Special Article

Opioid Therapies and Cytochrome P450 Interactions

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Abstract
Adverse drug reactions are common and associated with substantial economic and human costs. Particularly among older adult populations, preventable adverse drug reactions are often caused by drug-drug interactions. All analgesics have side effect profiles and many have known drug-drug interactions. Opioids are recognized as a necessary option for managing moderate-to-severe pain, yet many opioid side effects can be enhanced by metabolic interactions within the liver, involving other drugs, diseases, or genetics. J Pain Symptom Manage 2012;44:S4–S14. © *2012 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Adverse drug reactions, cytochrome P450, CYP3A4, CYP2D6, drug-drug interactions, inhibitor, inducer, metabolism, prodrug, substrate, opioids

Adverse Drug Reactions From Interacting Drugs

An Institute of Medicine report in 2000 found that the incidence of adverse drug reactions (ADRs) is one of the most common, although avoidable, mistakes made in medicine, leading to more deaths than motor vehicle accidents, AIDS, or breast cancer.[1] Authors of a subsequent systematic review concurred with the finding that 59% of drug-related hospital admissions were caused by preventable, inappropriate use of medicines, such as the coprescription of interacting drugs.[2] Notably, the incidence of ADRs increases linearly along with the number of medications taken.[3] Compared with younger individuals, older adults are prescribed a disproportionate amount of drugs,[4] which is perhaps an important factor why preventable ADRs are commonly seen among older adults,[5] with the rates of adverse drug events escalating along with advancing age.[6] Efforts to reduce unnecessary prescribing are important, but for many patients, the number of medications cannot always be reduced without losing benefit. Therefore, understanding the basis of drug-drug interactions can facilitate appropriate choices in prescribing, thereby helping to avoid preventable ADRs.

The potential for ADRs is a well-known concern of patients and clinicians alike. The American public has a much greater level of concern about ADRs associated with drug-drug interactions than most health care providers would suspect. A random telephonic survey of 1004 U.S. adults conducted by the American Society of Health-System Pharmacists found that the

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concern about "being given two or more medicines that interact in a negative way" outweighed concerns about being given the wrong medicine, prescription drug cost, complications, high doses, harmful side effects, pain, or even developing an infection.[7] Approximately 70% of the respondents gave the highest ratings (either "concerned" or "very concerned") for their level of concern for "drug-drug interactions."[7]

Drug-drug interactions are also a concern within the field of pain medicine. Multimodal analgesia is often used to block pain signals at multiple stages in the pathway of pain from initiation to perception, resulting in additive and perhaps even synergistic analgesic effects (Fig. 1).[8] This commonly involves combining one or more of the four main types of analgesics: acetaminophen, anti-inflammatory medicines (aspirin, steroids, and nonsteroidals), multimechanism agents (tramadol and tapentadol), and opioids. Also, because lower doses of analgesics in a multimodal strategy can be effective via synergy, the side effect burden can be reduced. Striking a balance between analgesia and adverse effects can involve combining medications that target distinct components of the pain-signaling pathway, such as a local anesthetic to block nociception, along with an opioid, which also inhibits pain transmission and perception. Additionally, treating certain pain syndromes such as neuropathic pain often requires the addition of other agents with analgesic activity, such as antidepressants, anticonvulsants, and topical local anesthetics. Yet, the risk of ADRs is significantly increased with polypharmacy. The use of combination therapies for treating low back and osteoarthritis pain is already common, particularly among older adults.[5,9–11] For managing the symptoms of pain, patients can be prescribed a multitude of short- and/or long-acting analgesics, along with agents for other pain-associated morbidities, such as spasm, sleep disturbance, and depression. In managing patients with pain, clinicians should regularly include the consideration of potential drug-drug interactions between all analgesics, adjuvant agents, and patients' baseline medication regimens.

