Clinicians are witnessing differences in the doses required for induction and maintenance of anesthesia, as well as prolonged recovery in some patients. Predictable factors like patient characteristics, factors related to the procedure, pharmacological characteristics of anesthetics and adjunctive drugs, might explain some of the observed differences. However, the role of various polymorphisms of genes encoding for drugs’ molecular targets, transporters and metabolic enzymes can have a significant impact on anesthesia outcome, too. In the present paper, we critically discuss pharmacological characteristics of the most common drugs used in anesthesia, with a focus on the possible genetic background of unpredictable diversities in anesthesia outcomes.

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Keywords: anesthesia ● epigenetics ● genotype ● inhalational anesthetics ● intravenous anesthetics ● neuromuscular blockers ● opioids ● pharmacological characteristics ● sedatives
### Table 1. The possible influence of pharmacogenomics on clinical outcomes of drugs used in anesthesia.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>Protein</th>
<th>Gene</th>
<th>Genotype (important allelic variants)</th>
<th>Effect on drug PK/PD and clinical outcomes</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volatile anesthetics</strong></td>
<td>Desflurane</td>
<td>RYR1</td>
<td>RYR1</td>
<td>Multiple (48 variants) at 19q13.1</td>
<td>Safety: increased risk of malignant hyperthermia because of Ca(^{2+}) leakage from the intracellular source</td>
<td>[13,15]</td>
</tr>
<tr>
<td></td>
<td>Isoflurane</td>
<td>DHPFR</td>
<td>CACNA1S</td>
<td>rs772226189 (c.520C&gt;T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td></td>
<td></td>
<td>rs1800559 (c.3257G&gt;A)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Nitrous oxide</td>
<td>MTHFR</td>
<td>MTHFR</td>
<td>rs1801133 (677T&gt;C)</td>
<td>Safety: Abnormal plasma homocysteine concentration; potential cardiotoxicity?</td>
<td>[17]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>rs1801131 (1298A&gt;C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intravenous anesthetics</strong></td>
<td>Propofol</td>
<td>CYP2B6</td>
<td>CYP2B6</td>
<td>rs3745274 (G&gt;T)</td>
<td>Decreased metabolism of the drug; dosage adjustment (decreased dose needed)</td>
<td>[69]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>rs2279343 (A&gt;G)</td>
<td>Decreased elimination rate from the central compartment; dosage adjustment</td>
<td>[22]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ABCB1</td>
<td>rs1128503; (1236C&gt;T)</td>
<td>Increased response to propofol anesthesia due to enhanced activity in efflux transporter</td>
<td>[70]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADRB2</td>
<td>rs1042718 (C&gt;A)</td>
<td>Safety: Risk of hypotension in combinations with fentanyl/remifentanil, and sevoflurane</td>
<td>[71]</td>
</tr>
<tr>
<td></td>
<td>Ketamine</td>
<td>CYP2B6</td>
<td>CYP2B6</td>
<td>CYP2B6*1</td>
<td>CYP2B6*6;*6 diplotype may have decreased clearance; Safety: increased risk of adverse effects</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CYP2B6*6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Local anesthetics</strong></td>
<td>Lidocaine/procaine</td>
<td>G6PD</td>
<td>G6PD</td>
<td>Multiple (more than 200 variants) at Xq28</td>
<td>Safety: Drug-induced methemoglobinemia</td>
<td>[50]</td>
</tr>
<tr>
<td><strong>Sedatives</strong></td>
<td>Diazepam</td>
<td>CYP2C19</td>
<td>CYP2C19</td>
<td>CYP2C19*2</td>
<td>Reduced enzymatic activity; elevated diazepam concentration increased risk for adverse events</td>
<td>[38]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CYP2C19*3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Midazolam</td>
<td>CYP3A5</td>
<td>CYP3A5</td>
<td>CYP3A5*22</td>
<td>Reduced enzymatic activity; increased midazolam plasma concentrations; increased risk for adverse events</td>
<td>[3,39,40]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CYP3A5*1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>POR</td>
<td>POR</td>
<td>POR*28</td>
<td>Decreased midazolam metabolism; enhanced effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GABRA1</td>
<td>GABRA1</td>
<td>187 + 3553 (A&gt;G)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexametomidine</td>
<td>ADRA2A</td>
<td>ADRA2A</td>
<td>rs180054 (C1291G)</td>
<td>Change in (\alpha_2A) receptor structure and decreased drug activity; reduced sedative effect</td>
<td>[44]</td>
</tr>
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<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>PKCB</td>
<td>PKCB</td>
<td>PKCB</td>
<td>rs923216 (T&gt;A)</td>
<td>Safety: Transient hypertension</td>
<td>[42,45]</td>
</tr>
<tr>
<td><strong>Opioid analgesics</strong></td>
<td>Alfentanil</td>
<td>MOR</td>
<td>OPRM1</td>
<td>rs1799971 (A&gt;G)</td>
<td>Loss of a N-glycosylation site in the extracellular region of the receptor; reduced analgesic effect</td>
<td>[50,55]</td>
</tr>
<tr>
<td></td>
<td>Fentanyl</td>
<td>P-gp</td>
<td>ABCB1</td>
<td>rs1045642 (A&gt;G)</td>
<td>Decreased excretion of drug from CNS and plasma because of reduced expression of P-gp; dosage adjustment may be required</td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td>Sufentanil</td>
<td>COMT</td>
<td>COMT</td>
<td>rs4680 (G&gt;A)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Remifentanil</td>
<td></td>
<td></td>
<td></td>
<td>Increased drug response – dosage adjustment (reduced dose)</td>
<td>[57]</td>
</tr>
<tr>
<td><strong>Muscle relaxants</strong></td>
<td>Rocuronium</td>
<td>OATP1A2</td>
<td>SLOC1A2</td>
<td>rs3834099 (-189L-188InsA)</td>
<td>A lower rate of drug elimination by the liver and slower decline in plasma concentration; prolonged duration and recovery time</td>
<td>[3,6,65]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OATP1B1</td>
<td>SOLB1B1</td>
<td>rs306233 (388A&gt;G)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>P-gp</td>
<td>ABCB1</td>
<td>rs1128503; (1236C&gt;T)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Applicable also for succinylcholine (suxamethonium) and it is drug labeled (level 1A evidence).
2 Drug labeled.
3 Applicable for remifentanil.
CNS: Central nervous system; PK/PD: Pharmacokinetics/pharmacodynamics.
Table 1. The possible influence of pharmacogenomics on clinical outcomes of drugs used in anesthesia (cont.).

