

Opioid Pharmacokinetic Drug-Drug Interactions

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Abstract

Pharmacokinetic drug-drug interactions (DDIs) involving opioid analgesics can be problematic. Opioids are widely used, have a narrow therapeutic index, and can be associated with severe toxicity. The purpose of this review is to describe pharmacokinetic DDIs associated with opioids frequently encountered in managed care settings (morphine, codeine, oxycodone, oxymorphone, hydrocodone, hydromorphone, fentanyl, tramadol, and methadone). An introduction to the pharmacokinetic basis of DDIs is provided, and potential DDIs associated with opioids are reviewed. Opioids metabolized by the drug metabolizing enzymes of the cytochrome P450 (CYP450) system (codeine, oxycodone, hydrocodone, fentanyl, tramadol, and methadone) are associated with numerous DDIs that can result in either a reduction in opioid effect or excess opioid effects. Conversely, opioids that are not metabolized by that system (morphine, oxymorphone, and hydromorphone) tend to be involved in fewer CYP450-associated pharmacokinetic DDIs.

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For author information and disclosures, see end of text.

Adverse drug reactions (ADRs) are a significant problem, resulting in substantial morbidity, mortality, and healthcare expenses.¹ In 2004, 1.2 million hospitalized patients experienced an ADR, 90% of which were due to a medication that was properly administered.² Drug-drug interactions (DDIs) are an important and potentially preventable source of ADRs. DDIs can be broadly categorized as pharmacokinetic or pharmacodynamic; pharmacokinetic DDIs occur when a drug (the “precipitant drug”) causes a change in the absorption, distribution, metabolism, and/or elimination (“ADME”) of another drug (the “object drug”). These interactions can lead to either loss of efficacy or toxicity of the object drug. Pharmacodynamic DDIs result when 2 drugs are coadministered and the concentration-response curve of 1 or both drugs is altered without a change in the object drug’s pharmacokinetics.³

Opioid analgesics are widely used in the treatment of both cancer-related and noncancer-related pain. In consensus guidelines, chronic opioid therapy is proposed as an option for patients with moderate to severe chronic noncancer pain, where the pain is impacting their quality of life, and the potential benefits of opioids are expected to outweigh the risks.⁴ Similarly, in elderly patients, consideration of opioid therapy is recommended for all patients with moderate to severe pain, pain-related functional impairment, or pain-related diminished quality of life.⁵

As a drug class, opioids are associated with a narrow therapeutic index, wide interindividual variability in response (eg, doses used in an opioid-tolerant patient can be fatal to an opioid-naïve patient), and potentially life-threatening toxicity. As the prevalence of opioid use has increased, serious adverse reactions and deaths associated with opioids have also increased.⁶ Although there have been substantial efforts to improve the safety of opioids in clinical practice, much of this effort has been directed to prevention of misuse and diversion, and management of chronic adverse effects.⁷ In contrast, the importance of pharmacokinetic DDIs related to opioids has received little attention. For example, in a systematic review of publications that described “opioid related problems,” 105 publications including 156 patients were identified; of these, approximately 30% described opioid-associated DDIs.⁸ Moreover, in a series of analyses evaluating opioid users with chronic low back pain and osteoarthritis in a managed care

database, approximately 30% of patients identified were taking opioids metabolized by the cytochrome P450 (CYP450) system and were also exposed to other CYP450 substrates, including potentially interacting drugs.^{9,10} Consequences of pharmacokinetic DDIs associated with opioids can include excess opioid effects (including fatal toxicity), loss of analgesic efficacy, predisposition to other adverse effects, relapse to illicit or inappropriate drug use, and misinterpretation of opioid screening results.

Purpose and Scope

The purpose of this review is to describe potential DDIs associated with opioids that are frequently encountered in managed care (morphine, codeine, oxycodone, oxycodone, hydrocodone, hydromorphone, fentanyl, tramadol, and methadone). The focus will be on pharmacokinetic DDIs involving the CYP450 system where the opioid is the object drug (ie, we will not address the potential for some opioids to impact the disposition of other drugs, nor will we address pharmacodynamic interactions such as excessive sedation when an opioid is used with a benzodiazepine; although each of these categories of interactions can be clinically important, they are beyond the scope of this review). We will first provide a brief overview of the pharmacokinetic basis of opioid drug interactions, and then will review potential DDIs associated with opioids. Where relevant, we will also briefly address the impact of genetic factors (ie, “pharmacogenetics”) on predisposition to drug interactions. A complete review of the pharmacogenetics of opioids is outside of the scope of this manuscript.