Hepatic Pathways for Opioid Metabolism

Opioids are the cornerstone for the management of patients with severe pain, and are

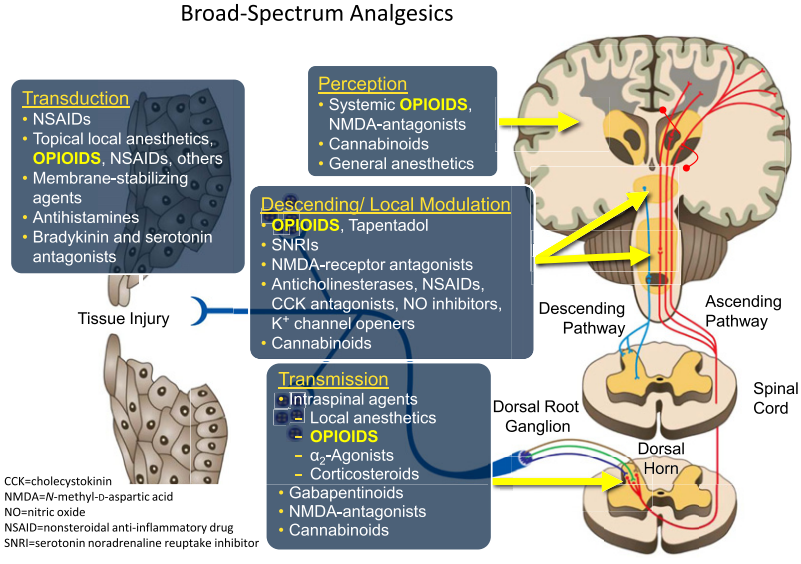

Fig. 1. The sites of action of broad-spectrum analgesics. Targeting multiple distinct components in the pain-signaling pathway—transduction, transmission, perception, and modulation—is increasingly viewed as offering additive, perhaps even supra-additive (synergistic) pain reduction. Coadministration of the α_2-receptor agonist clonidine along with an opioid, for example, may yield significantly greater analgesic effects when compared with either agent alone. Although the neural pathways that govern pain are yet to be fully elucidated, a balanced analgesic approach using multiple agents with unique modes of action is thought to reduce the peripheral and central sensitization and inflammation that often characterize chronic pain disorders. Adapted from Kelly et al.[8]

recognized in both guidelines and evidenced-based systematic reviews to be necessary for malignant and nonmalignant chronic pain.[12–16] However, the occurrence of opioid side effects (e.g., respiratory depression, somnolence, and possibly overdose) can be enhanced by metabolic interactions within the liver, such as drug-drug, drug-disease, or drug-genetic interactions, or a combination thereof (see case presentations in the following article by Dr. Brennan).

The μ-opioid analgesics have varied responses among individuals, partly because of their unique pharmacodynamics and pharmacokinetics. Pharmacodynamics refers to a drug's effect on the body and involves the receptor-binding properties of a particular drug; pharmacokinetics refers to how the body affects the drug and is influenced by its absorption, distribution, metabolism, and elimination, processes that ultimately affect drug bioavailability.[17,18] This article focuses on the metabolic effects on bioavailability of opioids.

Drugs are metabolized through an array of chemical processes that enhance elimination, generally by making compounds more water soluble for excretion in urine;[17,19] these chemical reactions fall into two categories, both of which are important to opioids. *Phase II reactions* make substances more hydrophilic by conjugation to water-loving substances, such as glucuronic acid, sulfate, glycine, or glutathione. Glucuronidation is the most important Phase II reaction and is catalyzed by uridine diphosphate glucuronosyltransferase (UGT), the enzyme primarily responsible for metabolizing morphine, oxymorphone, tapentadol, and hydromorphone. *Phase I reactions* include hydrolysis and oxidation. Most opioids are oxidatively metabolized; most oxidative metabolism is catalyzed by cytochrome (CY) P450 enzymes, located primarily in the liver, but also in enterocytes in the epithelium of the small intestine.[19] These enterocytes can be an important source of first-pass metabolism by members of the CYP3A enzyme family, in particular, reducing the amount of drug that reaches circulation and becomes bioavailable.[19] Most opioids are lipophilic, allowing them to easily cross the cellular membranes to reach their targets; some undergo extensive first-pass metabolism, reducing their bioavailability.[17] In addition to catalyzing the synthesis and degradation of endogenous steroids, lipids, and vitamins, the CYP450 enzyme system is integral to the metabolism of 40%–50% of all medications, including many opioids.[19–21] The opioids that undergo Phase I metabolism (Table 1) have reactions catalyzed primarily by CYP3A4 and CYP2D6 and are, therefore, more prone to drug-drug interactions with commonly prescribed drugs also metabolized through the CYP450 system (termed *substrates*), such as certain statins, selective serotonin reuptake inhibitors (SSRIs), macrolide antibiotics (e.g., clarithromycin and erythromycin), anti-HIV agents (e.g., ritonavir and delavirdine), calcium channel blockers (e.g., verapamil and diltiazem), steroids,[22] benzodiazepines, β-blockers, and warfarin (Tables 2 and 3).[23]

