Towards personalized opioid dosing: A concise overview of CYP polymorphisms

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Abstract

Concern about excess opioid prescribing and abuse makes it is more important than ever that the dose of opioid prescribed be sufficient to relieve pain, but not excessive. The wide variation among patients regarding opioid response poses clinical challenges to prescribers seeking to offer patients adequate but safe levels of analgesia. While many factors (pharmacodynamics and pharmacokinetic) can influence drug response, growing understanding of the genomic influences on the cytochrome (*CYP*) P450 enzymes may help better identify patients who will most benefit from opioid therapy and direct their dosing regimen. Since many opioids are primarily metabolized by Phase 1 *CYP450* enzymes, *CYP* enzyme polymorphisms can result in variations in patient response. Many opioids and other drug classes are metabolized by the *CYP* families *CYP2D6*, *CYP3A4*, and to lesser extent *CYP2B6* enzymes. Thus, patients who have genotype polymorphisms in these enzymes are phenotypically (clinically) poor, intermediate, extensive, or ultra-rapid metabolizers, affecting how rapidly or to what extent an individual patient metabolizes opioids. Moreover, these enzymes may be induced or inhibited by drugs or other substances. While phenotyping and genotyping individual patients is not yet a practical everyday solution, the advent of personalized medicine will likely allow for cost-effective, rapid testing that may better identify a patient's metabolic type prior to prescribing opioid therapy. With better matching of the effective dose for each patient, it should be possible to avoid excess dosing, resulting in fewer prescribed pills and, presumably, fewer unused pills that are at risk for diversion.

Keywords: Opioid, Metabolism, Cytochrome P450, Pharmacogenomics, Polymorphism.

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Introduction

CYP450 enzymes

Cytochrome P450 (*CYP450*) describes a family of isoenzymes located in the endoplasmic reticulum of liver cells, which catalyze metabolic conversion (biotransformation) of endogenous and exogenous compounds. Part of Phase I metabolism (oxidation, reduction, and hydrolysis), oxidation by way of *CYP450* enzymes results in metabolic conversion of parent drugs to metabolites that are often (but not always) with reduced affinity and efficacy target receptors, and often (but not always) more water-soluble (more unlikely to be reabsorbed through kidney convoluted tubules and hence, more likely to be excreted in the urine) [1,2].

The human genome contains 70 *CYP* genes, which have been classified based on sequence homology, resulting in 18 families and 44 subfamilies [3,4]. Thus, *CYP450* is the name of a superfamily of isoenzymes; drugs may be metabolized by one or more of its subfamilies, acting as enzymatic pathways [5]. The main enzymes involved in the metabolism of current drugs belong to the *CYP*1, *CYP*2, and *CYP*3 families and include these isoforms: 1A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4, and 3A5. In fact, about 90% of all current pharmaceutical products are metabolized by *CYP1A2*, 2C8/9, 2C19, 2D6, and 3A4 [6] (Figure 1).

CYP polymorphisms

Nucleotides are the building blocks of DNA and a single nucleotide polymorphism (SNP) represents a difference in one of those nucleotides. SNPs are often seen in the DNA between genes, but SNPs can occur within a gene or within the regulatory region near a gene, in which case they may affect the gene's function [7]. Most variability in *CYP450* activity can be traced to SNPs at the *CYP450* gene locus [6].

A SNP can change the composition of the protein transcribed by the gene, which, in turn, leads to changes in gene expression and/or activity. New SNPs and their corresponding functional effects have recently been discovered and, indeed, continue to be discovered [6]. Changes in transcribed proteins may cause changes to enzymes, drug transporters, and drug receptors which can make the functional effect greater, less, or nil [8]. Because of the heritability of SNPs, the prevalence of certain polymorphisms can vary markedly between ethnic groups or races [9]. These changes can be of great clinical relevance in that they can result in unexpected drug metabolism (more rapid metabolism, shorter half-lives, or, conversely, significantly elevated circulating plasma concentrations of the agent), which may lead to toxicity even within normally therapeutic dosing ranges [10].