Pharmacokinetic Basis of Opioid Drug Interactions

The manifestation of opioid toxicity or lack of efficacy can occur due to several clinical consequences including pharmacokinetic DDIs. In general, opioids share common metabolic pathways, many through the CYP450 enzymatic system. Therefore, clinicians have the tools to avoid potential DDIs by switching the precipitating drug or altering the opioid dose. However, given the common use of opioids, many patients are concurrently prescribed drugs that could precipitate a DDI.^{9,10} The focus of this section is to review fundamental concepts of drug metabolism as they relate to the opioid analgesics. Additionally, this section will introduce pharmacogenetic concepts as they relate to variability in DDIs with opioids.

Fundamental Concepts of Pharmacokinetics and Opioid Metabolism

Drugs that interfere with the pharmacokinetics of opioids generally do so by altering their elimination.¹¹ The overall

elimination of opioids from the systemic circulation refers to the irreversible removal from the body by all routes. The concept of drug elimination can be divided into 2 major physiologic components, metabolism and excretion.³ Excretion refers to the removal of drug from the body, commonly through the kidney or biliary secretion. Clearance describes the efficiency of irreversible drug elimination from the body through metabolism or excretion.³

In general, the clinically significant DDIs that involve opioids occur through modulation of drug metabolism. The major metabolizing organ in the body is the liver, although the gastrointestinal tract and other organs also have metabolizing capacity.³ Drug metabolism can be broken down into 2 fundamental elements termed Phase I and Phase II metabolism.³

Phase I Opioid Metabolism

Phase I metabolism refers to the modulation of a molecular structure of endogenous or exogenous substances (eg, drugs) through chemical reactions such as oxidation, reduction, or hydrolysis. The predominant catalysts for Phase I metabolism of drugs are found in the CYP450 enzymatic system.³ The opioids that are metabolized by CYP450 include codeine, hydrocodone, oxycodone, methadone, tramadol, and fentanyl.¹² The CYP450 system comprises distinct isozymes that are responsible for drug metabolism. Of these isoenzymes, CYP3A and CYP2D6 are primarily responsible for opioid metabolism through the CYP450 system, with CYP2B6 also contributing to methadone metabolism. The metabolic pathways of the opioids are presented in **Table 1**.

The CYP3A isoenzyme is responsible for the metabolism of approximately 50% of all drugs currently available. The functional component of the CYP3A enzyme that is most likely relevant to opioid metabolism is CYP3A4.¹³ In general, CYP3A4 is responsible for opioid metabolism but the capability of CYP3A5 to metabolize opioids has not been thoroughly assessed for many of the drugs. CYP3A5 is polymorphically expressed, and some patients do not have functional CYP3A5 alleles.¹³ This is important because many CYP3A4 substrates have overlap with CYP3A5 and catalyze the formation of the same metabolites. Therefore, patients without functional CYP3A5 alleles may appear to have decreased CYP3A4 activity and this may influence the degree of DDI.

The CYP2D6 isoenzyme is also an important CYP450 enzyme that metabolizes several opioid analgesics.¹² The CYP2D6 enzyme is polymorphically expressed and patients have varying degrees of CYP2D6 activity with a small percentage of the population having no enzyme activity.^{14,15}

■ **Table 1.** Metabolic Pathways of Common Opioids^{12,83}

Opioid	Phase I Metabolism	Phase II Metabolism
Codeine	CYP2D6 CYP3A	UGT2B7
Hydrocodone	CYP2D6 CYP3A	UGT1A3 UGT2B7 Dihydromorphone ketone reductase
Oxycodone	CYP3A CYP2D6	UGT2B7
Methadone	CYP3A CYP2B6 CYP2D6 CYP2C9 ^a CYP2C19 ^a	
Tramadol	CYP3A CYP2D6	
Fentanyl	CYP3A	
Morphine	CYP3A	UGT2B7
Hydromorphone		UGT1A3 UGT2B7 Dihydromorphone ketone reductase
Oxymorphone		UGT2B7

^aMinor pathways/clinical significance unknown.
Adapted from Smith HS. *Mayo Clin Proc.* 2009;84(7):613-624 and Fredheim OM, Moksnes K, Borchgrevink PC, Kaasa S, Dale O. *Acta Anaesthesiol Scand.* 2008;52(7):879-889.