Opioid metabolism results in the production of both inactive and active metabolites. For example, hydrocodone undergoes oxidative metabolism to form the *inactive metabolite* norhydrocodone by CYP3A4 and the *active metabolite* hydromorphone by CYP2D6 (Table 1).[17] Hydromorphone is 30 times more potent than the *parent compound*, hydrocodone, and also is produced commercially as an opioid analgesic in its own right (a potential misunderstanding in urine toxicology testing).[24] Indeed, several pharmaceutical opioids have active metabolites more potent than their parent compounds, and in the case of prodrugs (e.g., codeine), the parent compound itself is inactive. Furthermore, opioid metabolites can have analgesic activity and/or toxicity. Although the morphine-6-glucuronide metabolite of morphine is better tolerated with higher analgesic potency than its parent compound,[25] morphine-3-glucuronide can cause neurotoxicity, including symptoms such as allodynia and myoclonus.[26]

Sources of Variation in Opioid Hepatic Metabolism

In the pain management setting, use of prescription opioids with other analgesics that use the CYP450 pathway also can lead to drug interactions, which affect the metabolism of both substances. These substrates, inhibitors, or inducers of CYP450 include several antidepressants (e.g., fluoxetine, fluvoxamine, amitriptyline, clomipramine, desipramine, imipramine, and

Table 1
The Metabolism of Opioids[17,20,32,39]

Opioid	Phase I Metabolism	Phase II Metabolism
Morphine	None	Glucuronidated by UGT2B7 (to morphine-3-glucuronide and morphine-6-glucuronide) and by UGT1A3
Codeine	10% *N*-demethylated by CYP3A4 (to norcodeine) 5% *O*-demethylated by CYP2D6 (to morphine)	80% glucuronidated by UGT2B7
Hydrocodone	*O*-demethylated by CYP2D6 (to hydromorphone) *N*-demethylated by CYP3A4 (to norhydrocodone)	CYP-metabolized products (e.g., hydromorphone) glucuronidated by UGTs
Oxycodone	*N*-demethylated by CYP3A4 (to noroxycodone) *O*-demethylated by CYP2D6 (to oxymorphone)	CYP-metabolized products (e.g., oxymorphone) glucuronidated by UGTs
Methadone	*N*-demethylated by CYP3A4, CYP2B6 Minor roles: CYP2C8, CYP2C19, CYP2D6, and CYP2C9	Glucuronidated by UGT2B7 and UGT1A3
Tramadol	*N*-demethylated by CYP3A4 and CYP2B6 *O*-demethylated by CYP2D6	None
Fentanyl	*N*-dealkylated by CYP3A4 (to norfentanyl)	None
Hydromorphone	None	Hepatic glucuronide conjugation by UGT2B7 and UGT1A3 (to hydromorphone-3-glucuronide)
Oxymorphone	None	Hepatic glucuronide conjugation by UGT2B7 and UGT1A3 (minor)
Tapentadol	None	Hepatic glucuronide conjugation by UGT2B7 and UGT1A9

CYP = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferase.

paroxetine),[27–29] cyclooxygenase-2 inhibitor and traditional nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, diclofenac, naproxen, meloxicam, and celecoxib),[27,30] and antiepileptic agents (e.g., diazepam and phenytoin).[27,31] The CYP450 drug-drug interactions are, therefore, relevant to most practitioners, whether primary care or specialty based.

In contrast, opioids metabolized through Phase II reactions (Table 1) have a much lower potential for drug-drug interactions.[17] Few potent inhibitors of the UGT enzymes have been identified and clinically relevant drug-drug interactions involving this enzyme system are uncommon.[32] Hence, the opioids metabolized primarily through the UGT pathways

