Pharmacogenomic considerations for medications in the perioperative setting

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Several high-profile examples of adverse outcomes from medications used in the perioperative setting are well known (e.g., malignant hyperthermia, prolonged apnea, respiratory depression, inadequate analgesia), leading to an increased understanding of genetic susceptibilities underlying these risks. Pharmacogenomic information is increasingly being utilized in certain areas of medicine. Despite this, routine preoperative genetic screening to inform medication risk is not yet standard practice. In this review, we assess the current readiness of pharmacogenomic information for clinical consideration for several common perioperative medications, including description of key pharmacogenes, pharmacokinetic implications and potential clinical outcomes. The goal is to highlight medications for which emerging or considerable pharmacogenomic information exists and identify areas for future potential research.

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Nearly half of anesthesia-related deaths are attributable to adverse drug events (ADEs) or overdose [1], and one in 20 perioperative medication administrations causes an unpredictable ADE or involves a medication error [2,3]. Furthermore, it has been reported that three in four surgical patients in the USA do not have adequate analgesia in the acute postoperative setting [4]. The perioperative period involves the introduction of several drugs and drug classes, and any specific individual's response may be unpredictable.

Several examples describing this heterogeneity have been known for decades. In the 1950s, one landmark discovery was the identification of genetic variants in pseudocholinesterase that alter the kinetics of succinylcholine [5–7], causing prolonged apnea in individuals with a genetic predisposition. Separately, in 1960, the first documented individual to survive malignant hyperthermia (MH) was reported, ushering in extensive research about this disorder as being caused by genetic variation in calcium channels [8].

Pharmacogenomics involves the study of how genes affect drug response. Pharmacogenomics may have a role during preoperative evaluation by the anesthesiologist as it offers an opportunity to personalized anesthetic plans (Figure 1) [9]. Perisurgical care often involves medications that individuals may have never been exposed to before, including sedative-hypnotics, inhaled anesthetics, analgesics and cardiovascular drugs, among others. Although not yet available as standard of practice because of several barriers to implementation, pharmacogenomic information may offer an opportunity to potentially reduce ADEs, optimize drug efficacy and lower costs associated with surgery. In this review, we address one barrier to pharmacogenomic implementation: the need for an accurate understanding of the current evidence regarding medications and genes that may be actionable.

Figure 1. Potential clinical components of a comprehensive perioperative prescribing evaluation.

Perioperative evaluation considerations are adapted from Butterworth et al. 2013 [9] and Sanford et al. 2015 [10].

PONV: Postoperative nausea and vomiting.

For a set of commonly used perioperative medications, we examined all major pharmacogenomic clinical studies. Our primary data source was PubMed, using algorithmic [11] and manual medication searches. When available, we reviewed clinical guidelines provided by the Clinical Pharmacogenetics Implementation Consortium (CPIC) [12], the Royal Dutch Association for the Advancement of Pharmacy – Pharmacogenetics Working Group (DPWG) [13], information from the pharmacogenomics knowledge base (PharmGKB) and information from FDA drug labels. We regard these resources to be the most authoritative guidelines in pharmacogenomics. We present the synthesized pharmacogenomic evidence surrounding several key perioperative medications. Drugs with the best clinical evidence are described in detail. The review is organized by drug classes and then individual drugs. Of note, it should be taken into consideration that genetic effects of a medication account for a part of the total variability in response. Other factors such as drug–drug interactions, coexisting diseases or environmental factors are not covered in this review. Furthermore, disease-associated genetic variants that may have associated medication effects are also not reviewed.

Anesthetics

In a prior study examining anesthesia-related mortality in the USA, 46.6% of deaths were related to anesthetic overdose and 42.5% attributable to anesthetic ADEs [1]. Two of the most concerning ADEs associated with anesthetic administration are prolonged apnea and MH. Pharmacogenomic considerations for these ADEs will be reviewed, in addition to key pharmacogenetics studies for the frequently used agent propofol.

Succinylcholine & mivacurium (prolonged apnea)

Over 60 years ago, succinylcholine was introduced for clinical use, and not long afterwards, consequent cases of prolonged apnea were reported [5]. These cases were commonly associated with the atypical form (A-variant) of pseudocholinesterase, which was found to have approximately 100-fold lower affinity for succinylcholine than the usual form (U-variant) [7]. This missense polymorphism in the *BCHE* gene, also referred to as position 70 or rs1799807, results in an aspartic acid to glycine change [14]. Inactivation of succinylcholine to succinylmono-

choline [15] is greatly decreased in persons with the A-variant. The clinical consequence is that the respiratory muscles of the individual are immobilized for a longer period of time than in individuals with the U-variant, increasing the time to resumption of spontaneous breathing [15]. For short surgical procedures at doses of 0.3–1.1 mg/kg in U-variant adults, neuromuscular blockade is detected in 1 min with a maximum blockade continuing for 2 min and subsequent recovery within 4–6 min [16]. The A-variant has been reported to prolong this time to 6–20 min in heterozygous individuals [17] and 1–6 h in homozygous individuals [14,18,19]. Mivacurium, a nondepolarizing muscle relaxant with two- to 2.5-times the clinical effective duration of action to succinylcholine, is also metabolized by pseudocholinesterases [20]. A-variant carriers who receive mivacurium have also been shown to have prolonged duration of recovery with times between 30 min and 12 h after a standard dose [19].

