Published in final edited form as:
Pharmacogenomics. 2009 September ; 10(9): 1489–1510. doi:10.2217/pgs.09.82.

Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies

Elizabeth B Daily and **Christina L Aquilante**†

Abstract

Cytochrome P450 (CYP) 2C8 is responsible for the oxidative metabolism of many clinically available drugs from a diverse number of drug classes (e.g., thiazolidinediones, meglitinides, NSAIDs, antimalarials and chemotherapeutic taxanes). The CYP2C8 enzyme is encoded by the *CYP2C8* gene, and several common nonsynonymous polymorphisms (e.g., *CYP2C8*2* and *CYP2C8*3*) exist in this gene. The *CYP2C8*2* and **3* alleles have been associated *in vitro* with decreased metabolism of paclitaxel and arachidonic acid. Recently, the influence of *CYP2C8* polymorphisms on substrate disposition in humans has been investigated in a number of clinical pharmacogenetic studies. Contrary to *in vitro* data, clinical data suggest that the *CYP2C8*3* allele is associated with increased metabolism of the CYP2C8 substrates, rosiglitazone, pioglitazone and repaglinide. However, the *CYP2C8*3* allele has not been associated with paclitaxel pharmacokinetics in most clinical studies. Furthermore, clinical data regarding the impact of the *CYP2C8*3* allele on the disposition of NSAIDs are conflicting and no definitive conclusions can be made at this time. The purpose of this review is to highlight these clinical studies that have investigated the association between *CYP2C8* polymorphisms and CYP2C8 substrate pharmacokinetics and/or pharmacodynamics in humans. In this review, CYP2C8 clinical pharmacogenetic data are provided by drug class, followed by a discussion of the future of CYP2C8 clinical pharmacogenetic research.

Keywords

amodiaquine; CYP2C8; cytochrome P450 2C8; human; ibuprofen; NSAID; paclitaxel; repaglinide; thiazolidinedione

The field of pharmacogenetics is aimed at understanding how genetic variation contributes to interindividual variability in drug disposition (i.e., pharmacokinetics) and drug response (i.e., pharmacodynamics). In terms of drug disposition, the cytochrome P450 (CYP) metabolizing enzymes are a major area of study, as they catalyze the oxidative metabolism of numerous drugs and endogenous compounds. Enzymes in the CYP2C family (e.g., CYP2C8, CYP2C9, CYP2C18 and CYP2C19) are significant contributors to drug disposition and metabolize 20% of clinically available drugs [1,2]. Recently, the role of the CYP2C8 isoenzyme has garnered considerable interest in the fields of drug metabolism and pharmacogenetics. This is largely a

†Author for correspondence: University of Colorado Denver, School of Pharmacy, Department of Pharmaceutical Sciences, 12700 East 19th Avenue, Box C238-P15, Aurora, CO 80045, USA, Tel.: +1 303 724 6126; Fax: +1 303 724 7266; christina.aquilante@ucdenver.edu.

Financial & competing interests disclosure

Dr Aquilante currently holds investigator-initiated research grants from the NIH (K23 DK073197), American College of Clinical Pharmacy and Tibotec Therapeutics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

result of the elucidation of the structure of the CYP2C8 enzyme, characterization of polymorphisms within the *CYP2C8* gene and identification of clinically relevant CYP2C8 substrates, such as the thiazolidinediones and repaglinide [1].

In 2005, Totah and colleagues published a comprehensive review describing CYP2C8 substrates, inhibitors, inducers and pharmacogenetics [1]. Since that time, the field of *CYP2C8* pharmacogenetics has expanded dramatically, and numerous clinical studies have been published regarding the association between *CYP2C8* polymorphisms and the disposition of various substrates. As such, the purpose of this review is to discuss clinical studies that have examined the influence of *CYP2C8* polymorphisms on the pharmacokinetics and/or pharmacodynamics of CYP2C8 substrates in humans. First, we present a brief discussion of the CYP2C8 enzyme and *CYP2C8* polymorphisms (for a comprehensive background discussion of CYP2C8 and *in vitro* data, the reader is referred to the review by Totah and Rettie) [1]. Next, we place major focus on the relevant clinical *CYP2C8* pharmacogenetic data by drug class, followed by a discussion of the future of *CYP2C8* clinical pharmacogenetic research.

CYP2C8 enzyme

CYP2C8 comprises 7% of the total hepatic CYP content and plays an important role in the metabolism of a diverse number of exogenous and endogenous compounds [1]. It is highly expressed in liver, but is also found in extrahepatic sites such as the kidney, heart, adrenal gland, brain, uterus, mammary gland, ovary and duodenum [3,4]. CYP2C8 plays a major role in the metabolism of many clinically available drugs [5,6]. These drugs are summarized in Table 1 and include: thiazolidinediones (i.e., rosiglitazone, pioglitazone and troglitazone), meglitinides (i.e., repaglinide), 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (i.e., cerivastatin), chemotherapeutic agents (i.e., paclitaxel and all-*trans*-retinoic acid), antimalarials (i.e., amodiaquine and chloroquine), antiarrhythmics (i.e., amiodarone) and retinoid derivatives (i.e., tazarotenic acid) [1]. Other data suggest that CYP2C8 plays only an intermediate or minor role in the metabolism of other agents such as NSAIDs (i.e., ibuprofen, diclofenac and tenoxicam), fluvastatin, simvastatin acid, carbamazepine, cyclophosphamide, dapsone, diltiazem, ifosfamide, loperamide, methadone, morphine, torsemide, verapamil and zopiclone [1]. CYP2C8 also converts endogenous compounds such as arachidonic acid to biologically active epoxide metabolites, which are important regulators of vascular tone and blood pressure [1,7].

CYP2C8 gene & polymorphisms

The CYP2C8 enzyme is encoded by the *CYP2C8* gene, which spans 31 kb and is located on chromosome 10q24 [3]. *CYP2C8* is located in close proximity to *CYP2C9*, *CYP2C19* and *CYP2C18*, which are also located on chromosome 10q24. In total, the *CYP2C* gene family spans approximately 400 kb and there is linkage between genes [3,8]. The *CYP2C8* gene shares 74% sequence homology with *CYP2C9* and is transcriptionally regulated by nuclear receptors such as androstane receptor, pregnane X receptor, glucocorticoid receptor and hepatic nuclear factor-4α [9–11]. The wild-type gene is referred to as *CYP2C8*1* (or **1A*). A number of common nonsynonymous SNPs have been identified in *CYP2C8* including: *CYP2C8*2* (Ile269Phe), *CYP2C8*3* (linked polymorphisms Arg139Lys and Lys399Arg) and *CYP2C8*4* (Ile264Met) (Figure 1). Of note, the *CYP2C8*3* allele is in partial linkage disequilibrium with the *CYP2C9*2* allele, which is associated with impaired metabolism of many CYP2C9 substrates [8]. Common polymorphisms in the CYP2C8 promoter, -271C>A and -370T>G, have also been identified [12,13]. Additionally, data from the Human Cytochrome P450 Allele Nomenclature Committee and dbSNP show that a number of other rare nonsynonymous polymorphic *CYP2C8* alleles exist, including *CYP2C8*5* through *CYP2C8*14*, and several that have not yet been assigned a ‘star’ designation [201,202]. The

description, location and frequencies of nonsynonymous and promoter *CYP2C8* polymorphic alleles are summarized in Table 2.

Recently, several groups have characterized *CYP2C8* haplotypes in different racial groups. Using data from the International HapMap Project, Rodriguez-Antona and colleagues characterized *CYP2C8* haplotypes in 54 unrelated Caucasian individuals [13]. They inferred haplotypes from 12 HapMap tag SNPs and SNPs with a putative functional significance. Seven common haplotypes (frequency greater than 2%) were identified and named (A, B, C1, C2, C3, D and E). The SNPs included in these haplotypes are shown in Table 3.

Considering that there is a large degree of racial diversity in *CYP2C8* haplotype structure, Saito and colleagues set out to characterize *CYP2C8* haplotypes using 40 polymorphisms in 437 Japanese individuals [14]. A total of 40 haplotypes without amino acid changes and nine haplotypes with amino acid changes were inferred. The most common haplotypes were **1d* (36.6%), **1e* (28.9%), **1f* (11.3%), **1B* (8.5%). Using network analysis, haplotypes that were found in more than two patients were further classified into six groups, **IA* (2.1%), **IB* (10.3%), **ID* (38.1%), **IE* (43.5%), **IG* (3%) and **IJ* (1.3%).

Given the close proximity of *CYP2C8* and *CYP2C9* on chromosome 10, and the linkage that exists between these two genes [8], Speed and colleagues recently characterized haplotypes containing *CYP2C8* and *CYP2C9* polymorphisms in 2500 individuals from 45 populations around the world [15]. Ten SNPs were studied across a 132 kb region containing *CYP2C8* and *CYP2C9*. These SNPs included: rs4918758 (*CYP2C9*), rs1799853 (*CYP2C9*, Arg144Cys), rs1934953 (*CYP2C8*), rs10509681 (*CYP2C8*, Lys399Arg), rs11572103 (*CYP2C8*, Ile269Phe), rs1058930 (*CYP2C8*, Ile264Met), rs11572093 (*CYP2C8*), rs11572080 (*CYP2C8*, Arg139Lys), rs11572076 (*CYP2C8*) and rs17110453 (*CYP2C8*). From these SNPs, 17 common haplotypes were inferred (haplotypes A through Q). Haplotype G contained three coding region SNPs, *CYP2C9* Arg144Cys, *CYP2C8* Arg139Lys and *CYP2C8* Lys399Arg and occurred at a frequency of 10% in Europeans. The investigators also found that 89% of chromosomes with either the *CYP2C8* Arg139Lys or *CYP2C8* Lys399Arg variants also carried the *CYP2C9* Arg144Cys variant allele. The investigators went on to hypothesize that due to the strong association of these three variants, it may be difficult in clinical studies to differentiate if observed associations are a result of *CYP2C8* or *CYP2C9* polymorphisms [15]. Of note, haplotypes B, L and M, which contain the *CYP2C8* Ile269Phe (**2*) polymorphism, were common in Africans (frequency of 6–28%), but were absent in other races studied. The investigators were unable to compare their haplotype results to those of Rodriguez-Antona and colleagues because only four polymorphisms were studied in common between the two studies. Future investigations elucidating the optimal panel of polymorphisms to include in *CYP2C8* haplotype analysis are needed.

CYP2C8 clinical pharmacogenetic research is a direct result of *in vitro* work, which identified some *CYP2C8* polymorphisms to have putative functional significance. Specifically, *CYP2C8*3* is associated with reduced CYP2C8 metabolic activity for the substrates, paclitaxel and arachidonic acid, compared with wild-type enzyme [12,16,17]. Decreased CYP2C8 metabolic activity has also been demonstrated for *CYP2C8*2* [16]. Although not statistically significant, data suggest that median *CYP2C8*4* metabolic activity for paclitaxel is lower than wild-type enzyme [12]. More recently, *in vitro* analysis of promoter polymorphisms showed that the *CYP2C8*1B* allele (-271C>A) is associated with higher rates of transcription compared with wild-type [13]. In regards to less common polymorphisms, the *CYP2C8*8* allele (Arg186Gly) is associated with reduced enzymatic activity compared with wild-type, and the *CYP2C8*7* allele (Arg186X) results in a prematurely terminated protein. However, these polymorphisms are rare and appear to be race specific, occurring primarily in Asian populations [18].

While *in vitro* data suggest that variant *CYP2C8*3* and *CYP2C8*2* alleles result in decreased metabolism of CYP2C8 substrates, clinical pharmacogenetic data have yielded sometimes contradictory results. Hereafter, we present *CYP2C8* clinical pharmacogenetic data for clinically available drugs, by drug class. This is followed by a discussion of the future of *CYP2C8* clinical pharmacogenetic research. For a review of the influence of *CYP2C8* polymorphisms on arachidonic acid metabolism and clinical outcomes, the reader is referred to a recent review by Theken and Lee [7].

Antidiabetic agents

Thiazolidinediones

The thiazolidinediones, rosiglitazone and pioglitazone, are peroxisome-proliferator-activated receptor-γ agonists that modulate the transcription of numerous genes involved in glucose metabolism, lipid metabolism, adipocyte differentiation and insulin sensitivity [19]. Rosiglitazone and pioglitazone are indicated for the treatment of Type 2 diabetes [20]. Both rosiglitazone and pioglitazone are extensively metabolized in the liver by CYP2C8 [3,21,22]. Troglitazone, a thiazolidinedi-one that was withdrawn from the market due to idiosyncratic hepatotoxicity, is also a CYP2C8 substrate [23]. Other CYP enzymes that contribute a lesser degree to rosiglitazone and pioglitazone metabolism include CYP2C9 (rosiglitazone), CYP3A4 (pioglitazone) and CYP1A1 (pioglitazone) [24,25]. Rosiglitazone undergoes CYP2C8-mediated *N*-demethylation and hydroxylation, followed by sulfate and glucuronic acid conjugation [21,24]. *N*-desmethylrosiglitazone and para-*O*-sulfate rosiglitazone are the primary metabolites, and both are considered less potent than the parent drug. Pioglitazone undergoes CYP2C8-mediated hydroxylation and oxidation, followed by sulfate and glucuronide conjugation. M-IV (hydroxy-derivative of pioglitazone) and M-III (keto-derivative) are the principal metabolites found *in vivo* [25].

Recent clinical data suggest that *CYP2C8* polymorphisms contribute to interindividual variability in thiazolidinedione pharmacokinetics (Table 4). Kirchheiner and colleagues considered the influence of the *CYP2C8*3* polymorphism on single dose and multiple-dose rosiglitazone (8 mg) pharmacokinetics in German healthy volunteers [26]. Following a single-dose, mean rosiglitazone area under the plasma concentration–time curve (AUC) was 36% lower and weight-adjusted oral clearance was 39% higher in *CYP2C8*3* homozygotes compared with wild-type homozygotes ($p = 0.03$, both comparisons). Rosiglitazone AUC was 7% lower and weight-adjusted oral clearance was 15% higher in heterozygotes compared with wild-type homozygotes (not statistically significant, both comparisons). Similar pharmacokinetic results by genotype were found after 14 days of rosiglitazone administration. In multivariate regression analysis, significant predictors of rosiglitazone AUC were *CYP2C8*3* genotype and body weight, which accounted for 48% of the variability in rosiglitazone AUC. The investigators also conducted a population pharmacokinetic analysis of their data, which revealed a 23 and 46% higher rosiglitazone oral clearance in heterozygotes and *CYP2C8*3* homozygotes, respectively, compared with wild-type homozygotes.