Table 2
Cytochrome P450 2D6 Substrates, Inhibitors, and Inducers

Substrates		Inhibitors		Inducers
Antiarrhythmic agents	***SSRIs***	***Antiarrhythmic agents***	***Antihistamine***	***Antibiotic***
Encainide	Fluoxetine	Amiodarone	Chlorpheniramine	Rifampin
Flecainide	Fluvoxamine	Quinidine	***Histamine H_2-receptor antagonists***	***Glucocorticoid***
Lidocaine	Paroxetine	***Antipsychotic agents***	Cimetidine	Dexamethasone
Mexiletine	***Tricyclics***	Chlorpromazine	Ranitidine	
Propafenone	Amitriptyline	Reduced haloperidol	***Other drugs***	
Sparteine	Amoxapine	Levomepromazine	Celecoxib	
β-Blockers	Clomipramine	***SNRI***	Doxorubicin	
Alprenolol	Desipramine	Duloxetine	Ritonavir	
Carvedilol	Doxepin	***SSRIs***	Terbinafine	
Metoprolol	Imipramine	Citalopram		
Propranolol	Nortriptyline	Escitalopram		
Timolol	***Other drugs***	Fluoxetine		
Antipsychotic agents	Amphetamine	Paroxetine		
Aripiprazole	Chlorpheniramine	Sertraline		
Haloperidol	Debrisoquine	***Tricyclic***		
Perphenazine	Dextromethorphan	Clomipramine		
Risperidone	***Histamine H_1-receptor antagonists***	***Other antidepressant/ antianxiolytic agents***		
Thioridazine	Metoclopramide	Bupropion		
Zuclopenthixol	Phenformin	Moclobemide		
SNRIs	Tamoxifen			
Duloxetine				
Venlafaxine				

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
Reprinted with permission from Smith.[17]

Table 3

Cytochrome P450 3A4 Substrates, Inhibitors, and Inducers

Substrates			Inhibitors			Inducers
CCBs	***Other psychiatric drugs***	***Antiretroviral agents***	***CCBs***	***Antibiotics***	***Chemotherapeutic agents***	***Statins***
Amlodipine	Aripiprazole	Indinavir	Amlodipine	Ciprofloxacin	4-Ipomeanol	Atorvastatin
Diltiazem	Bromocriptine	Lopinavir	Diltiazem	Clarithromycin	Imatinib	Fluvastatin
Felodipine	Buspirone	Nelfinavir	Felodipine	Erythromycin	Irinotecan	Lovastatin
Nicardipine	Carbamazepine	Nevirapine	Nicardipine	Josamycin	Tamoxifen	Simvastatin
Nifedipine	Donepezil	Ritonavir	Nifedipine	Norfloxacin	***Hormonal therapies***	***Antiretroviral agents***
Verapamil	Haloperidol	Saquinavir	Verapamil	Oleandomycin	Ethinyl estradiol	Efavirenz
Statins	Mirtazapine	Tipranavir	***Statin***	Roxithromycin	Levonorgestrel	Lopinavir
Atorvastatin	Nefazodone	***Chemotherapeutic agents***	Simvastatin	Telithromycin	Raloxifene	Nevirapine
Lovastatin	Pimozide	Cyclophosphamide	***Antiarrhythmic agents***	***Azole antifungal agents***	***Other drugs***	***Hypnotic agent***
Simvastatin	Reboxetine	Docetaxel	Amiodarone	Clotrimazole	Cimetidine	Pentobarbital
Other cardiovascular agents	Risperidone	Doxorubicin	Quinidine	Fluconazole	Disulfiram	***Anticonvulsant agents***
Amiodarone	Valproate	Etoposide	***Phosphodiesterase inhibitor***	Itraconazole	Methylprednisolone	Carbamazepine
Digoxin	Venlafaxine	Gefitinib	Tadalafil	Ketoconazole	Phenelzine	Oxcarbazepine
Ivabradine	Ziprasidone	Ifosfamide	***Psychiatric drugs***	Miconazole	***Foods***	Phenobarbital
Quinidine	***Sleep aids***	Paclitaxel	Bromocriptine	Voriconazole	Bergamottin (grapefruit juice)	Phenytoin
Warfarin	Zolpidem	Tamoxifen	Clonazepam	***Antiretroviral agents***	Star fruit	Primidone
Phosphodiesterase inhibitors	Zopiclone	Teniposide	Desipramine	Amprenavir		Valproic acid
Sildenafil	***Antibiotics***	Vinblastine	Fluoxetine	Atazanavir		***Food***
Tadalafil	Azithromycin	Vindesine	Fluvoxamine	Delavirdine		Cafestol (caffeine)
Benzodiazepines	Clarithromycin	***Hormonal therapies***	Haloperidol	Efavirenz		
Alprazolam	Erythromycin	Estradiol	Nefazodone	Indinavir		
Clonazepam	Oleandomycin	Ethinyl estradiol	Norclomipramine	Lopinavir		
Flunitrazepam	***Azole antifungal agents***	Levonorgestrel	Nortriptyline	Ritonavir		
Midazolam	Itraconazole	Raloxifene	Sertraline	Nelfinavir		
Triazolam	Ketoconazole	Testosterone		Nevirapine		
SSRIs				Saquinavir		
Citalopram				Tipranavir		
Fluoxetine						

CCB = calcium channel blocker; SSRI = selective serotonin reuptake inhibitor.
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(morphine, oxymorphone, tapentadol, and hydromorphone) are less prone to drug interactions than those eliminated using the CYP450 pathways.[33] Indeed, oxymorphone and tapentadol have no known pharmacokinetic drug-drug interactions, and morphine has few.