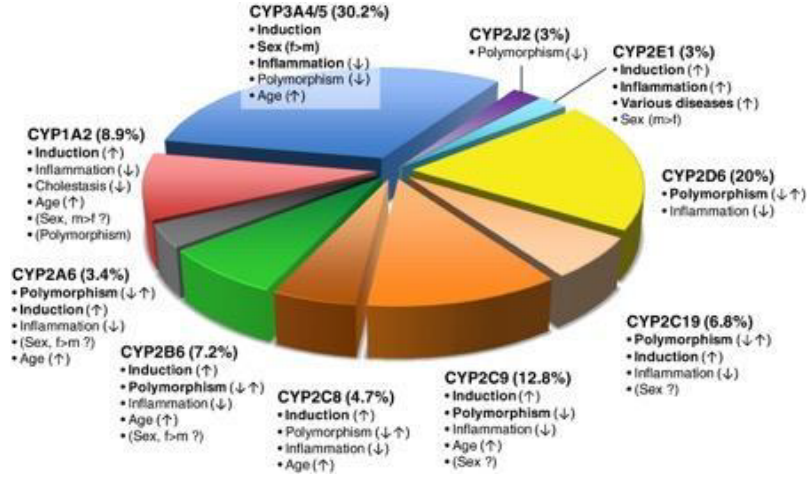

Figure 1. *Graphical representation of the approximate fraction of common current drugs that are metabolized by specific P450 isozymes, and some factors that are known or suspected to alter the activity of each isozyme (↑,increase; ↓, decrease; ?, suspected). [source: From Zanger & Schwab (2013) Pharmacol Thera 138:103-141 with permission].*

CYP2D6

Although the *CYP2D6* enzyme accounts for only about 5% of the *CYP* content in the liver [2] it is responsible for the oxidative metabolism for about 25% of currently commercialized pharmaceutical agents, [4,11] —including opioids—along with antidepressants, antipsychotics, and antiarrhythmic agents [2]. The *CYP2D6* enzyme is encoded by the *CYP2D6* gene, located on human chromosome 22. With more than 60 known alleles (defined as two or more alternative forms of a gene that occur by mutation and can be found at the same place on a chromosome) [5,12] *CYP2D6* has numerous polymorphisms resulting in at least 130 possible genetic variations [2]. The extensive effect of *CYP2D6* on drug metabolism has made it the subject of considerable study [13].

An individual's drug-metabolizing phenotype is based on the combination of *CYP2D6* alleles, which are expressed as normal, reduced, or enhanced catalytic activity [14]. Individuals with two normal function alleles are called "extensive metabolizers" and have normal enzymatic activity.

Individuals with two nonfunctional or null alleles have little to no enzymatic activity and are called "poor metabolizers"; the majority of *CYP2D6* polymorphisms result in decreased enzymatic activity i.e., poor metabolism [10,15-17]. Individuals with one null allele or two deficient alleles are called "intermediate metabolizers" and have compromised (but not absent) enzymatic activity. This particular polymorphism is common among Asian patients, affecting as many as 50% of certain Asian populations [6,18]. Gene duplication, that is, having more than two copies of the *CYP2D6* gene in one chromosome, may occur; individuals with more than two functional *CYP2D6* alleles are known as "ultra-rapid metabolizers" [19]. This polymorphism is particularly high among Saudi Arabians (20%) and Ethiopians (29%) [6,18]. Within these four broad metabolic types there can still be considerable variability in metabolic rates.

An alternative method for describing metabolic type is to assign a number to the alleles. Normal function alleles count as 1, reduced-function alleles as 0.5, and non-functional alleles as 0. Tallying the individual's alleles will result in any of six possible scores: 0, 0.5, 1, 1.5, 2, and >2.

Those who score 0 are poor metabolizers, intermediate metabolizers score 0.5 to 1, extensive metabolizers' rate 1 to 2, and those with a score over 2 are ultra-rapid metabolizers [14]. In this connection, it should be noted that patients who score 1 on this test may be grouped into the intermediate metabolizer or the extensive metabolizer category. They are considered intermediate if their score is obtained by two alleles of 0.5 points each (0.5 + 0.5 = 1), but if they achieve their score by having one functional allele (1 point), they are categorized as extensive metabolizers (1 + 0 = 1) [14].

CYP2D6 polymorphisms may explain at least in part the interpatient differences in opioid response and the variations in circulating plasma levels of opioid agents [20]. *CYP2D6* polymorphisms may affect analgesic benefit, side effects, and tolerability of opioids in individual patients.

