Pharmacogenomics

Personalized Therapy in Pain Management: Where do we Stand?
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Disclosures

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Genetic Variants Influencing Pharmacokinetics

The catalytic activity of drug-metabolizing enzymes and the function of drug transporters are crucial for the concentrations of substances in the blood and their target site. A considerable amount of data on genetic variants and their impact on drug metabolism has been published; however, its value in daily clinical practice is still a matter of debate.[3,6,7]

CYP2D6: Metabolism of Opioids

Of all drug therapies, 20–25% are estimated to be influenced by genetic variants of drug-metabolizing enzymes,[8] with CYPs playing a pivotal role, as these enzymes are responsible for approximately 80% of all phase I metabolism.[9] Thus, CYP pharmacogenomics has a significant impact on pharmacotherapy in clinical practice as well as for drug development. Critical base changes or deletions in the gene result in qualitative and/or quantitative variation in mRNA and proteins with resulting consequences for the metabolizing capacity of
CYPs. CYP2D6 accounts for only a small percentage of all hepatic CYPs (<2%); however, it metabolizes a broad spectrum of frequently used drugs, for example, β-blockers, antiarrhythmics, antidepressants, neuroleptics and analgesics\textsuperscript{[10]} (for a detailed overview see\textsuperscript{[201]}). More than 80 distinct allelic variants for CYP2D6 are known, which lead to a wide spectrum of metabolic and phenotype diversity within populations.\textsuperscript{[11]} The variants can be associated with four metabolism phenotypes – poor, intermediate, extensive and ultrarapid metabolism – thereby characterizing the phenotypes of poor metabolizers (PM), intermediate metabolizers, extensive metabolizers (EM) and ultrarapid metabolizers (UM). A detailed list of all known cytochrome alleles is available at the website of the CYP Allele Nomenclature Committee.\textsuperscript{[202]}

The genetic variability of CYP2D6's metabolizing capacity is of clinical importance since approximately 7–10% of the Caucasian population is affected by this autosomal recessive trait of nonfunctional alleles.\textsuperscript{[11]} Approximately a quarter of all commonly used drugs are predominantly or partly metabolized by CYP2D6,\textsuperscript{[12]} underlining the impact of CYP2D6 activity on daily clinical routine. Relevant polymorphisms resulting in nonfunctional alleles are single base exchanges (CYP2D6*4 [rs3892097], *7 [rs5030867] and *8 [rs5030865]) or deletions (CYP2D6*3 [rs35742686] and *6 [rs5030655]) within the CYP2D6 gene locus. Deletion of the entire CYP2D6 gene (CYP2D6*5) also leads to the absence of CYP2D6 protein production. Subjects with these homozygous PM-associated variants are at an increased risk of suffering from adverse side effects owing to drug concentrations exceeding the therapeutic level (i.e., tricyclic antidepressants or antiarrhythmics) or therapeutic failure due to poor metabolism of a prodrug to its active metabolite.

By contrast, duplication or multiduplication of the CYP2D6 gene is related to an increased enzyme activity and ultrarapid metabolism in UMs, resulting in a rapid decline of respective substrates' blood concentrations. Thus, therapeutic effects cannot be obtained in UMs at conventional doses of an active drug.

Diverse frequencies among individuals from various racial and ethnic backgrounds can result in modified therapeutic strategies. Whereas the CYP2D6*4 allele is present at a high frequency in Caucasians (allele frequency: ~20%) and accounts for more than 75% of the mutant CYP2D6 alleles, this SNP is almost absent in the Chinese population. By contrast,
other polymorphisms related to the intermediate metabolism, such as CYP2D6*10, are particularly common in Asian subjects and the *45 and *46 alleles in subjects from black African origin. Within a middle European population, 3–5% are UMs, whereas in Scandinavia, this figure decreases to 1–2%; however, this increases for subjects from the Mediterranean (10–12%), Saudi Arabia (21%) and Ethiopia (29%). This varying metabolic capacity can have considerable impact on the efficacy, tolerability and dosing regimes of various drugs in different ethnic populations.

Opioids are the mainstay of pharmacological pain management. Several opioids are metabolized by CYPs, with CYP2D6 playing a pivotal role for the formation of active metabolites from codeine, dihydrocodeine, hydrocodone, oxycodone and tramadol, although with varying effects on analgesic efficacy. Meanwhile, a plethora of case reports have been published indicating therapeutic failure (no analgesia-/opioid-related side effects) in specific genotypes receiving these opioids. However, these single cases can hardly give evidence of the overall impact of CYP variants on treatment efficacy and side-effect profile, particularly if one considers the numerous further variables influencing response to analgesic treatment.