It is important to recognize that, in addition to pharmacokinetic interactions, all drugs can undergo pharmacodynamic drug-drug interactions.[17] Opioids are affected pharmacodynamically at a receptor level by the antagonists naltrexone and naloxone. In addition, there is an additive effect of opioids with other drugs that affect the central nervous system, such as benzodiazepines, antihistamines, and alcohol. Concomitant administration of these agents can lead to toxicity.[34,35]

The CYP3A4 and CYP2D6 enzymes are prevalent in the liver and are particularly important to drug metabolism, including that of most opioids.[21,36] Moreover, drugs that interact with the CYP450 enzyme system are among the more frequently prescribed.[37] The activity of CYP450 enzymes naturally varies among individuals, but drugs can inhibit or induce enzymatic activity, greatly enhancing variability. For example, CYP3A activity naturally varies fivefold, but drug interactions with the enzyme can increase the range of variability to approximately 400-fold.[19] If unrecognized, these large differences in metabolic activity can affect the substrates of the enzyme, leading to changes in the systemic concentrations of affected medications.

Many drugs can affect the metabolism of opioids and, therefore, their clinical effects. Altered metabolism can result in an opioid or its metabolite exiting the body too rapidly, missing the location of its therapeutic target, or lingering in the body too long and causing toxic effects.[17] For example, drugs that use or inhibit the CYP450 enzyme pathways have the potential to prolong or intensify the effects of opioids such as hydrocodone and oxycodone that use those enzymes for elimination.[24] If metabolism by CYP2D6 and CYP3A4 is blocked or reduced, the systemic concentrations of the opioid can escalate, leading to toxicity through the amplification of both analgesic and adverse μ-receptor effects (including somnolence and respiratory depression).[38] This overt negative outcome is perhaps more dangerous and easily recognized than in the case of inhibition of the bioactivation of a compound, as in the following example.

CYP2D6 *inhibitors* have the potential to obstruct the effects of the prodrug codeine.[28] *Prodrugs* require biotransformation to an active metabolite to achieve the desired effect, such as the oxidation of codeine to morphine to produce analgesia. Blocking codeine metabolism can present as a nonresponse to drug therapy (inadequate or complete lack of analgesia)[28] and may yield a clinical picture of pseudoaddiction and perhaps cause the inappropriate labeling of a patient as a drug seeker. Notably, inhibiting the same enzyme results in opposite effects, either overdosage or nonresponse, dependent on whether the parent opioid taken is an active compound or a prodrug, respectively.[27] According to the authors of a study of drug dispensing data that included the CYP2D6-inhibiting SSRI antidepressants fluoxetine and paroxetine, drug-drug interactions that result in a nonresponse can easily be overlooked and neglected in clinical practice.[28]

Alternatively, *inducers* of CYP2D6 activity would have the opposite effect—boosting the enzymatic activity. This may cause rapid elimination of certain opioids (such as hydrocodone), thereby minimizing the analgesic benefit; on the other hand, it may foster the rapid conversion of the prodrug codeine to morphine, potentially causing overdose. Table 2 lists the inhibitors, substrates (which compete for binding to the same enzyme and have outcomes similar to inhibitors), and inducers of the CYP2D6 enzyme. The time course of the effects of inducers can be difficult to predict because of several factors, including drug half-lives and enzyme turnover.[39] As described in the review by Lin and Lu,[40] large interindividual variability in P450 induction has been recorded in the literature from human studies. In addition to the polymorphisms of P450 genes, genetic variations of the receptors, intracellular and tissue concentration of the inducers, physiological factors (hormones, development, and disease), and environmental elements (diet and pollutants) can all affect the induction of drug-metabolizing enzymes.[40] Thus, it is the interaction of genetic and epigenetic factors that determines an individual's responsiveness to a given inducer. Substrates,

inhibitors, and inducers of CYP3A4 enzyme, such as carbamazepine, statins, benzodiazepines, and chemotherapeutic agents, also are prone to involvement in clinically important drug-drug interactions (Table 3).[17] Drug interactions involving CYP3A4 affect the opioids metabolized primarily through that enzyme family: fentanyl, oxycodone, and methadone.[17] Oxycodone also is partially metabolized through CYP2D6, whereas tramadol, another prodrug, undergoes metabolism through both as well.[17]