CYP3A4 and 3A5

CYP3A4 is the most abundant of all of the *CYP450* isoforms and accounts for about half of all of the *CYP450* enzymes in the liver, but there is little polymorphism and thus little variation in *CYP3A4* expression in humans [21]. On the other hand, *CYP*3A5 is far less abundant (making up about 2% of the *CYP450* enzymes in the liver in Caucasians), but is highly polymorphic and its contributory role to *CYP3A4* activity accounts for the overall variability observed in the *CYP3A4*/5 enzyme [21].

Owing to linkage disequilibrium and other factors, *CYP3A4* and *CYP*3A5 overlap to the extent that it is difficult to draw clear conclusions about one genotype or the other [6]. These two isoforms have similar sequence homology and nearly identical substrate specificity, but differ in functional activity. When appropriate, we will describe them as they are often described in the literature, that is, as *CYP3A4*/5.

CYP2B6

The *CYP2B6* gene on chromosome 19 is responsible for coding metabolic enzymes of the *CYP450* family [22-24] and exhibits marked variations among individuals in terms of mRNA expression which has been attributed to genetic polymorphisms [25]. *CYP2B6**6 has been reported to be implicated in opioid

addiction as well as response to methadone maintenance therapy [24,26]. The *CYP2B6* enzyme is not a major metabolic pathway for the most commonly prescribed opioids.

Literature Review

Opioid substrates

An enzyme molecule typically has an "active site" that binds to a substrate (e.g., drug) and orients it for catalysis. The substrate is changed by the action of the enzyme, which then releases the product. Two theoretic models explain how this might work. The "lock-and-key" hypothesis supposes that the substrate and the active site of the enzyme are a close match and allow for a tight fit with no further modification [27]. By contrast, the "induced fit" hypothesis proposes that the active site and substrate are not a close match but the active site has sufficient flexibility to morph into the appropriate shape to form a close match with the substrate. The induced fit hypothesis holds that the interaction between enzyme and substrate is weak, but cumulative weak interactions cause conformational changes to the enzyme that jointly contribute to its binding strength.

The following section presents a summary of some opioids that undergo metabolism involving *CYP450* enzymes. Some opioids, notably but not exclusively morphine, are mainly metabolized via non-*CYP450* pathways (e.g. phase 2 glucuronidation).

Buprenorphine (CYP3A4)

Buprenorphine is available for parenteral, oral, sublingual, and transdermal administration. Buprenorphine is metabolized via the *CYP3A4* isoform as its primary metabolic pathway with a contribution from UDP-glucuronosyltransferase (UGT) 2B enzymes [28]. The UGT enzymes are not part of the cytochrome superfamily of enzymes. The major metabolite of buprenorphine is norbuprenorphine, a pharmacologically active compound that is then metabolized to its glucuronide conjugates [29].

Codeine (CYP2D6)

Codeine is primarily considered a prodrug that is converted by *CYP2D6* first to morphine and then to morphine-6-glucuronide (M6G) [14]. Codeine *O*-demethylation conversion to morphine occurs mainly in the liver microsomes, but some metabolism takes place in the intestine and the brain. Codeine is also *N*-demethylated to the metabolite norcodeine via its minor metabolic pathway *CYP3A4* [19]. Codeine is eliminated mainly by glucuronidation with *O*-demethylation to morphine and *N*-demethylation to norcodeine [30]. Since the analgesic benefit of codeine derives mainly from its morphine metabolite, the *O*-demethylation pathway via the *CYP2D6* enzyme is of particular interest, in that it produces the active metabolite [31]. While the analgesic effect of codeine is largely attributable to the metabolism of codeine to morphine [19]. other pathways and metabolites come into play. Conversion of codeine to codeine-6-glucuronide occurs via UGT2B7, which also catalyzes morphine glucuronidation to morphine-3-glucuronide (M3G) and M6G.