The association between the *CYP2C8*3* polymorphism and rosiglitazone pharmacokinetics in healthy Caucasian volunteers was recently evaluated in our laboratory [27]. No *CYP2C8*3* homozygotes were identified in our population. Following a single dose of rosiglitazone 4 mg, mean AUC was 29% lower and weight-adjusted oral clearance was 39% higher in heterozygotes compared with wild-type homozygotes ($p = 0.002$ and $p = 0.03$, respectively). The half-life of rosiglitazone was also shorter in heterozygotes compared with wild-type homozygotes (3.5 h versus 4 h), although this did not reach statistical significance ($p = 0.09$). In multivariate regression analysis, significant predictors of rosiglitazone AUC were *CYP2C8*3* genotype and body weight, which accounted for 42% of the variability in rosiglitazone AUC.

Tornio and colleagues evaluated the effects of the *CYP2C8*3* allele on single-dose pioglitazone (15 mg) pharmacokinetics in healthy volunteers [28]. The weight-adjusted pioglitazone AUC was 34% lower in *CYP2C8*3* homozygotes and 26% lower in heterozygotes compared with wild-type homozygotes ($p < 0.05$, both comparisons). The half-life of pioglitazone was significantly shorter in heterozygotes (3.4 h) and *CYP2C8*3* homozygotes (3.3 h) compared with wild-type homozygotes (4.5 h). The investigators also evaluated the effects of trimethoprim (a *CYP2C8* inhibitor) on pioglitazone pharmacokinetics, but found that *CYP2C8* genotype did not significantly influence the extent to which trimethoprim increased the plasma concentrations of pioglitazone.

While these three studies demonstrated lower rosiglitazone and pioglitazone plasma exposure in carriers of the *CYP2C8*3* allele, two other studies reported no association between *CYP2C8* polymorphisms and thiazolidinedione pharmacokinetics. As part of a healthy volunteer drug–drug interaction study between trimethoprim and rosiglitazone, Hruska and colleagues found that rosiglitazone AUC did not differ significantly between wild-type homozygotes and those carrying a *CYP2C8*3* or **2* allele [29]. In a different healthy volunteer study, Pederson and colleagues found that the pharmacokinetics of a single dose of rosiglitazone 4 mg did not differ significantly by *CYP2C8* genotype, nor did genotype influence the magnitude of the drug–drug interaction between rosiglitazone and fluvoxamine (a CYP2C8 inhibitor) [30].

Although the data are not entirely consistent, three of five studies suggest that the *CYP2C8*3* allele is associated with increased rosiglitazone and pioglitazone metabolism. In studies that included *CYP2C8*3* homozygotes, a gene–dose effect appears to be present, both for rosiglitazone and pioglitazone. Of note, variability in the magnitude of the differences in AUC and oral clearance between heterozygotes and wild-type homozygotes was evident upon comparison of some of the studies. This may be explained by differences in body weight and gender distribution between genotype groups. Additionally, all studies did not genotype for the *CYP2C9*2* and *CYP2C9*3* alleles, which may have confounded the study findings, particularly for rosiglitazone, which undergoes some CYP2C9 metabolism. In terms of the studies that did not find an association between *CYP2C8* polymorphisms and rosiglitazone pharmacokinetics, this is most likely to be due to small sample sizes and the fact that these studies were not originally powered to detect differences between genotype groups (i.e., both were drug–drug interaction studies).

In terms of clinical relevance, the issue that remains to be determined is whether these modest thiazolidinedione pharmacokinetic differences by *CYP2C8* genotype will translate into pharmacodynamic differences in patients with Type 2 diabetes. Both rosiglitazone and pioglitazone have wide therapeutic indices. However, changes in plasma drug exposure, as a result of *CYP2C8* polymorphisms, may influence the risk of concentration-dependent adverse effects (e.g., weight gain, edema) or the magnitude of glucose reductions or insulin sensitization. In light of recent cardiovascular risk findings surrounding rosiglitazone, it seems prudent at this point in time to focus attention on the potential influence of *CYP2C8* polymorphisms on pioglitazone pharmacokinetics and pharmacodynamics in long-term studies of patients with Type 2 diabetes. Additionally, recent data suggest that polymorphisms in drug receptor and effector protein genes (e.g., PPAR-γ, adiponectin) influence response to thiazolidinediones [31]. Thus, consideration of both drug–metabolism and drug–target genetics must be given to comprehensively elucidate interindividual variability in thiazolidinedione response.

Repaglinide

Repaglinide, an agent in the meglitinide class, is a nonsulfonylurea insulin secretagogue that is used to lower postprandial glucose levels in patients with Type 2 diabetes. Repaglinide is

metabolized through oxidative biotransformation and glucuronidation to several metabolites, M1, M2 and M4 [32,33]. Both CYP2C8 and CYP3A4 have been implicated in the metabolism of repaglinide; however, *in vivo* it appears that CYP2C8 may contribute to a greater extent than CYP3A4 [33,34]. This is supported by drug–drug interaction data that showed that gemfibrozil (a CYP2C8 inhibitor) increased repaglinide plasma concentrations to a greater extent than the CYP3A4 inhibitors, itraconazole and clarithromycin [35,36]. Given the important role of CYP2C8 in repaglinide metabolism, investigations have been conducted examining the influence of *CYP2C8* polymorphisms on repaglinide pharmacokinetics (Table 5).

Niemi and colleagues set out to determine whether *CYP2C8* genotype affects the pharmacokinetics of single-dose repaglinide 0.25 mg in healthy Caucasian volunteers [37]. Repaglinide mean AUC and maximium plasma concentration ($C_{max)}$ were 45 and 39% lower, respectively, in subjects with the *CYP2C8*1/*3* genotype compared with wild-type homozygotes. Repaglinide AUC was also 13% lower in subjects with the *CYP2C8*1/*4* genotype compared with wild-type homozygotes, although this was not statistically significant. Niemi and colleagues then went on to expand their study of repaglinide pharmacogenetics in a larger analysis of their completed or ongoing repaglinide healthy volunteer cohorts [38]. In this analysis, they evaluated the effects of polymorphisms in the *CYP2C8* and *CYP3A5* genes, and the drug transporter genes, *ABCB1* and *SLCO1B1*, on the pharmacokinetics of repaglinide following a single 0.25 mg dose. Consistent with their previous data, repaglinide were significantly 48 and mean AUC and C_{max} 44% lower, respectively, in subjects with the *CYP2C8*1/*3* genotype compared with wild-type homozygotes. Significant predictors of repaglinide AUC in multiple regression analysis were *CYP2C8*1/*3* genotype and *SLCO1B1* genotype. Taken together, these two investigations were the first to suggest that the *CYP2C8*3* allele is associated with increased metabolism *in vivo* for certain substrates, namely repaglinide.

Given the association between *CYP2C8* genotype and repaglinide pharmacokinetics, these investigators went on to conduct a *CYP2C8* haplotype–phenotype study of repaglinide [13]. First, *CYP2C8* haplotypes were characterized in 54 Caucasian liver samples and CYP2C8 activity was assessed by measuring paclitaxel 6α-hydroxylation. Of 12 tagging polymorphisms, 7 common haplotypes were inferred (i.e., A, B, C1, C2, C3, D and E). *In vitro*, haplotype B was associated with increased paclitaxel metabolism, while haplotype C was associated with decreased paclitaxel metabolism. Of note, the *CYP2C8*3* and *CYP2C8*4* alleles were not significantly associated with paclitaxel metabolism in the liver samples. Next, the investigators studied the influence of these haplotypes on single-dose repaglinide 0.25 mg pharmacokinetics in 68 Caucasian healthy volunteers. Carriers of haplotype B had a 34% reduction in repaglinide AUC compared with noncarriers ($p = 0.036$), and carriers of haplotype C had a 34% increase in repaglinide AUC compared with noncarriers ($p = 0.046$). Haplotype D, which contains the *CYP2C8*3* allele, had 50% lower repaglinide AUC compared with noncarriers ($p = 0.035$). Of note, these findings were observed in *SLCO1B1* c.521 T/C heterozygotes, and the *CYP2C8* haplotype findings did not reach statistical significance in *SLCO1B1* c.521 wild-type homozygotes. In further functional analyses, the investigators characterized *CYP2C8* -271C>A as the putative polymorphism causing increased activity of haplotype B. These data suggest that, in humans, haplotypes B and D are associated with increased repaglinide metabolism, while haplotype C is associated with decreased repaglinide metabolism.

CYP2C8 genotyping has been conducted in a few repaglinide drug–drug interaction studies. In a drug–drug interaction study of ciclosporin (inhibitor of organic anion-transporting polypeptide 1B1, which is encoded by the *SLCO1B1* gene) and repaglinide, *CYP2C8* polymorphisms did not affect the extent of the interaction or the baseline pharmacokinetics of repaglinide [39]. However, there was only one subject with the *CYP2C8*1/*3* genotype and

one subject with the *CYP2C8*1/*4* genotype in this study. Thus definitive *CYP2C8* genotype conclusions cannot be drawn due to an inadequate sample size for comparisons. Another study evaluated the interaction between gemfibrozil and repaglinide in healthy volunteers. In the study population, the ratios of M2 and M4 to parent repaglinide were highest in the 3 subjects possessing the *CYP2C8*1/*3* genotype [40]. Although the number of heterozygotes was small, these data are consistent with previous findings of increased repaglinide metabolism associated with the *CYP2C8*3* allele. In a drug–drug interaction study of grapefruit juice and repaglinide, the *CYP2C8*3* allele was not significantly associated with repaglinide pharmacokinetics when repaglinide was administered alone [41].

Most studies have found the *CYP2C8*3* allele to be associated with increased repaglinide metabolism, while one study found no association. A possible explanation for this discrepancy is that a higher dose of repaglinide (2 mg) was used in the drug–drug interaction study that observed no *CYP2C8* genotype association. The authors hypothesized that the effects of the *CYP2C8*3* allele on repaglinide pharmacokinetics may be relevant at lower doses (e.g., 0.25 mg used in most studies), but at higher clinically relevant doses other factors, such as CYP3A4 metabolism, may come into play diluting the *CYP2C8* genotype effect. Additionally, it is well-recognized that *SLCO1B1* polymorphisms are important predictors of repaglinide pharmacokinetics [38]. *SLCO1B1* polymorphisms were evaluated in most, but not all, repaglinide studies. Thus, imbalances in *SLCO1B1* genotypes between *CYP2C8* genotype groups may have confounded the results. In future repaglinide *CYP2C8* pharmacogenetic studies, consideration should be given to stratification by *SLCO1B1* genotype and evaluation of *CYP2C8* haplotypes should be conducted across a range of clinically applicable doses. Furthermore, the clinical implication of *CYP2C8* and *SLCO1B1*-mediated variability in repaglinide pharmacokinetics on repaglinide pharmacodynamics merits investigation in patients with Type 2 diabetes.

HMG-CoA reductase inhibitors

The HMG-CoA reductase inhibitors, ‘statins’, are used extensively in the treatment of hyperlipidemia. CYP2C8 is thought to play a major role in the metabolism of cerivastatin and a minor role in the metabolism of fluvastatin and simvastatin acid.

Cerivastatin

Cerivastatin is a lipophilic statin that undergoes CYP2C8-mediated metabolism to the active metabolites M-1 and M-23 [42]. *In vitro*, gemfibrozil markedly inhibited the formation of the M-23 metabolite, and to a lesser extent the M-1 metabolite, presumably through CYP2C8 inhibition [43]. CYP3A4 contributes to a minor extent in the formation of M-1 [42]. In 2001, cerivastatin was withdrawn from the worldwide market due to a higher incidence of rhabdomyolysis compared with other statins [44,45]. Rhabdomyolysis is the consequence of excessive muscle breakdown that results in acute renal failure, cardiac complications and compression of the nerves and blood vessels [46]. Although the mechanisms of statin-induced rhabdomyolysis remain uncertain, one possible risk factor for rhabdomyolysis is elevated concentrations of statins in the plasma [46]. This may be a result of high statin doses, drug–drug interactions that increase statin plasma exposure or dysfunctional CYP metabolizing enzymes [46]. An important risk factor for cerivastatin-associated rhabdomyolysis was concomitant treatment with gemfibrozil, which increased cerivastatin concentrations several-fold through inhibition of CYP2C8-mediated metabolism [47].

The association between *CYP2C8* polymorphisms and cerivastatin-associated side effects, such as rhabdomyolysis, has not been formally assessed. However, a case report identified three *CYP2C8* polymorphisms, 475delA (exon 3), G874T (exon 6) and T1551C (exon 9), in a Japanese woman who developed rhabdomyolysis after 22 days of cerivastatin therapy [48].

The authors concluded that the 475delA polymorphism, which results in a frameshift and premature protein truncation, was the putative polymorphism causing decreased CYP2C8 metabolizing enzyme activity. In a subsequent analysis, the authors evaluated the cerivastatin metabolite ratios in this patient's serum, and found the ratio of M-23:M-1 to be lower than in control patients [49]. This finding suggests that decreased metabolism of cerivastatin was evident in this patient, and this may be due to *CYP2C8* gene polymorphisms, as previously discussed. While the potential associations between *CYP2C8* polymorphisms and decreased cerivastatin metabolism are intriguing, the clinical relevance of the 475delA polymorphism is unclear, as homozygozity for this allele is extremely rare [48].