**Codeine** Codeine is a prodrug with a low affinity and low intrinsic activity at the µ-opioid receptor (200-times and 50-times less than morphine, respectively). It is eliminated primarily by glucuronidation (50–70% to codeine-6-glucuronide) with O-demethylation to morphine and N-demethylation to norcodeine being minor pathways (Figure 1). The O-demethylation of codeine to the active metabolite morphine depends on CYP2D6 activity. Study data so far mainly depend on trials in volunteers, single case reports or only small clinical trials enrolling a very limited number of PMs.

![Diagram of drug-metabolizing enzymes involved in the metabolism of codeine](image-url)
Codeine is widely administered for the treatment of postoperative pain, especially in pediatric patients. Furthermore, codeine is used as a component of certain drug combinations, for example, paracetamol (acetaminophen) plus codeine, which is frequently used for acute and chronic pain management, as well as in cough and cold medicines, owing to its antitussive properties. As codeine is a less potent μ-opioid receptor agonist than morphine, it is classified as a weak opioid (WHO class II) and, in the past, has been considered as a safe alternative to other opioids in an outpatient setting.

Williams and coworkers studied the analgesic efficacy of codeine in children undergoing adenotonsillectomy. Plasma morphine concentrations were very low and were correlated with the metabolizing phenotype, with no morphine and metabolites (morphine-6-glucuronide and morphine-3-glucuronide) measurable in the two PMs and some heterozygous patients with declining metabolic capacity. Codeine analgesia was less reliable than analgesia with morphine in the control group, and was not well correlated with either phenotype or plasma morphine in that study. Overall, evidence for impaired analgesic outcome in CYP2D6 PMs is sparse, and large-scale studies are needed to demonstrate genetically determined unresponsiveness to codeine analgesia.

On the other hand, subjects carrying a gene duplication or multiduplication may experience exaggerated pharmacologic effects in response to regular doses of codeine. Enhanced CYP2D6 activity in these genotypes predisposes to life-threatening opioid intoxication. Respiratory depression was observed after a small dose of codeine in a patient with an additional inhibition of CYP3A4 activity by other medications and a transient reduction in renal function. The CYP2D6 genotype predicting ultrarapid metabolism resulted in 50% higher plasma concentrations of morphine and its glucuronides compared with EMs. However, a publication highlighted that the prediction of extremely high morphine formation from codeine in particular can currently only be obtained by combining genotyping with phenotyping.
Recent case reports of codeine fatalities highlighted that the use of this weak opioid, particularly in young children, is associated with a substantial risk in those subjects displaying the UM genotype (Table 1). A boy aged 2 years died owing to codeine overdose after adenotonsillectomy; another previously healthy child aged 29 months of North African descent experienced apnea resulting in brain injury following a dose of acetaminophen and codeine 2 days after an uneventful anesthesia for a tonsillectomy. Owing to the ethnic background of this child, the risk of carrying a CYP2D6 gene duplication was increased approximately threefold compared with Caucasian subjects.

A breastfed neonate whose mother received codeine 30 mg/day died on day 13 owing to morphine-related respiratory depression. The mother had an UM genotype; thus, high amounts of morphine were formed from codeine, which then were transferred via breastmilk to the baby. A systemic review of the literature was conducted on CNS depression in breastfed infants owing to the maternal use of codeine. In total, 35 infants were identified. Adverse drug reactions were described as unexplained episodes of drowsiness, apnea, bradycardia and cyanosis in suckling infants, and codeine was found to be a definite cause of this CNS depression. A possible additional role of the polymorphic uridyl glucuronosyl transferase (UGTB7), which catalyzes the glucuronidation of morphine to morphine-6-glucuronid and morphine-3-glucuronid, has been suggested. In a case–control study, two mothers with symptomatic infants were identified as carrying the combined genotypes of a CYP2D6 UM and UGT2B7*2/*2; however, to date, the impact of UGT2B7 on codeine toxicity has not been well described. In general, these data question the use of codeine in the postpartal period, particularly if the mother is breastfeeding, and have led to an US FDA warning on the prescription of codeine to nursing mothers.