The CYP2D6 metabolizing phenotypes can be described as ultrarapid metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM), and poor metabolizer (PM). CYP2D6 PMs have little to no CYP2D6 function and therefore do not metabolize opioid substrates through this pathway. This can greatly diminish the analgesic effects of opioid prodrugs (as discussed below) that require CYP2D6 to form active metabolites, such as hydrocodone and codeine.

Phase II Opioid Metabolism

Phase II metabolism refers to a chemical reaction in which a drug is conjugated with a chemical moiety such as a glucuronide, which promotes drug excretion through the kidneys.³ In almost all cases, the conjugated drug is rendered inactive and loses biological activity. However, morphine represents an important exception and is an example of a conjugated compound (morphine-6-glucuronide) that maintains its analgesic effect. The most abundant Phase II enzyme to metabolize the opioid analgesic class is UDP-glucuronosyltransferase-2B7 (UGT2B7).¹⁶ This enzyme is the primary route of elimination for morphine, hydromorphone, and oxymorphone.

Prodrugs

A drug that is administered in a biologically inactive form and is biotransformed into an active metabolite is termed a prodrug. Hydrocodone and tramadol are prodrugs that are converted to active forms by CYP450 isoenzymes.¹² Additionally, codeine is metabolized into morphine through CYP2D6, which contributes a greater analgesic effect than codeine.¹⁷⁻¹⁹ The consideration of drug interactions involving opioid prodrugs is important because they can be clinically manifested in the opposite manner from an active parent drug. For example, the decreased metabolism of a prodrug would result in a decreased analgesic effect and potential treatment failure, whereas the decreased metabolism of an active parent drug would enhance an analgesic effect and potentially lead to opioid toxicity.

CYP450 Inhibition vs Induction—Potential DDIs and Clinical Manifestations

Drugs that are metabolized by CYP450 enzymes are considered substrates for that system. In general, the coadministration of an opioid that is metabolized by the CYP450 system and another substrate of the same enzyme will not result in a drug interaction. The metabolic capacity of the P450 system can maintain the burden of 2 substrates in most situations. However, when a substrate has a high affinity for the CYP450 isoenzyme and is at a concentration that can occupy most or all of the enzyme’s catalytic sites, there can be competition. This drug would be considered a substrate and also a competitive inhibitor of the CYP450 isoenzyme. Some drugs can inhibit CYP450 isoenzymes by other mechanisms and even without being substrates. For the purposes of this review drugs that inhibit CYP450 by any mechanism will be referred to as CYP450 inhibitors. Drugs that can inhibit CYP3A or CYP2D6 and are most likely to interact with certain opioids are presented in **Table 2**.

In addition to inhibition, drugs can induce the activity of CYP450 isoenzymes and enhance the metabolism and, therefore, clearance of certain opioids. Drugs

that induce CYP450 enzymes predominantly do so by activating transcription factors that upregulate enzyme expression.³ Therefore, a drug interaction manifested following the administration of a CYP450 inducer generally takes longer to reach maximal effect (eg, several days to weeks) than a drug interaction due to inhibition, which can manifest immediately. Inducers of CYP450 generally enhance the activity of more than 1 isoenzyme. CYP3A is an inducible enzyme but CYP2D6 does not respond to CYP450 induction. Therefore, DDIs with opioids due to induction are mainly limited to those that are metabolized by CYP3A and CYP2B6. The drugs that can induce CYP3A and CYP2B6 that are likely to interact with the opioids that are metabolized by these pathways are also presented in Table 2.

The clinical effects of drug interactions with opioids that are metabolized by UGT2B7 have not been well delineated. In vitro data suggest that inhibition of UGT2B7 may confer a drug interaction, although clinical data are very limited.²⁰⁻²⁶ This review will focus on clinically relevant CYP450 interactions given the current lack of data with UGT2B7.

