

# Opioid Metabolism

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Clinicians understand that individual patients differ in their response to specific opioid analgesics and that patients may require trials of several opioids before finding an agent that provides effective analgesia with acceptable tolerability. Reasons for this variability include factors that are not clearly understood, such as allelic variants that dictate the complement of opioid receptors and subtle differences in the receptor-binding profiles of opioids. However, altered opioid metabolism may also influence response in terms of efficacy and tolerability, and several factors contributing to this metabolic variability have been identified. For example, the risk of drug interactions with an opioid is determined largely by which enzyme systems metabolize the opioid. The rate and pathways of opioid metabolism may also be influenced by genetic factors, race, and medical conditions (most notably liver or kidney disease). This review describes the basics of opioid metabolism as well as the factors influencing it and provides recommendations for addressing metabolic issues that may compromise effective pain management. Articles cited in this review were identified via a search of MEDLINE, EMBASE, and PubMed. Articles selected for inclusion discussed general physiologic aspects of opioid metabolism, metabolic characteristics of specific opioids, patient-specific factors influencing drug metabolism, drug interactions, and adverse events.

Mayo Clin Proc. 2009;84(7):613-624

CYP = cytochrome P450; M1 = O-desmethytramadol; M3G = morphine-3-glucuronide; M6G = morphine-6-glucuronide; UGT = uridine diphosphate glucuronosyltransferase

Opioids are a cornerstone of the management of cancer pain<sup>1</sup> and postoperative pain<sup>2</sup> and are used increasingly for the management of chronic noncancer pain.<sup>3,4</sup> Understanding the metabolism of opioids is of great practical importance to primary care clinicians. Opioid metabolism is a vital safety consideration in older and medically complicated patients, who may be taking multiple medications and may have inflammation, impaired renal and hepatic function, and impaired immunity. Chronic pain, such as lower back pain, also occurs in younger persons and is the leading cause of disability in Americans younger than 45 years.<sup>5</sup> In younger patients, physicians may be more concerned with opioid metabolism in reference to development of tolerance, impairment of skills and mental function, adverse events during pregnancy and lactation, and prevention of abuse by monitoring drug and metabolite levels.

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Experienced clinicians are aware that the efficacy and tolerability of specific opioids may vary dramatically among patients and that trials of several opioids may be needed before finding one that provides an acceptable balance of analgesia and tolerability for an individual patient.<sup>6,9</sup> Pharmacodynamic and pharmacokinetic differences underlie this variability of response. *Pharmacodynamics* refers to how a drug affects the body, whereas *pharmacokinetics* describes how the body alters the drug. Pharmacokinetics contributes to the variability in response to opioids by affecting the bioavailability of a drug, the production of active or inactive metabolites, and their elimination from the body. Pharmacodynamic factors contributing to variability of response to opioids include between-patient differences in specific opioid receptors and between-opioid differences in binding to receptor subtypes. The receptor binding of opioids is imperfectly understood; hence, matching individual patients with specific opioids to optimize efficacy and tolerability remains a trial-and-error procedure.<sup>6,9</sup>

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This review primarily considers drug metabolism in the context of pharmacokinetics. It summarizes the basics of opioid metabolism; discusses the potential influences of patient-specific factors such as age, genetics, comorbid conditions, and concomitant medications; and explores the differences in metabolism between specific opioids. It aims to equip physicians with an understanding of opioid metabolism that will guide safe and appropriate prescribing, permit anticipation and avoidance of adverse drug-drug interactions, identify and accommodate patient-specific metabolic concerns, rationalize treatment failure, inform opioid switching and rotation strategies, and facilitate therapeutic monitoring. To that end, recommendations for tailoring opioid therapy to individual patients and specific populations will be included.

## METHODS

Articles cited in this review were identified via a search of MEDLINE, EMBASE, and PubMed databases for literature published between January 1980 and June 2008. The opioid medication search terms used were as follows: *codeine*, *fentanyl*, *hydrocodone*, *hydromorphone*, *methadone*, *morphine*, *opioid*, *opioid analgesic*, *oxycodone*, *oxymorphone*, and *tramadol*. Each medication search term was combined

with the following general search terms: *metabolism, active metabolites, pharmacokinetics, lipophilicity, physiochemical properties, pharmacology, genetics, receptor, receptor binding, receptor genetics or variation, transporter, formulations, AND adverse effects, safety, or toxicity*. The reference lists of relevant papers were examined for additional articles of interest.

## BASICS OF OPIOID METABOLISM

Metabolism refers to the process of biotransformation by which drugs are broken down so that they can be eliminated by the body. Some drugs perform their functions and then are excreted from the body intact, but many require metabolism to enable them to reach their target site in an appropriate amount of time, remain there an adequate time, and then be eliminated from the body. This review refers to opioid metabolism; however, the processes described occur with many medications.

Altered metabolism in a patient or population can result in an opioid or metabolite leaving the body too rapidly, not reaching its therapeutic target, or staying in the body too long and producing toxic effects. Opioid metabolism results in the production of both inactive and active metabolites. In fact, active metabolites may be more potent than the parent compound. Thus, although metabolism is ultimately a process of detoxification, it produces intermediate products that may have clinically useful activity, be associated with toxicity, or both.

