONV.

5-HT₃ (Serotonin) Antagonists

5-HT₃ (serotonin) receptor antagonists are relatively safe, efficacious, and cost-effective first-line therapy for the prevention of PONV.^{2,6} Activation of the 5-HT₃ receptors has a role in sympathetic, parasympathetic, and sensory functions, which affect nausea and vomiting.¹⁶ On the other hand, 5-HT₃ receptor antagonists competitively and selectively bind to 5-HT₃ receptors and block serotonin binding sites in the vomiting centers, chemoreceptor trigger zone, and nucleus tractus solitarius (NTS).¹⁷ Antiemetic medications approved for use in the United States that target these receptors include granisetron (Kytril), dolasetron (Anzemet), ondansetron (Zofran), and palonosetron (Aloxi). Although these medications function similarly and are all metabolized via a common pathway, significant interpatient variability in the efficacy of these drugs has been reported.¹⁷ As a result, it has been suggested that genetic polymorphism of the genes that encode the 5-HT₃ receptor subunits may have a role in patients' responses to 5-HT₃ receptor antagonists and the antiemetic efficacy thereof.¹⁸

SEROTONIN RECEPTOR POLYMORPHISMS.

Genetic variations (eg, SNPs and indels) of the 5-HT₃ receptor genes have been investigated for association with PONV. Joy Lin et al¹⁸ investigated the impact of *5HT3A* polymorphisms on the risk of PONV after general anesthesia in 369 Taiwanese subjects. Two SNPs (rs33940208 and rs10160548) were associated with postoperative nausea, and two haplotypes (CCT and TAG) showed a significant risk effect on PONV, with odds ratios (ORs) of 2.31 and 0.23, respectively.¹⁸ Similarly, Kim et al¹⁹ found that among the *5HT3B* deletion genotypes (-100_-102delAAG), a homozygous mutant was associated with a higher incidence of PONV during the first 2 hours after surgery. Interestingly, this genotype difference did not affect clinical

response to ondansetron 24 hours after surgery.¹⁹ Being female, a nonsmoker, and having the *5HT3A* variant c1377A>G were each associated with higher risk of postoperative vomiting (POV) (OR for the variant 2.97, 95% confidence interval [CI] 1.47 to 6.02, $P = .003$), whereas having the *5HT3B* variant c5 201_202delCA or c6-137C>T significantly reduced the risk of POV (OR 0.42, 95% CI 0.26 to 0.69, $P = .001$ and OR 0.034, 95% CI 0.003 to 0.033, $P = .004$, respectively).²⁰ In contrast, Wesmiller et al²¹ did not find any significant association between SNPs in the *5HT3A* gene (rs1176713) and PONV in women after surgery for breast cancer (OR 0.48, 95% CI 0.17 to 1.37). Thus, 5-HT₃ receptor subunit polymorphism appears to have a role in the occurrence of PONV, but replicative and more comprehensive studies are needed before the adoption of this genetic information into clinical practice.

TRANSPORT PROTEIN POLYMORPHISM.

Overall, 5-HT₃ receptor antagonists are moderately hydrophobic organic cations (basic amines with a rigid aromatic ring and carbonyl group) that are transported by the human organic cation transporters (OCTs)¹⁶ and the ATP binding cassette member B1 (ABCB1) transporter.⁷ These transporters regulate cellular uptake and transportation across the blood-brain barrier, respectively, of some 5-HT₃ receptor antagonists, including ondansetron. Among patients suffering from chemotherapy-induced nausea and vomiting, the SNP *ABCB1* C3435T was associated with the efficacy of 5-HT₃ receptor antagonism.²² Thus, genetic polymorphism in genes coding for these drug transporters may affect the concentration of the antiemetic medications that must be transported into and out of the central nervous system (CNS), which in turn would directly or indirectly affect efficacy.