Recently, a drug-opioid interaction study demonstrated the significance of the combined effect of inhibiting both the CYP3A4 (by an antifungal agent, itraconazole) and CYP2D6 pathways (by the SSRI, paroxetine) on oxycodone metabolism.[29] Notably, because oxycodone is metabolized through two different CYP450 isoforms, if one mechanism is blocked, then typically the other can compensate, reducing the risk of clinically important drug-drug interactions. Inhibiting one path did not have a significant effect on the pharmacokinetics of oxycodone; however, inhibiting both CYP450 pathways decreased the oral clearance of oxycodone by 64% and increased the systemic concentrations by 188% ($P < 0.001$ for both).[29]

Because the adverse events associated with drug-drug interactions can be serious, and as more drug metabolic pathways are being characterized, CYP450 information is now more commonly included in prescribing information. For example, a black box warning in the prescribing information for oxycodone hydrochloride controlled-release tablets advises that the risks associated with drug-oxycodone metabolic interactions are serious. Enhanced monitoring and dosage adjustments are required if the opioid is concomitantly used with CYP450 3A4 inhibitors.[41] Furthermore, if oxycodone is taken with a CYP450 3A4 inducer, then either the lack of efficacy or the development of a withdrawal/abstinence syndrome may result.[41] Meanwhile, the blueprint for the Prescriber Continuing Education Program element of the U.S. Food and Drug Administration's Risk Evaluation and Mitigation Strategies, developed to enhance the safe management of patients taking extended-release or long-acting opioids, recommends knowledge of the underlying pharmacodynamics and pharmacokinetics of opioids, as well as of their potential drug interactions. Specifically, CYP450 inducers and inhibitors are highlighted for their potential interactions with some opioids.[42]

To avoid the potential for drug-drug interactions in patients who have complicated medication regimens, such as older adults, treatment with an opioid that is not metabolized by the CYP450 system can be prescribed. Potential interactions between CYP450-metabolized opioids and other concomitantly administered drugs that use or affect this pathway should be monitored by careful dose adjustments, vigilant therapeutic drug monitoring, and prompt medication changes in the event of toxicities.[17,22]

A broad range of foods and beverages also can alter hepatic CYP450 enzyme activity, again having the potential to affect opioid metabolism. For example, CYP1A2 activity can be enhanced by smoked foods[43] and induced by indole-containing foods and vegetables such as cabbage and cauliflower, as well as by components of garlic.[44,45] Organosulfur compounds such as diallyl sulfide—a major flavor component in garlic—as well as its metabolites are known to competitively inhibit CYP2E1.[45] CYP3A4 also can be induced by garlic[45,46] and a component of unfiltered coffee, cafestol,[17] and grapefruit phytochemicals strongly inhibit CYP3A4 and CYP2C9.[47] CYP3A4 activity is also significantly induced by St. John's Wort, a perennial weed commonly used to treat mild-to-moderate depression.[48,49]

Clinical Implications of Genotype and Phenotypic Alterations in Metabolism

Pharmacogenetic testing represents an emerging technology in medicine. Inherent pharmacogenetic differences such as duplications, deletions, and single nucleotide polymorphisms in the genes that encode the CYP450 enzymes, particularly CYP3A4 and CYP2D, can dramatically affect the metabolic capacity of an individual, leading to the under- or overexposure to an opioid. Many of these genetic alterations from wild-type genes lead to changes in enzyme capacity; they are well characterized through studies such as the Human Genome Project and they are not rare.[20] Indeed, more than 100 different alleles of

CYP2D6 have been identified, with various combinations resulting in activity levels described as ultrarapid, extensive, intermediate, or poor metabolizers.[20,50,51] Extensive metabolizers are considered normal, and standard drug dosing schedules are configured for people with this enzyme capacity. Intermediate metabolizers have a range of metabolic capacity less than extensive metabolizers. A range of severity within the poor metabolizer group also has been observed, with the most extreme cases associated with a serious inability to clear medications and the potential for serious side effects because of lack of any functional CYP2D6 enzyme.