Opioids differ with respect to the means by which they are metabolized, and patients differ in their ability to metabolize individual opioids. However, several general patterns of metabolism can be discerned. Most opioids undergo extensive first-pass metabolism in the liver before entering the systemic circulation. First-pass metabolism reduces the bioavailability of the opioid. Opioids are typically lipophilic, which allows them to cross cell membranes to reach target tissues. Drug metabolism is ultimately intended to make a drug hydrophilic to facilitate its excretion in the urine. Opioid metabolism takes place primarily in the liver, which produces enzymes for this purpose. These enzymes promote 2 forms of metabolism: phase 1 metabolism (modification reactions) and phase 2 metabolism (conjugation reactions).

Phase 1 metabolism typically subjects the drug to oxidation or hydrolysis. It involves the cytochrome P450 (CYP) enzymes, which facilitate reactions that include *N*-, *O*-, and *S*-dealkylation; aromatic, aliphatic, or *N*-hydroxylation; *N*-oxidation; sulfoxidation; deamination; and dehalogenation. Phase 2 metabolism conjugates the drug to hydrophilic substances, such as glucuronic acid, sulfate, glycine, or glutathione. The most important phase 2 reaction is

glucuronidation, catalyzed by the enzyme uridine diphosphate glucuronosyltransferase (UGT). Glucuronidation produces molecules that are highly hydrophilic and therefore easily excreted. Opioids undergo varying degrees of phase 1 and 2 metabolism. Phase 1 metabolism usually precedes phase 2 metabolism, but this is not always the case. Both phase 1 and 2 metabolites can be active or inactive. The process of metabolism ends when the molecules are sufficiently hydrophilic to be excreted from the body.

## FACTORS INFLUENCING OPIOID METABOLISM

### METABOLIC PATHWAYS

Opioids undergo phase 1 metabolism by the CYP pathway, phase 2 metabolism by conjugation, or both. Phase 1 metabolism of opioids mainly involves the CYP3A4 and CYP2D6 enzymes. The CYP3A4 enzyme metabolizes more than 50% of all drugs; consequently, opioids metabolized by this enzyme have a high risk of drug-drug interactions. The CYP2D6 enzyme metabolizes fewer drugs and therefore is associated with an intermediate risk of drug-drug interactions. Drugs that undergo phase 2 conjugation, and therefore have little or no involvement with the CYP system, have minimal interaction potential.

### PHASE 1 METABOLISM

The CYP3A4 enzyme is the primary metabolizer of fentanyl<sup>10</sup> and oxycodone,<sup>11</sup> although normally a small portion of oxycodone undergoes CYP2D6 metabolism to oxymorphone (Table 1<sup>10-18</sup>). Tramadol undergoes both CYP3A4- and CYP2D6-mediated metabolism.<sup>16</sup> Methadone is primarily metabolized by CYP3A4 and CYP2B6; CYP2C8, CYP2C19, CYP2D6, and CYP2C9 also contribute in varying degrees to its metabolism.<sup>19-23</sup> The complex interplay of methadone with the CYP system, involving as many as 6 different enzymes, is accompanied by considerable interaction potential.

Each of these opioids has substantial interaction potential with other commonly used drugs that are substrates, inducers, or inhibitors of the CYP3A4 enzyme (Table 2).<sup>24,25</sup> Administration of CYP3A4 substrates or inhibitors can increase opioid concentrations, thereby prolonging and intensifying analgesic effects and adverse opioid effects, such as respiratory depression. Administration of CYP3A4 inducers can reduce analgesic efficacy.<sup>10,11,16</sup> In addition to drugs that interact with CYP3A4, bergamottin (found in grapefruit juice) is a strong inhibitor of CYP3A4,<sup>26</sup> and cafestol (found in unfiltered coffee) is an inducer of the enzyme.<sup>27</sup>

Induction of CYP3A4 may pose an added risk in patients treated with tramadol, which has been associated with seizures when administered within its accepted dos-

TABLE 1. Metabolic Pathway/Enzyme Involvement

Opioid	Phase 1 metabolism	Phase 2 metabolism	Comment
Morphine <sup>12</sup>	None	Glucuronidation via UGT2B7	
Codeine <sup>13</sup>	CYP2D6	None	
Hydrocodone <sup>14</sup>	CYP2D6	None	One of the metabolites of hydrocodone is hydromorphone, which undergoes phase 2 glucuronidation
Oxycodone <sup>11</sup>	CYP3A4 CYP2D6	None	Oxycodone produces a small amount of oxymorphone, which must undergo subsequent metabolism via glucuronidation
Methadone <sup>15</sup>	CYP3A4 CYP2B6 CYP2C8 CYP2C19 CYP2D6 CYP2C9	None	CYP3A4 and CYP2B6 are the primary enzymes involved in methadone metabolism; other enzymes play a relatively minor role
Tramadol <sup>16</sup>	CYP3A4 CYP2D6	None	
Fentanyl <sup>10</sup>	CYP3A4	None	
Hydromorphone <sup>17</sup>	None	Glucuronidation via UGT2B7	
Oxymorphone <sup>18</sup>	None	Glucuronidation via UGT2B7	

CYP = cytochrome P450; UGT2B7 = uridine diphosphate glucuronosyltransferase 2B7.

age range.<sup>16</sup> This risk is most pronounced when tramadol is administered concurrently with potent CYP3A4 inducers, such as carbamazepine, or with selective serotonin reuptake inhibitors, tricyclic antidepressants, or other medications with additive serotonergic effects.<sup>16</sup>

The CYP2D6 enzyme is entirely responsible for the metabolism of hydrocodone,<sup>14</sup> codeine,<sup>13</sup> and dihydrocodeine to their active metabolites (hydromorphone, morphine, and dihydromorphone, respectively), which in turn undergo phase 2 glucuronidation. These opioids (and to a lesser extent oxycodone, tramadol, and methadone) have interaction potential with selective serotonin reuptake inhibitors, tricyclic antidepressants,  $\beta$ -blockers, and antiarrhythmics; an array of other drugs are substrates, inducers, or inhibitors of the CYP2D6 enzyme (Table 3<sup>28</sup>).