Codeine is considered a "weak opioid" agonist by the World Health Organization (WHO) [32] and is widely prescribed around the world for relief of moderate pain. It has low affinity for the μ-opioid receptor (200 times less than morphine) and low intrinsic activity there (50 times less than morphine) [33]. Because it has been categorized as a "weak opioid," it has been considered a safer alternative for pain control than many other strong opioids, which may account for its widespread use in treating pain, including pediatric patients [33]. Patients with gene duplication (ultrarapid metabolizers) may be predisposed to opioid toxicity even at therapeutic or very low doses of codeine, since they can produce large amounts of morphine and M6G from relatively small amounts of codeine [34]. A case report in 2006 identified a neonate who died of opioid toxicity after his mother was prescribed codeine plus acetaminophen to control episiotomy-related pain. The mother had a *CYP2D6* polymorphism and was an ultra-rapid metabolizer and the baby ingested quantities of morphine via her breast milk [35,36].

Since *CYP2D6* ultrarapid metabolism is not rare and consequences are potentially lethal, codeine currently is one of two opioids in the United States which is required by the Food and Drug Administration (FDA) to include pharmacogenetic information about *CYP2D6* metabolism on its labeling [37]. (The other is tramadol.)

Fentanyl (CYP3A4/5)

Fentanyl is a highly lipophilic opioid distributed extensively throughout the body and metabolized via *CYP3A4*/5 primarily to the inactive metabolite norfentanyl [38]. The pharmacokinetic activity of norfentanyl depends on the patient's ability to metabolize and excrete fentanyl.

Variations in the alleles *CYP3A4**1B and *CYP*3A5*3 have been associated with variations in fentanyl metabolism. A study of 25 fentanyl-related deaths found evidence that *CYP*3A5*3 is associated with impaired fentanyl metabolism [39]. In a study of cancer patients administered transdermal fentanyl for pain control, patients with homozygous *CYP*3A5*3 alleles had a two-fold increase in fentanyl plasma concentration compared to other patients [40]. In a study of postoperative pain patients, the *CYP*3A5*3 allele affected plasma exposure of fentanyl but did not impact urinary excretion of fentanyl in the early postoperative period [38].

Hydrocodone (CYP2D6)

Hydrocodone may be considered a type of prodrug, in that it is metabolized via *CYP2D6* into hydromorphone, which is five times more potent than the parent drug hydrocodone [11]. Hydrocodone metabolism is similar to that of codeine, in that *CYP2D6* catalyzes *O*-demethylation to dihydromorphine (an active metabolite similar to morphine) and *N*-demethylation to norhydrocodone [5,41]. The analgesic effect of hydrocodone derives mainly from its metabolites [42]. About 40% of hydrocodone is cleared via non-*CYP* pathways [42].

A case report describes a fatal case of hydrocodone toxicity in a five-year-old developmentally delayed girl who had been administered hydrocodone for a respiratory tract infection. The patient had a *CYP2D6* polymorphism, resulting in the hydrocodone metabolizing to large amounts of hydromorphone, exacerbated by polypharmacy [43].

Hydromorphone (UGT2B7)

The metabolism of hydromorphone has not yet been entirely elucidated but takes place largely via the UGT2B7 pathway. It is thought that hydromorphone metabolism might involve some *CYP*3A and *CYP*2C9 activity, but *CYP2D6* is not involved in the agent's therapeutic activity [44,45].

Levorphanol (UGT2B7)

Levorphanol (levo-3-hydroxy-N-methylmorphinan) is anopioid that was originally marketed as an alternative to morphine [46,47]. It undergoes glucuronidation in the liver via the UGT2B7 enzyme, similar to morphine.

G. Meperidine (CYP2B6)

Meperidine is an opioid analgesic agent that is metabolized via multiple enzymes. Most of the metabolism occurs via *CYP2B6* (57%) with contributions from *CYP3A4* (28%) and *CYP*2C19 (15%) and very minor contributions (<1%) from isoforms *CYP*3A5 and *CYP2D6* [48].

Methadone (CYP3A4 and CYP2B6)

Methadone is a racemic compound (*R*- and *S*- enantiomers). Methadone is metabolized via isoenzymes *CYP3A4* and *CYP2B6*. *CYP2B6* preferentially metabolizes the *S*- enantiomer and can affect clearance and plasma concentrations of methadone [49]. The clinical disposition of methadone has historically been attributed largely to *CYP3A4*, although *CYP2B6* plays an important role [50]. While methadone is not a substrate for *CYP2D6* [51] methadone can inhibit *CYP2D6 in vitro* and *in vivo* [51,52]. Methadone reduces the clearance of tramadol in patients and for that reason; tramadol may not be optimal for use as an analgesic agent in patients receiving methadone maintenance treatment [52].