<table>
<thead>
<tr>
<th>Drug class (depolarizing)</th>
<th>Drug (Suxamethonium)</th>
<th>Protein</th>
<th>Gene</th>
<th>Genotype (important allelic variants)</th>
<th>Effect on drug PK/PD and clinical outcomes</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle relaxants</td>
<td>Succinylcholine</td>
<td>BChE</td>
<td>BChE</td>
<td>A-variant: rs1799807; (c.293T&gt;C)</td>
<td>Reduction of drug metabolism due to reduced enzyme activity; prolonged muscle relaxation (paralysis) and apnea</td>
<td>[2,11,68]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K-variant: rs1803224 (c.1699C&gt;T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F-variant: rs28933390 (c.1253C&gt;A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>S-variant: rs104893684 (c.1004A&gt;G)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Applicable also for succinylcholine (suxamethonium) and it is drug labeled (level 1A evidence).
‡ Drug labeled.
§ Applicable for remifentanil.

CNS: Central nervous system; PK/PD: Pharmacokinetics/pharmacodynamics.
In the present review, we discuss more comprehensively and critically pharmacological characteristics of drugs commonly used in anesthesia according to the latest data, with a special focus on genetic variability as a possible explanation for unpredictable diversities in anesthesia outcomes. Other factors influencing anesthetic drug action, like the interactions with other drugs and xenobiotics, are not in the scope of this review article.

**Inhalational anesthetics**

Volatile anesthetics are halogenated methyl-ethyl ether derivatives and differ according to their physicochemical properties (flammability, odor, volatility); potency (minimal alveolar concentration, [MAC]), and solubility in blood and tissues. Their exact mechanism of action is not fully elucidated and is historically grounded on two basic theories. The older one, now mostly abandoned, suggested a nonspecific anesthetic interaction with hydrophobic lipid components of the cell, while the newer theory proposes specific membrane proteins as sites for anesthetic binding [1]. Among those membrane proteins, neuronal ion channels are the most likely molecular targets. They are a part of complex neurotransmitter receptors, such as nicotinic acetylcholine (nAch), GABAA, glutamate N-methyl-D-aspartate (NMDA) and serotonin 5-HT3, although voltage-gated sodium, potassium and calcium channels can be affected at higher anesthetic concentrations [4,5]. The overall anesthesia results from either a reduction of presynaptic excitatory neurotransmitter release or an increased inhibition of postsynaptic excitability or both, while one recent study proposed a decrease in intracellular ATP level due to mitochondrial dysfunction as a key for general anesthetic effects [6].

Since the protein theory is largely accepted, a relevance of genes coding for a specific receptor subunit is largely under-investigated in the context of anesthetic drug action. Although single nucleotide polymorphisms for different GABA subunits or sodium channels have been described in the literature, it is unrealistic to expect that a single gene polymorphism would significantly change the anesthesia outcomes, especially in light of the existence of such a diversity of the anesthetic molecular targets.

Differences in inhalational anesthetics’ potency, the speed of induction and recovery from anesthesia, as well as some specific adverse-effects profile might govern the use of one drug over others in special situations.

Isoflurane produces concentration-dependent profound respiratory depression and hypotension because of decreased systemic vascular resistance. With rapid changes in concentration, it can cause transient tachycardia and hypertension as a consequence of sympathetic stimulation [7]. Because of its pungent odor, it is not used for induction of anesthesia and is an airway irritant causing cough and laryngospasm. Almost 99% of the drug is eliminated unchanged via the lungs [1].

In contrast to isoflurane, sevoflurane induces the rapid onset of anesthesia because of lower solubility in blood and other tissues. Therefore, it is often used for induction in outpatient anesthesia. Sevoflurane does not irritate the airways and has a strong bronchodilator effect. Moreover, it is an anesthetic of choice in patients with risk for myocardial infarction because it does not influence the heart rhythm. This cardiac stability appears to extend for several days, which may convey additional benefits for reducing morbidity and mortality in a postoperative period [8]. Although around 5% of the inhaled dose is metabolized in the liver via CYP2E1 to hexafluoroisopropanol and fluoride, there are no clinically relevant data regarding a potential nephrotoxic effect of fluoride [9].

Desflurane has the lowest potency and solubility in blood and other tissues compared with other inhalational anesthetics. Therefore, it induces rapid induction and fast recovery from anesthesia and can be used for outpatient surgery. Furthermore, it has the lowest fat-to-blood solubility of the inhaled anesthetics and is suitable for obese patients undergoing prolonged surgery. Because of the strong irritating effect in airways and a high incidence of moderate to severe upper airway adverse events, it is not suitable for the induction of anesthesia. It is almost completely exhaled by lungs unchanged and does not carry a risk of hepatic- or nephrotoxicity [10].

One of the rare but very serious adverse effects of all potent halogenated anesthetic agents is malignant hyperthermia (MH). The core pathophysiological feature of MH is dysregulation of Ca$^{2+}$ homeostasis as a result of uncontrolled Ca$^{2+}$ leakage from the sarcoplasmic or endoplasmic reticulum into the cytoplasm mediated by functionally altered ryanodine receptor (RYR1) and a type of dihydropyridine calcium channel (DHPR) in different muscle cells as well as in B lymphocytes. This leads to a life-threatening hypermetabolic state characterized by fever, tachycardia, hyperthermia, skeletal muscle rigidity, metabolic and respiratory acidosis, increased level of IL-6 secreted by B lymphocytes, hypoxia and potential death if the condition is left untreated [11–13].