Although CYP2D6-metabolized drugs have lower interaction potential than those metabolized by CYP3A4, genetic factors influencing the activity of this enzyme can introduce substantial variability into the metabolism of hydrocodone, codeine, and to a lesser extent oxycodone. An estimated 5% to 10% of white people possess allelic variants of the *CYP2D6* gene that are associated with reduced clearance of drugs metabolized by this isoenzyme,<sup>29,31</sup> and between 1% and 7% of white people carry CYP2D6 allelic variants associated with rapid metabolism.<sup>32,33</sup> The prevalence of poor metabolizers is lower in Asian populations ( $\leq 1\%$ )<sup>34</sup> and highly variable in African populations (0%-34%).<sup>35-39</sup> The prevalence of rapid metabolizers of opioids has not been reported in Asian populations; estimates in African populations are high but variable (9%-30%).<sup>35,36</sup>

The clinical effects of CYP2D6 allelic variants can be seen with codeine administration. Patients who are poor opioid metabolizers experience reduced efficacy with codeine because they have a limited ability to metabolize codeine into the active molecule, morphine. In contrast, patients who are rapid opioid metabolizers may experience increased opioid effects with a usual dose of codeine because their rapid metabolism generates a higher concentration of morphine.<sup>40</sup> Allelic variants altering CYP2D6-mediated metabolism can be associated with reduced efficacy of hydrocodone or increased toxicity of codeine, each of which relies entirely on the CYP2D6 enzyme for phase 1 metabolism.<sup>41,42</sup> In patients treated with oxycodone, which relies on CYP3A4 and to a lesser extent on CYP2D6, inhibition of CYP2D6 activity by quinidine increases noroxycodone levels and reduces oxymorphone production. In one study, such alterations were not accompanied by increased adverse events.<sup>30</sup> However, individual cases of reduced oxycodone efficacy<sup>42</sup> or increased toxicity<sup>41</sup> in CYP2D6 poor metabolizers have been reported.

#### PHASE 2 METABOLISM

Morphine, oxymorphone, and hydromorphone are each metabolized by phase 2 glucuronidation<sup>17,18,43</sup> and therefore have little potential for metabolically based drug interactions. Oxymorphone, for example, has no known pharmacokinetic drug-drug interactions,<sup>18</sup> and morphine has few.<sup>43</sup> Of course, pharmacodynamic drug-drug interactions are possible with all opioids, such as additive interactions with benzodiazepines, antihistamines, or alcohol, and antagonistic interactions with naltrexone or naloxone.

TABLE 2. Cytochrome P450 3A4 Substrates, Inhibitors, and Inducers

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

CCB = calcium channel blocker; SSRI = selective serotonin reuptake inhibitor. From *The Drug Monit.*<sup>24</sup> with permission.

However, the enzymes responsible for glucuronidation reactions may also be subject to a variety of factors that may alter opioid metabolism. The most important UGT enzyme involved in the metabolism of opioids that undergo glucuronidation (eg, morphine, hydromorphone, oxycodone)<sup>12,44</sup> is UGT2B7. Research suggests that UGT2B7-mediated opioid metabolism may be altered by interactions with other drugs that are either substrates or inhibitors of this enzyme.<sup>45</sup> Moreover, preliminary data indicate that UGT2B7 metabolism of morphine may be potentiated by CYP3A4, although the clinical relevance of this finding is unknown.<sup>46-48</sup>

The activity of UGT2B7 shows significant between-patient variability, and several authors have identified allelic variants of the gene encoding this enzyme.<sup>12,44</sup> Although the functional importance of these allelic variants with respect to glucuronidation of opioids is unknown, at least 2 allelic variants (the UGT2B7-840G and -79 alleles) have been linked to substantial reduction of morphine glucuronidation, with resulting accumulation of morphine and reduction in metabolite formation.<sup>49,50</sup> Moreover, research has shown that variation in the amount of messenger RNA for hepatic nuclear factor 1 $\alpha$ , a transcription factor

responsible for regulating expression of the *UGT2B7* gene, is associated with interindividual variation in UGT2B7 enzyme activity.<sup>51</sup>

#### CLINICAL IMPLICATIONS OF METABOLIC PATHWAYS

Most opioids are metabolized via CYP-mediated oxidation and have substantial drug interaction potential. The exceptions are morphine, hydromorphone, and oxycodone, which undergo glucuronidation. In patients prescribed complicated treatment regimens, physicians may consider initiating treatment with an opioid that is not metabolized by the CYP system. However, interactions between opioids that undergo CYP-mediated metabolism and other drugs involved with this pathway often can be addressed by careful dose adjustments, vigilant therapeutic drug monitoring, and prompt medication changes in the event of serious toxicity.