Among 311 children undergoing tonsillectomy for obstructive sleep apnea, the T-allele of the *OCT1* SNP rs12208357 was associated with an increased risk of PONV and prolonged postanesthesia care unit stay ($P < .05$).²³ These findings were consistent with prior in vitro and in vivo studies which showed that 5-HT₃ receptor antagonists inhibit OCT1-mediated transport and *OCT1* overexpression in liver cells increases uptake of drugs.²⁴ In vivo, *OCT1* genotype was significantly

associated with the plasma concentration and efficacy of ondansetron and tropisetron—a 5HT₃ antagonist that is approved in some countries. Among patients receiving moderately high doses of emetogenic chemotherapeutic drugs, compared with the fully functioning OCT1*1 allele, loss-of-function mutations (mutations that result in gene products with less or no function) in two *OCT1* alleles (*OCT1**2, *OCT1**3, *OCT1**4, *OCT1**5, and *OCT1**6) were associated with higher plasma concentrations and higher clinical efficacy of tropisetron and ondansetron ($P < .04$).²⁴

Choi et al.²⁵ investigated whether the *ABCB1* 2677G>T/A and 3435C>T polymorphisms alter the efficacy of ondansetron in preventing PONV in patients after laparoscopic cholecystectomy. They found that compared with patients with other genotypes, patients with the *ABCB1*2677TT or 3435TT genotype had a lower incidence of PONV during the first 2 hours after surgery (relative risk [RR] 0.5, 95% CI 0.3 to 0.9 and RR 0.4, 95% CI 0.1 to 0.9, respectively).²⁵ Similarly, Farhat et al.²⁶ found that the homozygous TT variant (*ABCB1*2677TT) conferred a lower risk of PONV up to 24 hours after surgery. However, other researchers did not find any significant association between the *ABCB1* C3435T genotype and PONV.²⁷ Among patients who had undergone abdominal surgery with colorectal anastomosis, those with TT alleles had higher nausea scores than those with CT and CC alleles.²⁷ These findings suggest that polymorphism of the *OCT1* and *ABCB1* genes may have a role in determining the therapeutic efficacy of 5-HT₃ antagonists for preventing PONV.

CYTOCHROME P450 POLYMORPHISMS. Hepatic cytochrome p450 enzymes metabolize granisetron, ondansetron, and palonosetron at variable rates and to variable extent. Granisetron is metabolized primarily by CYP3A4 enzymes (via *N*-demethylation), whereas ondansetron is metabolized predominantly by CYP2D6 enzymes (via hydroxylation), with contributions from CYP1A1, CYP1A2, and CYP3A4 enzymes.²⁸ *CYP2D6* is a highly polymorphic gene that codes for enzymes with a 10-fold to 10,000-fold variation in drug metabolizing activity.²⁹ Four groups of *CYP2D6* patients have been identified based on variations in the enzyme activity: poor metabolizers (PMs),

intermediate metabolizers, extensive metabolizers (EMs), and ultrarapid metabolizers (UMs).³⁰

Patients metabolize ondansetron at different rates depending on the *CYP2D6* group to which they belong. The rate at which ondansetron is metabolized differs by *CYP2D6* group, thus the risk for PONV after ondansetron administration also may vary by group. After the administration of ondansetron (4 mg) to patients undergoing general anesthesia, the incidence of PONV is higher in patients with more than three copies of the normal *CYP2D6* gene (UMs) than in patients in all other *CYP2D6* categories ($P < .01$).³¹ At the other end of the classification spectrum, compared with EMs, PMs are at a decreased risk for PONV and require smaller amounts of ondansetron.^{32,33} However, other investigators did not find this protective effect in PMs among Taiwanese women undergoing a total abdominal hysterectomy.³⁴ One potential reason for this difference could be that the Taiwanese women who experience severe PONV in the latter study were treated with prochlorperazine, not ondansetron.³⁴ Ondansetron is administered as a racemic mixture of *R*- and *S*-enantiomers, and its *CYP2D6* metabolism appears to be enantiomer specific.³⁵ Stamer et al.³⁵ examined the relationship between *CYP2D6* polymorphisms and the plasma concentration of the *S*- and *R*-enantiomers of ondansetron. PMs had a significantly higher plasma concentration of *S*-ondansetron than UMs had ($P = .003$), but the plasma concentration of the *R*-enantiomer did not vary with *CYP2D6* category.³⁵ The Clinical Pharmacogenetic Implementation Consortium has developed guidelines for ondansetron therapy based on genotype.³⁰ The guidelines recommend standard therapy for *CYP2D6* EMs, and the selection of an alternative drug such as granisetron, which is not metabolized primarily by *CYP2D6*, for UMs.³⁰ Unfortunately, there is insufficient evidence to support any recommendations for intermediate metabolizers and PMs.³⁰