**Dihydrocodeine & Hydrocodone** The metabolism of the semisynthetic dihydrocodeine displays many parallels to codeine. CYP2D6 catalyzes O-demethylation to dihydromorphine, which is an active metabolite with an opioid receptor activity comparable to morphine. CYP3A4 catalyzes N-demethylation to nordihydrocodeine and nordihydromorphine. For CYP2D6 PMs, the area under the serum concentration–time curve (AUC), partial metabolic clearance and total urinary recovery of dihydromorphine were sevenfold lower (10.3 ± 6.1 nmol·h/l; 7.0 ± 4.1 ml/min; 1.3 ± 0.9% of dose) compared with EMs (75.5 ± 42.9 nmol·h/l; 49.7 ± 29.9 ml/min; 8.9 ± 6.2%). In quinidine-induced poor
metabolism, the plasma concentrations of dihydromorphine were reduced three- to four-fold, and urinary excretion of dihydromorphine in the first 12 h was decreased from 0.91 to 0.28% of the dihydrocodeine dose. However, quinidine did not change the effects of a single dose of dihydrocodeine on pain thresholds in an experimental setting, and there was no difference in the reduction of pupillary diameter in five CYP2D6 EM and four PM volunteers. The authors concluded that the metabolism of dihydrocodeine to dihydromorphine may, therefore, not be of clinical importance for analgesia.

Analogous to codeine and dihydrocodeine, the production of the active metabolite hydromorphone from hydrocodone is reduced in CYP2D6 PMs. In vitro studies revealed that the O-demethylation of hydrocodone is predominantly catalyzed by CYP2D6 and, to a lesser extent, by an unknown low-affinity CYP enzyme. Norhydrocodone formation was attributed to CYP3A4. The authors estimated that 40% of the clearance of hydrocodone is via non-CYP pathways. In a volunteer trial, CYP2D6 EMs and PMs were equally responsive to oral hydrocodone, and quinidine had no consistent effect on their responses, even though quinidine abolished the pre-existing metabolic differences in hydromorphone production, as measured in urine. Data from patients receiving hydrocodone for pain management are not available.

**Tramadol** Tramadol is a synthetic opioid, and studies document its analgesic efficacy with a low potential for the depression of respiration and the development of tolerance, dependence and abuse. This racemic mixture produces analgesia by a synergistic action of its two enantiomers and their metabolites. Hepatic CYP metabolizes tramadol to 11 demethylated compounds, of which M1 (O-demethyltramadol) predominates and possesses analgesic properties. (+)O-demethyltramadol has been demonstrated to have an affinity for μ-opioid receptors that is approximately 200-times greater than that of the parent compound. Thus, it is largely responsible for opioid receptor-mediated analgesia, whereas (+)tramadol and (-)tramadol inhibit the re-uptake of neurotransmitters serotonin and noradrenaline. O-demethylation to M1 requires CYP2D6 for its formation. Experimental pain models and prospective clinical studies demonstrated that the analgesic effect of tramadol is linked to CYP2D6 genotype and that the active (+)M1 mainly contributes to analgesia. The proportion of nonresponders more than doubled (21.6 vs 46.7%) in the
PM group as opposed to the patients with functionally active CYP2D6 alleles. In a Chinese population, patients homozygous for CYP2D6*10, which is known to reduce enzyme activity, needed more tramadol compared with heterozygous patients and patients without this genetic variation, owing to the lack of analgesia mediated by the opioid receptor agonists O-demethyltramadol.

These results were confirmed by analysis of the serum concentrations of (+)O-demethyltramadol in different CYP2D6 genotypes. PMs had negligible concentrations of this active metabolite compared with heterozygous individuals carrying one functionally active CYP2D6 allele, EMs and UMs. Thus, PMs lacking CYP2D6 activity demanded and received more tramadol doses via patient-controlled analgesia compared with individuals with preserved catalytic CYP2D6 activity.

Kirchheiner and colleagues reported relatively small differences in plasma concentrations between EM and UM volunteers after receiving tramadol 100 mg orally. By contrast, PMs showed significantly elevated concentrations for tramadol and reduced concentrations for O-demethyltramadol. Lower opioid effects were detected with decreasing CYP2D6 activity. An increased pain threshold and pain tolerance, a more pronounced decrease in pupil diameter and an increase in nausea and vomiting were observed in UMs compared with the other genotypes. The authors stated that UMs were more sensitive to tramadol; however, they speculated that enzymes other than CYP2D6 or transporter proteins might also contribute to tramadol and metabolite concentrations.