Since methadone is widely used in treatment programs for opioid addiction, genetic variability must be considered to better gauge therapeutic response. In a meta-analysis (n=7 articles), trough (*R*-) methadone plasma concentrations were higher in homozygous carriers of *CYP2B6**6 compared to non-carriers (p=0.03) and trough (*S*-) methadone plasma concentrations were also higher in homozygous carriers of the *CYP2B6**6 haplotype compared to non-carriers (p=0.02) [53]. However, among the carriers of the *CYP2B6**6 haplotype, there can still be considerable heterogeneity. This suggests that patients who are homozygous for the *CYP2B6**6 genotype metabolize methadone more slowly and therefore have higher trough concentrations of *R*- and *S*-methadone in plasma. The ATP-binding cassette, subfamily B, member 1 (ABCB1) gene is probably the most consistently mentioned gene with respect to response to methadone therapy [53]. However, there is no significant association found with the ABCB1 polymorphism and trough plasma concentrations of *R*-, *S*-, methadone dose, and response [53].

Methadone has complicated pharmacokinetics, may be used as an alternative opioid agent in patients who do not respond well to other opioids, and is sometimes considered as a second-line treatment for cancer pain. Clinicians may prescribe racemic methadone (*R*- and *S*-methadone) and levomethadone (*R*-methadone) [31]. Both enantiomers are known to bind to NMDA-receptor sites, making them effective in treating neuropathic pain. Most studies of methadone have been conducted in cohorts of opioid addicts receiving methadone maintenance therapy, which may impact the overall generalizability of their findings [31].

Morphine (UGT2B7)

The main metabolic pathway for morphine in mammals is glucuronidation catalyzed by UGT enzymes [54]. Variations in morphine response have been attributed to differing individual abilities to glucuronidate morphine or to UGT2B7 polymorphisms or both [55]. Morphine's main metabolite is morphine-3-glucuronide (M3G) which has central nervous system stimulatory effects but is thought to be inactive in analgesia [56]. Morphine-6-glucuronide (M6G) is a minor metabolite, but is thought to play a role in pain relief.

Oxycodone (CYP2D6 and CYP3A4/5)

Oxycodone undergoes *N*-demethylation as its main metabolic pathway, mediated by *CYP*3A, and also undergoes *O*-demethylation mediated by the *CYP2D6* enzyme, which accounts for only about 10% of metabolites excreted in the urine [57,58]. The *CYP2D6* oxycodone metabolite of oxymorphone has a 40-fold higher mu-opioid-receptor binding affinity than the parent drug oxycodone [57] and is a more potent mu-opioid-receptor agonist than oxycodone, yet it is thought to play only a minor role in analgesia. Quantitatively, the *CYP2D6* pathway is the more important one [57]. In contrast to certain other opioids, the main effects of oxycodone in humans appear to be governed by the parent drug rather than its oxidative and reductive metabolites [57].

While women have greater *CYP3A4*/5 activity in relation to *CYP2D6* activity, there is no evidence in the literature that supports sex-based differences in oxycodone metabolism or use patterns [59]. When concern was raised about the use of codeine in pediatric patients, there was a tendency to regard oxycodone as a "safer" alternative. However, maternal use of oxycodone during breastfeeding has been associated with a 20.1% rate of infant central nervous system (CNS) depression compared to 16.7% for mothers taking codeine and 0.5% for mothers taking acetaminophen [60].

One hundred twenty-one surgical patients who received oxycodone 0.05 mg/kg before emergence from anesthesia and then had oxycodone via patient-controlled analgesia (PCA) for the first 48 postsurgical hours were evaluated in a clinical trial [61]. Blood samples were taken at 30, 90, and 180 minutes after the initial dose of oxycodone. The primary endpoint of the study was the plasma concentration ratios of oxymorphone (metabolite) to oxycodone and the second was postoperative analgesic consumption. The ratios of oxymorphone to oxycodone were 0.10 (poor metabolizers), 0.13 (intermediate metabolizers), 0.18 (extensive metabolizers), and 0.28 (ultrarapid metabolizers), p=0.005. At 12 hours, oxycodone consumption was significantly highest in the poor metabolizer group compared to the other groups (p=0.005). Pain intensity scores were similar across groups [61]. This study underscores how metabolic type can affect opioid dose, serum concentrations, and opioid consumption.