NK-1 Receptor Antagonists and Polymorphisms

Aprepitant (Emend) is the only FDA-approved and most widely available NK-1 receptor antagonist used for the prevention of PONV. It is most effective when administered in combination with other

antiemetic therapy.^{6,36,37} Aprepitant exerts its effect in the NTS, where it blocks the vagal terminals and decreases afferent messages sent from the periphery.³⁶ Genetic polymorphism of the tachykinin receptor 1 gene (*TACR1*), which encodes the NK-1 receptor, has been examined among patients undergoing lower abdominal surgery.³⁸ The presence of the rs3821313 or rs3755468 SNP in the *TACR1* gene was associated with a higher incidence of PONV ($P < .01$ and $P = .016$, respectively). Also, having the TT haplotype, defined by two SNPs (rs3771836 and rs3755468), in the *TACR1* gene was associated with decreased frequency and severity of PONV. In the latter study, female patients had a more significant reduction in the severity of PONV than male patients had ($P < .01$).³⁸ Additional studies are needed to examine the relationship between NK-1 receptor polymorphisms and the efficacy of NK-1 receptor antagonists in preventing PONV.

DOPAMINE RECEPTOR POLYMORPHISMS.

Drugs that block DRD2 exert antiemetic effects by blocking adenylate cyclase to decrease the amount of cyclic adenosine monophosphate (cAMP) in the NTS and chemoreceptor trigger zone.³⁹ Antiemetic medications in this class include droperidol (Inapsine), metoclopramide (Reglan), promethazine (Phenergan), and prochlorperazine (Compazine).^{6,40} Although metoclopramide also blocks histamine and serotonin receptors and enhances gastrointestinal motility,⁴⁰ promethazine and prochlorperazine are phenothiazines, which have antidopaminergic properties. The sedative effects of promethazine can reduce anxiety-mediated nausea, but also limit its clinical use in the management of PONV.⁴¹

The Taq1A polymorphism of the *DRD2* gene, which produces the A2 allele, may also influence the occurrence of PONV.^{21,42,43} Among 1,000 Japanese patients undergoing elective surgery, being homozygous A2A2 for the *DRD2* Taq1A polymorphism was associated with an increased risk of PONV within the first 6 hours after surgery (RR 1.58, $P = .028$) compared with being A1A1 homozygous or A1A2 heterozygous.⁴³ Among patients undergoing strabismus surgery, the A2 allele was associated with a higher incidence of PONV ($P = .02$) but not nausea.⁴² However, Wesmiller et al²¹ did not find any significant relationship be-

tween dopamine receptor polymorphism (*DRD2* and *DRD3*) and PONV. Thus, additional studies are needed before the pharmacogenetics of dopamine receptor antagonists can be incorporated into clinical practice.

Pharmacogenetics of Opioid-Induced PONV

Opioids are frequently administered during the perioperative period for pain management. Activation of the mu-opioid receptors (encoded by the *OPRM1* gene) mediates supraspinal analgesia and the common side effects of opioids, including decreased gastrointestinal (GI) motility as well as nausea and vomiting.^{4,44} The highly polymorphic nature of the *OPRM1* gene may explain some of the interpatient variability in opioid-induced PONV. Several studies, including a genome-wide association study,⁴¹ have investigated the influence of *OPRM1* polymorphism on the incidence and severity of PONV.^{41,45,46} Also, a systematic review (59 studies) and meta-analysis (23 studies) found that the presence of the G allele (*OPRM1* 118A>G) is associated with higher postoperative opioid consumption ($P < .001$) and lower risk of PONV ($P = .01$).⁴⁶ These findings are consistent with those of a double-blind, randomized control trial of over 400 Korean women who underwent breast surgery under general anesthesia⁴⁵ and 85 Japanese patients who underwent elective surgery.⁴⁷ These findings suggest that inheritance of the G allele is associated with decreased opioid efficacy and side effects. However, more studies are needed to investigate the dimorphic relationships between *OPRM1* polymorphism, opioid efficacy, and opioid-induced PONV.