Based on the substantial evidence from a systematic literature review, there is a strong correlation between one of the 48 pathogenic variants in gene *RYR1* (encoding for RYR) or one of two variants of *CACNA1S* (calcium voltage-gated channel subunit α1 S gene encoding for an α1s subunit of the DHPR) and MH. Although the
exact mechanism is not known, these mutations might be responsible for rendering the channels more sensitive to activation by depolarization or by volatile anesthetics [14,15]. Therefore, based on a high level of evidence, the Clinical Pharmacogenetics Implementation Consortium (CPIC) launched the guidelines in which they recommend that halogenated anesthetics should not be used in patients with the established genetic risk for MH [15].

Among general anesthetics, nitrous oxide (N₂O) is the only gas with specific features and significant positive impact on anesthesia outcome. Although unable to produce surgical anesthetic depth in applied concentrations (MAC higher than 100 vol%), it is commonly applied as an adjunct to halogenated anesthetics to reduce their effective concentrations and thus improve the safety of anesthesia. It is the least soluble of all general anesthetics and therefore induces rapid onset and fast emergence from anesthesia after discontinuation. Furthermore, it produces a strong analgesic effect (comparable to morphine) because of the stimulation of central opioidergic and adrenergic system [1,16]. N₂O stimulates the sympathetic nervous system and when administered with halogenated agents, increases blood pressure, heart rate and cardiac output, while the opposite is seen after concomitant administration with opioids. Because of rapid entering in the body cavities, which cannot be accompanied by equally fast N₂ escape, it can cause an increase of volume or pressure in cavities. This can lead to certain risks, like pneumothorax, air embolus, obstruction of the middle ear or intraocular air bubble [16].

Patients who are suffering from alcoholism, vitamin B12 deficiency, malnutrition, as well as those who are homozygous for MTHFR and having 677 C>T or 1298 A>C polymorphism (a prevalence of both SNPs is 20% in the Western European population) are at increased risk for hyperhomocysteinemia and decreased folate synthesis after N₂O administration. N₂O irreversibly oxidizes the cobalt in vitamin B12, a cofactor for the enzyme methionine synthase thereby reducing remethylation of homocysteine to methionine and folate synthesis. This could result in DNA hypomethylation, defective DNA synthesis, apoptosis of rapidly dividing cells, and signs of megaloblastic anemia and peripheral neuropathy [17,18]. The significance of MTHFR polymorphisms for these N₂O adverse effects seems to be relevant; however, further investigation is warranted.

**Intravenous (parenteral) anesthetics**

When appropriate, considering the duration and type of surgery, and in patients with absolute or relative contraindications for volatile anesthetics, intravenous anesthetics can be applied not only for induction but for the maintenance of general anesthesia as well. Being small, highly lipophilic substituted aromatic or heterocyclic compounds, they share a similar pattern of distribution and redistribution to the higher and less perfused tissues, respectively. Drug clearance and the speed of recovery from anesthesia depend on the amount of drug stored in peripheral tissues, its lipid solubility, and the rate of metabolism and elimination. Thus, the dosage of intravenous anesthetics should be carefully determined taking into account patient age, cardiovascular and pulmonary status, hepatic and renal function, concomitant therapy, but also a specific genotype, where appropriate [1].

Propofol is the most frequently used parenteral anesthetic for the induction and maintenance of anesthesia. Fospropofol is a prodrug metabolized by ALPs to propofol. Since it is in the form of an aqueous solution, in contrast to propofol which is prepared as a lipid emulsion, it has better tolerability during application. Propofol has sedative-hypnotic, but also anxiolytic, anticonvulsant, anti-inflammatory, antiemetic, anti-oxidative and possibly neuroprotective effect [19]. The adverse effects of propofol are well-documented, and the most common is pain after injection, while others may include bradycardia, hypotension, loss of airway reflexes, apnea and hyperlipidemia secondary to the infusion of lipid formulation [19,20]. It was repeatedly shown that individual susceptibility to propofol’s anesthetic effect and risk for adverse effects significantly vary, and often cannot be estimated from patient’s characteristics and health status. It is possible that polymorphisms in genes coding for molecular targets or enzymes involved in drug’s clearance might influence individual variability to propofol effects, although clear evidence for the gene role is still lacking.

Propofol activates the GABA₄ receptors, blocks NMDA glutamate receptors and interferes with calcium influx into the cell [19,20]. One recent study performed SNP analysis for multiple genes possibly related to propofol pharmacological profile. It was found that carriers of the minor allele (G) in the gene for serotonin receptor – 5HT2A (SNP rs6313) required less propofol and had a 40% decrease in the time needed to induce anesthesia. Associations were found between the GABA₄ receptor SNPs rs2279020 and the sodium channel gene SCN9A SNP rs6746030 and the depth of anesthesia. In addition, dominant mutations in GABA₄ rs2279020, GABA2 rs11503014 and cholinergic muscarinic receptor – CHRM2 rs1824024 were associated with cardiovascular susceptibility to propofol [21].

Furthermore, the contribution of polymorphisms in genes coding for metabolic enzymes CYP2B6 and uridine 50-diphosphate (UDP) glucuronosyltransferase might be relevant for a variable response to propofol. Propofol
is mostly conjugated to glucuronide (70%) while 30% of the drug first undergoes hydroxylation via CYP2B6. Since the gene for CYP2B6 is one of the most polymorphic CYP genes (more than 100 SNPs), several recent clinical studies investigated its importance for propofol dosing [22,23]. Model-based dosing simulations for SNP rs2279343 in CYP2B6 suggest a 50% decrease in propofol infusion dose in AA and AG patient genotypes during the maintenance of general anesthesia. Without dosage adjustments, a 250% higher propofol exposure will occur within 1 h from the start of infusion in these patients thus indicating a significance of this particular polymorphism for dose adjustment in order to secure optimal anesthesia and avoid adverse effects [22].