Fluvastatin

Fluvastatin is a racemic mixture of an active (+)-3R, 5S form and an inactive (−)-3S, 5R form. Both enantiomers are principally metabolized by CYP2C9 (75%) and to a lesser extent by CYP3A4 (~20%) and CYP2C8 (~5%) [50,51]. Given the small contribution of CYP2C8 to fluvastatin's overall metabolism, it would not be expected that *CYP2C8* polymorphisms would contribute in a major way to the disposition of the drug. Furthermore, gemfibrozil, a CYP2C8 inhibitor, was shown to have no effect on the pharmacokinetics of fluvastatin [52]. Kirchheiner and colleagues evaluated the influence of *CYP2C9* and *CYP2C8* polymorphisms on fluvastatin pharmacokinetics in 26 healthy German volunteers [53]. Neither *CYP2C8*3*, nor *CYP2C9*2*, significantly influenced the pharmacokinetics of fluvastatin 40 mg following 14 days of therapy. Of note, the mean AUC of the active (+)-3R, 5S enantiomer was threefold higher and the mean AUC of the inactive (−)-3S, 5R enantiomer was fourfold higher in *CYP2C9*3* homozygotes (n = 3) compared with wild-type homozygotes (n = 5). In summary, although *CYP2C9* polymorphisms influence the pharmacokinetics of fluvastatin, genetic variation in *CYP2C8* does not contribute to a significant extent.

Other statins

Most of the other statins (e.g., atorvastatin and lovastatin) do not undergo CYP2C8-mediated metabolism [54]. *In vitro* data from human liver microsomes showed that CYP2C8 contributed only a minor extent to the metabolism of simvastatin acid [55]. Rosuvastatin, the newest statin, does not undergo extensive metabolism; however, approximately 10% of the parent drug is metabolized by CYP2C9 [56]. Thus, it is unlikely that the *CYP2C9*2* polymorphism, or the partially linked *CYP2C8*3* polymorphism, would significantly influence the disposition or response of rosuvastatin. This hypothesis is supported by drug–drug interaction data, which showed that CYP2C9 inhibition with fluconazole only modestly increased the AUC of rosuvastatin by 14% [57]. Furthermore, genome-wide studies have not identified *CYP2C9* or *CYP2C8* polymorphisms as key determinants of statin response. Instead, it appears that polymorphisms in other CYP enzyme genes (e.g., *CYP3A5*), drug-transporter genes (e.g., *SLCO1B1*) and drug-target genes (e.g., apolipoprotein E and *HMGCR*) may be more likely contributors to interpatient variability in statin response and adverse events [58–61].

NSAIDs

Drugs in the nonsteroidal anti-inflammatory class are some of the most widely prescribed and over-the-counter medications. While CYP2C9 contributes to the metabolism of most NSAIDS, recent data show that *CYP2C8* polymorphisms may influence interindividual variability in the pharmacokinetics of some NSAIDs, namely ibuprofen and diclofenac [62].

Ibuprofen

Ibuprofen, a racemic mixture of S-(+) and R-(−) enantiomers, is one of the most commonly used NSAIDs. The S-enantiomer is mainly responsible for the anti-inflammatory pharmacologic activity of ibuprofen, and the R-enantiomer is capable of conversion to the S-

enantiomer *in vivo* [63,64]. CYP2C9 contributes to the metabolism of both the S- and R-enantiomers, and CYP2C8 plays a role in the metabolism of the R-enantiomer [65]. However, recent data suggest controversy in the extent to which CYP2C8 is involved in R-ibuprofen metabolism. For example, *in vitro* data suggest that CYP2C8 contributes less than 10% to the clearance of R-ibuprofen [66]. However, *in vivo*, administration of gemfibrozil, a CYP2C8 inhibitor, increased the AUC of R-ibuprofen to a greater extent than S-ibuprofen (34 vs 7%, respectively) [67]. Studies have been conducted that examined the effects of *CYP2C8* polymorphisms on the disposition of ibuprofen in humans (Table 6).

In a healthy volunteer study, Spanish Caucasians were administered a single dose of ibuprofen 400 mg [68]. In order to minimize the potential confounding of *CYP2C9* genotype on ibuprofen pharmacokinetics, subjects with the *CYP2C9*3/*3* genotype were excluded from the study. R-ibuprofen clearance was significantly 1.7-fold and 1.6-fold lower in *CYP2C8*3* homozygotes and heterozygotes, respectively, compared with wild-type homozygotes ($p = 0.03$). R-ibuprofen half-life was also significantly longer in *CYP2C8*3* homozygotes (9 h) and heterozygotes (4.2 h) compared with *CYP2C8*1* homozygotes (2 h, $p < 0.025$). These data suggest that the *CYP2C8*3* genotype is associated with decreased R-ibuprofen metabolism. However, 13 of the 16 individuals who carried a *CYP2C8*3* allele were also carriers of at least one copy of the *CYP2C9*2* allele, therefore, it is difficult to draw definitive conclusions regarding the relative contributions of *CYP2C8*3* versus *CYP2C9*2* on interindividual variability in R-ibuprofen metabolism.

In another healthy volunteer study, Spanish Caucasian individuals were administered a single dose of ibuprofen 400 mg [69]. *CYP2C8*3* homozygotes had approximately ninefold lower R-ibuprofen clearance and S-ibuprofen clearance than wild-type homozygotes. Of note, the *CYP2C9*2* allele was associated with ibuprofen pharmacokinetics only in individuals who also carried the *CYP2C8*3* allele. In regards to the enantiospecific clearance of ibuprofen, a modest genotype effect was observed, with the *CYP2C8*3* allele being associated with reduced R-ibuprofen clearance, and both the *CYP2C8*3* and *CYP2C9*3* alleles being associated with reduced S-ibuprofen clearance. In contrast to these findings, a healthy volunteer bioequivalence study of single-dose ibuprofen 600 mg showed 24% higher clearance of R-ibuprofen in subjects with the *CYP2C8*1/*3* genotype compared with wild-type homozygotes [70]. Given these conflicting findings, controversy exists regarding the role of *CYP2C8* and *CYP2C9* polymorphisms in ibuprofen metabolism. Potential explanations for the discrepancies between studies include differences in sample size, differences in *CYP2C8* and *CYP2C9* genotype combinations, linkage between the *CYP2C8*3* and *CYP2C9*2* polymorphisms, small number of *CYP2C8*3* homozygotes evaluated in most studies, lack of control for body weight in some studies, and differences in the extent of conversion of R-ibuprofen to S-ibuprofen *in vivo*.

Diclofenac

Diclofenac is a phenylacetic acid NSAID that is metabolized by CYP2C9 to the major metabolite 4-hydroxydiclofenac, and by CYP2C8, CYP3A4 and CYP2C19 to the minor metabolite, 5-hydroxydiclofenac [62,71,72]. Diclofenac is also glucuronidated by UGT2B7 to diclofenac acyl glucuronide, which is subsequently metabolized by CYP2C8 to 4-hydroxydiclofenac acyl glucuronide [62,71,72]. Dorado and colleagues sought to determine the impact of *CYP2C8* polymorphisms on diclofenac metabolism, with a particular focus on the 5-hydroxylation pathway [73]. The investigators analyzed data from healthy Spanish volunteers who had previously participated in a diclofenac *CYP2C9* pharmacogenetic study. The subjects had received a single dose of enteric-coated diclofenac 50 mg followed by an 8 h urine collection for evaluation of diclofenac and its metabolites. In this analysis, the study population was genotyped for the *CYP2C8*2*, **3* and **4* alleles. The mean urinary ratio of diclofenac:5-hydroxydiclofenac was significantly higher in carriers of the *CYP2C8*3* or

*CYP2C8*4* alleles compared with wild-type homozygotes. However, there was substantial overlap in the urinary ratios between genotype groups and plasma concentrations of diclofenac and its metabolites were not reported. As such, definitive conclusions regarding the impact of *CYP2C8* polymorphisms on diclofenac metabolism cannot be drawn from this study. Considering that only 65% of diclofenac and its metabolites are renally eliminated, with biliary excretion accounting for the other 35%, it is likely that other polymorphisms, or non-genetic factors, may contribute to diclofenac metabolism and excretion [74].

Diclofenac has been associated with rare, but serious, hepatotoxicity [75]. It is hypothesized that the 5-hydroxydiclofenac metabolic pathway or the UGT2B7 glucuronidation pathway may play a role in diclofenac adduct formation, which may subsequently contribute to hepatotoxicity [72]. Aithal and colleagues previously demonstrated that the *CYP2C9* genotype was not associated with the risk of diclofenac-induced hepatitis [76]. The investigators then went on to assess the role of *CYP2C8* polymorphisms on the risk of diclofenac hepatotoxicity [72]. The study included 24 case patients who had experienced diclofenac hepatotoxicity, and 160 control patients (i.e., those who had received diclofenac but who had not developed hepatotoxicity). This control group was comprised of 48 patients from a hospital setting and 112 patients from the community setting. All patients were genotyped for the *CYP2C8*3* and **4* alleles and haplotypes were assigned. The overall frequency of *CYP2C8* haplotypes differed significantly between cases and hospital controls ($p = 0.04$). Case patients who carried the *CYP2C8*4* allele had a non-significant increased odds of hepatotoxicity compared with the hospital control group. In contrast, genes involved in the metabolism and biliary excretion (i.e., *UGT2B7* and *ABCC2*, respectively) of diclofenac were associated more strongly with diclofenac hepatotoxicity. Thus, it appears that *CYP2C8* polymorphisms are not the strongest predictors of diclofenac hepatic adverse events in patients.

Tenoxicam

Tenoxicam is an NSAID that is available in Europe and Canada. It is extensively metabolized by CYP2C9 and possibly to a lesser extent by CYP2C8 [62,77]. Peiro and colleagues sought to determine if polymorphic *CYP2C9* and *CYP2C8* alleles influence variability in tenoxicam pharmacokinetics [77]. In this cohort of Spanish healthy volunteers, *CYP2C8* polymorphisms (**2*, **3* and **4*) were not significantly associated with the pharmacokinetics of a single 20 mg dose of tenoxicam. However, significant increases in tenoxicam AUC and elimination half-life were observed for *CYP2C9*3* carriers compared with noncarriers. Although the sample size of this study was small, these data suggest that CYP2C9, rather than CYP2C8, is the principal determinant of tenoxicam pharmacokinetics in humans.

Effects of genotype on NSAID-related bleeding

Studies have also been conducted evaluating the association between *CYP2C8* genotype and NSAID-induced adverse effects (e.g., gastrointestinal bleeding) and NSAID-induced protective effects (e.g., decreased colorectal cancer risk). Acute gastrointestinal bleeding is one of the most common adverse effects of NSAID therapy. Previously, *CYP2C9* genetic variation, namely *CYP2C9*2*, was associated with an increased risk of gastrointestinal bleeding in patients receiving NSAID therapy [78]. Given that *CYP2C9*2* is in partial linkage disequilibrium with *CYP2C8*3*, and many NSAIDs are substrates for both enzymes, Blanco and colleagues set out to determine whether *CYP2C9* and *CYP2C8* polymorphisms were associated with gastrointestinal bleeding in a cross- sectional study of NSAID users ($n = 134$ bleeding cases, $n = 177$ nonbleeding controls) [79]. The use of a number of different NSAIDs was observed in this study, some of which have not been documented to be CYP2C8 substrates. Nonetheless, the frequencies of the *CYP2C8*3* and C*YP2C9*2* alleles were higher in NSAID users who experienced a bleed versus those that did not experience a bleed (*CYP2C8*3*, odds ratio: 3.4, $p < 0.002$; *CYP2C9*2*, odds ratio: 2.7, $p = 0.013$). In multivariable regression

analysis, significant predictors of NSAID-induced bleeding were *CYP2C8*3* genotype and drinking habits. Further analysis of the data revealed that the highest bleeding risk was in patients who possessed both the variant *CYP2C8*3* and *CYP2C9*2* alleles. The authors hypothesized that these polymorphisms conferred an increased risk of gastrointestinal bleeding due to decreased metabolic clearance, and increased plasma concentrations of NSAIDs. Given the limitations of this study (e.g., case–control design, small sample size, multiple NSAIDs included – some of which are metabolized by multiple CYP isoforms, small number of *CYP2C8*3* homozygotes, and lack of pharmacokinetic correlates), these findings merit replication in additional populations. In regards to protective effects, NSAIDs (i.e., aspirin and ibuprofen) have been associated with a reduction in the risk of colorectal cancer. McGreavey and colleagues hypothesized that individuals who possessed variant *CYP2C8* or *CYP2C9* alleles would have decreased NSAID metabolism, which may lead to an enhanced protective effect from these agents [80]. They evaluated this hypothesis in a case–control study of 478 patients with colorectal cancer and 733 controls. NSAID use was associated with a significant reduction in the risk of colorectal cancer. However, the *CYP2C8*3, CYP2C9*2* and *CYP2C9*3* alleles did not modify the protective effects of NSAIDs in this population.

In summary, available data suggest that *CYP2C8* polymorphisms may contribute to interindividual variability in the pharmacokinetics and risk of adverse events of certain NSAIDs, namely ibuprofen and possibly diclofenac. However, given the conflicting genetic associations observed in these studies, particularly for ibuprofen, definitive conclusions cannot be made at this time. Futhermore, future NSAID *CYP2C8* pharmacogenetic studies should include well-characterized groups in regards to the *CYP2C8* and *CYP2C9* alleles. Additionally, studies are needed to determine if the observed decreased metabolism of ibuprofen and diclofenac in carriers of polymorphic *CYP2C8* alleles is associated with differences in clinical response to these agents. Lastly, while many NSAIDs are known to be CYP2C9 substrates, the contribution of CYP2C8 metabolism has not been elucidated for many agents (e.g., naproxen, piroxicam and celecoxib) [62]. Given the high sequence homology between the two enzymes, it is possible that CYP2C8 contributes to the metabolism of some of these substrates. Additional *in vitro* studies are needed to assess the contribution of CYP2C8 versus CYP2C9 to the metabolism of clinically available NSAIDs.

Cancer drugs

Paclitaxel is a chemotherapeutic agent that is used in the treatment of solid tumors, particularly breast, lung and ovarian cancer. CYP2C8 is the principal enzyme that catalyzes the formation of the major metabolite, 6α-hydroxypaclitaxel [81]. CYP3A4 and CYP3A5 have also been shown to contribute to the metabolism of paclitaxel to a lesser extent [82]. Given paclitaxel's affinity for CYP2C8, it has been used as the primary probe in studies examining the effects of *CYP2C8* polymorphisms on substrate disposition *in vitro*. These studies have demonstrated a significant reduction in paclitaxel metabolism associated with the *CYP2C8*3* allele, and a modest reduction in paclitaxel metabolism with the *CYP2C8*4* allele [12,16,17]. It is well recognized that a high degree of inter-individual variability exists in paclitaxel clearance [83]. Consequently, a number of clinical pharmacogenomic studies have been conducted to determine if *CYP2C8* polymorphisms, namely *CYP2C8*3*, explain interindividual variability in paclitaxel disposition in cancer patients (Table 7).