In Caucasians, the A-variant is relatively rare, with a population allele frequency of 1.7%, meaning approximately one in 30 are heterozygotes and three in 10,000 are homozygotes [14]. Other racial/ethnic populations show similarly low frequency rates [21]. The A-variant is often found in linkage disequilibrium with the K-variant (rs1803274), a quantitative variant affecting the amount of pseudocholinesterase enzyme that is produced. The K-variant has an average global frequency of 15.9% [22]. The K-variant is also a missense variant that results in approximately 30% decrease in pseudocholinesterase activity for individuals with the heterozygous genotype (U/K) when compared with homozygous U-variant (U/U) samples [23]. Despite this, the K-variant has at most a modest clinical effect with succinylcholine. In a study of 70 adult surgical patients, it was shown that patients heterozygous for the K-variant (U/K) had approximately a 4-min mean difference in the duration of action of succinylcholine relative to U/U patients, a difference that was small compared with the wide variability present among all patients [24]. Nevertheless, for mivacurium, it has been reported that individuals with the U/K genotype will have a duration of action that is on average 6–8 min longer, and thus, possibly a clinically significant effect during a short-term surgery [25].

Other variants within *BCHE* that associate with prolonged apnea include F-variants (flu-1, rs28933389; flu-2, rs28933390), J-variant (rs121918556) and S-variant (rs104893684), among others, occurring in much lower frequencies than the K- and A-variants [15]. The US FDA labeling for succinylcholine includes a warning about prolonged apnea in individuals, who are A/A homozygous and recommends a 5–10 mg test dose prior to therapeutic use, if the drug is to be used at all [16]. For heterozygous individuals, the FDA label recommends cautious use of succinylcholine. For mivacurium, the FDA label cautions that the duration of action may be as long as 8–11 min longer in individuals with heterozygosity for the A-variant; use of mivacurium in homozygous A-variant individuals is not recommended [20].

Volatile anesthetics & succinylcholine (malignant hyperthermia)

MH is a disorder of skeletal muscle calcium regulation [8]. Details of the disorder have been extensively described elsewhere [15,26,27]. Briefly, a rapid increase in myoplasmic calcium levels and consequent hypermetabolic state characterizes MH, and the current gold standard diagnosis is via *in vitro* muscle contracture test in Europe or the caffeine halothane contracture test in North America [15,28]. Sensitivity is nearly 100% with a specificity of 80% [29]. Taking a comprehensive family history is the accepted screening tool to detect possible genetic susceptibility to MH. Caffeine halothane contracture test and *in vitro* muscle contracture test are not offered as screening tools for the general population, but there is a growing sentiment that germline genetic testing could be used as a screening tool in appropriate individuals.

MH has been shown to associate with the administration of succinylcholine and/or volatile anesthetics. Given that MH is a rare ADE, practically all studies describing MH have been case series of at-risk patients. In a multicenter European MH study that included five different countries, 101 of 196 MH patients carried a ryanodine receptor (*RYR1*) gene variant [30]. Over 400 genetic variants have been identified in *RYR1* and the European Malignant Hyperthermia Group has determined 48 to be causal, in addition to two other variants in the dihydropyridine receptor (*CACNA1S*) gene (Supplementary Table 1) [31]. These variants are confirmed to have functional pathogenicity. Some have argued for genetic screening panels to be increasingly utilized in appropriate clinical settings as a primary diagnostic tool [31]. However, the full extent of genes and variants involved are not yet thoroughly known, and genetic screening will not accomplish the goal of completely preventing this disease.

At present, desflurane, isoflurane, sevoflurane and succinylcholine have US FDA labels with contraindications for patients with known or suspected susceptibility to MH. CPIC has recently published a clinical guideline for triggering agents of MH [32].

Propofol

Propofol is commonly used in induction and maintenance phases of anesthesia. It is metabolized by CYP2B6, CYP2C9 and UGT1A9 [33]. The most commonly studied, however, is the CYP2B6 enzyme, and is the only gene in propofol's metabolic pathway with several clinical pharmacogenetics studies to date, particularly for the rs3742574 (G516T, Gln172His) polymorphism.

In a study of patients undergoing a variety of surgical procedures, anesthesia was induced by propofol, fentanyl and atracurium, and maintained with sevoflurane and remifentanyl. In a regression model including several covariates such as sex, age, weight, surgery duration, smoking status, various medication use and doses and rs3742574 genotype (GG vs GT/TT), it was found that T allele carriers associated with a lower total propofol dose than the GG genotypes for a subset of 64 patients undergoing general anesthesia (151.5 ± 64.2 vs 129.3 ± 43.6 mg, in GG vs GT/TT genotypes, respectively; $p = 0.043$) [34]. Another study showed that nine out of ten women displaying propofol blood levels one standard deviation above the mean were T allele carriers, while only 16 of 34 women were carriers when displaying propofol levels one standard deviation below the mean ($p = 0.027$) [35]. Higher maximum propofol concentrations during infusion were also observed in T allele carriers for a study of 51 patients undergoing anesthesia [36].