Response to individual opioids varies substantially, and factors contributing to this variability are not clearly understood. Because an individual patient's response to a given opioid cannot be predicted, it may be necessary to administer a series of opioid trials before finding an agent that provides effective analgesia with acceptable tolerability.<sup>6-9</sup>

TABLE 3. Cytochrome P450 2D6 Substrates, Inhibitors, and Inducers

Substrates		Inhibitors		Inducers
<i>Antiarrhythmic agents</i>	<i>SSRIs</i>	<i>Antiarrhythmic agents</i>	<i>Antihistamine</i>	<i>Antibiotic</i>
Encainide	Fluoxetine	Amiodarone	Chlorpheniramine	Rifampin
Flecainide	Fluvoxamine	Quinidine	<i>Histamine H<sub>2</sub> receptor antagonists</i>	<i>Glucocorticoid</i>
Lidocaine	Paroxetine	<i>Antipsychotic agents</i>	Cimetidine	Dexamethasone
Mexiletine	<i>Tricyclics</i>	Chlorpromazine	Ranitidine	
Propafenone	Amitriptyline	Reduced haloperidol	<i>Other drugs</i>	
Sparteine	Amoxapine	Levomepromazine	Celecoxib	
<i>β-Blockers</i>	Clomipramine	<i>SNRI</i>	Doxorubicin	
Alprenolol	Desipramine	Duloxetine	Ritonavir	
Carvedilol	Doxepin	<i>SSRIs</i>	Terbinafine	
Metoprolol	Imipramine	Citalopram		
Propranolol	Nortriptyline	Escitalopram		
Timolol	<i>Other drugs</i>	Fluoxetine		
<i>Antipsychotic agents</i>	Amphetamine	Paroxetine		
Aripiprazole	Chlorpheniramine	Sertraline		
Haloperidol	Debrisoquine	<i>Tricyclic</i>		
Perphenazine	Dextromethorphan	Clomipramine		
Risperidone	<i>Histamine H<sub>1</sub> receptor antagonists</i>	<i>Other antidepressant/</i>		
Thioridazine	Metoclopramide	<i>antianxiolytic agents</i>		
Zuclopenthixol	Phenformin	Bupropion		
<i>SNRIs</i>	Tamoxifen	Moclobemide		
Duloxetine				
Venlafaxine				

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.  
From Indiana University School of Medicine,<sup>28</sup> with permission.

In some patients, the most effective and well-tolerated opioid will be one that undergoes CYP-mediated metabolism. For example, in a 2001 clinical trial, 50 patients with cancer who did not respond to morphine or were unable to tolerate it were switched to methadone, which undergoes complex metabolism involving up to 6 CYP enzymes. Adequate analgesia with acceptable tolerability was obtained in 40 (80%) of these patients.<sup>52</sup>

In short, for some patients, selecting an opioid without considerable potential for drug interactions may not be possible. Under such conditions, an understanding of opioid metabolism can guide dose adjustments or the selection of a different opioid when analgesia is insufficient or adverse events are intolerable.

### PRODUCTION OF ACTIVE METABOLITES

Some opioids produce multiple active metabolites after administration (Table 4<sup>10,11,16-18,28,43,53-60</sup>). Altered metabolism due to medical comorbidities, genetic factors, or drug-drug interactions may disrupt the balance of metabolites, thereby altering the efficacy and/or tolerability of the drug. Moreover, opioids that produce metabolites chemically identical to other opioid medications may complicate the interpretation of urine toxicology screening.

### CODEINE

Codeine is a prodrug that exerts its analgesic effects after metabolism to morphine. Patients who are CYP2D6 poor or

rapid metabolizers do not respond well to codeine. Codeine toxicity has been reported in CYP2D6 poor metabolizers who are unable to form the morphine metabolite<sup>42</sup> and in rapid metabolizers who form too much morphine.<sup>61,62</sup> In fact, a recent study found that adverse effects of codeine are present irrespective of morphine concentrations in both poor and rapid metabolizers,<sup>63</sup> suggesting that a substantial proportion of patients with CYP2D6 allelic variants predisposing to poor or rapid codeine metabolism will experience the adverse effects of codeine without benefitting from any of its analgesic effects. Codeine is also metabolized by an unknown mechanism to produce hydrocodone in quantities reaching up to 11% of the codeine concentration found in urinalysis.<sup>58</sup> The clinical effect of the hydrocodone metabolite of codeine is unknown.

### MORPHINE

In addition to its pharmacologically active parent compound, morphine is glucuronidated to 2 metabolites with potentially important differences in efficacy, clearance, and toxicity: morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). Morphine may also undergo minor routes of metabolism, including *N*-demethylation to normorphine or normorphine 6-glucuronide, diglucuronidation to morphine-3, 6-diglucuronide, and formation of morphine ethereal sulfate. A recent study found that a small proportion of morphine is also metabolized to hydromorphone,<sup>55</sup> although there are no data suggesting a meaningful clinical effect.