Henningsson and colleagues considered the influence of *CYP2C8* polymorphisms on high-dose paclitaxel pharmacokinetics in a retrospective study of 97 Caucasian patients with breast, ovarian or esophageal cancer [84]. The *CYP2C8*3* allele was not significantly associated with paclitaxel clearance. Additional genetic analysis revealed that polymorphisms in *CYP3A4*, *CYP3A5* and the *ABCB1* drug transporter gene were also not associated with paclitaxel pharmacokinetics. In another study, Marsh and colleagues evaluated the association between

CYP2C8 polymorphisms and paclitaxel pharmacokinetics and progression-free survival in 93 patients with breast cancer [85]. *CYP2C8*3* and *CYP2C8*4* alleles were not significantly associated with paclitaxel clearance or treatment outcomes. Additionally, polymorphisms in the *CYP3A4*, *CYP3A5*, *CYP1B1*, *ABCB1* and *ABCG2* genes were not significantly associated with paclitaxel clearance. Marsh and colleagues then went on to study the influence of 27 polymorphisms in 16 candidate genes on paclitaxel and docetaxel (both in combination with carboplatin) treatment outcomes and toxicity in a retrospective analysis of 914 patients in the Scottish Randomized Trial in Ovarian Cancer [86]. *CYP2C8* polymorphisms were not significantly associated with paclitaxel or docetaxel progression-free survival or toxicity in this retrospective analysis. Other groups set out to determine the influence of polymorphic *CYP2C8* alleles on paclitaxel disposition and outcomes in Japanese cancer patients. However, no polymorphic *CYP2C8*2* or **3* alleles were found in their respective populations [87–89]. Thus, these polymorphisms are unlikely to be the causative factors to explain interindividual variability in paclitaxel pharmacokinetics or response in Japanese patients.

Along these lines, Saito and colleagues set out to determine *CYP2C8* haplotype structure in a Japanese population (n = 437), and to determine the association between *CYP2C8* haplotypes and paclitaxel pharmacokinetics in 199 Japanese cancer patients [14]. The investigators found nonsynonymous *CYP2C8* polymorphisms to be rare, and focused their analysis on 40 haplotypes that contained only synonymous polymorphisms. Haplotypes were classified into six groups (**IA*, **IB*, **ID*, **IE*, **IG* and **IJ*). The pharmacokinetics of paclitaxel and paclitaxel metabolites (major, 6α-hydroxypaclitaxel; minor, 3′-*p*-hydroxypaclitaxel and 3′-*p*-dihydroxypaclitaxel) were then compared between haplotype groups. The 3-*p*-hydroxypaclitaxel median AUC was 2.5-fold higher, and the 3-*p*-hydroxypaclitaxel to paclitaxel AUC ratio was 64% higher, in carriers of the **IG* group haplotype compared with noncarriers of the **IG* group haplotype. CYP3A4 is the primary enzyme responsible for the metabolism of paclitaxel to 3-*p*-hydroxypaclitaxel, and CYP2C8 is responsible for the subsequent conversion of 3-*p*-hydroxypaclitaxel to 3′-*p*-dihydroxypaclitaxel. The investigators reported that the observed pharmacokinetic differences of 3′-*p*-hydroxypaclitaxel were not due to differences in polymorphic *CYP3A4* alleles between the *CYP2C8* diplotype groups. The authors hypothesized that the **IG* group haplotype, which is comprised of intronic polymorphisms (mainly IVS3–21T>A and IVS4+151G>A), confers reduced CYP2C8 activity. However, no significant associations were observed between the *CYP2C8 *IG* group haplotype and paclitaxel or 6-hydroxypaclitaxel pharmacokinetics. It is unclear why the **IG* haplotype was not associated with 6-hydroxypaclitaxel pharmacokinetics given that CYP2C8 is the principal enzyme responsible for the formation of this metabolite. Nonetheless, the role of the *CYP2C8*IG* haplotype in paclitaxel pharmacokinetics, clinical response and toxicity merits further analysis in additional studies, particularly in Asian populations.

More recently, Green and colleagues evaluated the role of *CYP2C8*, *CYP3A4* and *ABCB1* polymorphisms on paclitaxel pharmacokinetics and toxicity in 38 Caucasian ovarian cancer patients [90]. *CYP2C8*3* heterozygotes (n = 2) had a 55% lower clearance than *CYP2C8* wild-type homozygotes, but these results were observed only in patients who were *ABCB1* 2677G/T heterozygotes. In multivariable regression analysis, both *CYP2C8*3* and *ABCB1* 2677G/T were modest predictors of paclitaxel clearance (p = 0.076 for both factors). In terms of toxicity, patients with the *CYP2C8*1/*3* genotype had a higher risk of motor neuropathy and hematological toxicities.

When evaluated together, most studies did not find an association between the *CYP2C8*3* allele and paclitaxel pharmacokinetics. Discrepancies between the data could be due to inadequate study sample sizes to assess these genetic effects, different paclitaxel doses and infusion times, and the infrequency of the *CYP2C8*3* allele in Asian patients. Furthermore, paclitaxel is a substrate for P-glycoprotein; therefore, differences in the frequencies of

polymorphic *ABCB1* alleles between *CYP2C8* genotype groups may have potentially confounded the results between studies. Recent *in vitro* data suggest that common *CYP2C8* haplotypes are associated with altered paclitaxel 6α-hydroxylation [13]. Specifically, haplotype B was associated with increased paclitaxel metabolism, while haplotype C was associated with decreased paclitaxel metabolism *in vitro*. Whether these haplotypes explain inter-individual variability in paclitaxel pharmacokinetics in humans has yet to be determined. In the future, pharmacokinetic studies that include patient groups that are well-characterized for pertinent population-specific *CYP2C8* and *ABCB1* haplotypes may help elucidate the role of genetic polymorphisms on interindividual variability in paclitaxel pharmacokinetics and clinical response.

Antimalarial drugs

Amodiaquine

Amodiaquine is an antimalarial drug that is used as monotherapy, or in combination therapy, in many countries, particularly Africa. Amodiaquine undergoes CYP2C8-mediated metabolism to *N*-desethylamodiaquine, which has a longer half-life than the parent drug (9–18 days versus 5.2 h) [91]. Other enzymes that have been suggested to contribute a small extent to amodiaquine metabolism include CYP3A4 and extrahepatic CYP1A1 and CYP2B1 [91, 92]. One study evaluated the effects of *CYP2C8* polymorphisms on the efficacy and toxicity of amodiaquine monotherapy in a group of patients (n = 275) infected with malaria in West Africa [93]. The *CYP2C8*2* allele was common in this population (11.5%) but was not associated with malaria treatment outcomes compared with wild-type homozygotes. In terms of adverse events, an increased incidence of self-reported abdominal pain was observed in *CYP2C8*2* carriers compared with wild-type homozygotes (52 vs 30%, respectively). In this same report, amodiaquine metabolism was evaluated in recombinant CYP2C8 proteins and showed threefold and sixfold lower intrinsic clearance higher K_m in *CYP2C8*2* compared with *CYP2C8*1*. The *CYP2C8*3* enzyme also demonstrated decreased activity compared with *CYP2C8*1*. Another study evaluated the pharmacokinetics of amodiaquine, in combination with artesunate, in 103 Ghanian children [94]. In this population pharmacokinetic analysis, the *CYP2C8*2* allele was associated with lower plasma concentrations of *N*-desethylamodiaquine compared with wild-type homozygotes; however, this difference was not statistically significant. *CYP2C8* genotype was not associated with efficacy or toxicity in this study. Together, these two clinical studies suggest that *CYP2C8*2* is not a major determinant of amodiaquine efficacy or toxicity in adults or children. This is hypothesized to be due to the fact that both the parent drug and metabolite are pharmacologically active. *In vitro* data suggest that the *CYP2C8*3* allele is associated with marked reductions in amodiaquine metabolism [93]. Given that *CYP2C8*3* is more prevalent in Caucasians, and *CYP2C8*2* is more prevalent in Africans, the *in vitro* finding of marked reduction in amodiaquine metabolism with the *CYP2C8*3* allele is most relevant for Caucasian populations. Additional studies are needed to more comprehensively elucidate the effects of *CYP2C8*2* and *CYP2C8*3* alleles on pharmacokinetics, efficacy and toxicity of amodiaquine in both African and Caucasian populations.

Chloroquine

Chloroquine is another agent used in the prevention and treatment of malaria. Chloroquine is metabolized to desethylchloroquine and bisdesethylchloroquine, both of which are pharmacologically active metabolites. *In vitro*, CYP2C8, CYP3A4 and CYP3A5 were significant contributors to chloroquine metabolism [95]. The influence of *CYP2C8* polymorphisms on chloroquine pharmacokinetics and pharmacodynamics in humans has yet to be determined.

Other CYP2C8 substrates

A diverse number of other drugs have been implicated as CYP2C8 substrates through *in vitro* studies. However, to our knowledge, clinical studies evaluating the effects of polymorphic *CYP2C8* alleles on drug disposition or response of these agents have not been published. Brief descriptions of these drugs and relevant available *in vitro CYP2C8* pharmacogenetic data are provided below.

All-*trans*-retinoic acid

All-*trans*-retinoic acid (ATRA), or tretinoin, is the acid form of vitamin A and is used in the treatment of acute promyelocytic leukemia. It is also used topically in the treatment of acne. *In vitro* data suggest that CYP2C8 is a major contributor to the formation of 4-hydroxy-ATRA, which is the first step in the termination of ATRA action. Significant variability exists in the pharmacokinetics of ATRA in cancer patients [96]. To our knowledge, the extent to which *CYP2C8* polymorphisms influence ATRA metabolism and therapeutic efficacy or toxicity has yet to be determined in clinical studies.

Loperamide

Loperamide is a μ-opioid receptor agonist that is used in the treatment of diarrhea. In human liver microsomes, loperamide was shown to be metabolized by CYP2C8, CYP3A4, CYP2B6 and CYP2D6 [97]. In this study, CYP2C8 and CYP3A4 played the most important roles in loperamide *N*-demethylation [97]. In a healthy volunteer drug–drug interaction study, gemfibrozil increased loperamide AUC and C_{max} 2.2-fold and 1.6-fold, respectively [98]. To our knowledge, the impact of *CYP2C8* polymorphisms on loperamide pharmacokinetic has not yet been published.

Methadone

Methadone is an opioid receptor antagonist that is used in the treatment of chronic pain and opioid dependence. *In vitro*, CYP2C8 was shown to metabolize both the R- and S-enantiomers of methadone, with a greater effect on the R-enantiomer [99]. Considering that the R-enantiomer is the more pharmacologically active form *in vivo*, the potential influence of *CYP2C8* polymorphisms on the metabolism of the R-enantiomer may be clinically significant and warrants further study.

Morphine

Morphine is an opioid analgesic that is glucuronidated to morphine-3-glucuronide and morphine-6-glucuronide. In addition, morphine undergoes *N*-demethylation to normorphine. In human liver microsomes, CYP3A4 was found to contribute a major extent, and CYP2C8 a minor extent, to normorphine formation [100]. Given that the *N*-demethylation pathway is a minor contributor to morphine metabolism, and CYP2C8 contributes only a small extent, it is unlikely that polymorphisms in *CYP2C8* would explain a significant amount of the variability in morphine pharmacokinetics or pharmacodynamics.

Amiodarone

Amiodarone is an antiarrhythmic agent used in the treatment of supraventricular and ventricular arrhythmias. Amiodarone is metabolized by CYP2C8 to desethylamiodarone, which is a pharmacologically active metabolite [101]. An *in vitro* study examining the effects of the *CYP2C8*1*, *CYP2C8*3* and *CYP2C8* P404A alleles on amiodarone metabolism was carried out in Hep G2 cells [102]. *CYP2C8*3* was not associated with a reduction in amiodarone metabolism in this study. Instead, the study found that *CYP2C8* 404A was associated with 48% lower amiodarone intrinsic clearance compared with the wild-type allele. This was

hypothesized to be due to decreased expression of the protein compared with wild-type. The implications of this finding on the pharmacokinetics and pharmacodynamics of amiodarone in patients remains to be determined. However, considering that the 404A allele has only been identified at low frequency in Japanese individuals, it is unlikely that it will have broad clinical effects in patients treated with amiodarone [17].

Zopiclone

Zopiclone is a nonbenzodiazepine sedative hypnotic that is used in the treatment of insomnia. Zopiclone is extensively hepatically metabolized to *N*-oxide-zopiclone, which has low pharmacologic activity, and *N*-desmethyl-zopiclone, which is pharmacologically inactive. An *in vitro* study showed that CYP3A4 was the major enzyme involved in the metabolism of zopiclone to both metabolites, and that CYP2C8 contributed to the metabolism of *N*-desmethyl-zopiclone [103]. However, in a healthy volunteer drug–drug interaction study, gemfibrozil did not significantly increase the plasma concentrations of zopiclone [104]. Thus, *in vivo*, it appears that CYP2C8 contributes a minor extent to zopiclone metabolism and *CYP2C8* polymorphisms are unlikely to have clinically significant effects on zopiclone pharmacokinetics.

Tazarotenic acid

Tazarotenic acid (tazarotene) is used in the topical treatment of psoriasis and acne. It is a retinoid prodrug that is converted to its active metabolite tazarotenic acid, which is subsequently converted to an inactive sulfoxide metabolite. In human liver microsomes, the metabolism of tazarotenic acid was mediated, in part by CYP2C8 [105]. Topical administration results in low plasma concentrations of tazarotenic acid. Thus it is unlikely that *CYP2C8* polymorphisms would contribute a significant extent to variability in the pharmacokinetics of tazarotenic acid when it is used in topical administration [106]. However, *CYP2C8* polymorphisms may be relevant to the pharmacokinetics of an oral formulation of tazarotenic acid, which is under development for the treatment of psoriasis.