The rs3742574 T allele was observed to cause altered splicing and loss of exons 4–6, leading to decreased expression and activity of the enzyme [37]. This functional difference may contribute to pharmacogenomic differences in patients. The magnitude of effect that this difference will have in clinical practice is not yet known.

Analgesics

Successful multimodal perioperative analgesia remains a challenging problem. ADEs related to opioid administration following surgery has been associated with increased length of stay and hospital costs [38]. Consideration of genetic variability may offer a means to partially address these shortcomings. The following section examines pharmacogenomic evidence for several different analgesics.

Codeine

Codeine is a prodrug where 5–15% of its dose is metabolized by CYP2D6 to morphine, the active metabolite [39]. *CYP2D6* is a considerably polymorphic gene with predictable metabolizer phenotypes based on the presence of certain alleles. Poor metabolizers (PM) carry no functional alleles; for codeine, *o*-demethylation to morphine is significantly reduced resulting in decreased morphine levels and decreased analgesia compared with normal metabolizers [39,40]. In stark contrast, CYP2D6 ultra rapid metabolizers (UM) carry additional gene copies and convert a higher percentage of codeine to morphine which can result in toxic concentrations of morphine even with small doses of codeine. Intermediate metabolizers (IM) have lower than normal activity, but higher than PMs. The vast majority of individuals are normal metabolizers (extensive metabolizers, EM), which constitutes 77–92% of individuals [39].

In a study of 26 Caucasian male volunteers, plasma morphine concentrations after one dose of 30 mg codeine were significantly different between metabolizer phenotypes: 0.5, 11 and 16 $\mu\text{g h/l}$ (PM, EM and UM, respectively; $p = 0.02$ between EM and UM) [41]. In this study, ten of the 11 UM patients displayed sedation compared with only six out of 12 EM patients ($p = 0.03$). In another randomized placebo-controlled double-blind trial between nine EMs and nine PMs prescribed 170 mg codeine [42], only traces of morphine were found in the plasma in PMs (C_{max} : 2 ± 1 nmol/l; area under plasma-concentration time curve, AUC: 10 ± 7 nmol $\times$ h/l), while EMs had adequate morphine concentrations (C_{max} : 38 ± 16 nmol/l; AUC: 173 ± 90 nmol $\times$ h/l). Analgesia was only observed in EM patients.

A case–control study of 111 mother–infant pairs showed that mothers taking codeine with the UM phenotype were significantly more likely to have breastfed infants displaying CNS depression (odds ratio, OR = 4.19, $p = 0.043$) [43]. Increasing CYP2D6 activity was also associated with an increased risk of maternal CNS depression (OR = 8.62, $p = 0.012$). This finding was corroborated by another case–control study of 72 mother–child pairs where it was found that mothers whose infants exhibited CNS depression after codeine therapy were six-times more likely to be of the UM phenotype [44]. At least one case report described morphine poisoning and death of a neonate after 13 days of breastfeeding from a mother with the UM phenotype [45]. There is a black box warning recommending against codeine use in all children under the age of 12, a warning against use in children 12–18 years with certain conditions, and a strong warning against use of codeine in nursing mothers [46,47]. Recently, the US FDA has required labeling changes to limit the use of codeine in cough and cold medicines to adults 18

years and older. Clinical guidelines from CPIC [39] recommend alternatives to codeine therapy for UMs and PMs. DPWG [13] recommends alternatives or to be alert to ADEs associated with UMs, and use of alternatives or to be alert to insufficient pain relief in PMs. For IMs, CPIC and DPWG recommend alternatives to codeine therapy if analgesia is less than optimal.

Tramadol

Tramadol is a drug with both parent and metabolite compounds that likely work not only on opioid mediated but also monoaminergic mediated mechanisms for analgesia [48]. Tramadol is metabolized by the CYP2D6 enzyme to the main active metabolite (+)-O-des-methyltramadol (ODT), which is responsible for the opioid receptor mediated analgesia and has approximately 200-times greater affinity for the opioid receptor than the parent drug [49]. Tramadol itself likely has analgesic activity, with (+) and (-) tramadol enantiomers as the most potent inhibitor of serotonin and norepinephrine reuptake, respectively [48].

In a study of 271 Caucasian patients undergoing major abdominal surgery, CYP2D6 PM patients required a 33% higher postoperative tramadol loading dose compared with EMs due to insufficient analgesia (144.2 vs 108.3 mg, $p < 0.001$) [50]. In addition, the response rate for PM patients was 53.3 versus 78.4% found in EMs assessed for 48 h after the loading dose ($p = 0.005$). In a different study observing single oral dose, multiple oral dose and IV tramadol, tenfold lower area under the curve (AUC) and $C_{\max}$ of ODT in PM patients was found when compared with normal metabolizers ($p < 0.0001$) for 48 h after dosing [48]. Furthermore, a study of 187 major abdominal surgery patients given IV tramadol 3 mg/kg postoperatively showed ten of 18 PMs needing rescue medication in the postanesthetic care unit, significantly more than in any other metabolizer phenotype ($p < 0.001$) [51].

As of April 2017, the US FDA revised tramadol labeling to include a contraindication in all children under the age of 12, a warning for use in children 12–18 years with certain conditions, and a stronger warning against the use of tramadol in nursing mothers [46]. The US FDA also included a black box warning for tramadol in children after tonsillectomy and/or adenoidectomy.