Tramadol (CYP2D6)

Tramadol is a racemic mixture and its analgesic effect results from a synergistic interaction of its two enantiomers and their metabolites. Of the 11 demethylated compounds resulting from tramadol metabolism, analgesic properties are thought to reside primarily in *O*-desmethyltramadol which is metabolized via *CYP2D6*. *O*-desmethyltramadol possesses a 200-times greater affinity for mu-opioid-receptors than the parent compound [41,62,63].

Like codeine, tramadol carries pharmacogenetic information about *CYP2D6* polymorphisms on its labeling [37]. Individuals with more than two functional *CYP2D6* genes (ultrarapid metabolizers) may be at elevated risk for opioid-associated side effects [14,31] and they have higher peak plasma concentration, greater miosis, and experience a greater degree of analgesic effect than *CYP2D6* extensive metabolizers [64].

By contrast, poor *CYP2D6* metabolizsers may require higher doses of tramadol in order to achieve the same analgesic effect. An analysis of serum concentrations of the (+)*O*-desmethyltramadol in different *CYP2D6* genotypes found that poor metabolizers had smaller quantities of the active metabolite compared to others.

Other factors that affect opioid metabolism

Drug response involves a complex interplay of factors. These include environment, age, sex, ethnic group, comorbid conditions, concurrent medication use, and organ dysfunction [58]. Drug response may be further affected by diet, lifestyle, and smoking [65-68]. Inflammation has been associated with a reduced expression of *CYP3A4* via proinflammatory cytokines (such as interleukin [IL] 6), which might potentially affect opioid metabolism [69].

Polypharmacy refers to taking multiple agents concurrently; it is prevalent among chronic pain patients, cancer patients, and the elderly [70]. Drug metabolism is clearly impacted by polypharmacy, that is, taking agents known to inhibit certain *CYP* pathways can disrupt metabolism or, in other cases, block alternative biotransformative pathways [14]. Renal dysfunction can decrease elimination, allowing for a potentially toxic build-up of metabolites [34]. Powerful *CYP2D6* inhibitors can cause poor metabolism of a drug even in a patient who might otherwise be considered an ultrarapid metabolizer. This effect is known as "phenoconversion" [14]. It is important to be aware of potential drug-drug interactions with opioids and agents that may inhibit or induce the catalysis of opioid analgesics.

Inhibitors

Inhibitors refer to prescription drugs, over-the-counter medications, supplements, and even foods that can disrupt *CYP* activity and affect how a concurrently taken drug is metabolized. Powerful *CYP2D6* inhibitors which can cause a > 5-fold increase in the plasma area-under-the-curve concentration (AUC) or more than an 80% decrease in clearance include bupropion, cinacalcet, fluoxetine, paroxetine, and quinidine. Other but less potent *CYP2D6* inhibitors are amiodarone, chlorpromazine, cimetidine, duloxetine, flecainide, haloperidol, metoclopramide, propafenone, risperidone, ritonavir, sertraline, and terbinafine [2,14].

CYP3A4/5 inhibitors include amiodarone, carbamazepine, cyclosporine, dexamethasone, dihydralazine, diltiazem, doxycycline, erythromycin, imatinib, meprobamate, metamizole, methylprednisolone, nefazodone, nelfinavir, phenobarbital, phenytoin, ritonavir, topiramate, verapamil, and others. St. John's Wort, a popular herbal supplement, [71] grapefruit, and licorice[2] are also *CYP3A4*/5 inhibitors.

Inducers

Inducers are molecules that promote gene expression by enhancing activators or disabling repressors. *CYP2D6* inducers include dexamethasone, glutethimide, and rifampicin. *CYP3A4*/5 inducers include carbamazepine, clotrimazole, dexamethasone, phenobarbital, phenytoin, rifampin, and sulfinpyrazone [71].