Despite some positive correlation between specific genotypes and propofol-induced anesthesia features, a lack of data reproducibility limits the implementation of preoperative genetic screening to identify individuals for whom dosage adjustment may be necessary [21].

Etomidate is primarily used for the induction of anesthesia in patients with the risk of hypotension (those undergoing cardiac surgery or with poor cardiac function) because it has a favorable effect on the cardiovascular system [1]. It has a unique toxic effect as significantly inhibits an enzyme 11-β-hydroxylase and aldosterone synthesis in the adrenal gland. Since this effect outlasts the hypnosis and sedation (6–8 h after bolus injection), it may be detrimental for the survival of critically ill patients. Being a hydrophobic imidazole derivative, etomidate is formulated with propylene glycol and injection of this solution is highly irritating and accompanied by intense pain. In contrast to propofol, etomidate has simpler pharmacological properties: it primarily activates GABA<sub>A</sub> receptors, while biotransformation involves hydrolyzation by hepatic esterases to inactive metabolites that are excreted by urine [24].

Genetic contribution to etomidate effectiveness and safety profile has not been investigated so far. One study revealed that GABA<sub>A</sub> receptors containing β2 and β3 subunits as well as γ are sensitive to etomidate since some point mutations significantly affected etomidate binding affinity; however, the clinical relevance of these is uncertain [25].

Ketamine is the most distinctive among all anesthetic agents. Because of its water solubility and good absorption, can be applied in different ways, intramuscularly, orally, rectally, and intranasally, which can be useful in uncooperative or with limited intravenous access [1]. It exerts a strong analgesic effect, and produces hypnosis and amnesia, while patients are able to breathe spontaneously. It is a noncompetitive antagonist of glutamate NMDA receptors thus interfering with calcium ion influx in the cell, although it has other putative lower-affinity pharmacological targets [26]. Also, ketamine diminishes the requirement for opioid analgesic drugs since reduces overall muscle tone, spontaneous movement of extremities, but also hallucinations, delusions, vivid dreams) that bring limitation of usage [28].

Ketamine has extensive hepatic metabolism. It is oxidized mostly by CYP3A4, and to a lesser extent by CYP2B6 to the active norketamine which is conjugated and as glucuronide eliminated via the kidney [29]. As stated previously, CYP2B6 is highly polymorphic and relevance of different genotypes for ketamine effectiveness was investigated in several in vitro and clinical studies [30–32]. According to one clinical study, CYP2B6*6 allele is associated with decreased clearance and resultantly increased plasma concentrations leading to a higher incidence of adverse effects [30]. However, additional data about a potential clinical significance of the CYP2B6 genotypes is warranted.

Thiopental is the only thiobarbiturate that is still, although rarely, used for induction of anesthesia because of strong sedative and hypnotic effect, rapid onset and ultra-short duration of action as consequence of very high lipid solubility [33]. Although after single bolus injection the anesthetic effect lasts less than 10 min, after prolonged infusion more than 24 h is needed for a patient to fully recover from anesthesia. This is because of rapid thiopental redistribution from CNS and slow elimination from the peripheral, especially fat tissue where it accumulates. It is extensively metabolized in the liver in several steps (desulfuration, N-dealkylation to the active pentobarbital) and excreted in the urine [1].

Acting as a positive allosteric modulator of GABA<sub>A</sub> receptors, thiopental increases the time in which GABA<sub>A</sub>-associated chloride channels are in open state, while higher doses can directly activate the channel opening. Additionally, thiopental modulates the nAch receptor and Ca<sup>2+</sup>-ATPase involved in Ca<sup>2+</sup> homeostasis [3,34]. Despite a long history of use, a possible pharmacogenomics’ influence on its pharmacological properties, as well as efficacy and safety is currently obscure [3].
Sedatives
Barbiturates, like amobarbital, pentobarbital, secobarbital were mostly used in preoperative anesthesia as sedatives because of their profound depressant effect on the CNS and other excitable tissue. Considering that barbiturates are likely to cause respiratory depression, they have mostly been replaced by safer depressants benzodiazepines [35].

Benzodiazepines, like midazolam and diazepam, have a strong sedative-hypnotic effect and more favorable pharmacological and safety profile than barbiturates. They also act as positive-allosteric modulators of the GABA_A receptor, leading to increased receptor affinity for GABA and more frequent Cl- channel opening. Despite some differences in their affinity toward the binding site, potency and selectivity for receptor subunits, they considerably differ in their pharmacokinetic properties (protein plasma binding, volume of distribution, half-life, biotransformation), as well as onset and duration of action [35]. Patient-related factors, such as older age, a lower amount of fatty tissue, decreased renal and liver function are known to slow down drug elimination. Unlike diazepam which has several active metabolites which further prolong the duration of action, midazolam does not. In addition to being the most lipophilic of all benzodiazepines, and because of its short half-life and duration of effect, midazolam is the most suitable for continuous infusion. Another shortcoming of diazepam is that it needs to be prepared with propylene glycol for intravenous administration in order to increase its solubility in water, which also increases the risk of thrombophlebitis [36,37].

Diazepam has complex hepatic biotransformation, utilizing CYP3A4 and CYP2C19 to yield several active metabolites that are finally conjugated to glucuronides. Several allelic variants of the CYP2C19 have been identified as influencing diazepam metabolism. Presence of the *2 and *3 alleles are associated with decreased metabolism of diazepam (higher area under the curve and lower clearance) resulting in a significantly longer time to recover from anesthesia and an increased risk of toxicity [38].