Implications for Practice

The occurrence of PONV depends on surgical, anesthetic, and patient risk factors, including genetic makeup. The pharmacogenomics of PONV are not yet fully understood, in part, because of the relatively small number of studies exploring these important phenomena (Table 1). PONV remains one of the most common side effects of anesthesia, and in this era of precision medicine, the effect of genetic variability on PONV susceptibility should not be overlooked. Clinically, opioids are frequently used for the management of

Table 1. Summary of Reviewed Articles

Study	Purpose	Sample	Gene(s)	Findings	Implications for Practice and Research
Hromatka et al ⁸	To describe genome-wide association with motion sickness	80,494 customers of 23andMe	<i>Genome-wide</i>	35 SNPs were associated with motion sickness. Many of the SNPs are in genes involved in balance, and eye, ear, and cranial development. The 35 SNPs also correlated with PONV ($P < .003$), migraine, altitude sickness, hay fever, and vertigo	There is a genetic correlation between motion sickness and PONV. Patients with a history of motion sickness are at higher risk for PONV
Joy Lin et al ¹⁸	To clarify the impact of HTR3A polymorphisms on risks of PONV after general anesthesia	369 Taiwanese	<i>HTR3A</i>	Two SNPs of the <i>HTR3A</i> gene were significantly associated with PON (rs33940208 and rs10160548). Two haplotypes CTT and TAG showed a significant risk effect with OR of 2.31 and 0.23, respectively	HTR3A genetic polymorphism may be a strong predictor of PON
Kim et al ¹⁹	To investigate whether the Y129S and -100_-102AAG deletion polymorphisms as variants of the 5-HT3B receptor gene affect the efficacy of ondansetron in preventing PONV in patients undergoing general anesthesia for laparoscopic surgery	245 Adults	<i>HT3B</i>	Among the 5- <i>HT3B</i> -100_102AAG deletion genotypes, the incidence of PONV was higher in patients with a homomutant genotype than other genotypes during the first 2 h after surgery. There was also a statistically significant difference with and without the Ins/Ins or the Del/del genotype. No difference by genotype at 2-24 h	Response to ondansetron is significantly influenced by the 100_102AAG deletion polymorphism. Patients with homozygous deletion may not respond to ondansetron in the PACU

(Continued)

Table 1. Continued

Study	Purpose	Sample	Gene(s)	Findings	Implications for Practice and Research
Rueffert et al ²⁰	To investigate both HTR3A and HTR3B genes in patients with postoperative vomiting after general anesthesia	189 Adults	<i>HT3A, HT3B</i>	Females with 5-HT3A variant c1377A>G were associated with higher risk of PONV (OR 2.97, 95% CI 1.47-6.02, <i>P</i> = .003), whereas those with 5-HT3B variants c5+201_+202delCA and c6-137C>T were associated with lower risk for PONV (OR 0.42, 95% CI 0.26-0.69, <i>P</i> = .001 and OR 0.03 95% CI 0.003-0.033, <i>P</i> = .004). Being homozygous for the HTR3B -100_-102AAG deletion was not associated with PONV	Being a pilot study, clinical implications would be premature
Wesmiller et al ²¹	To describe the incidence and explore the risk factors associated with PONV after surgery in women diagnosed with early stage breast cancer after surgery for breast cancer	90 Adult women	<i>HTR3A, DRD2, DRD3, SLC6A, TPH, ANKK, COMT</i>	Polymorphisms of 5- <i>HTR3A</i> (rs1176713) and <i>DRD3</i> (Ser9Gly) were associated with decreased risk for PONV (OR 0.48, 95% CI 0.73-5.86 and OR 0.432, 95% CI 0.173-1.079, respectively). Women with the COMT Val/Val genotype experienced the highest level of pain, received the highest amount of opioids in morphine equivalents, and also reported the highest severity of nausea in the PACU. Heterozygous group had	PONV is complex and multifactorial. Additional studies are needed