■ **Table 2.** CYP2D6, CYP3A, and CYP2B6 Inhibitors and Inducers^{91,a}

CYP450 Inhibitors			CYP450 Inducers	
CYP2D6	CYP3A	CYP2B6	CYP3A4	CYP2B6
Amiodarone ^b	Amiodarone ^b	Clopidogrel	Carbamazepine	Artemisinin
Bupropion	Chloramphenicol	Thiotepa	Dexamethasone	Carbamazepine
Celecoxib	Cimetidine	Ticlopidine	Efavirenz	Efavirenz
Chlorpromazine	Ciprofloxacin	Voriconazole	Modafinil	Nevirapine
Cimetidine	Clarithromycin ^b		Nevirapine	Phenobarbital
Cinacalcet	Delavirdine		Oxcarbazepine	Phenytoin
Citalopram	Diltiazem ^b		Phenobarbital	Rifampin
Clemastine	Dronedarone		Phenytoin ^b	
Diphenhydramine	Erythromycin ^b		Rifabutin	
Doxepin ^c	Fluconazole ^b		Rifampin ^b	
Doxorubicin ^c	Fluoxetine		St. John's wort	
Dronedarone	Fluvoxamine		Troglitazone ^b	
Duloxetine ^c	Gestodene			
Escitalopram ^c	Indinavir			
Fluoxetine ^b	Itraconazole ^b			
Haloperidol	Ketoconazole ^b			
Hydroxyzine	Mibefradil			
Levomopromazine	Mifepristone			
Methadone	Nefazodone			
Metoclopramide	Nelfinavir			
Mibefradil ^b	Norfloxacin ^c			
Paroxetine ^b	Ritonavir			
Perphenazine	Saquinavir			
Quinidine ^b	Telithromycin			
Ranolazine	Verapamil ^b			
Ritonavir	Voriconazole ^b			
Sertraline				
Terbinafine ^b				
Thioridazine ^b				
Tripelennamine				

CYP450 indicates cytochrome P450.

^aData are compiled from in vitro and in vivo evidence.

^bThese drugs may have the most clinically significant interactions with opioids due to strength of CYP450 inhibition or induction and frequency of administration.

^cWeak or questionable inhibitors.

Adapted from Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>. Published 2007. Accessed July 1, 2011.

General Clinical Manifestations of Drug Interactions With Opioids

CYP450 inhibitors can lead to excessively high serum concentrations of the parent opioid drug. This may increase the incidence of side effects if the parent drug is active, or it may decrease efficacy if it is a prodrug. In contrast, inducers

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can lead to lower than expected serum concentrations of the parent drug. This can lead to a reduced effect if the parent drug is active or an enhanced effect if it is a prodrug. For example, if hydrocodone is administered with a CYP2D6 inhibitor, a decreased analgesic effect would be expected, with the potential for a treatment failure. However, if a CYP2D6 inhibitor was administered with the CYP2D6 substrate, methadone, an enhanced analgesic effect and potential toxicity could be expected. The differences in the clinical manifestations of interactions with hydrocodone and methadone are due to the difference between active and inactive (prodrug) parent drugs.

Metabolism and Interactions With Opioids

Morphine

Morphine can be administered directly as a parent drug, or it can be formed following the administration of prodrug opioids (eg, codeine). Morphine is primarily metabolized via UGT2B7. The resulting metabolites are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The M6G metabolite contributes an analgesic effect that has been suggested to be greater than the parent, morphine.²⁷ The M6G is produced to a lesser extent (15%) compared with the inactive M3G metabolite (55%) from morphine.^{28,29} There are minimal pharmacokinetic changes between morphine, M6G, and M3G in human studies with UGT inhibitors.^{21,30,31} In addition to UGT2B7, other Phase II enzymes may contribute to morphine's metabolism to a lesser extent.³²

There are data to suggest that CYP3A and potentially other isoenzymes convert morphine into an inactive metabolite, normorphine.³³ However, the clinical relevance of CYP3A modulation through drug interactions has not been adequately documented.

Codeine

Codeine has a high potential for drug interactions since it is metabolized by both the CYP450 2D6 and 3A isoenzymes. Codeine confers most of its analgesic effects through the formation of its metabolites.¹⁷⁻¹⁹ The metabolites that account for the analgesic effects of codeine are morphine and M6G.³⁴ Morphine is formed following an *O*-demethylation of codeine catalyzed by CYP2D6. Morphine is then converted to M3G and M6G by glucuronidation, as previously mentioned. Thus, if CYP2D6 is pharmacologically or genetically inhibited, morphine and M6G formation will be inhibited. Indeed, codeine has been reported to be devoid of analgesic activity in patients that exhibit the CYP2D6 PM phenotype or when CYP2D6 is inhibited with quinidine.³⁵ Table 2 lists

CYP2D6 inhibitors that may interact with codeine. In addition to CYP2D6, codeine is metabolized by CYP3A to the inactive metabolite norcodeine.

Codeine also undergoes Phase II metabolism to codeine-6-glucuronide (C6G) by UGT2B7. However, the UGT2B7 inhibitor diclofenac did not influence the transformation of codeine to codeine-6-glucuronide in a pharmacokinetic study in healthy volunteers.²¹ Thus this pathway seems unlikely to contribute to drug interactions with codeine.