TABLE 4. Major Opioid Metabolites

Opioid	Inactive metabolites	Active metabolites identical to pharmaceutical opioids	Active metabolites that are not pharmaceutical opioids
Morphine <sup>28,43,53-55</sup>	Normorphine	Hydromorphone <sup>a</sup>	Morphine-3-G glucuronide Morphine-6-G glucuronide
Hydromorphone <sup>17</sup>	Minor metabolites	None	Hydromorphone-3-glucuronide
Hydrocodone <sup>56</sup>	Norhydrocodone	Hydromorphone	None
Codeine <sup>57,58</sup>	Norcodeine	Hydrocodone <sup>a</sup>	None
Oxycodone <sup>11</sup>	None	Morphine	Noroxycodone
Oxymorphone <sup>18</sup>	Oxymorphone-3-glucuronide	Oxymorphone	6-Hydroxy-oxymorphone
Fentanyl <sup>10</sup>	Norfentanyl	None	None
Tramadol <sup>16</sup>	Nortramadol	None	<i>O</i> -desmethyltramadol
Methadone <sup>59</sup>	2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine 2-Ethyl-5-methyl-3,3-diphenylpyrroline	None	None
Heroin <sup>60</sup>	Normorphine	Morphine	6-Monoacetylmorphine

<sup>a</sup> Only very low levels are seen in the urine: less than 11% for hydrocodone after codeine administration and less than 2.5% for hydromorphone after morphine administration.<sup>53,54,58</sup>

Like morphine, M6G is a  $\mu$ -opioid receptor agonist with potent analgesic activity. However, morphine has greater affinity than M6G for the  $\mu_2$ -opioid receptor thought to be responsible for many of the adverse effects of  $\mu$ -receptor agonists,<sup>64,65</sup> most notably respiratory depression, gastrointestinal effects, and sedation.<sup>65,66</sup> Although the affinities of morphine and M6G for the  $\mu_1$ -opioid receptor are similar, a study of low-dose morphine, M6G, and M3G found that morphine had greater analgesic efficacy.<sup>67</sup> The M3G metabolite of morphine lacks analgesic activity, but it exhibits neuroexcitatory effects in animals and has been proposed as a potential cause of such adverse effects as allodynia, myoclonus, and seizures in humans.<sup>68-70</sup> In a clinical trial, however, low-dose M3G exhibited no analgesic effects, did not potentiate the analgesic effects of morphine or M6G, and did not produce adverse effects.<sup>67</sup>

Clinical data regarding morphine and its glucuronide metabolites are unclear. Two studies found no correlation between plasma concentrations of morphine, M6G, or M3G in either clinical efficacy or tolerability.<sup>71,72</sup> Moreover, in patients with impaired renal function, the pharmacokinetics of morphine appear to be less affected than that of its M6G and M3G metabolites, which were found to accumulate.<sup>73-76</sup> Although M6G appears to be better tolerated than morphine, increased toxicity in patients with reduced clearance was primarily related to the accumulation of the M6G metabolite.

#### HYDROMORPHONE

The production of active metabolites is also an issue with hydromorphone. The primary metabolite of hydromorphone, hydromorphone-3-glucuronide, has neuroexcitatory potential similar to<sup>68,70</sup> or greater than<sup>69</sup> the M3G metabolite of morphine. Clinical data on the neuroexcitatory potential of hydromorphone during long-term therapy are unavailable. However, hydromorphone is available only in short-

acting formulations and extended-release formulations are recommended in patients with chronic pain requiring long-term therapy.<sup>3,4</sup>

#### TRAMADOL

Like codeine, tramadol requires metabolism to an active metabolite, *O*-desmethyltramadol (M1), to be fully effective. The parent compound relies on both CYP3A4 and CYP2D6, with metabolism of M1 relying on CYP2D6.<sup>16</sup> In a group of patients receiving multiple medications and treated with tramadol under steady-state conditions, the concentration of M1 after correcting for dose and the M1/tramadol ratio were each approximately 14-fold higher in patients with a CYP2D6 allelic variant associated with extensive metabolism than in poor metabolizers.<sup>77</sup> Both tramadol and its M1 metabolite exert analgesic effects through opioidergic mechanisms ( $\mu$ -opioid receptor) and through 2 nonopioidergic mechanisms, serotonin reuptake inhibition and norepinephrine reuptake inhibition. Although M1 has more potent activity at the  $\mu$ -opioid receptor,<sup>16,78</sup> tramadol is the more potent inhibitor of serotonin and norepinephrine reuptake and the more potent promoter of serotonin and norepinephrine efflux.<sup>79,80</sup> Although the precise function of M1 in humans remains unclear, tramadol-mediated analgesia appears to depend on the complementary contributions of an active metabolite with a route of metabolism that differs from that of the parent compound.

#### OXYCODONE

Oxycodone is metabolized by CYP3A4 to noroxycodone and by CYP2D6 to oxymorphone.<sup>11</sup> Noroxycodone is a weaker opioid agonist than the parent compound, but the presence of this active metabolite increases the potential for interactions with other drugs metabolized by the CYP3A4 pathway. The central opioid effects of oxycodone

are governed primarily by the parent drug, with a negligible contribution from its circulating oxidative and reductive metabolites.<sup>81</sup> Oxymorphone is present only in small amounts after oxycodone administration, making the clinical relevance of this metabolite questionable. Although the CYP2D6 pathway is thought to play a relatively minor role in oxycodone metabolism, at least 1 study has reported oxycodone toxicity in a patient with impaired CYP2D6 metabolism.<sup>41</sup> The authors of this report suggested that failure to metabolize oxycodone to oxymorphone may have been associated with accumulation of oxycodone and noroxycodone, resulting in an inability to tolerate therapy.