Balyan et al ²³	To identify associations between OCT1-specific polymorphisms and postoperative RD and PONV in children undergoing tonsillectomy	311 Children (262 White and 49 Black)	<i>OCT1</i>	less pain, less opioid, and less PONV compared with Val/Val and met/met Subjects with the T-allele of OCT1 SNP are associated with increased risk of PONV and extended PACU stay ($P < .05$)	OCT1 may place a significant role in morphine-related PONV and PACU length of stay
Tzvetkov et al ²⁴	To determine whether OCT1 mediates the cellular uptake of tropisetron and ondansetron and, whether and to what extent, genetic polymorphisms in OCT1 contribute to the variability in pharmacokinetics and therapeutic efficacy of tropisetron and ondansetron in cancer patients	270 Adults	<i>OCT1</i>	Subjects with 2 loss-of-function OCT1 alleles had higher plasma concentration and efficacy of tropisetron and ondansetron ($P < .04$)	Lacking a fully active OCT1 may decrease the metabolism of tropisetron and ondansetron, with improved efficacy
Choi et al ²⁵	To investigate whether the ABCB1 2677G>T/A and 3435C>T polymorphisms of ABCB1 affect the efficacy of ondansetron in preventing PONV in patients undergoing general anesthesia	198 Adults	<i>ABCB1</i>	The incidence of PONV was lower in patients with 2677TT (25.9% vs 53%) and 3435TT (21.7% vs 52.5%) genotypes than other genotypes during the first 2 h after surgery. The RRs of suffering from PONV were 0.5 (95% CI 0.3-0.9) and 0.4 (95% CI 0.1-0.9) with the 2677TT and 3435TT genotypes, respectively	ABCB1 gene polymorphism may be a predictor of response to ondansetron

(Continued)

Table 1. Continued

Study	Purpose	Sample	Gene(s)	Findings	Implications for Practice and Research
Farhat et al ²⁶	To determine the association of ABCB1 polymorphism G2677T with antiemetic efficacy in patients treated with ondansetron for preventing PONV	426 Adults (225 with PONV, 201 no-PONV)	<i>ABCB1</i>	<i>ABCB1</i> 1236TT genotype has a significantly lower incidence of PONV during the first 2 h and between 2 and 24 h after surgery compared with other genotypes (1236CT and 1236CC). The occurrence of PONV was significantly higher in patients with CC genotype at 2 h than other genotypes	ABCB1 polymorphism may be a predictor of PONV in the immediate postoperative period
Dzambazovska-Trajkovska et al ²⁷	To evaluate the association between C3435T and the opioid consumption in the acute postoperative period in patients who have undergone abdominal surgery with colorectal anastomosis	99 Adults	<i>ABCB1</i>	At 6 and 18 h postoperatively, CC genotype had significantly higher VAS pain scores than CT and TT. TT genotype associated with higher nausea scores. But there was no significant difference among the three genotypes regarding vomiting and sedation scores	SNPs of the ABCB1 gene may be associated with opioid consumption and PONV
Candiotti et al ³¹	To evaluate whether patients who do not respond to ondansetron for prophylaxis of PONV possess an increased wild-type CYP2D6 gene copy number	250 Adults	<i>CYP2D6</i>	Subjects with three copies of CYP2D6 allele (UM) are more likely to experience vomiting (but not nausea) compared with EM ($P < .01$) and all others groups ($P < .01$)	CYP2D6 enzymatic activity may influence ondansetron metabolism and efficacy