While there are limited data, inhibitors of CYP3A would be expected to increase concentrations of codeine, and therefore, enhance its conversion to morphine.³⁶ In 1 reported case, a breast-feeding mother who was a CYP2D6 UM received a CYP3A inhibitor with codeine. The inhibition of the CYP3A pathway paired with the genetically rapid formation of morphine resulted in toxic morphine concentrations in the breast milk and subsequent infant death.³⁷ Alternatively, CYP450 inducers such as rifampin have similar clinical consequences to CYP2D6 inhibitors when coadministered with codeine. The induction of CYP3A by rifampin will enhance codeine's conversion to the inactive metabolite, norcodeine. Since CYP2D6 is not an inducible enzyme, the conversion to morphine may be decreased when CYP3A is induced.³⁸

Oxycodone

Oxycodone is metabolized in the liver by CYP3A (approximately 80%) to the inactive metabolite noroxycodone, and to a lesser extent by CYP2D6 (less than 10%) to the active metabolite oxymorphone; oxymorphone is subsequently inactivated by UGT2B7 (and potentially other UGT enzymes, including UGT1A3) to oxymorphone-6-glucuronide.^{12,39,40} Numerous interactions between oxycodone and CYP3A inhibitors and inducers have been reported. In controlled trials with healthy volunteers, the CYP3A inhibitors telithromycin, itraconazole, ketoconazole, miconazole, voriconazole, ritonavir, lopinavir, and grapefruit juice all substantially increased oxycodone exposure, generally resulting in increased opioid effects.⁴¹⁻⁴⁹ The product information for oxycodone products contains a "black box warning" cautioning about the concomitant use of oxycodone and CYP3A4 inhibitors, due to the potential risk of adverse effects, including potentially fatal respiratory depression.⁵⁰ Of note, inhibition of CYP3A may also result in increased oxymorphone exposure, which could also contribute to the increase in opioid effects.⁴⁷ Conversely, CYP3A inducers, including rifampin and St. John's wort, substantially decrease oxycodone (and potentially oxymorphone) exposure, resulting in diminished opioid effects.^{51,52} In general, concomitant

use of documented CYP3A inhibitors and inhibitors (Table 2) results in clinically important DDIs in patients using oxycodone.

In contrast to the well-defined role of CYP3A in contributing to drug interactions with oxycodone, the role of CYP2D6-mediated drug interactions on the effects of oxycodone is controversial. The parent molecule (oxycodone) has potent analgesic activity, and plasma concentrations of the active metabolite, oxymorphone, are much lower than those of oxycodone, so that the relative importance of oxymorphone is not clear.⁴⁵ In a controlled clinical trial, the CYP2D6 inhibitor paroxetine decreased oxymorphone exposure following oxycodone administration; however, this had limited effects on plasma concentrations of oxycodone and minimal impact on opioid pharmacodynamic effects.^{45,51} Similar results were also observed with the CYP2D6 inhibitor quinidine.⁵³ In contrast, in a recent controlled study conducted by Kummer et al, paroxetine blunted the pupillary response and analgesic effects of oxycodone in 12 healthy CYP2D6 EMs.⁴² Moreover, in a study by Samer et al, quinidine-mediated CYP2D6 inhibition in subjects administered oxycodone resulted in both a reduction in oxymorphone exposure and some reduced opioid effects.⁴¹

Oxymorphone

As indicated above, oxymorphone undergoes minimal CYP450 metabolism, and is metabolized primarily by UGT2B7 (and potentially UGT1A3) to the inactive metabolite noroxymorphone.^{12,39,40} As such, pharmacokinetic DDIs are not expected with oxymorphone.

Hydrocodone

Hydrocodone is a prodrug opioid, and the parent compound is a relatively weak μ -receptor agonist.⁵⁴ Hydrocodone is metabolized into its active moiety, hydromorphone, by CYP2D6.^{55,56} Hydromorphone is subsequently metabolized via UGT enzymes and dihydromorphone ketone reductase.^{57,58} Hydrocodone may also be metabolized by CYP3A to the inactive metabolite norhydrocodone, although the extent of CYP3A metabolism of hydrocodone is unclear.⁵⁵ Despite the known metabolism of hydrocodone by CYP2D6 and CYP3A, very limited clinical data exist regarding drug interactions due to changes in hydrocodone metabolism.⁵⁵ Intuitively, CYP2D6 inhibitors would be expected to decrease hydromorphone formation, and potentially result in diminished opioid analgesia. Conversely, it is possible that use of CYP3A inhibitors and inducers could result in potentiated or diminished opioid actions, respectively. CYP2D6 inhibition by quinidine in CYP2D6 EMs resulted in diminished hydromorphone