Tramadol is categorized by CPIC to have moderate to strong recommendation status for CYP2D6 (cpicpgx.org/genes-drugs, last updated April 26, 2019). The DPWG recommends selecting an alternative drug (not oxycodone or codeine) or to be alert to suboptimal analgesia in PMs, tramadol dose increase or an alternative drug if there is decreased efficacy for IMs, and a dose reduction of tramadol by 30% or use of an alternative drug for UMs [13].

Morphine

The μ -opioid receptor is encoded by the *OPRM1* gene, and is the most commonly studied pharmacogene for morphine. Of greatest interest has been the SNP resulting in an asparagine to aspartic acid change at amino acid 40 (Asn40Asp, A118G, rs1799971), with the G-variant conferring higher binding affinity to β -endorphin, but lower potency from exogenous opioids [52].

Studies of *OPRM1* rs1799971 have investigated multiple different pain populations, several different outcomes phenotypes, and many have been conducted primarily in Asian populations. In a study of 588 Chinese Singaporean women who were evaluated for pain (visual analog scale) and patient-controlled intravenous morphine consumption for postcesarean analgesia, each additional copy of the risk G allele increased morphine usage by 1.87 mg ($p < 0.0001$) in the 24 h after surgery [53]. This would mean that if an individual had the GG genotype, their morphine intake would be an additional 3.74 mg relative to the wild-type AA genotype. This represents 2.28% of the variation in morphine consumption explained by genotype [53]. Another study observing morphine use following abdominal hysterectomy in 973 Asian women showed patients with GG genotypes also required the most morphine (19.22 vs 14.83 and 16.23 mg in wild-type and heterozygous genotype, respectively; $p = 0.005$) [54]. These findings are supported by a meta-analysis of 18 studies involving 4607 patients taking various opioids (morphine, fentanyl, hydrocodone and oxycodone) that showed that G allele carriers required statistically significant higher mean opioid doses than AA homozygotes ($p = 0.003$) [52]. The standard mean difference (SMD) was -0.18 between these two groups, meaning a small effect size. Of note, 12 of the 18 studies were performed in Asian patients, and half the studies used morphine. Subgroup analyses found the Asian population as a major contributor to the effect (SMD = -0.21, $p = 0.001$) and strongest significance in morphine users (SMD = -0.29, $p < 0.001$) and those undergoing viscus surgery (SMD = -0.20, $p = 0.008$).

The US FDA currently does not have pharmacogenomic information for morphine in its labels. It is also among the list of CPIC genes–drugs that currently does not have any prescribing actions recommended (cpicpgx.org/genes-

Table 1. Key pharmacogenomic anesthesia drugs in the perioperative setting.

Drug	Gene	Variant	Clinical outcome risk	US FDA label has pharmacogenetic information?	Study (year)	Reference type	Ref.
Mivacurium, succinylcholine	BCHE	Multiple	Prolonged apnea	Yes	Alvarellos <i>et al.</i> (2015)	PharmGKB [†] summary	[15]
					Bartel <i>et al.</i> (1992)	Pharmacokinetic	[23]
					Bretlau <i>et al.</i> (2013)	Pharmacokinetic-pharmacodynamic	[24]
					Cerf <i>et al.</i> (2002)	Pharmacokinetic-pharmacodynamic	[19]
					Drug label	Clinical guideline (FDA)	[20]
					Drug label	Clinical guideline (FDA)	[16]
					Gätke <i>et al.</i> (2005)	Pharmacodynamic	[25]
					Kalow (1964)	Review article	[7]
					Rubinstein <i>et al.</i> (1960)	Case report	[5]
Desflurane, enflurane, halothane, isoflurane, sevoflurane, succinylcholine	RYR1 CACNA1S	Multiple	Malignant hyperthermia	Yes	Hopkins <i>et al.</i> (2015)	Clinical guideline (EMHG)	[31]
					Alvarellos <i>et al.</i> (2015)	PharmGKB summary	[15]
					Alvarellos <i>et al.</i> (2016)	PharmGKB summary	[91]
					www.MHAUS.org [‡]	Organization	[29]
					Drug label	Clinical guideline (FDA)	[92]
					Drug label	Clinical guideline (FDA)	[93]
					Drug label	Clinical guideline (FDA)	[94]
					Drug label	Clinical guideline (FDA)	[16]
					Gonsalves <i>et al.</i> (2018)	Clinical guideline (CPIC)	[32]
Propofol	CYP2B6	rs3745274	Awakening time	No	Restrepo <i>et al.</i> (2009)	Review article	[33]
					Mourao <i>et al.</i> (2016)	Pharmacokinetic	[34]
					Mastrogianni <i>et al.</i> (2014)	Pharmacokinetic	[35]
					Kansaku <i>et al.</i> (2011)	Pharmacokinetic	[36]

[†]PharmGKB = The Pharmacogenomics Knowledgebase.

[‡]www.MHAUS.org; (Malignant Hyperthermia Association of the United States).

CPIC: Clinical Pharmacogenetics Implementation Consortium; EHM: European Malignant Hyperthermia Group.

drugs, last updated April 26, 2019). DPWG does not list any recommendations. Given the reproducibility of the above findings across multiple studies and the large number of patients examined, we conclude that *OPRM1* genotyping warrants further evaluation to better determine its role in modulating morphine analgesic requirements.