Janicki et al ³²	To compare the therapeutic effectiveness of dolasetron and granisetron and obtain preliminary data for CYP2D6 guided therapy	150 Adults with moderate to high risk for PONV	<i>CYP2D6</i>	There was no significant difference in efficacy between dolasetron and granisetron in preventing PONV in PACU ($P = .62$) and 24 h after PACU discharge ($P = .74$). In dolasetron group, those classified as UM had more episodes of PONV than those treated with granisetron ($P = .033$)	CYP2D6 genotype may influence efficacy and dolasetron and granisetron
Wesmler et al ³³	To explore the association between PONV and CYP2D6 genotypes in trauma patients admitted for surgical repair of a single extremity fracture	112 Adults	<i>CYP2D6</i>	Compared with EM, patients classified as PM (homozygous <i>CYP2D6*4</i>) had a decreased risk for PONV ($P = .003$) and received higher doses of opioid ($P = .007$). PM received smaller amounts of ondansetron (2.28 ± 3.15 mg) compared with EM (3.88 ± 4.38 mg) for PONV	CYP2D6 genotype appears to influence PONV, but this study had small samples size PM (n = 7) and UM (n = 0) groups
Chen et al ³⁴	To examine what genes in the pathway from morphine metabolism to distribution have a biggest influence on morphine-induced nausea and vomiting	129 Taiwanese women for total abdominal hysterectomy and PCA IV morphine	<i>CYP2D6, CYP3A4, UGT2B7, ABCB1, ABCB3, OPRK1, OPRD1, KCNJ6, KCNJ9</i>	There is no relationship between CYP2D6 and CYP3A4 and the incidence of PONV ($P > .65$). Those with TT genotype of KCNJ9 C/T rs2737703 had lower odds of PONV compared with CC genotype (OR 0.09, 95% CI 0.01-0.83, $P = .033$). After controlling for multiple regression, there is no association between SNPs	PONV may not be related to opioid pharmacogenetics

(Continued)

Table 1. Continued

Study	Purpose	Sample	Gene(s)	Findings	Implications for Practice and Research
Stamer et al ³⁵	To examine whether CYP2D6 and CYP3A genetic variants influence plasma concentrations of ondansetron enantiomers	141 Adults	<i>CYP2D6, CYP3A4</i>	of the genes studied and morphine-induced PONV The plasma concentration of <i>S</i> -ondansetron varied with CYP2D6 activity ($P = .01$). PM had highest concentration (362.5 [238.4/486.6] h ng/mL) and UM had the lowest (149.6 [114.5/184.8] h ng/mL, $P = .003$). The <i>R</i> -ondansetron varied with CYP3A4 genotype: the plasma concentration of <i>R</i> -enantiomer was 2-fold higher in low expressors of CYP3A (281.5 [249.6/314.3] h ng/mL) compared with high expressors (142.5 [92.4/192.7] h ng/mL, $P = .003$)	Enantiomerism appears to play a role on metabolism of ondansetron by polymorphic CYP3A4 and CYP2D6. CYP3A4 and CYP2D6 may influence the efficacy of ondansetron
Hayase et al ³⁸	To determine the genetic influence of various SNPs in the TACR1 gene on the sex difference in PONV	200 Adults for abdominal surgery	<i>TACR1</i>	32 SNPs in the <i>TACR1</i> gene were explored: 2 SNPs (rs3821313, $P < .01$ and rs3755468, $P = .016$) were associated with incidence of PONV and 2 other SNPs (rs3771836, $P = .055$ and rs1477156, $P = .089$) were associated with severity of PONV. The TT haplotype defined by 2 SNPs (ie, rs3771836 and rs3755468) was associated with decreased incidence and severity of PONV. This haplotype association differed	Genetic differences in TACR1 gene (which encodes the neurokinin 1 receptor) may explain the observed sex differences in PONV