exposure, and similar subjective responses to hydrocodone as reported by PMs.⁵⁶ In contrast, in another study conducted in healthy volunteers, hydrocodone effects were similar in CYP2D6 PMs and EMs and CYP2D6 inhibition with quinidine did not affect hydrocodone-mediated changes in pupil diameter or subjective opioid effects.⁵⁹ In summary, CYP2D6 inhibitors decrease the formation of the active hydrocodone metabolite hydromorphone. Although the clinical importance of this reduction in hydromorphone is not clear, this may result in a reduction in opioid effects, particularly in CYP2D6 EMs.

Hydromorphone

Hydromorphone is primarily metabolized via UGT1A3, UGT2B7, and dihydromorphone ketone reductase, and undergoes minimal CYP450 metabolism.^{57,58,60,61} Based on information available to date, hydromorphone is unlikely to be associated with pharmacokinetic DDIs based on its metabolism.

Fentanyl

Fentanyl undergoes extensive hepatic metabolism. CYP3A enzymes are predominantly responsible for the metabolism of fentanyl to norfentanyl, although other CYPs may play a minor role.^{62,63} Multiple studies have demonstrated the presence of interactions between fentanyl and CYP3A modulators. CYP3A inhibitors (including fluconazole, voriconazole, ritonavir, and troleandomycin) increased fentanyl exposure and decreased fentanyl clearance in controlled clinical trials, and case reports suggest similar interactions with the CYP3A inhibitors diltiazem and cyclosporine.⁶⁴⁻⁶⁸ Although data regarding the effects of CYP3A induction on fentanyl disposition are more limited, at least 2 case reports and 1 controlled study indicate increased fentanyl clearance and diminished fentanyl concentrations and opioid effects when fentanyl is coadministered with rifampin.⁶⁹⁻⁷¹ Interactions between fentanyl and CYP3A inhibitors are well documented, and are of clinical importance. The product information for fentanyl products contains a "black box warning" cautioning about the concomitant use of fentanyl and all CYP3A4 inhibitors, due to the potential risk of adverse effects, including potentially fatal respiratory depression.⁷² Similarly, the use of CYP3A inducers may be associated with a reduction in response to fentanyl. Therefore, coadministration of fentanyl and CYP3A inhibitors and inducers (Table 2) should be avoided.

Tramadol

Over 70% of a dose of tramadol is metabolized by CYP2D6 and CYP3A.^{73,74} Tramadol and its CYP2D6 metabolite (M1) are both active and contribute to the analgesic effects of

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tramadol. The CYP3A metabolite (M2) is inactive. Both metabolites are further metabolized (via demethylation, glucuronidation, and sulfation) and eliminated via urinary excretion.^{75,76} CYP2D6 inhibition results in decreased formation of the active M1 metabolite, and increased exposure to the parent drug; however, because both the parent compound and the M1 metabolite are active, the clinical importance of CYP2D6 inhibition is not clear.⁷⁷⁻⁸⁰ In studies conducted in CYP2D6 EMs, CYP2D6 inhibition with paroxetine resulted in a reduction of tramadol-associated pupillary dilation, and a diminishment of some, but not all, opioid effects.^{78,79} In contrast, escitalopram, a weak CYP2D6 inhibitor, has no effects on the analgesic effects associated with tramadol.⁸⁰ Data regarding CYP3A modulation of tramadol are sparse. Cimetidine (a combined CYP2D6 and CYP3A inhibitor) moderately increases exposure to tramadol (although these changes are not likely to be clinically important) and carbamazepine (a CYP3A inducer) reduces exposure to tramadol.^{74,81} Based on studies conducted in healthy volunteers, CYP2D6 inhibitors appear to reduce some analgesic effects of tramadol, although this effect is variable. Therefore, concurrent use of CYP2D6 inhibitors (Table 2) and tramadol should be avoided if possible. Despite the limited data regarding the impact of CYP3A inhibition, CYP3A inhibitors (Table 2) may be expected to increase exposure to tramadol, and if possible, should be avoided in patients using tramadol. Conversely, use of CYP3A inducers (Table 2) may reduce tramadol exposure, and patients should be monitored for inadequate analgesia if such combinations cannot be avoided. It is important to note that tramadol has been associated with serious adverse effects including serotonin syndrome and seizures, and inhibition of tramadol metabolism either via CYP2D6 or CYP3A inhibition could raise safety concerns.⁸¹