Verapamil

Verapamil is an L-type calcium channel blocker used in the treatment of cardiovascular conditions such as hypertension, angina and arrhythmias. Verapamil is administered as a racemic mixture of R- and S-enantiomers, with the S-enantiomer being the more pharmacologically active form [107]. Additionally, the S-enantiomer undergoes a quicker rate of hepatic first pass metabolism than the R-enantiomer [108]. *In vitro* data have demonstrated that CYP2C8 contributes to the metabolism of both R-verapamil and S-verapamil, and further contributes to the metabolism of norverpamil, one of the primary metabolites [109]. The extent to which *CYP2C8* polymorphisms influence the pharmacokinetics and pharmacodynamics of verapamil in humans has not been assessed.

Other agents

In vitro studies have also demonstrated that CYP2C8 has a minor role in the metabolism of other substrates such as: diltiazem, carbamazepine, cyclophosphamide, dapsone, ifosfamide and torsemide [110–114]. To our knowledge the influence of *CYP2C8* polymorphisms has not been studied for these drugs. However, given that CYP2C8 plays only a minor role in the metabolism of these substrates, it is unlikely that *CYP2C8* polymorphisms would have clinically relevant effects for these particular drugs.

Conclusion

CYP2C8 has emerged as an important enzyme that is responsible for the metabolism of a diverse group of substrates in humans. Available data suggest that genetic variation in

CYP2C8 alters the *in vivo* disposition of many commonly used drugs. In clinical studies, the polymorphic *CYP2C8*3* allele is associated with increased metabolism of thiazolidinediones and repaglinide. By contrast, all but one study showed no effect of the *CYP2C8*3* allele on paclitaxel pharmacokinetics. At this time, the data regarding the impact of the *CYP2C8*3* allele on ibuprofen metabolism are conflicting and inconclusive. The *CYP2C8*2* allele, which is common in Africans, has not been associated with altered pharmacokinetics of the substrate amodiaquine in humans. Unfortunately, data regarding the effects of *CYP2C8*4* on substrate pharmacokinetics are unclear, as too few subjects with this variant genotype were included in clinical studies. More recently, novel *CYP2C8* haplotypes in Caucasians and Japanese patients have been identified, and these have been associated with altered pharmacokinetics of repaglinide and paclitaxel.

Future perspective

While the CYP2C8 clinical pharmacogenetic data are intriguing, there are several issues that merit consideration in future clinical studies. First, future *CYP2C8* pharmacogenetic–pharmacokinetic studies should conduct *a priori* sample size calculations based on the differences that would like to be detected between genotype groups. In turn, subjects should be prospectively stratified and enrolled based on these *CYP2C8* genotype numbers. This will ensure suitable power to detect potential pharmacokinetic differences between genotype groups. While some investigators have done this, in most situations, this has not been the case. This is likely due to the fact that prospectively-stratified genotype panel studies are difficult to conduct because it is often challenging to find a sufficient number of subjects who possess *CYP2C8* homozygous variant genotypes. Second, population-specific studies are needed to assess the effects of certain *CYP2C8* alleles on substrate pharmacokinetics. A good example of this is *CYP2C8*2*. To date, few studies, with the exception of amodiaquine, have attempted to elucidate the role of this polymorphism on substrate pharmacokinetics in individuals of African descent. Along these lines, the enrollment of patients with the *CYP2C8*4* allele has been too few in most studies to make meaningful conclusions regarding the role of this polymorphism on substrate pharmacokinetics in humans. Third, future studies should consider characterizing *CYP2C8* haplotypes rather than focusing on single polymorphisms, as has been the case in most studies to date. Fourth, for drugs that are metabolized by both *CYP2C8* and *CYP2C9*, polymorphisms within both of these genes should be evaluated in order to provide a more comprehensive assessment of their relative contribution to drug disposition and response. Fifth, human *CYP2C8* is transcriptionally regulated by nuclear receptors. The extent to which polymorphisms in nuclear receptor genes influence the downstream transcriptional regulation of *CYP2C8* has not been assessed. Future clinical studies examining polymorphisms in these regulator genes and their association with CYP2C8 substrate pharmacokinetics are needed. In addition, many of the CYP2C8 substrates discussed in this review are also substrates for drug transporters. In many cases, drug-transporter polymorphisms influence the pharmacokinetics of the substrate (e.g., *SLCO1B1*–repaglinde; *ABCB1*–paclitaxel). As such, future pharmacokinetic studies should carefully consider the confounding influence of these drug transporter polymorphisms when evaluating *CYP2C8* genetics. In addition, future analysis of studies should include important nongenetic covariates, such as body weight, to improve the statistical power of genotype comparisons. Lastly, for drugs in which the pharmacokinetics are affected by *CYP2C8* genotype (e.g., repaglinide, rosiglitazone and pioglitazone), pharmacodynamic studies are needed in relevant patient populations to determine if CYP2C8-mediated differences in pharmacokinetics translate into meaningful inter-individual differences in pharmacodynamics.

Executive summary

CYP2C8 enzyme

- CYP2C8 plays an important role in the metabolism of a diverse number of exogenous and endogenous compounds.

CYP2C8 gene & polymorphisms

- Common nonsynonymous polymorphisms exist in the *CYP2C8* gene and the *CYP2C8*3* and *CYP2C8*2* polymorphisms have been studied most often in clinical investigations.
- The frequency of polymorphic *CYP2C8* alleles differs by race and ethnicity. *CYP2C8*2* is common in Blacks, but is rare in Caucasians and Asians. In contrast, *CYP2C8*3* is common in Caucasians, but is rare in Blacks or Asians.
- *In vitro*, the *CYP2C8*2* and **3* alleles have been associated with decreased metabolism of paclitaxel and arachidonic acid.
- Clinical data suggest that the *CYP2C8*3* allele is associated with increased metabolism of rosiglitazone, pioglitazone and repaglinide; however, for other substrates (e.g., ibuprofen and paclitaxel), the data regarding the association between *CYP2C8* polymorphisms and substrate pharmacokinetics are conflicting.

Antidiabetic agents

- In clinical studies, the *CYP2C8*3* allele is associated with increased metabolism, and decreased plasma concentrations, of the oral antidiabetic drugs rosiglitazone, pioglitazone and repaglinide.

HMG-CoA reductase inhibitors

- CYP2C8 plays a major role in the metabolism of cerivastatin, and a minor role in the metabolism of fluvastatin and simvastatin acid.
- To date, data suggest that *CYP2C8* polymorphisms do not influence fluvastatin pharmacokinetics in healthy volunteers.

NSAIDs

- The *CYP2C8*3* allele has been associated with decreased ibuprofen metabolism in two studies and increased ibuprofen metabolism in one study. Thus, the data regarding the influence of the *CYP2C8*3* allele on the metabolism of ibuprofen are inconclusive at this time.
- One pharmacokinetic study and one case–control study suggest *CYP2C8* polymorphisms may influence diclofenac metabolism and risk of hepatotoxicity, respectively. However, these data merit replication in additional populations.

Cancer drugs

- Paclitaxel is an *in vitro* probe drug for CYP2C8 activity; however, most clinical studies have reported no association between *CYP2C8* polymorphisms and paclitaxel pharmacokinetics or pharmacodynamics in cancer patients.

Antimalarial drugs

- The *CYP2C8*2* allele is not a significant predictor of the pharmacokinetics or clinical response of the antimalarial drug, amodiaquine, in African patients.

Bibliography

Papers of special note have been highlighted as:

▪ of interest

▪▪ of considerable interest

1 ▪▪. Totah RA, Rettie AE. Cytochrome P450 2C8: substrates, inhibitors, pharmacogenetics, and clinical relevance. Clin Pharmacol Ther 2005;77:341–352. [PubMed: 15900280]Comprehensive review of CYP2C8 substrates, inhibitors and pharmacogenetics

2. Evans WE, Relling MV. Moving towards individualized medicine with pharmacogenomics. Nature 2004;429:464–468. [PubMed: 15164072]

3. Klose TS, Blaisdell JA, Goldstein JA. Gene structure of *CYP2C8* and extrahepatic distribution of the human CYP2Cs. J Biochem Mol Toxicol 1999;13:289–295. [PubMed: 10487415]

4. Delozier TC, Kissling GE, Coulter SJ, et al. Detection of human CYP2C8, CYP2C9, and CYP2J2 in cardiovascular tissues. Drug Metab Dispos 2007;35:682–688. [PubMed: 17220242]

5. Schoch GA, Yano JK, Wester MR, Griffin KJ, Stout CD, Johnson EF. Structure of human microsomal cytochrome P450 2C8. Evidence for a peripheral fatty acid binding site. J Biol Chem 2004;279:9497–9503. [PubMed: 14676196]

6. Schoch GA, Yano JK, Sansen S, Dansette PM, Stout CD, Johnson EF. Determinants of cytochrome P450 2C8 substrate binding: structures of complexes with montelukast, troglitazone, felodipine, and 9-*cis*-retinoic acid. J Biol Chem 2008;283:17227–17237. [PubMed: 18413310]

7 ▪. Theken KN, Lee CR. Genetic variation in the cytochrome P450 epoxygenase pathway and cardiovascular disease risk. Pharmacogenomics 2007;8:1369–1383. [PubMed: 17979511] Comprehensive review of the influence of *CYP2C8* polymorphisms on arachidonic acid metabolism and clinical outcomes

8. Yasar U, Lundgren S, Eliasson E, et al. Linkage between the *CYP2C8* and *CYP2C9* genetic polymorphisms. Biochem Biophys Res Commun 2002;299:25–28. [PubMed: 12435384]

9. Johnson EF, Stout CD. Structural diversity of human xenobiotic-metabolizing cytochrome P450 monooxygenases. Biochem Biophys Res Commun 2005;338:331–336. [PubMed: 16157296]

10. Ferguson SS, Chen Y, LeCluyse EL, Negishi M, Goldstein JA. Human CYP2C8 is transcriptionally regulated by the nuclear receptors constitutive androstane receptor, pregnane X receptor, glucocorticoid receptor, and hepatic nuclear factor 4α. Mol Pharmacol 2005;68:747–757. [PubMed: 15933212]

11. Kojima K, Nagata K, Matsubara T, Yamazoe Y. Broad but distinct role of pregnane X receptor on the expression of individual cytochrome p450s in human hepatocytes. Drug Metab Pharmacokinet 2007;22:276–286. [PubMed: 17827782]

12. Bahadur N, Leathart JB, Mutch E, et al. *CYP2C8* polymorphisms in Caucasians and their relationship with paclitaxel 6α-hydroxylase activity in human liver microsomes. Biochem Pharmacol 2002;64:1579–1589. [PubMed: 12429347]

13 ▪. Rodriguez-Antona C, Niemi M, Backman JT, et al. Characterization of novel *CYP2C8* haplotypes and their contribution to paclitaxel and repaglinide metabolism. Pharmacogenomics J 2008;8:268–277. [PubMed: 17923851]Important study that characterized *CYP2C8* haplotypes and their functional significance in Caucasian individuals.

14 ▪. Saito Y, Katori N, Soyama A, et al. CYP2C8 haplotype structures and their influence on pharmacokinetics of paclitaxel in a Japanese population. *Pharmacogenet*. Genomics 2007;17:461–471.Important study that characterized *CYP2C8* haplotypes and their association with paclitaxel metabolism in Japanese cancer patients.

15 ▪. Speed WC, Kang SP, Tuck DP, Harris LN, Kidd KK. Global variation in *CYP2C8–CYP2C9* functional haplotypes. Pharmacogenomics J 2009;9(4):283–290. [PubMed: 19381162] Characterized *CYP2C8* and *CYP2C9* haplotypes in a large population of individuals from around the world.

16. Dai D, Zeldin DC, Blaisdell JA, et al. Polymorphisms in human *CYP2C8* decrease metabolism of the anticancer drug paclitaxel and arachidonic acid. Pharmacogenetics 2001;11:597–607. [PubMed: 11668219]

17. Soyama A, Saito Y, Hanioka N, et al. Non-synonymous single nucleotide alterations found in the *CYP2C8* gene result in reduced *in vitro* paclitaxel metabolism. Biol Pharm Bull 2001;24:1427–1430. [PubMed: 11767116]