Frey et al ⁴²	To examine the association between DRD2 TaqIA polymorphism and the occurrence of PONV in a White cohort undergoing strabismus repair surgery	306 Patients (2-21 y: n = 152; 22-80 y: n = 154)	DRD2	between female and male patients, with more greatly decreased severity of PONV in women than in men ($P < .01$)	Postoperative nausea was not associated with DRD2 TaqIA genotypes. Postoperative retching/vomiting was associated with genotype. Subjects with at least one A2 allele (A1A2 and A2A2) had higher risk of PONV than subjects with A1A1 genotype ($P = .022$)	Among patients undergoing strabismus surgery, polymorphism in dopamine type 2 receptor (DRD2) may play a role in PONV
Nakagawa et al ⁴³	To examine the relationship between the DRD2 TaqIA polymorphism and the occurrence of PONV, and to clarify the effect of the DRD2 TaqIA polymorphism on PONV	1,070 Japanese with cancer undergoing elective surgery under general anesthesia	DRD2	Being female ($P < .001$), never-smoker ($P = .021$), ex-smoker ($P = .008$), use of epidural anesthesia ($P = .005$), and the A2A2 genotype ($P = .028$) of the DRD2 TaqIA polymorphism were significant risk factors for the development of PONV 6 h after surgery		Dopamine type 2 receptor polymorphism may be a predictor of sex differences and occurrence of PONV in the PACU. Cancer patients undergoing neurosurgery and those with epidural anesthesia should be monitored closely
Lee et al ⁴⁵	To investigate association between PONV and A118G SNP with type distribution of the latter in Korean female adults undergoing breast surgery under general anesthesia with remifentanyl	416 Adults	OPRM1	Patients with GG genotype <i>OPRM1</i> A118G SNP showed lower PONV scale value on arrival at the PACU than the other AG and AA genotypes ($P = .003$). Over total intravenous anesthesia was better than inhalation agents except for patients with GG genotype where		Polymorphism of the mu opioid receptor may influence occurrence of PONV in the PACU

(Continued)

Table 1. Continued

Study	Purpose	Sample	Gene(s)	Findings	Implications for Practice and Research
Ren et al ⁴⁶	To summarize the literature of genetic studies of postoperative pain to clarify the effects of genetic variants on pain, the analgesic effects of opioids, and adverse effects during the postoperative period in patients with postoperative pain	23 Studies	<i>OPRM1</i>	anesthetic type did not make a difference Subjects with G allele of <i>OPRM1</i> experience less vomiting ($P = .01$) and consume larger amounts of opioids intraoperatively ($P < .00001$)	Polymorphism of mu-1 opioid receptor plays a role in opioid consumption and PONV
Janicki et al ⁴⁸	To combine the emerging technology of high-density SNP microarrays with a pooled genomic DNA design to identify novel loci for genes predisposing an individual to PONV in a Caucasian population during the perioperative period via GWAS	122 with severe PONV 129 Matched control subjects	<i>Genome-wide</i>	One single nucleotide polymorphism (rs2165870) in the promoter region of the M3 muscarinic acetylcholine receptor (<i>CHRM3</i>) gene was found to be significantly associated with PONV	Polymorphism of the muscarinic acetylcholine receptor may play a role in PONV. However, additional replication and functional validations studies are required.
Sugino et al ⁴⁷	To determine the genetic influence of various SNPs of the <i>OPRM1</i> gene and their combined effects on the variability of opioid analgesia and PONV in postoperative patients	85 Japanese patients for major elective surgery	<i>OPRM1</i>	Being heterozygous for SNP rs9397685 was significantly associated with a decrease severity of PONV ($P = .02$) and the minor G allele was associated with reduced severity of PONV ($P = .004$). Being female	Polymorphism of the mu-1 opioid receptor may play a role in the incidence and severity of PONV. <i>OPRM1</i> may be a predictor of PONV

<p>Zhang et al⁴⁹</p> <p>and lacking the GGAACGC haplotype significantly increased the OR of PONV by 4.95 and 10.5-fold, respectively</p>	<p>The <i>OPRM1</i> A118G genotype was not an important determinant in interindividual variation of postoperative fentanyl analgesia nausea and vomiting</p>	<p>OPRM1 polymorphism does not influence occurrence and severity of PONV</p>
<p>To determine whether polymorphic variations in the <i>OPRM1</i> A118G gene have an impact on PONV induced by fentanyl analgesia in Chinese women undergoing gynecologic surgery</p>	<p>165 Women undergoing elective total abdominal hysterectomy under general anesthesia</p>	<p><i>OPRM1</i></p>