Comparable to the cases with codeine, carriers of more than two functionally active CYP2D6 genes seem to be particularly prone for tramadol-related side effects. Opioid-induced respiratory depression was observed in one patient receiving tramadol via patient-controlled analgesia. Predisposing factors were the patient's genetic background and renal impairment (Table 1). Complete recovery occurred after naloxone administration, thus confirming opioid intoxication. Analysis of the patient's genotype revealed a CYP2D6 gene duplication resulting in ultrarapid metabolism of tramadol to its active metabolite (+)O-demethyltramadol. Concomitant renal impairment resulting in decreased metabolite clearance enhanced opioid toxicity.
**Oxycodone** For oxycodone, Lalovic and coauthors described CYP3A-mediated \( N \)-demethylation as the principal metabolic pathway in humans, whereas CYP2D6-mediated \( O \)-demethylation accounted for only 11% of the urinary metabolites.\(^{[47]}\) Although the CYP2D6 metabolite oxymorphone has a 40-fold higher \( \mu \)-opioid receptor binding affinity than oxycodone\(^{[47]}\) and proved to be a more potent \( \mu \)-opioid receptor agonist than oxycodone, it only plays an insignificant role in producing analgesic effects.\(^{[48]}\) The CYP3A4 pathway appears to be quantitatively more important.\(^{[47]}\) The central effects of oxycodone were governed by the parent drug, with a negligible contribution from its oxidative and reductive metabolites, thus demonstrating that CYP2D6 does not seem to play a major role for CNS effects or analgesic efficacy.\(^{[47,48]}\) Co-administration of the CYP2D6 inhibitor paroxetine in 20 chronic pain patients decreased the plasma levels (\( \text{AUC}_{0-12 \text{ h}} \)) of oxymorphone by 67%; however, paroxetine had no effect on oxycodone analgesia or the use of morphine rescue medication.\(^{[48]}\) In a postoperative setting, these results were confirmed with no difference in analgesic effect of intravenous oxycodone between EMs and PMs, although plasma concentrations of oxymorphone were significantly lower.\(^{[49]}\) By contrast, oxycodone analgesia was reduced in PMs compared with EMs in a human experimental pain model.\(^{[50]}\) Regarding CYP3A-dependent metabolism, comedication with rifampin decreased the AUC of intravenous and oral oxycodone by 53 and 86%, respectively, in volunteers.\(^{[51]}\) Plasma metabolite:parent drug ratios for noroxycodone and noroxymorphone were increased, whereas AUC of oxymorphone was reduced to 5–10% compared with controls. Oxycodone’s pharmacological effects were modestly attenuated by rifampin in this experimental setting. The authors stated that dose adjustment of oxycodone may be necessary when it is used concomitantly with rifampin to maintain adequate analgesia.\(^{[51]}\)

**Methadone** Racemic methadone (\( R \)- and \( S \)-methadone) or levomethadone (\( R \)-methadone) are used as second-line opioids for the treatment of patients suffering from cancer pain.\(^{[52,53]}\) Methadone is considered as a useful alternative in individuals refractory to other opioids or suffering from unresolved opioid-related side effects. Clinical experience has demonstrated its efficacy in neuropathic pain conditions, with several case reports highlighting this specific indication owing to methadone's NMDA-receptor agonistic properties. Both methadone enantiomers bind to the noncompetitive site of the NMDA receptor;\(^{[17]}\) however, levomethadone proved to be a stronger \( \mu \)-opioid receptor agonist
than S-methadone. This makes racemic methadone and levomethadone interesting drugs for the treatment of neuropathic (cancer) pain.

Studies on the metabolism of methadone have mainly been carried out on cohorts of opioid addicts under methadone maintenance treatment. In vivo, CYP3A4 and CYP2B6 are the major CYP isoforms involved in methadone metabolism, with CYP2D6 contributing to a minor extent, preferentially in metabolism of the R-enantiomer. The metabolites of methadone do not contribute to central nervous effects, as measured by means of pupil size in healthy volunteers, owing to low plasma concentrations and their 120- to 1300-fold lower affinities to the µ-opioid receptor.