18. Hichiya H, Tanaka-Kagawa T, Soyama A, et al. Functional characterization of five novel *CYP2C8* variants, G171S, R186X, R186G, K247R, and K383N, found in a Japanese population. Drug Metab Dispos 2005;33:630–636. [PubMed: 15716363]
19. Yki-Jarvinen H. Thiazolidinediones. N Engl J Med 2004;351:1106–1118. [PubMed: 15356308]
20. American Diabetes Association. Standards of medical care in diabetes – 2008. Diabetes Care 2008;31:S12–S54. [PubMed: 18165335]
21. Baldwin SJ, Clarke SE, Chenery RJ. Characterization of the cytochrome P450 enzymes involved in the *in vitro* metabolism of rosiglitazone. Br J Clin Pharmacol 1999;48:424–432. [PubMed: 10510156]
22. Jaakkola T, Laitila J, Neuvonen PJ, Backman JT. Pioglitazone is metabolised by CYP2C8 and CYP3A4 *in vitro*: potential for interactions with CYP2C8 inhibitors. Basic Clin Pharmacol Toxicol 2006;99:44–51. [PubMed: 16867170]
23. Yamazaki H, Shibata A, Suzuki M, et al. Oxidation of troglitazone to a quinone-type metabolite catalyzed by cytochrome P-450 2C8 and P-450 3A4 in human liver microsomes. Drug Metab Dispos 1999;27:1260–1266. [PubMed: 10534310]
24. Avandia Prescribing Information. GlaxoSmithKline (2007).
25. Actos Prescribing Information. Takeda Pharmaceuticals America, Inc. (2007)
26 ▪. Kirchheiner J, Thomas S, Bauer S, et al. Pharmacokinetics and pharmacodynamics of rosiglitazone in relation to *CYP2C8* genotype. Clin Pharmacol Ther 2006;80:657–667. [PubMed: 17178266]First study to show a significant association between *CYP2C8* polymorphisms and rosiglitazone pharmacokinetics.
27. Aquilante CL, Bushman LR, Knutsen SD, Burt LE, Rome LC, Kosmiski LA. Influence of *SLCO1B1* haplotype on rosiglitazone pharmacokinetics in healthy volunteers. Hum Genomics 2008;3(1):7–16. [PubMed: 19129086]
28 ▪. Tornio A, Niemi M, Neuvonen PJ, Backman JT. Trimethoprim and the *CYP2C8***3* allele have opposite effects on the pharmacokinetics of pioglitazone. Drug Metab Dispos 2008;36:73–80. [PubMed: 17913794]First study to show an association between *CYP2C8* polymorphisms and pioglitazone pharmacokinetics.
29. Hruska MW, Amico JA, Langaee TY, Ferrell RE, Fitzgerald SM, Frye RF. The effect of trimethoprim on CYP2C8 mediated rosiglitazone metabolism in human liver microsomes and healthy subjects. Br J Clin Pharmacol 2005;59:70–79. [PubMed: 15606443]
30. Pedersen RS, Damkier P, Brosen K. The effects of human *CYP2C8* genotype and fluvoxamine on the pharmacokinetics of rosiglitazone in healthy subjects. Br J Clin Pharmacol 2006;62:682–689. [PubMed: 16856883]
31. Aquilante CL. Pharmacogenetics of thiazolidinedione therapy. Pharmacogenomics 2007;8:917–931. [PubMed: 17716227]
32. Prandin Prescribing Information. Novo Nordisk, Inc. (2006)
33. Bidstrup TB, Bjornsdottir I, Sidelmann UG, Thomsen MS, Hansen KT. CYP2C8 and CYP3A4 are the principal enzymes involved in the human *in vitro* biotransformation of the insulin secretagogue repaglinide. Br J Clin Pharmacol 2003;56:305–314. [PubMed: 12919179]
34. Kajosaari LI, Laitila J, Neuvonen PJ, Backman JT. Metabolism of repaglinide by CYP2C8 and CYP3A4 *in vitro*: effect of fibrates and rifampicin. Basic Clin Pharmacol Toxicol 2005;97:249–256. [PubMed: 16176562]
35. Niemi M, Backman JT, Neuvonen M, Neuvonen PJ. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. Diabetologia 2003;46:347–351. [PubMed: 12687332]
36. Niemi M, Neuvonen PJ, Kivisto KT. The cytochrome P4503A4 inhibitor clarithromycin increases the plasma concentrations and effects of repaglinide. Clin Pharmacol Ther 2001;70:58–65. [PubMed: 11452245]
37 ▪. Niemi M, Leathart JB, Neuvonen M, Backman JT, Daly AK, Neuvonen PJ. Polymorphism in *CYP2C8* is associated with reduced plasma concentrations of repaglinide. Clin Pharmacol Ther 2003;74:380–387. [PubMed: 14534525]First study to show an association between *CYP2C8* polymorphisms and repaglinide pharmacokinetics.

38. Niemi M, Backman JT, Kajosaari LI, et al. Polymorphic organic anion transporting polypeptide 1B1 is a major determinant of repaglinide pharmacokinetics. Clin Pharmacol Ther 2005;77:468–478. [PubMed: 15961978]
39. Kajosaari LI, Niemi M, Neuvonen M, Laitila J, Neuvonen PJ, Backman JT. Cyclosporine markedly raises the plasma concentrations of repaglinide. Clin Pharmacol Ther 2005;78:388–399. [PubMed: 16198658]
40. Tornio A, Niemi M, Neuvonen M, et al. The effect of gemfibrozil on repaglinide pharmacokinetics persists for at least 12 h after the dose: evidence for mechanism-based inhibition of *CYP2C8 in vivo*. Clin Pharmacol Ther 2008;84:403–411. [PubMed: 18388877]
41. Bidstrup TB, Damkier P, Olsen AK, Ekblom M, Karlsson A, Brosen K. The impact of *CYP2C8* polymorphism and grapefruit juice on the pharmacokinetics of repaglinide. Br J Clin Pharmacol 2006;61:49–57. [PubMed: 16390351]
42. Muck W. Clinical pharmacokinetics of cerivastatin. Clin Pharmacokinet 2000;39:99–116. [PubMed: 10976657]
43. Wang JS, Neuvonen M, Wen X, Backman JT, Neuvonen PJ. Gemfibrozil inhibits CYP2C8-mediated cerivastatin metabolism in human liver microsomes. Drug Metab Dispos 2002;30:1352–1356. [PubMed: 12433802]
44. Lucas RA, Weathersby BB, Rocco VK, Pepper JM, Butler KL. Rhabdomyolysis associated with cerivastatin: six cases within 3 months at one hospital. Pharmacotherapy 2002;22:771–774. [PubMed: 12066968]
45. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006;97:C52–C60.
46. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. Ann Pharmacother 2001;35:1096–1107. [PubMed: 11573861]
47. Backman JT, Kyrklund C, Neuvonen M, Neuvonen PJ. Gemfibrozil greatly increases plasma concentrations of cerivastatin. Clin Pharmacol Ther 2002;72:685–691. [PubMed: 12496749]
48. Ishikawa C, Ozaki H, Nakajima T, et al. A frameshift variant of *CYP2C8* was identified in a patient who suffered from rhabdomyolysis after administration of cerivastatin. J Hum Genet 2004;49:582–585. [PubMed: 15365880]
49. Ozaki H, Ishikawa CT, Ishii T, et al. Clearance rates of cerivastatin metabolites in a patient with cerivastatin-induced rhabdomyolysis. J Clin Pharm Ther 2005;30:189–192. [PubMed: 15811174]
50. Scripture CD, Pieper JA. Clinical pharmacokinetics of fluvastatin. Clin Pharmacokinet 2001;40:263–281. [PubMed: 11368292]
51. Lescol Prescribing Information. Novartis Pharmaceuticals Corporation. (2006)
52. Spence JD, Munoz CE, Hendricks L, Latchinian L, Khouri HE. Pharmacokinetics of the combination of fluvastatin and gemfibrozil. Am J Cardiol 1995;76:A80–A83.
53. Kirchheiner J, Kudlicz D, Meisel C, et al. Influence of *CYP2C9* polymorphisms on the pharmacokinetics and cholesterol-lowering activity of (−)-3S,5R-fluvastatin and (+)-3R,5S-fluvastatin in healthy volunteers. Clin Pharmacol Ther 2003;74:186–194. [PubMed: 12891229]
54. Shitara Y, Sugiyama Y. Pharmacokinetic and pharmacodynamic alterations of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors: drug–drug interactions and interindividual differences in transporter and metabolic enzyme functions. Pharmacol Ther 2006;112:71–105. [PubMed: 16714062]
55. Prueksaritanont T, Ma B, Yu N. The human hepatic metabolism of simvastatin hydroxy acid is mediated primarily by CYP3A, and not CYP2D6. Br J Clin Pharmacol 2003;56:120–124. [PubMed: 12848784]
56. Crestor Prescribing Information. AstraZeneca Pharmaceticals (2009).
57. Cooper KJ, Martin PD, Dane AL, Warwick MJ, Schneck DW, Cantarini MV. The effect of fluconazole on the pharmacokinetics of rosuvastatin. Eur J Clin Pharmacol 2002;58:527–531. [PubMed: 12451430]
58. Link E, Parish S, Armitage J, et al. *SLCO1B1* variants and statin-induced myopathy – a genomewide study. N Engl J Med 2008;359:789–799. [PubMed: 18650507]
59. Chasman DI, Posada D, Subrahmanyan L, Cook NR, Stanton VP Jr, Ridker PM. Pharmacogenetic study of statin therapy and cholesterol reduction. JAMA 2004;291:2821–2827. [PubMed: 15199031]

60. Thompson JF, Man M, Johnson KJ, et al. An association study of 43 SNPs in 16 candidate genes with atorvastatin response. Pharmacogenomics J 2005;5:352–358. [PubMed: 16103896]
61. Wilke RA, Moore JH, Burmester JK. Relative impact of *CYP3A* genotype and concomitant medication on the severity of atorvastatin-induced muscle damage. Pharmacogenet Genomics 2005;15:415–421. [PubMed: 15900215]
62. Rodrigues AD. Impact of *CYP2C9* genotype on pharmacokinetics: are all cyclooxygenase inhibitors the same? Drug Metab Dispos 2005;33:1567–1575. [PubMed: 16118328]
63. Davies NM. Clinical pharmacokinetics of ibuprofen. The first 30 years. Clin Pharmacokinet 1998;34:101–154. [PubMed: 9515184]
64. Evans AM. Enantioselective pharmacodynamics and pharmacokinetics of chiral non-steroidal anti-inflammatory drugs. Eur J Clin Pharmacol 1992;42:237–256. [PubMed: 1577041]
65. Hamman MA, Thompson GA, Hall SD. Regioselective and stereoselective metabolism of ibuprofen by human cytochrome P450 2C. Biochem Pharmacol 1997;54:33–41. [PubMed: 9296349]
66. Chang SY, Li W, Traeger SC, et al. Confirmation that cytochrome P450 2C8 (CYP2C8) plays a minor role in (S)-(+)- and (R)-(−)-ibuprofen hydroxylation *in vitro*. Drug Metab Dispos 2008;36:2513–2522. [PubMed: 18787056]
67. Tornio A, Niemi M, Neuvonen PJ, Backman JT. Stereoselective interaction between the CYP2C8 inhibitor gemfibrozil and racemic ibuprofen. Eur J Clin Pharmacol 2007;63:463–469. [PubMed: 17333159]
68. Martinez C, Garcia-Martin E, Blanco G, Gamito FJ, Ladero JM, Agundez JA. The effect of the cytochrome P450 *CYP2C8* polymorphism on the disposition of (R)-ibuprofen enantiomer in healthy subjects. Br J Clin Pharmacol 2005;59:62–69. [PubMed: 15606441]
69. Garcia-Martin E, Martinez C, Tabares B, Frias J, Agundez JA. Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms. Clin Pharmacol Ther 2004;76:119–127. [PubMed: 15289789]
70. Lopez-Rodriguez R, Novalbos J, Gallego-Sandin S, et al. Influence of *CYP2C8* and *CYP2C9* polymorphisms on pharmacokinetic and pharmacodynamic parameters of racemic and enantiomeric forms of ibuprofen in healthy volunteers. Pharmacol Res 2008;58:77–84. [PubMed: 18694831]
71. Tang W. The metabolism of diclofenac – enzymology and toxicology perspectives. Curr Drug Metab 2003;4:319–329. [PubMed: 12871048]
72. Daly AK, Aithal GP, Leathart JB, Swainsbury RA, Dang TS, Day CP. Genetic susceptibility to diclofenac-induced hepatotoxicity: contribution of *UGT2B7*, *CYP2C8*, and *ABCC2* genotypes. Gastroenterology 2007;132:272–281. [PubMed: 17241877]
73. Dorado P, Cavaco I, Caceres MC, Piedade R, Ribeiro V, Llerena A. Relationship between *CYP2C8* genotypes and diclofenac 5-hydroxylation in healthy Spanish volunteers. Eur J Clin Pharmacol 2008;64:967–970. [PubMed: 18548238]
74. Voltaren Prescribing Information. Novartis Pharmaceuticals Corporation (2009).
75. de Abajo FJ, Montero D, Madurga M, Garcia Rodriguez LA. Acute and clinically relevant drug-induced liver injury: a population based case–control study. Br J Clin Pharmacol 2004;58:71–80. [PubMed: 15206996]
76. Aithal GP, Day CP, Leathart JB, Daly AK. Relationship of polymorphism in *CYP2C9* to genetic susceptibility to diclofenac-induced hepatitis. Pharmacogenetics 2000;10:511–518. [PubMed: 10975605]
77. Peiro AM, Novalbos J, Zapater P, et al. Pharmacogenetic relevance of the *CYP2C9*3* allele in a tenoxicam bioequivalence study performed on Spaniards. Pharmacol Res 2009;59:62–68. [PubMed: 18992346]
78. Martinez C, Blanco G, Ladero JM, et al. Genetic predisposition to acute gastrointestinal bleeding after NSAIDs use. Br J Pharmacol 2004;141:205–208. [PubMed: 14707031]
79. Blanco G, Martinez C, Ladero JM, et al. Interaction of *CYP2C8* and *CYP2C9* genotypes modifies the risk for nonsteroidal anti-inflammatory drugs-related acute gastrointestinal bleeding. Pharmacogenet Genomics 2008;18:37–43. [PubMed: 18216720]
80. McGreavey LE, Turner F, Smith G, et al. No evidence that polymorphisms in *CYP2C8*, *CYP2C9*, *UGT1A6*, *PPARδ* and *PPARγ* act as modifiers of the protective effect of regular NSAID use on the risk of colorectal carcinoma. Pharmacogenet Genomics 2005;15:713–721. [PubMed: 16141797]