Midazolam undergoes aliphatic hydroxylation via hepatic CYP3A4 and CYP3A5 followed by glucuronide conjugation [35]. There is limited evidence from the literature about the relevance of polymorphisms of CYP3A4, CYP3A5 and POR genes for midazolam efficacy and safety [39]. While CYP3A4*22 is found to be associated with decreased enzyme function, CYP3A5*1 results with increased midazolam metabolism. A relatively common POR*28 variant of POR (encodes a P450 oxidoreductase, an important part of all CYP enzymes), was in one study connected to 45% lower metabolism of midazolam via CYP3A5. For neither of these genetic polymorphisms, clear clinical applicability is not possible due to limited evidence and often contradictory results from the studies (e.g., POR*28 variant is associated with faster tacrolimus metabolism, thus indicating that the influence of this genotype depends on the substrate) [3,40].

Since the GABA_A receptors are the only target of benzodiazepine drugs, polymorphisms of different protein subunits of this complex receptor protein might, in theory, influence the benzodiazepines action. Choi et al. found that patients with SNP rs4263535 in GABRA1 encoding for alpha-1 (α1) subunit of the GABA_A receptor who are AA carriers have increased the risk for developing profound sedation during the surgery thus requiring dose adaptation (lower dose of midazolam). However, further studies are needed to confirm the relevance of this observation [41].

Dexmedetomidine, acting as a selective agonist of α2A adrenergic receptor (ADRA2A) either pre- or postsynaptic in locus coeruleus is also used for sedation and analgesia during surgical procedures [42]. Since dexmedetomidine is highly albumin and α1-glycoprotein bound, different factors such as bodyweight, fat-free mass, hypoalbuminemia and cardiac output should be taken into consideration before drug administration. Dexmedetomidine is mostly metabolized in the liver by UGT or via CYP2A6. Studies did not demonstrate any relevant SNP of genes affecting drug metabolism in intensive care unit patients [40,42,43].

However, several gene polymorphisms can be relevant to dexmedetomidine activity and safety. It was found that SNP rs1800544 in ADRA2A encoding for ADRA2A results with a decreased sedative response in patients with GG or GC genotype compared with the CC genotype [44]. Another SNP is rs9922316T>A in PKCB (protein kinase C β) coding for a same-named enzyme. This particular polymorphism for the A allele carrier can cause an increased risk for hypertensive crisis or even cardiac arrest. The clinical relevance of these polymorphisms needs confirmation [42,45].

Local anesthetics
Local anesthetics, such as tetracaine, lidocaine and bupivacaine are commonly used to produce spinal or epidural anesthesia. These drugs differ in their chemical structure (esters or amides), physicochemical properties (molecular size and hydrophobicity), pharmacological properties and duration of action [46,47].
Their mechanism of action is the prevention of transmission of nerve impulses by inhibiting passage of sodium ions through ion-selective voltage-gated sodium channels in nerve membranes. Since the primary binding site is in the open-channel inner pore, the drugs must cross the cell membrane to exert significant blockade. Moreover, local anesthetics bind more easily to channels which open more frequently (frequency dependence), and on membranes with more positive resting potentials (voltage dependence) [48]. Their unwanted effects are dependent on the concentration in the blood after systemic absorption and are the result of interference with impulse generation and conduction in excitable tissues, like the CNS, all type of muscles, autonomic ganglia. Clearance of drugs containing the amide group (lidocaine and bupivacaine) is dependent on the hepatic metabolism (mostly by CYP3A4), while the elimination of the ester-type drug (such as tetracaine and procaine) is dependent on plasma butyrylcholinesterase activity. Considering that the ester bonds are more prone to hydrolysis, amide-type of drugs usually has a longer duration [49,50].

Besides those drug-related characteristics, the clinical effectiveness of local anesthetics can be influenced by genetic predisposition, as well. Since voltage-gated sodium channels are the primary drug target, it is logical to expect that genetic mutations in the gene for sodium channel are likely to affect the efficacy of the local anesthetics. However, except for one in vitro experiment, which has shown that Asn395Lys mutation in the sodium voltage-gated channel α subunit 9 (SCN9A) could contribute to greater resistance to lidocaine, there are no clinical studies proving the significance of this mutation [50].

Some drug labels warn on the possibility, although rare, of hemolytic anemia after lidocaine and prilocaine application in patients with G6PD deficiency. G6PD is an enzyme that catalyzes the formation of NADPH, which maintains reduced glutathione within the cell, thus protecting cells against oxidative damage. Most cells have other metabolic pathways that can generate the intracellular NADPH; however, the red blood cells are reliant on this process. Therefore, local anesthetics which are known to induce methemoglobinemia, like prilocaine due to its metabolic pathways that can generate the intracellular NADPH; however, the red blood cells are reliant on this process. Therefore, local anesthetics which are known to induce methemoglobinemia, like prilocaine due to its conversion to 2-methylalanine, should be avoided in patients with G6PD deficiency [51].

**Opioids**

Fentanyl and its parenteral congeners sufentanil, remifentanil and alfentanil are synthetic opioids commonly used in anesthesia, either perioperative or postoperative because of their fast and strong analgesic effect. Besides relieving pain, and minimizing pain-evoked hemodynamic changes, in combination with general anesthetics they reduce the anesthetic requirements. Alfentanil has around 1/4 to 1/10 the potency of fentanyl, while sufentanil is five- to ten-times more potent than the parent drug, and is the most potent opioid analgesic for human use. The choice of drug depends primarily on the duration of its effect. Fentanyl and sufentanil have a short time to peak analgesic effect, rapid termination of effect after small bolus doses, 30 and 20 min, respectively, while recovery after prolonged administration varies considerably. Fentanyl's duration of action lengthens the most with infusion, and alfentanil's the least [52]. Since remifentanil has a duration of action <10 min and low potential for accumulation it is suitable for brief painful procedures [53]. Besides common opioid-specific adverse effects, remifentanil slows heart rate, decreases blood pressure and increases postoperative analgesic dose requirements due to acute opioid tolerance.