Methadone

Methadone has a complex pharmacokinetic profile marked by substantial interindividual pharmacokinetic variability and is associated with numerous drug interactions. Methadone exhibits a very long terminal elimination half-life (on average from 20 to 35 hours, ranging from 5 to 130 hours) and in general, steady-state is not achieved for approximately 2 weeks after initiation of therapy or changes in dose.^{82,83} Methadone is metabolized by CYP3A and CYP2B6, with potential contribution from CYP2D6, CYP2C9, and CYP2C19 (Table 1), and is a substrate for the transporter P-glycoprotein.^{82,84,85} Because of the complexity of methadone's metabolism and the numerous drug interactions associated with methadone, a complete review of these interactions is beyond the scope

of this review. In general, a multitude of interactions with CYP3A inhibitors have been reported, including but not limited to interactions with fluconazole, voriconazole, ciprofloxacin, erythromycin, and grapefruit juice, resulting in a reduction in methadone clearance and potential toxicity.^{82,86-89} Methadone has been associated with the ventricular arrhythmia torsades de pointes, and a potential association between methadone-induced torsades de pointes and CYP3A inhibition has been reported.⁹⁰ CYP3A inducers, including but not limited to rifampin, carbamazepine, phenobarbital, phenytoin, and St. John's wort, may induce the metabolism of methadone and reduce methadone exposure, to the extent that opioid withdrawal is possible.^{85,88} CYP2B6 inhibitors (Table 2) may also decrease the metabolism of methadone (increasing opioid effects) and CYP2B6 inducers (Table 2) can induce methadone metabolism, decreasing its effects.⁹¹ A number of the nonnucleoside reverse transcriptase inhibitors (NNRTIs), including efavirenz and nevirapine, induce CYP3A (and in the case of nevirapine, CYP2B6), and can increase methadone requirements and/or induce opioid withdrawal.^{84,88,92,93} Several protease inhibitors can cause a reduction in methadone concentrations and potential withdrawal, including darunavir/ritonavir, lopinavir/ritonavir, nelfinavir, and tipranavir/ritonavir.⁹² Atazanavir, indinavir/ritonavir, saquinavir/ritonavir, and fosamprenavir/ritonavir appear to have limited effects on methadone disposition.⁹² Selective serotonin reuptake inhibitors including sertraline, paroxetine, and fluvoxamine inhibit CYP2D6, and can increase methadone plasma concentrations, resulting in increased opioid effects or toxicity.^{82,94,95} Clinicians should carefully evaluate the interaction potential of any CYP3A4 or CYP2D6 inhibitor used concomitantly with methadone. Readers are directed to comprehensive reviews of pharmacokinetic interactions associated with methadone, and of interactions between methadone and antiretroviral drugs.^{85,92}

Conclusions

In general, opioids metabolized by CYP450 (Table 1) are more prone to clinically important pharmacokinetic DDIs than those that are not metabolized by CYP450. **Table 3** presents a generalized summary of potential opioid pharmacokinetic DDIs, based on published reports and known metabolic pathways, and Table 2 presents common CYP3A and CYP2D6 substrates, inhibitors, and inducers. While by no means an all-inclusive list, when used together, these tables can assist in the identification of opioid-related drug interactions.

General guidelines for managing opioid pharmacokinetic DDIs are summarized in Table 3, and discussed in detail else-

■ **Table 3.** Potential Effects of CYP3A and CYP2D6 Modulation on Opioid Pharmacokinetics^a