### OPIOIDS WITHOUT CLINICALLY RELEVANT ACTIVE METABOLITES

Fentanyl, oxymorphone, and methadone do not produce metabolites that are likely to complicate treatment. Fentanyl is predominantly converted by CYP3A4-mediated *N*-dealkylation to norfentanyl, a nontoxic and inactive metabolite; less than 1% is metabolized to despropionylfentanyl, hydroxyfentanyl, and hydroxynorfentanyl, which also lack clinically relevant activity.<sup>82</sup> An active metabolite of oxymorphone, 6-hydroxy-oxymorphone, makes up less than 1% of the administered dose excreted in urine and is metabolized via the same pathway as the parent compound, making an imbalance among metabolites unlikely.<sup>18</sup> Methadone does not produce active metabolites, exerting its activity—both analgesic and toxic—through the parent compound. However, methadone has affinity for the *N*-methyl-D-aspartate receptors<sup>83</sup>; this affinity is thought to account not only for a portion of its analgesic efficacy but also for neurotoxic effects that have been observed with this opioid.<sup>84-86</sup>

### ADHERENCE MONITORING: THE IMPORTANCE OF ACTIVE METABOLITES

Opioids that produce active metabolites structurally identical to other opioid medications can complicate efforts to monitor patients to prevent abuse and diversion. Current urine toxicology tests do not provide easily interpretable information about the source or dose of detected compounds. Thus, in a patient prescribed oxycodone, both oxycodone and oxymorphone will appear in toxicology results, but the urine test results will not establish whether the patient took the prescribed oxycodone alone or also self-medicated with oxymorphone.

Patients treated with codeine will have both codeine and morphine in urine samples. If too much morphine is present, the patient may be taking heroin or ingesting mor-

phine in addition to codeine. CYP2D6 rapid metabolizers may have an unusually high morphine-to-codeine ratio, making interpretation of the morphine-to-codeine ratio challenging.<sup>87</sup> However, in patients taking only codeine, the codeine-to-morphine ratio is less than 6, even in rapid metabolizers.<sup>87,88</sup> Additionally, morphine alone may be detectable in the urine 30 hours after ingestion of a single dose of codeine.<sup>89-92</sup>

The urine of patients treated with morphine may contain small amounts of hydromorphone ( $\leq 2.5\%$  of the morphine concentration).<sup>53,54</sup> Similarly, those treated with hydrocodone may test positive for both hydrocodone and hydromorphone, making it difficult to determine whether the parent opioid was taken as prescribed or a second opioid is being abused.

Clinicians may find it easier to monitor patients for adherence and abuse if the opioid prescribed does not produce active metabolites similar to other opioid medications. If abuse is suspected, choosing opioids such as fentanyl, hydromorphone, methadone, or oxymorphone may simplify monitoring. Sometimes an inactive metabolite provides a more reliable test of adherence than does the parent opioid. Urinary concentrations of methadone depend not only on dose and metabolism but also on urine pH. In contrast, the concentration of an inactive metabolite of methadone (via *N*-demethylation), 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, is unaffected by pH and is therefore preferable for assessing adherence to therapy.<sup>93,94</sup>

### POPULATION PHARMACOKINETICS

Opioid metabolism differs with individual opioids in populations stratified according to age, sex, and ethnicity (Table 5<sup>10,11,13-18,43</sup>). Reduced clearance of morphine,<sup>43</sup> codeine,<sup>13</sup> fentanyl,<sup>10</sup> and oxymorphone<sup>18</sup> has been reported in older patients. Oxycodone concentrations are approximately 25% higher in women than in men after controlling for differences in body weight, making it important for physicians to consider the patient's sex when prescribing this opioid.<sup>11</sup> Chinese patients have higher clearance and lower concentrations of morphine.<sup>43</sup> Similarly, codeine is a prodrug that exerts its analgesic effects after metabolism to morphine. Morphine concentrations were shown to be reduced in Chinese patients treated with codeine, providing confirmation of altered morphine metabolism in this large population.<sup>95</sup> As already stated, altered opioid metabolism in ethnic populations is also a byproduct of allelic variants of the gene encoding CYP2D6,<sup>32,33,41</sup> particularly in African populations.<sup>35-39</sup> Ethnic differences in the gene encoding UGT2B7 have also been identified, but these have not been associated with clinical differences in enzyme activity.<sup>44</sup>

TABLE 5. Demographic/Medical Factors Influencing Opioid Metabolism

Opioid	Age	Sex	Ethnicity	Hepatic impairment	Renal impairment
Morphine <sup>43</sup>	Clearance may be reduced in older patients	No effect	Chinese patients have higher clearance of morphine	Dose adjustment recommended	Dose adjustment recommended
Codeine <sup>13</sup>	Caution recommended in older patients	No effect	CYP2D6 allelic variants may alter metabolism, more common in populations of Asian or African descent	Dose adjustment recommended	Dose adjustment recommended
Hydrocodone <sup>14</sup>	Caution recommended in older patients	No known effect	CYP2D6 allelic variants may alter metabolism, more common in populations of Asian or African descent	Most frequently administered in combination with acetaminophen; liver function monitoring is advised during treatment in patients with hepatic impairment	Most frequently administered in combination with acetaminophen; renal function monitoring is advised during treatment in patients with severe renal impairment
Oxycodone <sup>11</sup>	Concentrations nominally higher in older patients	Concentrations ~25% higher in women than in men	No effect	Dose adjustment recommended	Dose adjustment recommended
Methadone <sup>15</sup>	Dose adjustment may be necessary in elderly patients	No effect	No effect	Dose adjustment recommended in patients with severe impairment	Dose adjustment recommended in patients with severe impairments
Tramadol <sup>16</sup>	Effects of age on pharmacokinetics have not been studied	No significant effect	No effect	Pharmacokinetics significantly altered in patients with severe hepatic impairment	Pharmacokinetics significantly altered only in patients with severe renal impairment
Fentanyl <sup>10</sup>	Clearance may be reduced in older patients	No effect	No effect	Dose adjustments may not be necessary in patients with hepatic impairment	Dose adjustments may not be necessary in patients with renal impairment
Hydromorphone <sup>17</sup>	No effect	C <sub>max</sub> 25% higher in women than in men with similar AUC <sub>0-24</sub>	No effect	Dose adjustment recommended	Dose adjustment recommended
Oxymorphone <sup>18</sup>	Steady-state concentrations ~40% higher in patients aged ≥65 y	Concentrations the same in men and women after controlling for body weight	No effect	Contraindicated in patients with moderate or severe hepatic impairment	Dose adjustment recommended