Data regarding the impact of CYP2D6 metabolizer status and comedication on the phenotype are conflicting. UMs showed lower plasma concentrations than the other genotypes and presented deficient satisfaction with methadone maintenance treatment. However, this was not found in all investigations enrolling methadone-maintained subjects. Respective data on pain patients are not available so far. One might speculate that analgesic efficacy is not substantially impaired by CYP genetic variants; however, comedication (e.g., with CYP2D6 inhibitors) might influence dose requirements.

Tricyclic Antidepressants Tricyclic antidepressants are used as co-analgesics in chronic pain management, particularly in the treatment of neuropathic pain. In contrast to their use in psychiatry, doses commonly administered in pain therapy are much lower. Tricyclic antidepressants undergo biotransformation in the liver, with CYP2D6 catalyzing hydroxylation reactions, whereas demethylation of the parent drug is mediated by CYP2C19. Both metabolites are pharmacologically active, and the demethylated metabolites are partially tricyclic drugs by themselves, such as nortriptyline and desipramine, which are demethylmetabolites of amitriptyline and imipramine, respectively.

CYP2D6 PMs have higher plasma concentrations of tricyclic antidepressants than EMs and are therefore more likely to experience dose-dependent adverse drug reactions. In 50 psychiatric patients receiving amitriptyline 150 mg/day, carriers of two functional CYP2D6 alleles had a significantly lower risk of side effects than carriers of only one functional allele (12.1 vs 76.5%). The lowest risk was observed for carriers of two functional CYP2D6 alleles combined with only one functional CYP2C19 allele. Conversely,
carriers of CYP2D6 gene duplications present ultrarapid metabolism of tricyclic antidepressants, which may result in subtherapeutic drug concentrations with a high risk of poor therapeutic response. One might speculate that amitriptyline therapy, for example, taking a single dose of 25 mg in the evening, used in a patient suffering from chronic pain and displaying the UM genotype, only produces placebo effects or no effects at all owing to insufficiently high plasma concentrations. This might be misinterpreted by the physician as a lack of patient compliance (i.e., not having taken the prescribed drug). Thus, genetically caused differences in blood concentrations of antidepressants make dose adjustments advisable. However, these findings and dose recommendations only relate to psychiatric doses, and no investigations on antidepressants as low-dose co-analgesics are available to date.

CYP2C9/CYP2C8: Metabolism of NSAIDs

The NSAIDs are a group of nonopioid analgesics widely used in the treatment of acute postoperative pain after minor surgery or in combination with opioids after major surgery, as well as for the treatment of chronic pain. They are an essential part of the recommended approach of 'multimodal pain management', as analgesics with different mechanisms of action should be combined to increase the efficacy of treatment and reduce adverse effects, such as opioid-induced nausea and vomiting, sedation or respiratory depression. However, adverse events, for example, gastrointestinal side effects, an influence on coagulation or cardiovascular side effects, have been reported, particularly with long-term treatment. There seems to be an interindividual variation in response to COX inhibitors, and this limits their clinical utility and safety.

More than 33 variants and a series of subvariants have been identified for CYP2C9 to date. The two missense mutations, CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910), encoding for Arg144>Cys and Ile359>Leu amino acid substitutions, yield enzymes with decreased activity. These alleles are mainly present in Caucasians (allele frequency: CYP2C9*2: 11% and CYP2C9*3: 7%), while their frequency is lower in African (4 and 2%, respectively) and Asian subjects (0 and 3%, respectively).

Human CYP2C9 metabolizes numerous drugs, for example, vitamin K antagonists (S-warfarin and penprocoumon), oral sulfonylurea hypoglycemics, antiepileptics, angiotensin II
receptor inhibitors, anticancer drugs and others (for a detailed review see[60]). In
addition, CYP2C9 polymorphism might play a significant role in the analgesic efficacy and
toxicity of traditional NSAIDs, for example, diclofenac, flubiprofen, ibuprofen, naproxen,
tenoxicam and piroxicam, as well as selective COX2 inhibitors, such as celecoxib or
valdecoxib.[62,63] However, the effect of CYP2C9 polymorphisms does not seem to be similar
for all NSAIDs.[64] In particular, conflicting data from in vitro and in vivo studies have been
discussed.[64,65]

**Studies in Healthy Volunteers** A more than twofold reduced clearance after oral intake of
celecoxib was observed in homozygous carriers of CYP2C9*3 compared with carriers of the
wild-type genotype CYP2C9*1/*1. Heterozygous carriers of *3 were inbetween.[63] Tang and
colleagues reported celecoxib concentrations in plasma after a single oral dose (AUC2–24 h)
to be increased 2.2-fold in two CYP2C9*1/*3 subjects and one *3/*3 subject.[66] Decreased
concentrations of carboxy- and hydroxy-celecoxib in heterozygous and homozygous carriers
of CYP2C9*3 were detected, supporting the proposition that CYP2C9 polymorphisms
influence celecoxib pharmacokinetic variability.