Antiepileptics

Several perioperative medications are known to reduce seizure threshold [55]. These include some inhaled volatile anesthetics, local anesthetics, opioids and sedative-hypnotic medications. In addition, it has been reported that in patients undergoing neurosurgery, 15–50% will experience seizures after surgery [56]. In line with these data, 70% of neurosurgery patients will be routinely administered a prophylactic antiepileptic drug after craniotomy, most commonly phenytoin [56]. We therefore evaluate two antiepileptic drugs for pharmacogenomic information relevant to the perioperative setting.

Carbamazepine & phenytoin

A severe cutaneous adverse reaction (SCAR) to a drug is a nonimmediate hypersensitivity reaction that causes significant morbidity or mortality [57]. SCAR includes Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms and acute generalized exanthematous pustulosis (AGEP). Genetic factors can predispose to SCAR [57]. Since December 2007, the US FDA has included a black box warning in the carbamazepine drug label [58] that recommends screening for HLA-B*15:02 prior to initiation of carbamazepine in individuals with Asian ancestry including South Asian Indians due to a strong association

Table 2. Key pharmacogenomic analgesia drugs in the perioperative setting.

Drug	Gene	Variant	Clinical outcome risk	US FDA label has pharmacogenetic information?	Study (year)	Reference type	Ref.
Codeine	CYP2D6	Metabolizer status	Analgesic response and toxicity	Yes	Crews <i>et al.</i> (2014)	Clinical guideline (CPIC)	[39]
					Drug label	Clinical guideline (FDA)	[39]
					Eckhardt <i>et al.</i> (1998)	Pharmacokinetic	[42]
					Gasche <i>et al.</i> (2004)	Case report	[40]
					Kirchheiner <i>et al.</i> (2006)	Pharmacokinetic	[41]
					Koren <i>et al.</i> (2006)	Case report	[45]
					Madadi <i>et al.</i> (2009)	Case-control	[44]
					Madadi <i>et al.</i> (2013)	Clinical guideline (CPND)	[95]
					Sistonen <i>et al.</i> (2012)	Case-control	[43]
					Swen <i>et al.</i> (2011)	Clinical guideline (DPWG)	[13]
Tramadol	CYP2D6	Metabolizer status	Analgesic response and toxicity	Yes	Drug label	Clinical guideline (FDA)	[96]
					Kirchheiner <i>et al.</i> (2008)	Pharmacokinetic-pharmacodynamic	[97]
					Pedersen <i>et al.</i> (2006)	Pharmacokinetic	[48]
					Stamer <i>et al.</i> (2003)	Pharmacodynamic	[50]
					Stamer <i>et al.</i> (2007)	Pharmacokinetic-pharmacodynamic	[51]
					Swen <i>et al.</i> (2011)	Clinical guideline (DPWG)	[13]
					Hwang <i>et al.</i> (2014)	Review article and meta-analysis	[52]
Morphine	OPRM1	rs1799971 (A118G, Asn40Asp)	Decreased analgesic response	No	Klepstad <i>et al.</i> (2011)	Pharmacodynamic	[98]
					Sanford <i>et al.</i> (2014)	Book chapter	[10]
					Sia <i>et al.</i> (2008)	Pharmacokinetic-pharmacodynamic	[53]
					Sia <i>et al.</i> (2013)	Pharmacokinetic-pharmacodynamic	[54]
					Walter <i>et al.</i> (2013)	Review article and meta-analysis	[99]

CPIC: Clinical Pharmacogenetics Implementation Consortium; CPND: Canadian Pharmacogenomics Network for Drug Safety; DPGW: Dutch Association for the Advancement of Pharmacy – Pharmacogenetics Working Group.

with this allele and SJS/TEN (pooled OR = 113.4) [59]. HLA-B (human leukocyte antigen B) is a cell surface protein that presents antigens to the immune system [60]. Greater than 15% of certain Asian populations carry *HLA-B*15:02* [58]. CPIC recommends against carbamazepine use in *HLA-B*15:02* carriers unless a patient has previously demonstrated tolerability for carbamazepine for >3 months without SCAR [60].

The association of SCAR and *HLA-B*15:02* with phenytoin shows a moderate association. In a case-control study, *HLA-B*15:02* was associated with phenytoin-induced SJS/TEN (OR: 5.1; 95% CI: 1.8–15.1; $p = 0.0041$) [61]. This finding was strongly demonstrated again in a subsequent meta-analysis (OR = 4.26; 95% CI: 1.93–9.39; $p < 3 \times 10^{-4}$) [62]. US FDA labeling warns against the use of phenytoin as an alternative to carbamazepine for patients with the *HLA-B*15:02* allele [63]. CPIC guidelines recommend against the initiation of phenytoin and fosphenytoin in patients with the *HLA-B*15:02* allele [64].