Opioid	CYP3A Inhibition	CYP3A Induction	CYP2D6 Inhibition ^b	Comments
Codeine ^{18,35-38,100}	Increase in opioid effects (limited clinical evidence); monitor for toxicity and avoid in highly susceptible populations	Decrease in opioid effects (limited clinical evidence); monitor for toxicity	Decrease in opioid effects (strong clinical evidence); avoid combination or use alternative analgesic agent	
Morphine ^{27,29-33}	Likely clinically inconsequential (limited clinical evidence); monitor for toxicity	Likely clinically inconsequential (limited clinical evidence); monitor for toxicity	NA	Primarily metabolized by phase II metabolism (UGT2B7 and other UGT enzymes), low likelihood for pharmacokinetic DDIs
Oxycodone ^{41-49,51,52}	Increase in opioid effects (strong clinical evidence, “black box warning”); avoid combination	Decrease in opioid effects (strong clinical evidence); avoid combination if possible	Potential reduction in opioid effects (contradictory clinical evidence); monitor patients closely	
Oxymorphone ^{12,39,40}	NA	NA	NA	Primarily metabolized by phase II metabolism (UGT2B7 and other UGT enzymes), low likelihood for pharmacokinetic DDIs
Hydrocodone ^{55,56,59}	Potential increase in opioid effects (limited clinical evidence); monitor for toxicity	Potential decrease in opioid effects (limited clinical evidence); monitor for loss of efficacy	Potential reduction in opioid effects, more likely in CYP2D6 EMs (some clinical evidence although data is contradictory); avoid if possible, if not possible to avoid monitor for loss of efficacy	
Hydromorphone ⁵⁷⁻⁶¹	NA	NA	NA	Primarily metabolized by phase II metabolism, low likelihood for pharmacokinetic DDIs
Fentanyl ^{64-71,101-103}	Increase in opioid effects (strong clinical evidence, “black box warning”); avoid combination	Decrease in opioid effects (strong clinical evidence); avoid combination if possible; monitor for loss of efficacy if not possible to avoid combination	NA	Some evidence that CYP3A polymorphisms influence disposition
Methadone ^{82-90,92-95}	Increase in opioid effects (strong clinical evidence); avoid combination	Decrease in opioid effects, withdrawal is possible (strong clinical evidence); avoid combination if possible; monitor for loss of efficacy if not possible to avoid combination	Increase in opioid effects (strong clinical evidence); avoid combination	Also a substrate for other CYP450 enzymes (Table 1) that may contribute to interactions. CYP2B6 inhibitors (Table 2) may also decrease the metabolism of methadone, and CYP2B6 inducers (Table 2) can increase methadone clearance. Long half-life means that time to new steady-state as a result of interactions can be substantial (eg, >2 weeks) Due to complex metabolism, clinicians should carefully evaluate the interaction potential of any drug used concomitantly with methadone. CYP3A inhibition may increase risk of methadone-related torsades de pointes.
Tramadol ^{77-81,104-106}	Potential increase in opioid effects (limited clinical evidence); avoid combination if possible	Potential decrease in opioid effects (limited clinical evidence); monitor for loss of efficacy	Potential decrease in opioid effects (limited clinical evidence); avoid combination if possible	Inhibition of tramadol metabolism either via CYP2D6 or CYP3A inhibition may increase the risk of these serious adverse effects including serotonin syndrome or seizures

DDI indicates drug-drug interaction; EM, extensive metabolizer; NA, not applicable; PM, poor metabolizer.

^aThese should be regarded as very general guidelines. In all cases, management of an opioid DDI needs to be individualized, and should include assessment of clinical and patient factors (eg, age, disease states, opioid tolerance, opioid dose, other drugs, genetic factors, etc).

^bCYP2D6 is generally not inducible.

Reports

where in this supplement. The information presented in this review should be regarded as a general guide. In all cases, detection and management of an opioid DDI needs to be individualized, and should include assessment of clinical and patient factors (eg, age, disease states, opioid tolerance, opioid dose, other opioid drugs, other nonopioid drugs, genetic factors). Some opioid interactions may only warrant close monitoring of the patient and/or dose adjustments. Examples may include the setting of CYP3A induction, where the consequence of the interaction (ie, diminished opioid effects) is not likely to be life threatening; however, it should be noted that even this is not an absolute, as CYP3A induction can cause withdrawal in methadone-treated patients. In contrast, some DDIs may be severe (eg, the use of CYP3A inhibitors with fentanyl, methadone, or oxycodone) and such combinations should be avoided if possible.^{50,72,85}

Opioids have a narrow therapeutic index, potentially fatal concentration-dependent toxicity, and wide interindividual variability, making them relatively challenging to manage even in the absence of a DDI. Given these challenges in management, the clinical impact of opioid DDIs is surprisingly poorly characterized. Many of the deaths associated with opioid prescribing involve at least 1 other offending drug, and several reports of fatal pharmacokinetic DDIs with the opioids have been published.^{6,96-99}

In summary, numerous pharmacokinetic DDIs involving the opioids are possible, and these can have important clinical implications. In general, opioids metabolized by the CYP450 system are more prone to pharmacokinetic DDIs. Future efforts are needed to better understand the clinical importance of DDIs, and identify strategies for avoiding and managing opioid DDIs.

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