Ibuprofen-mediated inhibition of COX1 and COX2 is significantly influenced
by CYP2C9 genotype. Clearance of racemic ibuprofen and S-ibuprofen was reduced by 50%
in carriers of two CYP2C9*3 alleles (1.52 l/h; 95% CI: 1.33–1.74) compared
with *1/*1 carriers (3.25 l/h; 95% CI: 2.84–3.73).[67] Ex vivo formation of thromboxane B(2),
reflecting COX1 inhibition, depended significantly on the type of CYP2C9 polymorphism. The
maximal inhibition of thromboxane B(2) formation and the area under the effect–time curve
were larger in *1/*3, *2/*3 and *3/*3 carriers than in *1/*1 carriers.[67] The same trend was
observed for prostaglandin E2, reflecting COX2 inhibition.[67] To date, clinical data are lacking;
thus, the influence of a reduced clearance of S-ibuprofen accompanied by increased
pharmacodynamic activity on efficacy and side effect profile has not been described in
patients receiving this NSAID.

Although CYP2C9 is the major determinant of clearance, it is necessary to also
consider CYP2C8 genotype, as it contributes to some small extent, to ibuprofen
metabolism.[66,68] García-Martín et al. measured the plasma concentration of ibuprofen in 130
healthy individuals who received a single oral dose of 400 mg racemic ibuprofen.[69] A low
ibuprofen clearance occurred in a substantial proportion of healthy subjects and was strongly linked to CYP2C8 and CYP2C9 polymorphisms.

Further investigations demonstrating the relevance of the CYP2C9*3 allele for tenoxicam, piroxicam, and lornoxicam pharmacokinetics have been published. Metabolism of orally dosed diclofenac by CYP2C8 and CYP2C9 was studied in 142 unrelated healthy Spanish volunteers. The results indicated that the diclofenac-to-5-hydroxydiclofenac urinary concentration ratio was higher in individuals carrying a CYP2C8*3 (rs10509681) or CYP2C8*4 (rs1058930) allele than in those homozygous for the wild-type allele. Furthermore, a linkage disequilibrium between CYP2C8*2 (rs11572103) and CYP2C9*3 alleles was confirmed in this Spanish population. In a recent review, the authors pointed out that overall clinical data regarding the impact of CYP2C8*3 allele on the disposition of NSAIDs are conflicting, and no definite conclusion can be made up to date.

Studies in Patients Whereas numerous clinical trials have demonstrated the impact of CYP2C9*3 on therapy with coumarins/warfarin, less information is available on the CYP2C9-related efficacy of NSAIDs in a clinical setting. Some publications focus on the incidence and severity of adverse events, for example, gastrointestinal complications (Table 2).

Acute gastrointestinal bleeding is a severe adverse drug reaction with a high rate of hospitalization and mortality in western countries. Risk factors for this complication include older age, a history of peptic ulcer, concomitant medication with steroids, coumarins and high-dose and/or long-term treatment with aspirin or NSAIDs, as well as combinations of these drugs. Blanco and colleagues performed a cross-sectional study involving 134 patients who experienced NSAID-induced gastrointestinal bleeding and 177 patients who received NSAID with no adverse effects. The combined presence of CYP2C8*3 and CYP2C9*2 was a relevant determinant in the risk of developing gastrointestinal bleeding in patients receiving NSAIDs metabolized by CYP2C8/9.

However, to date, study results are conflicting, with several other trials reporting no association. The recent review by Agundez et al. indicated CYP2C9*2 as a risk factor with an odds ratio of 1.58 (95% CI: 1.08–2.32) for patients receiving NSAIDs and 1.96 (95% CI: 1.00–2.56) for patients receiving NSAIDs that are substrates of CYP2C8 or CYP2C9.
the most common CYP2C9 alleles are taken together, the odds ratios increase to 1.78 (95% CI: 1.24–2.54) and 2.33 (95% CI: 1.45–3.75). However, more studies are necessary, and the relevance of the CYP2C8*3 allele in particular requires further investigation. Overall, differences in study designs (retrospective vs prospective), number of individuals enrolled, varying comedication, small numbers of homozygous subjects for CYP alleles resulting in reduced enzyme activity, and imbalance of genotype distribution might have contributed to inconsistent findings.