5HT, 5-hydroxytryptamine; CI, confidence interval; EM, extensive metabolizer; COMT, catechol-O-methyltransferase; GWAS, genome wide association study; OCT, organic cation transporter; OR, odds ratio; PACU, postanesthesia care unit; PCA IV, intravenous patient controlled analgesia; PM, poor metabolizer; PONV, postoperative nausea and vomiting; RD, respiratory depression; RR, relative risk; SNP, single-nucleotide polymorphism; UM, ultrarapid metabolizer; VAS, visual analog scale.

postoperative pain and have been associated with the occurrence of PONV. Emerging evidence from this review suggests that the *OPRM1* 118G allele is associated with decreased opioid analgesic effects and increased risk for nausea and vomiting after opioid use.⁴⁶ Thus, the *OPRM1* allele variant may be a good predictor of both postoperative pain management and PONV in patients receiving opioids.

Many pharmacogenomic studies of PONV have focused on the polymorphisms in the CYP genes, with particular attention to the inducible CYP2D6 enzyme. To date, there are no large randomized control trials or large multicenter trials investigating the association of *CYP2D6* polymorphism and PONV. However, several studies have linked PONV and *CYP2D6* genotype.³¹⁻³³ In addition, there are many alternative drugs for the management of PONV. The Clinical Pharmacogenetic Implementation Consortium guidelines for *CYP2D6* genotype-guided therapy of ondansetron recommend alternative 5-HT₃ receptor antagonists (eg, granisetron, dolasetron, palonosetron, and ramosetron) for *CYP2D6* UMs.³⁰ Given the increased enzyme activity in UMs and the availability of other effective antiemetics that are not metabolized by the CYP2D6 enzyme, choosing an alternative drug makes clinical sense.

The relationship between polymorphisms in *OPRM1* and *CYP2D6* genes, efficacy of opioids, and PONV highlights the multiplicity of genetic factors. This insight is relevant because, in the absence of genetic information, poor analgesic response to opioids such as morphine and codeine should alert the clinician to the possibility of increased risk for PONV. As the cost of genotyping decreases, one would expect the uptake of preemptive genotyping to increase in the clinical setting. However, until genetic information becomes readily available in medical records and point-of-care, knowledge of pharmacogenetics may be applied in all settings (with sound clinical judgment) to improve outcomes.

Conclusions

Studies have demonstrated that genetic differences have a relevant role in the occurrence and severity of PONV and the effectiveness of

antiemetic medications. In particular, the presence of three or more functional copies of the *CYP2D6* alleles (UM) is associated with a higher incidence of PONV and decreased efficacy of ondansetron, and the presence of the 118G allele in the *OPRM1* gene appears to protect against opioid-induced PONV (and decrease the analgesic response to opioids). In addition, *NK-1* receptor and dopamine receptor polymorphisms may affect the antiemetic efficacy of NK-1 receptor antagonists and DRD2 antagonists, respectively, yet these effects require further investigation. Overall, additional studies are needed to determine the biolog-

ical mechanism of PONV and the interaction between genetic polymorphisms, PONV, and other clinical factors such as hospital and postanesthesia care unit length of stay. Large-scale pharmacogenomic studies may contribute to increased satisfaction with care and improved perianesthesia outcomes.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jopan.2019.03.007>.

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Pharmacogenetics of Postoperative Nausea and Vomiting

2.5 Contact Hours

Purpose of the Journal of PeriAnesthesia Nursing: To facilitate communication about and deliver education specific to the body of knowledge unique to the practice of perianesthesia nursing.

Outcome of this CNE Activity: To enable the nurse to increase knowledge on the pharmacogenetics of postoperative nausea and vomiting

Target Audience: All perianesthesia nurses

Article Objectives

1. Discuss the genetic basis of inter-patient response to medication.
2. Explain the potential influence of genetic variations on PONV.
3. State the Clinical Pharmacogenetic Implementation Consortium (CPIC) *CYP2D6* guidelines for the management of PONV with ondansetron.

Accreditation

American Society of Perianesthesia Nurses is accredited with distinction as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

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Contact hours: Registered nurse participants can receive 2.5 contact hours for this activity.

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