81. Rahman A, Korzekwa KR, Grogan J, Gonzalez FJ, Harris JW. Selective biotransformation of taxol to 6 α-hydroxytaxol by human cytochrome P450 2C8. Cancer Res 1994;54:5543–5546. [PubMed: 7923194]
82. Harris JW, Rahman A, Kim BR, Guengerich FP, Collins JM. Metabolism of taxol by human hepatic microsomes and liver slices: participation of cytochrome P450 3A4 and an unknown P450 enzyme. Cancer Res 1994;54:4026–4035. [PubMed: 7913410]
83. Somlo G, Doroshow JH, Synold T, et al. High-dose paclitaxel in combination with doxorubicin, cyclophosphamide and peripheral blood progenitor cell rescue in patients with high-risk primary and responding metastatic breast carcinoma: toxicity profile, relationship to paclitaxel pharmacokinetics and short-term outcome. Br J Cancer 2001;84:1591–1598. [PubMed: 11401310]
84. Henningsson A, Marsh S, Loos WJ, et al. Association of *CYP2C8*, *CYP3A4*, *CYP3A5*, and *ABCB1* polymorphisms with the pharmacokinetics of paclitaxel. Clin Cancer Res 2005;11:8097–8104. [PubMed: 16299241]
85. Marsh S, Somlo G, Li X, et al. Pharmacogenetic analysis of paclitaxel transport and metabolism genes in breast cancer. Pharmacogenomics J 2007;7:362–365. [PubMed: 17224914]
86. Marsh S, Paul J, King CR, Gifford G, McLeod HL, Brown R. Pharmacogenetic assessment of toxicity and outcome after platinum plus taxane chemotherapy in ovarian cancer: the Scottish Randomised Trial in Ovarian Cancer. J Clin Oncol 2007;25:4528–4535. [PubMed: 17925548]
87. Yamaguchi H, Hishinuma T, Endo N, et al. Genetic variation in *ABCB1* influences paclitaxel pharmacokinetics in Japanese patients with ovarian cancer. Int J Gynecol Cancer 2006;16:979–985. [PubMed: 16803472]
88. Jiko M, Yano I, Sato E, et al. Pharmacokinetics and pharmacodynamics of paclitaxel with carboplatin or gemcitabine, and effects of *CYP3A5* and *MDR1* polymorphisms in patients with urogenital cancers. Int J Clin Oncol 2007;12:284–290. [PubMed: 17701008]
89. Nakajima M, Fujiki Y, Kyo S, et al. Pharmacokinetics of paclitaxel in ovarian cancer patients and genetic polymorphisms of *CYP2C8*, *CYP3A4*, and *MDR1*. J Clin Pharmacol 2005;45:674–682. [PubMed: 15901749]
90. Green H, Soderkvist P, Rosenberg P, et al. Pharmacogenetic studies of paclitaxel in the treatment of ovarian cancer. Basic Clin Pharmacol Toxicol 2009;104:130–137. [PubMed: 19143748]
91. Li XQ, Bjorkman A, Andersson TB, Ridderstrom M, Masimirembwa CM. Amodiaquine clearance and its metabolism to *N*-desethylamodiaquine is mediated by CYP2C8: a new high affinity and turnover enzyme-specific probe substrate. J Pharmacol Exp Ther 2002;300:399–407. [PubMed: 11805197]
92. Jewell H, Maggs JL, Harrison AC, O'Neill PM, Ruscoe JE, Park BK. Role of hepatic metabolism in the bioactivation and detoxication of amodiaquine. Xenobiotica 1995;25:199–217. [PubMed: 7618347]
93. Parikh S, Ouedraogo JB, Goldstein JA, Rosenthal PJ, Kroetz DL. Amodiaquine metabolism is impaired by common polymorphisms in *CYP2C8*: implications for malaria treatment in Africa. Clin Pharmacol Ther 2007;82:197–203. [PubMed: 17361129]
94. Adjei GO, Kristensen K, Goka BQ, et al. Effect of concomitant artesunate administration and cytochrome P4502C8 polymorphisms on the pharmacokinetics of amodiaquine in Ghanaian children with uncomplicated malaria. Antimicrob Agents Chemother 2008;52:4400–4406. [PubMed: 18779360]
95. Kim KA, Park JY, Lee JS, Lim S. Cytochrome P450 2C8 and CYP3A4/5 are involved in chloroquine metabolism in human liver microsomes. Arch Pharm Res 2003;26:631–637. [PubMed: 12967198]
96. Rigas JR, Francis PA, Muindi JR, et al. Constitutive variability in the pharmacokinetics of the natural retinoid, all-*trans*-retinoic acid, and its modulation by ketoconazole. J Natl Cancer Inst 1993;85:1921–1926. [PubMed: 8230282]
97. Kim KA, Chung J, Jung DH, Park JY. Identification of cytochrome P450 isoforms involved in the metabolism of loperamide in human liver microsomes. Eur J Clin Pharmacol 2004;60:575–581. [PubMed: 15365656]
98. Niemi M, Tornio A, Pasanen MK, Fredrikson H, Neuvonen PJ, Backman JT. Itraconazole, gemfibrozil and their combination markedly raise the plasma concentrations of loperamide. Eur J Clin Pharmacol 2006;62:463–472. [PubMed: 16758263]

99. Wang JS, DeVane CL. Involvement of CYP3A4, CYP2C8, and CYP2D6 in the metabolism of (R)- and (S)-methadone *in vitro*. Drug Metab Dispos 2003;31:742–747. [PubMed: 12756206]

100. Projean D, Morin PE, Tu TM, Ducharme J. Identification of CYP3A4 and CYP2C8 as the major cytochrome P450 s responsible for morphine *N*-demethylation in human liver microsomes. Xenobiotica 2003;33:841–854. [PubMed: 12936704]

101. Ohyama K, Nakajima M, Nakamura S, Shimada N, Yamazaki H, Yokoi T. A significant role of human cytochrome P450 2C8 in amiodarone *N*-deethylation: an approach to predict the contribution with relative activity factor. Drug Metab Dispos 2000;28:1303–1310. [PubMed: 11038157]

102. Soyama A, Hanioka N, Saito Y, et al. Amiodarone *N*-deethylation by CYP2C8 and its variants, *CYP2C8*3* and *CYP2C8* P404A. Pharmacol Toxicol 2002;91:174–178. [PubMed: 12530467]

103. Becquemont L, Mouajjah S, Escaffre O, Beaune P, Funck-Brentano C, Jaillon P. Cytochrome P-450 3A4 and 2C8 are involved in zopiclone metabolism. Drug Metab Dispos 1999;27:1068–1073. [PubMed: 10460808]

104. Tornio A, Neuvonen PJ, Backman JT. The CYP2C8 inhibitor gemfibrozil does not increase the plasma concentrations of zopiclone. Eur J Clin Pharmacol 2006;62:645–651. [PubMed: 16832679]

105. Attar M, Dong D, Ling KH, Tang-Liu DD. Cytochrome P450 2C8 and flavin-containing monooxygenases are involved in the metabolism of tazarotenic acid in humans. Drug Metab Dispos 2003;31:476–481. [PubMed: 12642475]

106. Tang-Liu DD, Matsumoto RM, Usansky JI. Clinical pharmacokinetics and drug metabolism of tazarotene: a novel topical treatment for acne and psoriasis. Clin Pharmacokinet 1999;37:273–287. [PubMed: 10554045]

107. Covera-HS Prescribing Information. Pfizer (2006).

108. Vogelgesang B, Echizen H, Schmidt E, Eichelbaum M. Stereoselective first-pass metabolism of highly cleared drugs: studies of the bioavailability of L- and D-verapamil examined with a stable isotope technique. Br J Clin Pharmacol 1984;58:S796–S803. [PubMed: 15595975]discussion S804–S796 (2004)

109. Tracy TS, Korzekwa KR, Gonzalez FJ, Wainer IW. Cytochrome P450 isoforms involved in metabolism of the enantiomers of verapamil and norverapamil. Br J Clin Pharmacol 1999;47:545–552. [PubMed: 10336579]

110. Kerr BM, Thummel KE, Wurden CJ, et al. Human liver carbamazepine metabolism. Role of CYP3A4 and CYP2C8 in 10,11-epoxide formation. Biochem Pharmacol 1994;47:1969–1979. [PubMed: 8010982]

111. Chang TK, Weber GF, Crespi CL, Waxman DJ. Differential activation of cyclophosphamide and ifosphamide by cytochromes P-450 2B and 3A in human liver microsomes. Cancer Res 1993;53:5629–5637. [PubMed: 8242617]

112. Winter HR, Wang Y, Unadkat JD. CYP2C8/9 mediate dapsone *N*-hydroxylation at clinical concentrations of dapsone. Drug Metab Dispos 2000;28:865–868. [PubMed: 10901692]

113. Miners JO, Coulter S, Birkett DJ, Goldstein JA. Torsemide metabolism by *CYP2C9* variants and other human CYP2C subfamily enzymes. Pharmacogenetics 2000;10:267–270. [PubMed: 10803683]

114. Sutton D, Butler AM, Nadin L, Murray M. Role of CYP3A4 in human hepatic diltiazem *N*-demethylation: inhibition of CYP3A4 activity by oxidized diltiazem metabolites. J Pharmacol Exp Ther 1997;282:294–300. [PubMed: 9223567]

115 ▪. Gil JP, Gil Berglund E. CYP2C8 and antimalaria drug efficacy. Pharmacogenomics 2007;8:187–198. [PubMed: 17286541]Comprehensive review of the association between *CYP2C8* polymorphisms and antimalaria drug efficacy.

Websites

201. CYP2C8 allele nomenclature. www.cypalleles.ki.se/cyp2c8.htm

202. dbSNP Home Page. www.ncbi.nlm.nih.gov/SNP

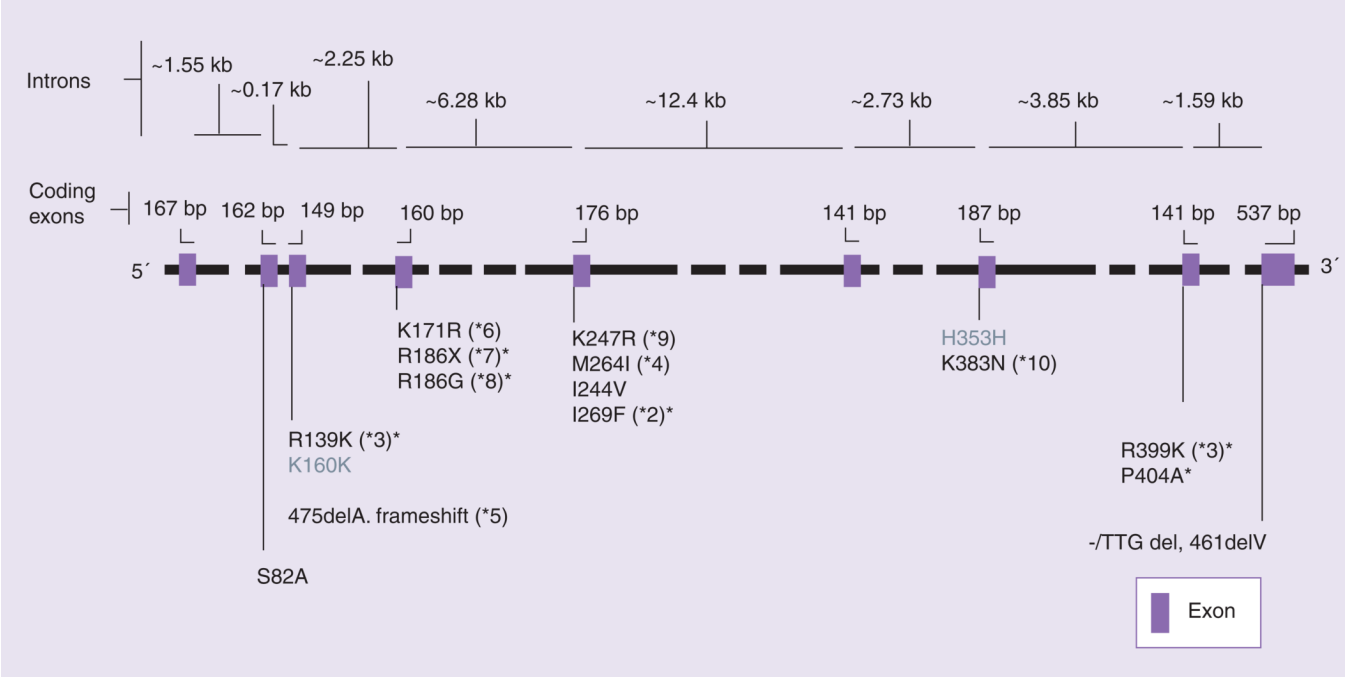

Figure 1. *CYP2C8* gene structure and coding region polymorphisms

The *CYP2C8* gene, located on chromosome 10q24, spans 31 kb and consists of nine exons. Coding region polymorphisms are shown in the figure. Gray text signifies synonymous polymorphisms, while the black text signifies nonsynonymous polymorphism.

*Alleles coding for documented or predicted reduced enzyme activity.

Figure reproduced from [115].

Table 1

Summary of CYP2C8 substrates.

Specific drugs	Drug class	Treatment indication	Other CYP enzymes that play a role in metabolism
Major contribution of CYP2C8 to metabolism			
All-*trans*-retinoic acid	Vitamin A derivative	Promyelocytic leukemia	CYP2C9
Amiodarone	Class III antiarrhythmic	Supraventricular and ventricular arrhythmias	CYP3A4, CYP1A2, CYP2C19, CYP2D6
Amodiaquine	4-aminoquinoline	Malaria	CYP3A4, CYP1A1, CYP1B1
Cerivastatin*	HMG-CoA reductase inhibitor	Hyperlipidemia	CYP3A4
Chloroquine	4-aminoquinoline	Malaria	CYP3A4, CYP2D6
Paclitaxel	Taxane	Solid malignant tumors (e.g., breast, ovarian, lung)	CYP3A4, CYP3A5
Repaglinide	Meglitinide	Type 2 diabetes	CYP3A4
Rosiglitazone Pioglitazone	Thiazolidinedione	Type 2 diabetes	CYP2C9, CYP3A4 CYP3A4, CYP1A1
Tazarotenic acid	Retinoid derivative	Acne and psoriasis	–
Troglitazone*	Thiazolidinedione	Type 2 diabetes	CYP3A4
Intermediate or minor contribution of CYP2C8 to metabolism			
Carbamazepine	Anticonvulsant	Epilepsy	CYP3A4 (major)
Cyclophosphamide	Nitrogen mustard alkylating agent	Lymphoma, leukemia, solid tumors	CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A
Dapsone	Antibacterial sulfone	Leprosy and pneumocystis pneumonia	CYP2C9 (major)
Diclofenac	NSAID	Pain and inflammation	CYP2C9 (major), CYP3A4, and CYP2C19
Diltiazem	Calcium channel blocker	Hypertension, arrhythmias, angina	CYP3A4, CYP2C9
Fluvastatin	HMG-CoA reductase inhibitor	Hyperlipidemia	CYP2C9 (major), CYP3A4
Ibuprofen	NSAID	Pain and inflammation	CYP2C9
Ifosfamide	Nitrogen mustard alkylating agent	Various cancers	CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A
Loperamide	μ-opioid receptor agonist	Antidiarrheal	CYP2B6, CYP2D6, CYP3A4
Methadone	Opioid antagonist	Pain and addiction to opioids	CYP3A4, CYP2D6, CYP2B6
Morphine	Opioid agonist	Pain	CYP3A4
Simvastatin acid	HMG-CoA reductase inhibitor	Hyperlipidemia	CYP3A4 (major)
Tenoxicam	NSAID	Pain and inflammation	CYP2C9 (major)
Torsemide	Loop diuretic	Edema	CYP2C9 (major)
Verapamil	Calcium channel blocker	Hypertension, arrhythmias, angina	CYP3A4 (major), CYP3A5
Zopiclone	Nonbenzodiazepine sedative hypnotic	Insomnia	CYP3A4 (major)

* Withdrawn from the market.