Phenytoin toxicities are also genetically mediated via CYP2C9, which converts phenytoin to 5-(4-hydroxyphenyl)-5-phenylhydantoin [65]. Two missense SNPs within CYP2C9 have shown to decrease enzyme activity and affect phenytoin pharmacokinetics: *2 allele (rs1799853) and *3 allele (rs1057910). These effects are more profound with the *3 allele. In a case-control genome-wide association study examining phenytoin-related SCAR in Taiwanese, Japanese and Malaysian individuals, it was discovered that the CYP2C9*3 variant was significantly associated with SCAR (OR = 12; 95% CI: 6.6–20; $p = 1.1 \times 10^{-17}$), and this was highly correlated with delayed clearance of plasma phenytoin [66]. In a study of 137 Caucasian patients with epilepsy, phenytoin ADEs (e.g., sleepiness, somnolence, fatigue, dizziness, vertigo) were associated with metabolizer status of CYP2C9 determined by *2 and *3 alleles ($p = 0.008$) [67]. Another toxicity study reported an increased risk for phenytoin

Table 3. Key pharmacogenomic antiepileptic drugs in the perioperative setting.

Drug	Gene	Variant	Clinical outcome risk	US FDA label has pharmacogenetic information?	Study (year)	Reference type	Ref.		
Carbamazepine	HLA-B	*15:02	SCAR [†]	Yes	Drug label	Clinical guideline (FDA)	[58]		
					Duong <i>et al.</i> (2017)	Review article	[57]		
					Leckband <i>et al.</i> (2013)	Clinical guideline (CPIC)	[60]		
Phenytoin	CYP2C9	rs1799853 (*2 allele,R144C)	Neurotoxicity and SCAR	Yes	Aynacioglu <i>et al.</i> (1999)	Pharmacokinetic	[70]		
					Caudle <i>et al.</i> (2014)	Clinical guideline (CPIC)	[64]		
					Chung <i>et al.</i> (2014)	Pharmacokinetic-pharmacodynamic	[66]		
					Drug label	Clinical guideline (FDA)	[63]		
		rs1057910 (*3 allele,I359L)			Depondt <i>et al.</i> (2011)	Pharmacodynamic	[67]		
					Hung <i>et al.</i> (2012)	Pharmacokinetic-pharmacodynamic	[69]		
					Kesavan <i>et al.</i> (2010)	Pharmacodynamic	[68]		
					Tate <i>et al.</i> (2005)	Pharmacodynamic	[71]		
					Caudle <i>et al.</i> (2014)	Clinical guideline (CPIC)	[64]		
					Cheung <i>et al.</i> (2013)	Pharmacodynamic	[62]		
					Drug label	Clinical guideline (FDA)	[63]		
					Hung <i>et al.</i> (2010)	Pharmacodynamic	[61]		
	HLA-B	*15:02	SCAR	Yes	Caudle <i>et al.</i> (2014)	Clinical guideline (CPIC)	[64]		
					Cheung <i>et al.</i> (2013)	Pharmacodynamic	[62]		
					Drug label	Clinical guideline (FDA)	[63]		
					Hung <i>et al.</i> (2010)	Pharmacodynamic	[61]		

†SCAR: Severe cutaneous adverse reaction.

CPIC: Clinical Pharmacogenetics Implementation Consortium.

toxicity with an OR = 15.3 for the *1/*3 genotype ($p < 0.0001$) [68]. The *2 allele carriers in this study showed a trend for toxicity OR = 3.5 ($p = 0.06$). Several pharmacokinetic studies further support the above studies [69,70]. A study involving 281 epilepsy patients showed that the *3 allele was associated with a lower required maximum phenytoin dose (*3 copy = 0, 1, 2; dose = 354, 309, 250 mg, respectively; $p = 0.0066$) [71].

CPIC and DPWG recommend 25 and 50% maintenance dose reductions for IMs (*1/*2, *1/*3) and PMs (*2/*2, *3/*3, *2/*3), respectively, due to possibility of toxicities associated with increased phenytoin plasma concentrations [13,64].

Cardiovascular drugs

Typically, pre-existing drugs such as statins and antihypertensives (especially β -blockers) with the possible exception of angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors are continued through the surgical period. Cooper-DeHoff and Johnson 2016 [72] previously reviewed the pharmacogenomics of hypertension medications, with the general consensus that clinical implementation may eventually require testing of multiple genetic markers to guide therapy. The International Consortium for Antihypertensive Pharmacogenomics Studies is an organization that promotes discovery of genetic markers that could ultimately aid in antihypertensive treatment decisions (icaps-htn.org). We also previously comprehensively assessed 71 cardiovascular drugs for pharmacogenomic evidence, of which 23 were found to be clinically actionable [73]. Our review here will focus on the current evidence surrounding two common medications, metoprolol and simvastatin.

Metoprolol

Metoprolol is one of the most commonly used β -blocker within the perioperative setting. It is metabolized to the inactive form, α -hydroxymetoprolol, by CYP2D6 [73,74]. In a study of 121 Caucasian hypertensive patients, it was observed that dose-normalized concentrations of metoprolol were significantly different between CYP2D6 phenotypes, with median levels in PMs/IMs 17-fold higher than EMs/UMs [75]. Another study showed that metoprolol plasma concentrations were 4.9-fold higher in the PM group than other phenotypes, which was associated with significantly greater reductions in heart rate, diastolic pressure and mean arterial pressure [76]. One large study reported that PM patients were fivefold more frequently found to exhibit metoprolol ADEs than a control population ($p < 0.0001$) [77]. A study of 187 Russian acute myocardial infarction patients observed that

Table 4. Key pharmacogenomic cardiovascular drugs in the perioperative setting.