AUC<sub>0-24</sub> = area under the plasma concentration vs time curve; C<sub>max</sub> = maximum plasma concentration; CYP = cytochrome P450.

In most cases, altered opioid metabolism in older patients, women, or specific ethnic groups can be addressed by careful dose adjustment. For example, morphine,<sup>43</sup> codeine,<sup>13</sup> fentanyl,<sup>15</sup> and oxymorphone<sup>18</sup> should be initiated at lower doses in older patients, and physicians prescribing oxycodone to women may consider starting at a lower dose relative to men. Morphine or codeine dose reductions may also be necessary in Asian populations. Given the genetic variability of metabolism in specific ethnic populations, it may make sense for patients with an unexplained history of poor response or an inability to tolerate a particular opioid to be switched to an opioid that relies on a different metabolic pathway.<sup>96,97</sup>

## MEDICAL CONDITIONS

### HEPATIC IMPAIRMENT

The liver is the major site of biotransformation for most opioids (Table 4). It is therefore not surprising that the

prescribing information for most frequently prescribed opioids recommends caution in patients with hepatic impairment.<sup>10,11,13,14,17,18,43</sup> For example, in patients with moderate to severe liver disease, peak plasma levels of oxycodone and its chief metabolite noroxycodone were increased 50% and 20%, respectively, whereas the area under the plasma concentration–time curve for these molecules increased 95% and 65%.<sup>11</sup> Peak plasma concentrations of another active metabolite, oxymorphone, were decreased by 30% and 40%, respectively. Although oxymorphone itself does not undergo CYP-mediated metabolism, a portion of the oxycodone dose is metabolized to oxymorphone by CYP2D6. Failure to biotransform oxycodone to oxymorphone may result in accumulation of oxycodone and noroxycodone, with an associated increase in adverse events.<sup>41</sup> The differential effect of hepatic impairment on the metabolism of oxycodone relative to its active metabolite illustrates the complexities associated with opioids that have multiple active metabolites.

Hepatic impairment may also affect metabolism of opioids that undergo glucuronidation rather than CYP-mediated metabolism, such as morphine and oxycodone. In a 1990 study, the elimination half-life and peak plasma concentrations of morphine were significantly increased in 7 patients with severe cirrhosis.<sup>98</sup> The bioavailability of morphine in these patients was 101% compared with approximately 47% observed in healthy participants. The ratio of morphine to its inactive metabolite M3G was significantly higher in cirrhotic patients than in controls. In another study, morphine hepatic extraction was compared in 8 healthy participants and 8 patients with cirrhosis. Hepatic extraction was 25% lower in patients with cirrhosis.<sup>99</sup> This reduction was attributed to reduced enzyme capacity rather than to impairment in blood flow. The authors of that study suggested that cirrhosis affected the metabolism of morphine less than other high-clearance oxidized drugs, perhaps indicating that cirrhosis has less of an effect on glucuronidation relative to CYP-mediated metabolism.

Currently, no comparable data exist on metabolism of oxycodone in patients with cirrhosis. However, hepatic disease may certainly have significant effects on oxycodone pharmacokinetics. Specifically, the bioavailability of oxycodone increased by 1.6-fold and 3.7-fold in patients with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment, respectively, compared with healthy controls. In 1 patient with severe hepatic impairment (Child-Pugh class C), the bioavailability was increased by 12.2-fold.<sup>18</sup>

The pharmacokinetics of fentanyl<sup>100</sup> and methadone,<sup>101</sup> 2 of the frequently used opioids, are not significantly affected by hepatic impairment. Although dose adjustments for these opioids may not be required in certain patients with hepatic impairment, clinicians should nonetheless be extremely cautious when prescribing any opioid for a patient with severe hepatic dysfunction.