This table was adapted and updated from that previously published [1].

Table 2

Putative functional *CYP2C8* polymorphisms and allele frequencies.

Allele **CYP2C8*1 *(also called *1A)***	dbSNP number or Human Genome Variation Society number ***Wild-type***	Nucleotide or amino acid change	Location	Allele frequency: Caucasian (%)	Allele frequency: Chinese (%)	Allele frequency: Japanese (%)	Allele frequency: African (%)
*CYP2C8*1B*	rs7909236	-271C>A	Promoter	23.3	10	8.9	0
*CYP2C8*1C*	rs17110453	-370T>G	Promoter	11.7	27.8	34.4	0
*CYP2C8*2*	rs11572103	Ile269Phe	Exon 5	0	0	0	19
*CYP2C8*3*	rs11572080	Arg139Lys	Exon 3	10.8	0	0	0
	rs10509681	Lys399Arg	Exon 8	11.7	0	0	0
*CYP2C8*4*	rs1058930	Ile264Met	Exon 5	5.8	0	0	0
*CYP2C8*5*	rs72558196	Thr159X	Exon 3	–	–	0.2‡	–
*CYP2C8*6*	NT_030059.12:g.15573214G>A	Gly171Ser	Exon 4	–	–	0.2‡	–
*CYP2C8*7*	rs72558195	Arg186X	Exon 4	–	–	0.1‡	–
*CYP2C8*8*	rs72558195	Arg186Gly	Exon 4	–	–	0.1‡	–
*CYP2C8*9*	NT_030059.12:g.15566697A>G	Lys247Arg	Exon 5	–	–	0.1‡	–
*CYP2C8*10*	NT_030059.12:g.15551173G>T	Lys383Asn	Exon 7	–	–	0.1‡	–
*CYP2C8*12*	rs3832694	461delV	Exon 9	–	–	0.1‡	–
*CYP2C8*13*	NT_030059.12:g.15566768T>G	Ile223Met	Exon 5	–	–	0.1‡	–
*CYP2C8*14*	NT_030059.12:g.15566725G>C	Ala238Pro	Exon 5	–	–	0.1‡	–
Not assigned	rs17851796	Ala82Ser	Exon 2	–	–	–	–
Not assigned	rs41286886	Val181Ile	Exon 4	–	–	–	–
Not assigned	rs11572102	Ile244Val	Exon 5	0	0	0	1.7
Not assigned	rs45438799	Leu361Phe	Exon 7	–	–	–	–
Not assigned		Pro404Ala	Exon 8	–	–	0.7‡	2.2

Polymorphisms are presented based on data summarized in dbSNP [201], the Human Cytochrome P450 Allele Nomenclature Committee [202] and previously published literature [1,7,14,115]. Allele frequencies for CYP2C8*1B, *1C, *2, *3, *4, Ile244Val and Pro404Ala are based on HapMap data available in dbSNP.

‡If polymorphism allele frequencies were not available in dbSNP, relevant published literature was used [14].

–: Allele frequency data were not available; Caucasian: Centre d'Etude du Polymorphisme Humain (Utah residents with ancestry from northern and western Europe); Chinese: Han Chinese in Beijing, China; Japanese: Japanese in Tokyo, Japan; African: Yoruba in Ibadan, Nigeria

Table 3

Common *CYP2C8* haplotypes in Caucasians[‡].

SNPs	Hap A	Hap B	Hap C1	Hap C2	Hap C3	Hap D	Hap E
rs11188172 G>A (-2048, promoter)	G	A	G	G	G	G	G
rs17110453 T>G (-370, promoter, *CYP2C8*1C*)	T	T	G	G	T	T	T
rs7909236 C>A (-271, promoter, *CYP2C8*1B*)	C	A	C	C	C	C	C
rs1934956 G>A (intron 1)	G	G	G	G	G	G	A
rs3216029 or rs11572078 (intron 2)	–	–	T	T	T	–	–
rs2275622 G>A (intron 2)	G	A	G	G	G	G	A
rs11572080 G>A (exon 3, Arg139Lys, *CYP2C8*3*)	G	G	G	G	G	A	G
rs2185571 G>A (intron 3)	A	G	G	G	G	G	G
rs1113129 C>G (intron 5)	C	C	G	G	G	C	C
rs1058930 C>G (exon 5, Ile264Met, *CYP2C8*4*)	C	C	C	G	C	C	C
rs2275620 A>T (intron 7)	A	T	A	A	A	A	T
rs10509681 A>G (exon 8, Lys399Arg, *CYP2C8*3*)	A	A	A	A	A	G	A

[‡]As reported by [13].

SNPs included in the haplotypes were HapMap tagging SNPs and CYP2C8 SNPs with putative functional significance.

The haplotypes were inferred using the CYP2C8 reference sequence (AL359672). Haplotype frequencies were 30.5% (Hap A), 19.6% (Hap B), 7.4% (Hap C1), 6.5% (Hap C2), 5.4% (Hap C3), 15.3% (Hap D) and 6.9% (Hap E).

This table was adapted from [13].

Table 4

Summary of thiazolidinedione CYP2C8 clinical pharmacogenetic–pharmacokinetic studies.

Drug	Study description	Sample size and genotype distributions	PK results in relation to *CYP2C8* genotype	Covariates	Ref.
Rosiglitazone	8 mg single dose and multiple-dose PK	*CYP2C8*1/*1*, n = 14 *CYP2C8*1/*3*, n = 13 *CYP2C8*3/*3*, n = 4	↓AUC and ↑CL in **3/*3* and **1/*3* vs *1/*1	Linear regression with inclusion of sex, age and weight	[26]
Rosiglitazone	4 mg single dose, PK	*CYP2C8*1/*1*, n = 19 *CYP2C8*1/*3*, n = 7	↓AUC and ↑CL in **1/*3* vs **1/*1*	Linear regression with inclusion of sex, age, weight, and *SLCO1B1* diplotype	[27]
Rosiglitazone	8 mg single-dose PK (cross-over trimethoprim drug interaction study)	*CYP2C8*1/*1*, n = 4 *CYP2C8*1/*3*, n = 3 *CYP2C8*1/*2*, n = 1	No association between *CYP2C8*2* or *CYP2C8*3* and PK	None reported	[29]
Rosiglitazone	4 mg single-dose PK (cross-over fluvoxamine drug interaction study)	*CYP2C8*1/*1*, n = 10 *CYP2C8*1/*3*, n = 10 *CYP2C8*3/*3*, n = 3	No association between *CYP2C8*3* allele and PK	None reported	[30]
Pioglitazone	15 mg single-dose PK (cross-over trimethoprim drug interaction study)	*CYP2C8*1/*1*, n = 8 *CYP2C8*1/*3*, n = 5 *CYP2C8*3/*3*, n = 3	↓AUC and ↓ $t_{1/2}$ in **3/*3* and **1/*3* vs **1/*1*	Weight	[28]

AUC: Area under the plasma concentration–time curve; CL: Oral clearance; PK: Pharmacokinetics; $t_{1/2}$: Half life.

Table 5

Summary of repaglinide CYP2C8 clinical pharmacogenetic–pharmacokinetic studies.

Drug	Study description	Sample size and genotype distributions	PK results in relation to *CYP2C8* genotype	Covariates	Ref.
Repaglinide	0.25 mg single-dose PK	*CYP2C8*1/*1*, n = 19 *CYP2C8*1/*3*, n = 6 *CYP2C8*1/*4*, n = 3	↓AUC and ↓ C_{max} in **1/*3* vs **1/*1* ↓AUC in **1/*4* vs **1/*1*, although not significant	None reported	[37]
Repaglinide	0.25 mg single-dose PK	*CYP2C8*1/*1*, n = 41 *CYP2C8*1/*3*, n = 10 *CYP2C8*1/*4*, n = 5	↓AUC and ↓ C_{max} in **1/*3* vs **1/*1*	Linear regression analysis with inclusion of *SLCO1B1*, *ABCB1* and *CYP3A5* genotype	[38]
Repaglinide	0.25 mg single-dose PK	Not described	↓AUC in haplotype B vs noncarriers; ↓AUC in haplotype D vs noncarriers; ↑AUC in haplotype C vs noncarriers	Data were stratified for the *SLCO1B1* 521T>C polymorphism	[13]
Repaglinide	0.25 mg single-dose PK (cross-over gemfibrozil drug interaction study)	*CYP2C8*1/*1*, n = 7 *CYP2C8*1/*3*, n = 3	↑ratio of M2 and M4 to parent in **1/*3* vs **1/*1*	None reported *SLCO1B1* genotype was also determined for each subject	[40]
Repaglinide	2 mg single-dose PK (cross-over grapefruit juice drug interaction study)	*CYP2C8*1/*1*, n = 24 *CYP2C8*1/*3*, n = 11 *CYP2C8*3/*3*, n = 1	No association between *CYP2C8*3* and PK	None reported	[41]

AUC: Area under the plasma concentration–time curve; C_{max}: Maximum plasma concentrations; PK: Pharmacokinetics.

Table 6

Summary of NSAID CYP2C8 clinical pharmacogenetic–pharmacokinetic studies.

Drug	Study description	Sample size and genotype distributions	PK results in relation to *CYP2C8* genotype	Covariates	Ref.
Ibuprofen	400 mg single-dose PK	*CYP2C8*1/*1*, n = 9 *CYP2C8*1/*3*, n = 10 *CYP2C8*3/*3*, n = 6	↓R-ibuprofen CL ↑ in **1/*3* and **3/*3* vs **1/*1*	*CYP2C9* genotype was also determined for each subject	[68]
Ibuprofen	400 mg single-dose PK	*CYP2C8*1/*1*, n = 93 *CYP2C8*1/*3*, n = 35 *CYP2C8*3/*3*, n = 2	↓Ibuprofen CL in **1/*3* and **3/*3* vs **1/*1* ↓R- and S-ibuprofen CL with **3* allele vs **1/*1*	*CYP2C9* genotype was also determined for each subject	[69]
Ibuprofen	600 mg single-dose PK (cross-over bioequivalence study	*CYP2C8*1/*1*, n = 43 *CYP2C8*1/*2*, n = 3 *CYP2C8*1/*3*, n = 11 *CYP2C8*1/*4*, n = 10 *CYP2C8*3/*3*, n = 2	↑R-ibuprofen CL in **1/*3* vs **1/*1*	*CYP2C9* genotype was also determined for each subject Weight-adjusted clearance was also assessed	[70]
Diclofenac	50 mg single-dose PK	*CYP2C8*1/*1*, n = 71 *CYP2C8*1/*3*, n = 19 *CYP2C8*1/*4*, n = 7 *CYP2C8*3/*3*, n = 5	↑Urinary ratio of parent to metabolite in **3* and **4* carriers vs **1/*1*	None reported	[73]
Tenoxicam	20 mg single-dose PK (cross-over bioequivalence study)	*CYP2C8*1/*1*, n = 10 *CYP2C8*1/*3*, n = 5 *CYP2C8*1/*4*, n = 2 *CYP2C8*3/*3*, n = 1	No association between *CYP2C8* polymorphisms and PK	Analysis of variance which included confounders such as age, sex, menstrual cycle phase, body weight and formulation of drug *CYP2C9* genotype was also determined for all subjects	[77]

CL: Oral clearance; PK: Pharmacokinetics.

Table 7

Summary of paclitaxel CYP2C8 clinical pharmacogenetic–pharmacokinetic studies

Drug	Study description	Sample size and genotype distributions	PK results in relation to *CYP2C8* genotype	Covariates	Ref.
Paclitaxel	80–225 mg/m^2, breast, ovarian, esophageal cancer (n = 97)	*CYP2C8*1/*2*, n = 1 *CYP2C8*1/*3*, n = 11 *CYP2C8*1/*4*, n = 4 *CYP2C8*3/*3*, n = 3	No association between *CYP2C8* genotype and PK	Population pharmacokinetic analysis was performed Additional genetic variables were *CYP3A4*3*, *CYP3A5*3C* and *ABCB1* 3435C>T	[84]
Paclitaxel	575–775 mg/m^2, breast cancer (n = 93)	*CYP2C8*1/*3*, n = 11 *CYP2C8*1/*4*, n = 6 *CYP2C8*3/*3*, n = 1 *CYP2C8*4/*4*, n = 1	No association between *CYP2C8* genotype and PK	Additional polymorphisms evaluated were *ABCB1* 1236C>T, *ABCB1* 2677G>T/A; ABCG2 421C>A; *CYP1B1*3; CYP3A4*1B*; and *CYP3A5*3C*	[85]
Paclitaxel	175–210 mg/m^2, lung, thymic, breast cancer (n = 199)	*CYP2C8*IA*, 2.1% *CYP2C8*IB*, 10.3% *CYP2C8*ID*, 38.1% *CYP2C8*IE*, 43.5% *CYP2C8*IG*, 3% *CYP2C8*IJ*, 1.3%	↑3-p-hydroxypaclitaxel AUC in haplotype **IG* group carriers vs noncarriers	*CYP3A4* genotypes were also determined	[14]
Paclitaxel	135–175 mg/m^2, ovarian cancer (n = 38)	*CYP2C8*1/*3*, n = 6 *CYP2C8*1/*4*, n = 4	↓CL in patients with the *CYP2C8*1/*3* and *ABCB1* 2677G/T vs *CYP2C8* wild-type homozygotes and *ABCB1* 2677G/T	Data were stratified according to the *ABCB1* 2677G>T/A polymorphism. The *ABCB1* 1236C>T, *ABCB1* 3435C>T, and *CYP3A4*1B* polymorphisms were also evaluated	[90]

Three other groups set out to determine the influence of polymorphic CYP2C8 alleles on paclitaxel disposition and outcomes in Japanese cancer patients. However, no polymorphic CYP2C8 alleles were found in their respective populations [87–89].

AUC: Area under the plasma concentration–time curve; CL: Clearance; PK: Pharmacokinetics.