As for metabolism, fentanyl undergoes CYP3A4/5 resulting in inactive metabolite norfentanyl [50]. Alfentanil and sufentanil are also biotransformed in the liver by N-dealkylation to inactive metabolites while remifentanil, with its unique pharmacokinetic characteristic, undergoes metabolism by nonspecific plasma and tissue esterases [54].

Regarding other opioid analgesics which can be used in the postoperative setting, only for codeine and tramadol, Clinical Pharmacogenetics Implementation Consortium has established guidelines on individualizing treatment based on the CYP2D6 genotype. Since both drugs are metabolized via CYP2D6 to more potent metabolites, individuals which are ultrarapid metabolizers have a higher risk of adverse effects and overdose, due to an increased concentration of morphine and O-desmethyltramadol, respectively [55,56].

Moderate quality evidence has shown that the variability of the analgesic effect is affected by genetic variants in opioid receptors (OPRM1), P-glycoprotein (P-gp) and catechol-O-methyltransferase (COMT). One of the most studied SNPs related to OPRM1 and the opioid analgesic action is the SNP rs1799971 (118 A>G). Persuasive evidence in favor of this functional polymorphism comes from a meta-analysis on morphine, where GG genotype was related to a reduced analgesic effect and requirements for higher opioid doses. Studies have confirmed this finding to be applicable for fentanyl, alfentanil and sufentanil as well [50,55]. Additionally, patients with the AA genotype of COMT, variant rs4680, may have increased response and therefore require a lower dose of opioids, including, sufentanil, as compared with patients with the AG or GG genotypes [57].

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**References**

1. [Bach-Rojecky, Vadunec, Lozić](#).
Contradictory results can be found in the literature regarding the \textit{ABCB1} polymorphisms, coding for P-glycoprotein. Variant rs1045642 AA seems to be associated with the efficacy of a lower dose of fentanyl; however, some studies with contradicting results have been also reported \cite{40}. Further research is needed to establish the clinical relevance of this gene polymorphism.

**Neuromuscular blocking agents**

Neuromuscular blocking agents (NMBs) are often used as anesthetic adjuncts during surgery. Based on differences in the mechanisms of action, they are divided into two groups: nondepolarizing (mivacurium, [cis] atracurium, rocuronium and vecuronium) and depolarizing (succinylcholine, known also as suxamethonium). Nondepolarizing drugs act as competitive antagonists of a nicotinic acetylcholine receptor (nAChR), while depolarizing act as the Ach, first briefly depolarizing the membrane of muscle cells followed by receptor desensitization \cite{58}.

Although all the NMBs are quaternary ammonium compounds, some structural differences might have clinical applicability. For example, succinylcholine and (cis)atracurium have two quaternary ammonium cations, unlike rocuronium and vecuronium which have only one quaternary cation and one tertiary amine. Tertiary amine group in acidic patients can be protonated and even more positively charged, thus rendering drugs like rocuronium and vecuronium more potent than other NMBs \cite{59}.

Within the nondepolarizing drugs, there are several pharmacokinetic differences. Regarding drug elimination, caution should be paid to patients with liver and kidney impairment. For example, the clearance of rocuronium, which is almost completely undergoing hepatic metabolism, might be reduced, and recovery time prolonged in patients with liver cirrhosis \cite{60,61}. Vecuronium should be used with caution in renal failure and in patients with burns because of lower drug elimination \cite{62,63}. (Cis)atracurium undergoes degradation by Hofmann elimination and ester hydrolysis. The rate of degradation \textit{in vivo} is under a strong influence of pH and temperature, where a decrease in body temperature and pH slows the degradation \cite{64}.

Rocuronium is eliminated mostly unchanged by biliary excretion which is reliant on hepatocellular uptake by organic anion transporting polypeptide 1A2 (OATP1A2) and OATP1B1. Later one is dependent on P-gp which is an efflux pump and exports rocuronium out of hepatocytes toward OATP1B1 \cite{61,65}. Since the before mentioned transporters are prone to genetic polymorphisms, several recent studies tested the influence of genetic polymorphisms on NMBs pharmacokinetics. Costa \textit{et al.} found that one functional SNP rs3834939 in SLOC1A2 gene encoding for the OATP1A2 affect rocuronium elimination, where T/del genotype may have decreased clearance of rocuronium as compared with patients with the del/del genotypes \cite{60}. In addition, a study testing the influence of polymorphisms of genes encoding for OATP1B1 (SLOB1B1) and P-gp (ABCB1) on the clinical effectiveness of rocuronium found that duration and recovery time of rocuronium were prolonged in patients with the \textit{ABCB1} rs1128503 TT and \textit{SLCO1B1} rs2306283 AG and GG genotypes because of decreased drug hepatic elimination. The latter one is connected with lower rocuronium hepatic elimination and its accumulation in plasma \cite{65}.

Although clinical data about the relevance of other genotypes for the efficacy of NMBs are currently lacking, we might speculate about a possible significance of polymorphisms of the gene encoding an \(\alpha\)-subunit of nACh receptor (responsible for NMB binding and channel opening) for their effectiveness \cite{3,65}.

In contrast to the nondepolarizing group of drugs, succinylcholine (suxamethonium, SCH) is hydrolyzed by enzyme butyrylcholinesterase (BChE) to succinylmonocholine, succinic acid and choline. BChE is synthesized in the liver and is not present in the synaptic cleft of the neuromuscular junction. This is the main reason why SCH is longer acting and longer bound to the nAChR than Ach which is metabolized very fast by acetylcholinesterase existing in neuromuscular junction \cite{11,66}. Increased activity and plasma levels of BChE have been found in patients with diabetes, uremia, hyperlipidemia, hyperthyroidism, but also in obese and high-protein dieters and in patients using protein-rich enteral nutrition. Decreased plasma levels of the enzyme are present in severe liver diseases, stress, inflammation (acute and chronic), cancer, eating disorders, cardiovascular disease, etc \cite{67}.