Discussion

Ethnicity and opioid metabolism

Since *CYP* polymorphisms are inheritable, ethnic, racial, and geographic variations in opioid response have been known for decades. Many polymorphisms and the resulting metabolic types are far from rare. For *CYP2D6*, for example, about 7% of the Caucasian population could be classified as poor metabolizers, while about 3.5% of this same population are ultrarapid metabolizers [72] *CYP2D6* gene duplication, resulting in ultrarapid metabolism, is highly prevalent in Saudi Arabia and Ethiopia (over 20%) but less common elsewhere. Reduced *CYP2D6* enzymatic activity is more common in Japanese (39% to 41%) and Chinese (50% to 70%) than the U.S. Caucasian population (2% to 8%) or African-American population (15% to 26%) [14].

Polymorphisms affecting the *CYP3A4*/5 enzymes also vary by race, ethnicity, and geography. Splice variants in the *CYP3A4**1B affect about 2% to 10% of Caucasians, 9% to 11% of Hispanics, and 35% to 67% of African-Americans in the United States; this polymorphism is very rare in China [21,73].

Clinical implications

While ethnic and racial distribution patterns of *CYP* polymorphisms can be interesting, they do not provide guidance on how to treat individual patients. In some cases, the history of an opioid-experienced patient may provide some insight into that patient's ability to metabolize opioids.

For others, it may be useful to phenotype or genotype the patient. Phenotyping is a relatively elaborate test in which the patient takes a probe drug and blood is drawn at various time points in order to analyze real-time *in vivo CYP* enzymatic activity. Phenotyping provides a good analysis of the interplay of genetic, environmental, and endogenous factors involved in drug response [74]. However, because phenotyping is a costly and time-consuming procedure, it is not a practical solution for all opioid patients [2]. Genotyping, on the other hand, relies on polymerase chain reactions (PCRs) to amplify the patient's DNA and applies other detection methods, such as restriction fragment length polymorphism after hydrolysis with restriction enzymes, among others, for each allele [75]. Alleles are assessed individually and thus only a subset of alleles can be analyzed. A number of commercial systems are available for this type of

testing. New test methods are being developed with the goal of finding a fast, inexpensive, reliable test method that can help guide opioid prescribing choices.

It will be interesting to see how our understanding of *CYP* polymorphisms will affect future prescribing practices [76]. As techniques become more practical, inexpensive, and easier to implement they will find more widespread use with the goal that opioid dosing can be safer, more rational, more effective, and more predictable.

Of great concern is the potential for drug-drug interactions when a patient takes an opioid analgesic agent along with other drugs, both prescription and over-the-counter medications. Pharmacokinetic drug-drug interactions with opioids are not uncommon [77-80]. And may have an adverse economic impact on the healthcare system which is not fully appreciated [81,82]. Since polypharmacy is common, particularly in the chronic pain population, [70] such drug-drug interactions must be considered carefully by clinicians. In a prospective observational study in academic U.S. emergency rooms (n=502) 250 patients had taken either one *CYP2D6* inhibitor or inducer (either pharmaceutical agent, supplement, or illicit drug) in the 48 hours before presenting to the emergency department. Patients who took a *CYP2D6* agent were one-third as likely to respond to hydrocodone (odds ratio 0.33, 95% confidence interval, 0.1 to 0.8) than non-users [11].

Drug-drug interactions appear to be more likely when a drug relies on one sole metabolic pathway of limited capacity, because substrates can saturate enzymatic action and inhibit catalysis. *CYP2D6* is such a pathway; on the other hand, *CYP3A4* has a higher capacity [11]. Thus, when assessing drug response, even if a polymorphism is known to prescribers in advance, there are several additional considerations that may influence prescribing choices. First, the affected pathway must be considered in that major pathway "collisions" are of greater concern than competition on minor pathways. When drugs compete for a single metabolic pathway it must also be considered what the therapeutic window of that other drug is. Other pathways of elimination may affect competition as well. When a pathway leads to an active metabolite, it is of greater concern than a pathway that does not. Thus, phenotyping or genotyping a patient at risk of drug-drug interactions must be balanced against other considerations [2].

Conclusion

Many commonly prescribed opioids are metabolized via the *CYP* enzyme family, and our evolving understanding of *CYP* polymorphisms is increasing the knowledge of how these drugs may be metabolized differently by different patients. Understanding polymorphisms allows clinicians to stratify patients into metabolic types which help guide – and ideally, optimize – prescribing and dosage choices. New tools to help classify patients and quantify doses may make opioid therapy safer, more effective, and more predictable in the future.

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