Ultrarapid metabolizers rapidly clear medications and thereby can minimize or eliminate the therapeutic response from active parent opioids. Individuals with ultrarapid or limited enzymatic capacity can have either an increased risk of adverse effects from higher than expected systemic concentrations of an active compound (either parent or metabolite) or be prone to inadequate analgesic responses when an active opioid does not become bioavailable. For example, rapid conversion of the prodrug tramadol to the active metabolite *O*-desmethyltramadol can result in an overdose, whereas rapid conversion of fentanyl to its inactive metabolite norfentanyl could lead to a lack of pain relief.[17] Although even extensive metabolizers can experience drug-drug interactions when CYP2D6 is inhibited or induced, individuals with ultrarapid or poor metabolic capacity have a higher risk of systemic drug concentrations straying outside the therapeutic range. For example, poor metabolizers of tramadol have 14-fold lower concentrations of the active metabolite *O*-desmethyltramadol and, therefore, may have inadequate pain relief.[17]

Still, a new study of a diverse cancer population treated with oxycodone did not find a relationship between genetic metabolic capacity and pain intensity after analgesic treatment.[52] Genomic testing of CYP2D6 categorized the participants as ultrarapid ($n = 10$), extensive ($n = 413$), or poor metabolizers ($n = 27$), and laboratory testing measured serum levels of oxycodone and its metabolites. Statistically significant different serum levels of the active metabolite oxymorphone among the genetic groups ($P < 0.000$) did not translate into a clinical difference in oxycodone requirements or analgesic efficacy ($P = 0.8$).[52]

Because of the research conducted, in particular by the Human Genome Project and by the SNP Consortium, the increased availability of genetic information has enabled better connections to be established between specific alleles of individual genes to painful disease states and responses to analgesics.[27,53–55] Genotyping is available to identify the known clinically relevant allelic variants of *CYP450* genes that have the potential to affect drug metabolism; indeed, genetic testing, already diagnostic for 2000 clinical conditions, is expected to undergo an exponential growth from that which is currently available.[56] Clinicians need to stay abreast of the clinical availability and utility of pharmacogenetic testing, especially as it relates to pain medicine.

Disease and Age-Associated Effects on Opioid Metabolism

Because the liver is the main site for most of opioid metabolism, hepatic impairment can significantly alter the bioavailability of an opioid and its metabolites.[17,57,58] Opioids metabolized through the CYP450 system as well as through glucuronidation can be affected by liver disease, such as cirrhosis.[17] Dose reductions for most opioids may be necessary for patients with hepatic impairment; indeed, some individuals with severe cirrhosis require higher doses of methadone to offset the loss of capacity of the sponge-like hepatic tissue that stores and releases methadone in healthy individuals.[59] Extreme caution is warranted when using any opioid in individuals with liver disease.[17]

Similarly, dose adjustments are necessary for patients with renal disease because most opioids are eliminated through urine, although methadone and fentanyl elimination seem to be less affected by renal impairment.[58] Furthermore, with older age, opioid doses may need to be reduced, as glomerular filtration rate declines.[60,61] Renal impairment can differentially affect various opioids and their metabolites.[17] For example, individuals with impaired kidney function have a higher risk of accumulating a metabolite of morphine, morphine-6-glucuronide, or a metabolite of hydromorphone, hydromorphone-6-glucuronide, and consequently experiencing neurotoxic effects.[59]

Certainly, dose reductions; prolongation of the dose interval; or at minimum, initiating therapy with a low dose and slowly titrating the dose upward is prudent in patients with renal impairment.

Conclusions

Individualized patient care is the future of medicine. Given the combination of genetic, physiological, nutritional, disease, pharmaceutical, and environmental factors that influence an individual's response to an opioid,[27] initiating opioid therapy should be considered a trial, wherein adjustments are to be expected to identify a regimen that provides adequate pain relief without intolerable adverse effects. The lowest dose should always be started, with appropriate interval titration, especially in the opioid-naïve patient. Multiple trials involving different opioids may be necessary to achieve this. Consideration should be given to analgesics not metabolized significantly via the CYP450 enzyme system. To avoid adverse effects associated with the drug-drug interactions, particular care should be taken with older adults, medically complicated patients (such as those with impaired immunity or inflammation), patients with impaired renal or hepatic function, and in cases involving polypharmacy.

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