BChE is highly polymorphic, with 62 SNPs identified in the coding region. Most of these mutations result in reduced enzyme activity and consequently increased the duration of SCH action, which might cause prolonged paralysis and apnea \cite{65}. The most common and significant variants of these genetic mutations are: atypical (A-variant, dibucaine resistant), Kalow (K-variant), fluoride (F-variant) and silent (S-variant). Among the white race, the most common are the A-variant (rs1799807) and the K-variant (rs1803274). In heterozygous individuals with the A variant, the drug effect is prolonged by three- to eight-times, but for homozygous it can be prolonged for up to 60-times \cite{14,66}. K-variant (SNP rs1803274) and F-variant (SNP rs28933390) are connected with decrement
of BChE activity [2,11,68]. The rarest but the most dangerous polymorphisms are for S-variant, for example, rs104893684 (c.1004A>G) which leads to the absence of BChE from plasma. This polymorphism is found only in the Indian population [11,68].

According to the European Malignant Hyperthermia Group, the safety of succinylcholine, as well as of volatile anesthetics, as described in more detail previously, may be influenced by 1 out of 50 polymorphisms in RYR1 and the CACNA1S genes. For individuals with muscle diseases caused by or associated with SNPs in the stated genes, SCH should be avoided because of increased MH susceptibility [15].

Epigenetics

Epigenetic changes, manifested in DNA methylation (CpG islands), modifications within histones, or in mRNA expression (miRNAs) can influence enzymes involved in drug biotransformation. Some of them like CYP2B6 and CYP3A4 are involved in the metabolism of drugs used in anesthesia, as previously mentioned in the text [72].

One particular condition which is commonly seen even after a short period of administration is opioid-induced hyperalgesia and has the highest occurrence for remifentanil. Among other factors, elevated DNA methylation is found to be a pathophysiological feature of this phenomenon [73]. In recent preclinical research conducted by Sabbaie et al., acetylation of H3K9 near BDNF (brain-derived neurotrophic factor) and PDYN (prodynorphin) promoters were found to be supportive factors for the development of opioid-induced hyperalgesia in mice. This is the first study that connects the opiates and nociception with epigenetic changes in genes coding for BDNF and PDYN. The relevance of these findings in humans needs further elucidation [74]. On the other hand, local anesthetics act the opposite, causing DNA demethylation. While for the ester group of local anesthetics (i.e., procaine) the underlying mechanism is the inhibition of DNA methyltransferase-1 (an important enzyme for DNA methylation), the mechanism for amide-type local anesthetics is unclear [75].

Metabolites generated during ethanol metabolism can impact gene expression by binding to transcription factors or modifying chromatin structure. Chronic alcohol consumption leads to significant reductions in S-adenosylmethionine levels, which cause DNA hypomethylation. Also, ethanol metabolism alters the ratio of NAD+ to reduced NAD (NADH) and contributes to the formation of reactive oxygen species and acetate. All of them can impact epigenetic regulatory mechanisms [75]. Ethanol abuse may lead to increased dose requirements for anesthetic agents, such as propofol, thiopental and opioids. However, this is thought to happen due to enzyme induction (particularly CYP2E1) or the development of cross-tolerance. Additionally, if the blood ethanol concentration is elevated, then competitive inhibition of metabolic enzymes can increase the sensitivity to other drugs such as volatile agents which compete with ethanol for binding on neuronal GABA and glycine receptors [76].

Cigarette smoking can induce liver enzymes. It was observed that chronic smokers need more benzodiazepines to achieve sedation. However, the incidence of postoperative nausea and vomiting are lower in smokers, probably due to antiemetic constituents of cigarettes. Discontinuing smoking prior to surgical procedures has produced mixed results, with studies reporting fewer pulmonary complications, but a higher incidence of purulent sputum in patients who discontinued smoking 8 weeks before surgery [77]. In cases of surgery without preoperative abstinence from smoking, nicotine-replacement therapy can be considered as adjuncts to treatment for pain possibly because of reducing the requirement for opioids [78].

Understanding this novel and a wide area of pharmacoeigipenetics certainly deserves detailed investigation in the near future, especially in relation to individual variability in response to drugs (Figure 1).

Conclusion & future perspective

Shocking data accumulated over time about the adverse drug reactions as the major cause of iatrogenic morbidity and mortality. They are one of the most common causes of death and billions of dollars are spent annually in the USA on their cost. It is estimated that genetic factors contribute to as far as 10–20% of the total number of reported adrenergic receptors, which indicates that timely pharmacogenomics testing could possibly prevent some of the ADRs and positively influence the therapeutic outcomes [79,80].

We have to remember that the perioperative period is the most vulnerable period for the patient and that individually tailored anesthesia care is the future mainstay. Also, some of the patients require postoperative intensive unit care due to their comorbidities and/or complexity of the operation. Taking into consideration all relevant patient-related factors, procedure- and anesthetic drugs-related factors, in addition to direct drug levels monitoring and automatic closed-loop control, implementation of pharmacogenomics, where appropriate, according to relevant
Factors that can influence anesthesia outcomes

Figure 1. Factors that can influence anesthesia outcomes. This scheme summarizes all the important factors, previously discussed in the paper, that need to be taken into consideration in tailored and individualized pharmacological approach and which may be influencing anesthesia outcome (efficacy, safety and ADRs).

ADR: Adrenergic receptor; NMB: Neuromuscular blockade; PK/PD: Pharmacokinetics/pharmacodynamics.

data from clinical studies (especially from real world), could aid anesthesiologists to interindividually guide their anesthesia care with little margin for possible errors or adverse effects.