Drug	Gene	Variant	Clinical outcome risk	US FDA label has pharmacogenetic information?	Study (year)	Reference type	Ref.
Metoprolol	CYP2D6	Metabolizer status	Efficacy; bradycardia	Yes	Drug label	Clinical guideline (FDA)	[100]
					Fux <i>et al.</i> (2005)	Pharmacokinetic-pharmacodynamic	[75]
					Goryachkina <i>et al.</i> (2008)	Pharmacokinetic-pharmacodynamic	[78]
					Rau <i>et al.</i> (2009)	Pharmacokinetic-pharmacodynamic	[76]
					Wuttke <i>et al.</i> (2002)	Pharmacodynamic	[77]
					Zineh <i>et al.</i> (2004)	Pharmacokinetic-pharmacodynamic	[79]
Simvastatin	SLCO1B1	rs4149056 (T521C, Val174Ala)	Myopathy	No	Drug label	Clinical guideline (FDA)	[101]
					Ramsey <i>et al.</i> (2014)	Clinical guideline (CPIC update)	[82]
					Wilke <i>et al.</i> (2012)	Clinical guideline (CPIC)	[81]
CPIC: Clinical Pharmacogenetics Implementation Consortium.							

UMs did not achieve therapeutic effects and plasma concentrations were significantly different from other genotypes ($p < 0.005$) [78].

Despite these findings and relatively consistent reporting of pharmacokinetic differences by CYP2D6 status, other studies have not been able to reproduce associations with ADEs [75,79].

Currently, US FDA labeling of metoprolol includes information about CYP2D6 and drug–drug interactions. Metoprolol and CYP2D6 are among the list of CPIC genes–drugs that currently do not have any prescribing actions that are recommended (cpicpgx.org/genes-drugs, last updated April 26, 2019). DPWG recommends dose adjustments or alternative treatments for heart failure patients where a 75% dose reduction may be required for PMs, 50% for IMs and a maximum titrated dose of 250% for UMs.

Simvastatin

Patients on chronic statin therapy are often advised to continue such therapy through surgery, and statins may also be started in certain previously untreated patients. Although evidence is still accumulating for statin use within the perioperative setting [80], we will review simvastatin pharmacogenomics as the level of evidence for this statin is substantial [73,81].

The *SLCO1B1* (solute carrier organic anion transporter family, member 1B1) gene, which codes for OATP1B1 (organic anion transporter protein B1) in the liver, contains a SNP (rs4149056, *SLCO1B1**5) that produces a valine to alanine change at amino acid 174, influencing the hepatic uptake of simvastatin [81,82]. Those carrying the CC genotype comparatively have 221% higher plasma AUC than TT wildtypes, with an OR for myopathy of approximately two to fourfold per copy of the C allele [82]. As a relatively frequent SNP (up to 16% C allele frequency in Africans, Americans, east Asians, south Asians, and Europeans) [22], the potential genetic risk applies to a large number of individuals.

US FDA labeling of simvastatin includes information about OATP1B1 and drug–drug interactions. The CPIC guideline [82] recommends a lower dose or alternative statin for C allele carriers.

Proton pump inhibitors

According to Practice Guidelines developed by the American Society of Anesthesiologists, evidence supports the use of PPIs, specifically omeprazole and lansoprazole, in preventing untoward effects of perioperative pulmonary aspiration [83]. Randomized controlled trials show reduced gastric volume and acidity with these two PPIs. Risk of aspiration occurs in approximately one in 3000 anesthetics with mortality accounting for 10–30% of all anesthesia-related deaths [84].

Table 5. Key pharmacogenomic proton pump inhibitors in the perioperative setting.

Drug	Gene	Variant	Clinical outcome risk	US FDA label has pharmacogenetic information?	Study (year)	Reference type	Ref.
Lansoprazole	CYP2C19	Metabolizer status	Inadequate efficacy	Yes	Adachi et al. (2000)	Pharmacodynamic	[88]
					Drug label	Clinical guideline (FDA)	[102]
					Furuta et al. (2002)	Pharmacokinetic-pharmacodynamic	[85]
					Gumus et al. (2012)	Pharmacokinetic	[87]
					Kawamura et al. (2003)	Pharmacodynamic	[86]
					Swen et al. (2011)	Clinical guideline (DPWG)	[13]
Omeprazole	CYP2C19	Metabolizer status	Inadequate efficacy	Yes	Baldwin et al. (2008)	Pharmacokinetic	[103]
					Drug label	Clinical guideline (FDA)	[104]
					Furuta et al. (1999)	Pharmacokinetic-pharmacodynamic	[105]
					Sagar et al. (2000)	Pharmacodynamic	[106]
					Sugimoto et al. (2006)	Pharmacodynamic	[90]
					Swen et al. (2011)	Clinical guideline (DPWG)	[13]
					Ohkusa et al. (2005)	Pharmacodynamic	[107]

DPWG: Dutch Association for the Advancement of Pharmacy – Pharmacogenetics Working Group.