**NSAID Adverse Effects on Coagulation** Another typical adverse event is the influence of classical NSAIDs on coagulation. This side effect is particularly a problem in the perioperative setting when exaggerated bleeding might lead to high blood loss, the need for blood transfusion or even re-surgery. Patients under coumarin anticoagulation therapy are a high-risk population as these drugs exhibit a narrow therapeutic window and CYP-dependent hepatic metabolism. Life-threatening drug–drug interactions are well described. Visser and coworkers conducted a population-based cohort study among 973 patients from an anticoagulation clinic who were treated with acenocoumarol or phenprocoumon. The authors found that comedication with several NSAIDs was associated with the risk of overanticoagulation. In NSAIDs that are known CYP2C9 substrates, the risk was modified by allelic variants of CYP2C9. The risk of overanticoagulation was 2.98 (95% CI: 1.09–7.02) in coumarin-treated patients taking NSAIDs with a CYP2C9*2 allele and 10.8 (95% CI: 2.57–34.6) in those with a CYP2C9*3 allele.

Other NSAID-related side effects, such as fluid and sodium retention and other renal adverse events, may also be related to CYP2C9 genotype. However, clinical studies supporting these hypotheses are lacking.

**Transmembrane Transporter ABCB1**

P-glycoprotein is a transmembrane transporter coded by the ATP-binding cassette subfamily B (ABCB1)/multidrug resistance (MDR1) gene. As a drug-efflux transporter, it is located in the GI tract, kidneys, liver and part of the blood–brain barrier. Genetic variants resulting in a functional impairment of P-glycoprotein are discussed, with most studies focusing on either the C3435T (rs1045642) variant or a diplotype consisting of three ABCB1 SNPs: C1236T (rs1128503), G2677T/A (rs2032582) and C3435T. Korean patients with a specific diplotype
(1236TT, 2677TT and 3435TT) showed increased susceptibility to intravenous fentanyl with early (2–3 min) and profound suppression of respiration (65–73% of initial respiratory rate) compared with those carrying an obviously more resistant diplotype (1236CC, 2677GG and 3435CC: 83–85% of initial respiratory rate). Although the need to supply oxygen was not significantly different between the genotypes, there was a trend for increased demand by patients carrying both 1236T and 3435T alleles. The results suggest that analysis of \textit{ABCB1} polymorphisms may have clinical relevance to the prevention of respiratory suppression by intravenous fentanyl or to anticipate its clinical effects. Zwisler et al. investigated oxycodone-related adverse drug reaction in an experimental pain setting enrolling 33 healthy volunteers. They found a strong association between less adverse drug reactions and the variant alleles 3453T and 2677A, and better antinociceptive effects of oxycodone for the variant 2677T.

Trials in patients suffering from chronic and cancer pain reported decreased opioid consumption in carriers of the 3435T allele. In line with this, methadone dose requirements in opioid-dependent subjects were influenced by \textit{ABCB1} genetic variability. The previously mentioned 3-locus genotype TT–TT–TT has an approximately fivefold chance of requiring a high methadone dose; individuals heterozygous for these SNPs have a threefold chance of stabilizing at lower doses. Coller and coauthors investigated five SNPs (A61G [rs9282564], G1199A [rs2229109], C1236T, G2677T/A and C3435T) and the respective haplotypes. Subjects carrying two copies of the wild-type haplotype required higher methadone doses compared with those with one copy and those with no copy (98.3 ± 10.4, 58.6 ± 20.9 and 55.4 ± 26.1 mg/day, respectively; \( p = 0.029 \)). In addition, carriers of the AGCTT haplotype required significantly lower doses than noncarriers (38.0 ± 16.8 vs 61.3 ± 24.6 mg/day). Contrasting results were published by Crettol and coworkers. In 279 methadone maintenance patients, no relationship between methadone dosages, response to treatment and \textit{ABCB1} haplotype was detected, although in a previous publication, the authors described that \textit{ABCB1} 3435TT carriers presented slightly lower trough (\( R,S \))-methadone plasma levels than CC carriers.