For some drugs, as discussed in the text, clinical guidelines have been developed based on collected evidence (i.e., for inhalational anesthetics and succinylcholine and RYR genotypes regarding the risk of malignant hyperthermia) [15]. However, for the majority of drugs, as well as for those described in the present review, robust clinical evidence regarding PGx tests’ efficacy and cost–effectiveness is currently missing [80]. Therefore, we are impatiently waiting for more proofs from high-quality clinical trials that PG testing is cost effective and lifesaving in different clinical settings.

Although, not in the scope of this review, we have to mention interactions of drugs used in anesthesia with other xenobiotics, where CYP3A4 is of special importance because of its involvement in metabolism of about 50% of all current drugs. Genotyping for this enzyme is not reasonable since significant genetic variants are of low prevalence but checking for clinically relevant interactions can certainly help in avoiding adverse reactions due to large number of drugs that either inhibit or induce its function.

Future perspective is to create an anesthesia-based software which is going to be able to guide the anesthesia care for each patient on predetermined parameters and data, among which pharmacogenetics information could have a substantial role. We believe that this paper will inspire further discussion in this specific area of pharmacology and pharmacogenomics.

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Executive summary

Inhalational anesthetics

• Various inhalational anesthetic drugs differ in potency, the speed of induction and recovery from anesthesia, as well as some specific adverse-effects which might govern the use of one drug over others.

• Some of the most dangerous adverse effects, like malignant hyperthermia (MH) caused by halogenated anesthetics are usually unpredictable and have a genetic background.

• Based on substantial evidence, Clinical Pharmacogenetics Implementation Consortium recommend that halogenated anesthetics should not be used in patients with the established genetic risk for MH (48 pathogenic variants in gene RYR1 or one of two variants of CACNA1S).

Intravenous anesthetics

• Among intravenous anesthetics propofol is the most frequently used for the induction and maintenance of anesthesia and positive correlation between specific CYP2B6 genotypes and propofol-induced anesthesia features have been found. A lack of data reproducibility limits the implementation of a preoperative genetic screening to identify individuals for whom dosage adjustment may be necessary.

Sedatives & opioid analgesics

• Presence of the *2 and *3 alleles of CYP2C19 has been associated with decreased metabolism of diazepam (higher area under the curve and lower clearance) resulting in significantly longer time to recover from anesthesia.

• Moderate quality evidence has shown that the variability of the analgesic effect and safety of fentanyl and its parenteral congeners is affected by variants in genes coding for opioid receptors (OPRM1), P-glycoprotein (ABCB1) and catechol-O-methyltransferase (COMT).

Neuromuscular blocking agents

• The risk of MH associated with application of succinylcholine may be influenced by 1 out of 50 polymorphisms in RYR1 and the CACNA1S genes.

• Nondepolarizing neuromuscular blocking agents differ in their physicochemical and pharmacokinetic features, which may influence their clinical applicability.

Epigenetics

• Epigenetic changes, manifested in DNA methylation, modifications within histones, or in mRNA expression can influence not only enzymes involved in drug biotransformation, but also other proteins that are more indirectly involved in drugs efficacy and safety.

• Alcohol drinking, cigarette smoking and other drugs/xenobiotics have been shown to influence the anesthesia outcome.

Conclusion

• Besides diverse predictable patient-related factors, individual genotype could also be included in decision making in order to achieve patient-tailored optimal anesthesia.

• Despite growing interest in the clarification of possible gene-anesthesia interaction, unequivocal evidence about the influence of respective genotype on drugs used in anesthesia effectiveness and safety profile is missing.

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References

Papers of special note have been highlighted as: • of interest; •• of considerable interest


•• Summarizes the latest knowledge about the pharmacogenetics of drugs used in general anesthesia and related complications.


• Describes neurophysiological research regarding anesthetic mechanism of action and identifying neuroanatomical locations mediating the actions of some anesthetic agents.
Challenges in anesthesia personalization Review


● Summarizes evidence from the literature supporting therapeutic recommendations for the use of volatile anesthetic agents and succinylcholine in patients with RYR1 or CACNA1S variants.


● The authors gave an overview of propofol pharmacological characteristics, its clinical uses and the advances in compartmental pharmacokinetic/pharmacodynamic modeling and drug interaction modeling of propofol.


● Describes in-depth pharmacological characteristics of ketamine and its metabolite, their clinical applications and future directions.


Review  Bach-Rojecky, Vadunec, Lozić et al.


38. Zhou S, Skaar DJ, Jacobson PA, Huang SR. Pharmacogenomics of medications commonly used in the intensive care unit.

39. Elens L, Nieuweboer A, Clarke SJ. Summarize the pharmacogenomics information for the medications commonly encountered in the intensive care unit.

40. Griffin CE 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects.

41. Choi YJ, Lee SY, Yang KS, Park JY, Yoon SZ, Yoon SM. Polymorphism rs4263535 in GABRA1 intron 4 was related to deeper sedation.

42. Weerink MAS, Struys MMR, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexametomidine.


47. Yagiela JA. Local anesthetics.

48. Fozzard HA, Sheets MF, Hanck DA. The sodium channel as a target for local anesthetic drugs.

49. Arthur GR, Covino BG. Pharmacokinetics of local anaesthetics.


51. Elyassi AR, Rowshan HH. Perioperative management of the glucose-6-phosphate dehydrogenase deficient patient: a review of literature.

52. Cherny NI. Opioid analgesics: comparative features and prescribing guidelines.

53. Stroumpos C, Manolaraki M, Paspatis GA. Remifentanil, a different opioid: potential clinical applications and safety aspects.


57. Yagiela JA. Local anesthetics.

58. Fozzard HA, Sheets MF, Hanck DA. The sodium channel as a target for local anesthetic drugs.

59. Arthur GR, Covino BG. Pharmacokinetics of local anaesthetics.

60. Cohen M, Sadhasivam S, Vinks AA. Pharmacogenetics in perioperative medicine.

61. Costa ACC, Coelho EB, Lanchote VL et al. The SLCO1A2 -188InsA polymorphism reduces clearance of rocuronium in patients submitted to elective surgeries.