Lansoprazole & omeprazole

Proton pump inhibitors are mainly metabolized by CYP2C19. In a study of gastroesophageal reflux disease patients [85], responses with 30 mg lansoprazole were significantly associated with CYP2C19 metabolizer status where EMs had the lowest cure rate, followed by IMs, while PMs had the highest cure rate (45.8, 67.9, 84.6%; $p = 0.035$). In a different study of 88 patients with erosive reflux esophagitis, healing rates were 77.4, 95.0 and 100% at 8 weeks for EMs, IMs and PMs, respectively ($p < 0.05$) [86]. Correspondingly, significant differences have been observed in mean intragastric pH and plasma levels of these PPIs, with PMs/IMs showing significantly higher mean intragastric pHs than EMs, and PMs showing the highest plasma drug levels followed by IMs and then EMs (745.4 ± 40.5 ng/ml, 439.9 ± 88.7 ng/ml, 312.3 ± 66.8 ng/ml, respectively after a single dose; $p < 0.0338$) [87–90].

US FDA labeling includes information about CYP2C19 enzyme activity differences and CYP2C19 drug–drug interactions for PPIs. Both lansoprazole and omeprazole are among the list of CPIC genes–drugs with recommended prescribing actions (cpicpgx.org/genes-drugs, last updated April 26, 2019). The DPGWG recommends that CYP2C19 UMs may need a 100–200% increase in lansoprazole/omeprazole doses, due to risk of insufficient response [13].

Future perspective

In this review, we summarized the current pharmacogenomic evidence for common perioperative medications from 5 different drug classes. The majority of these drugs have US FDA labeling and/or clinical guidelines that alert prescribers to the possible utility of considering genetic information when prescribing (Tables 1–5). This list is not meant to be exhaustive, but instead intends to highlight areas of accumulated evidence.

The perioperative setting is unique in that it is a high stakes, fast-paced environment where preoperative evaluation and preparation are important and critical factors that determine successful outcomes after surgery. This becomes a very appealing opportunity to use pharmacogenomics informed prescribing, considering the approximately 30 million inpatient and 53 million outpatient procedures performed each year.

Pre-emptive pharmacogenomic testing has shown promise in some clinical settings, including at our own institution during routine outpatient care [108]. Nevertheless, most of the genetic tests presented in this review are not readily available to the practicing anesthesiologist. Increased availability of testing platforms will likely occur either in response to increasing demand, or, more accurately, as clinical evidence of utility warrants. Future studies

aimed at evaluating the utility of having pharmacogenomic information for perisurgical prescribing are therefore warranted to thoughtfully consider the expanded integration of pharmacogenomic information into perioperative care. We have taken this opportunity to design a randomized prospective trial (clinicaltrials.gov #NCT03729180), where surgery patients at our institution will be enrolled for preemptive genetic screening, and anesthesiologists will have the option to use the pharmacogenomic results (with accompanying clinical decision support) for clinical decision making. The Department of Anesthesia and Critical Care at the University of Chicago is engaged to support this effort. These and other efforts represent a potential next frontier for precision medicine.

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Executive summary

Adverse events & the role of pharmacogenomics in perioperative care

- Perisurgical care often involves medications that patients may have never been exposed to before, including sedative-hypnotics, inhaled anesthetics, analgesics and cardiovascular drugs, among others.
- Although not yet available as standard of practice because of several barriers to implementation, pharmacogenomic information may offer an opportunity during perioperative care to potentially reduce adverse drug events, optimize drug efficacy and lower costs associated with surgery.

Anesthetics

- Data regarding the A and K variants of pseudocholinesterase, the two most common variants affecting succinylcholine and mivacurium duration of action, have compelling actionable information for prediction of prolonged apnea from these medications.
- Malignant hyperthermia resulting from the administration of volatiles anesthetics and/or succinylcholine has been studied for decades, but recent evidence and a growing knowledge about susceptibility variants suggests that genetic testing might be used as a primary screening method.
- Emerging evidence for propofol and *CYP2B6* rs3742574 shows pharmacokinetic and clinical outcome differences due to reduced function of the enzyme for select individuals.

Analgesics

- Codeine and tramadol have strong pharmacogenomic evidence based on *CYP2D6* metabolizer status, and US FDA information about these drugs is prominent.
- The largest studies for morphine and rs1799971 showed that G allele carriers require higher opioid doses.

Antiepileptics

- Severe cutaneous adverse reactions in carriers of *HLA-B* 15:02* is well known. Avoidance of these medications in individuals with genetic risk is now standard practice.
- Several studies show phenytoin toxicity associated with *CYP2C9* intermediate and poor metabolizers.

Cardiovascular medications

- Some data show variability in both efficacy and toxicity for metoprolol across individuals with varying *CYP2D6* metabolizer statuses.
- C allele carriers of rs4149056 (*SLCO1B1**5) have higher plasma concentrations of simvastatin and increased risk of myopathy.

Proton pump inhibitors

- Lansoprazole and omeprazole show both pharmacokinetic and clinical outcomes differences based on *CYP2C19* metabolizer status.

Future directions

- In this review, we summarize the current pharmacogenomic evidence for common perioperative medications from five different drug classes.
- Future studies including prospective trials aimed at evaluating the utility of having pharmacogenomic information for perisurgical prescribing are warranted to thoughtfully consider the expanded integration of pharmacogenomic information into perioperative care.

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