#### RENAL IMPAIRMENT

The incidence of renal impairment increases significantly with age, such that the glomerular filtration rate decreases by an average of 0.75 to 0.9 mL/min annually beginning at age 30 to 40 years.<sup>102,103</sup> At this rate, a person aged 80 years will have approximately two-thirds of the renal function expected in a person aged 20 or 30 years.<sup>102-104</sup> Because most opioids are eliminated primarily in urine, dose adjustments are required in patients with renal impairment.<sup>10,11,13,16-18,43</sup>

However, the effects of renal impairment on opioid clearance are neither uniform nor clear-cut. For example, morphine clearance decreases only modestly in patients with renal impairment, but clearance of its M6G and M3G metabolites decreases dramatically.<sup>105-107</sup> Accumulation of morphine glucuronides in patients with renal impairment

has been associated with serious adverse effects, including respiratory depression, sedation, nausea, and vomiting.<sup>73,74,108</sup> Similarly, patients with chronic renal failure who receive 24 mg/d of hydromorphone may have a 4-fold increase in the molar ratio of hydromorphone-3-glucuronide to hydromorphone.<sup>109</sup> Conversely, in patients treated with oxycodone, renal impairment increases concentrations of oxycodone and noroxycodone by approximately 50% and 20%, respectively.<sup>11</sup> Although renal impairment affects oxycodone more than morphine, there is no critical accumulation of an active metabolite that produces adverse events.<sup>11</sup> Thus, selecting an opioid in patients with renal impairment requires an understanding not only of the anticipated changes in concentrations of the opioid and its metabolites but also of the differential effects of parent compounds and metabolites when they accumulate.

As in liver disease, methadone and fentanyl may be less affected by renal impairment than other opioids. Methadone does not seem to be removed by dialysis<sup>110</sup>; in anuric patients, methadone excretion in the feces may be enhanced with limited accumulation in plasma.<sup>111</sup> However, for patients with stage 5 chronic kidney disease, the prudent approach remains to begin with very low doses, monitor carefully, and titrate upward slowly. Fentanyl is metabolized and eliminated almost exclusively by the liver; thus, it has been assumed that its pharmacokinetics would be minimally altered by kidney failure.<sup>112</sup> However, despite limited pharmacokinetic data, hepatic clearance and extraction of drugs with high hepatic extraction ratios (eg, fentanyl) could potentially be inhibited by uremia<sup>113</sup>; the theoretical potential for accumulation of fentanyl in patients with hepatic impairment makes caution advisable when prescribing opioids to these patients.

#### CLINICAL IMPLICATIONS OF MEDICAL CONDITIONS

The selection of an opioid analgesic may be affected by comorbidities and diminished organ reserve. Health care professionals need to be especially cautious when dealing with patients with diminished metabolic capacities due to organ dysfunction. In general, dose reduction and/or prolongation of dose intervals may be necessary depending on the severity of organ impairment. Moreover, clinicians should adopt a "start low and go slow" approach to opioid titration when hepatic or renal impairment is a factor.

Although metabolism of drugs undergoing glucuronidation rather than oxidation may be less affected by hepatic impairment, this does not appear to be a major advantage with respect to opioids. Morphine clearance and accumulation of its M3G metabolite are increased in cirrhosis, making dose adjustments advisable. Oxycodone, which also undergoes glucuronidation, is contraindicated

in patients with moderate or severe hepatic dysfunction.<sup>18</sup> Among opioids undergoing CYP-mediated metabolism, fentanyl<sup>100</sup> and methadone<sup>101</sup> appear to be less affected by liver disease. Nonetheless, data on these opioids are limited, making caution and conservative dosing advisable in this population.

In patients with substantial chronic kidney disease (stages 3-5), clinicians should carefully consider their options before choosing morphine. Nausea, vomiting, profound analgesia, sedation, and respiratory depression have been reported in patients who have kidney failure and are taking morphine.<sup>73,74,108,114,115</sup> Several authors have suggested that fentanyl and methadone are preferred in end-stage renal disease<sup>112,116</sup>; however, this advice needs to be tempered by the challenges inherent in dosing potent opioids in patients with poor renal function.

### CONCLUSION

Patient characteristics and structural differences between opioids contribute to differences in opioid metabolism and thereby to the variability of the efficacy, safety, and tolerability of specific opioids in individual patients and diverse patient populations. To optimize treatment for individual patients, clinicians must understand the variability in the ways different opioids are metabolized and be able to recognize the patient characteristics likely to influence opioid metabolism.

*Jeffrey Coleman, MA, of Complete Healthcare Communications (Chadds Ford, PA) provided research and editorial assistance for the development of the submitted manuscript, with support from Endo Pharmaceuticals (Chadds Ford, PA).*

### REFERENCES

- World Health Organization. Cancer Pain Relief: With a Guide to Opioid Availability. 2nd ed. Geneva, Switzerland: WHO Office of Publication; 1996.
- Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology*. 2004;100(6):1573-1581.
- AGS Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. *J Am Geriatr Soc*. 2002;50(6)(suppl):S205-S224.
- American Pain Society. *Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis and Juvenile Chronic Arthritis*. 2nd ed. Glenview, IL: American Pain Society; 2002:184.
- Andersson GB. Epidemiological features of chronic low-back pain. *Lancet*. 1999;354(9178):581-585.
- Grilo RM, Bertin P, Scotto F, Fazzino C, et al. Opioid rotation in the treatment of joint pain: a review of 67 cases. *Joint Bone Spine*. 2002;69(5):491-494.
- Mercadante S. Opioid rotation for cancer pain: rationale and clinical aspects. *Cancer*. 1999;86(9):1856-1866.
- Mercadante S, Bruera E. Opioid switching: a systematic and critical review. *Cancer Treat Rev*. 2006 Jun;32(4):304-315. Epub 2006 Apr 19.
- Quang-Cantagrel ND, Wallace MS, Magnuson SK. Opioid substitution to improve the effectiveness of chronic noncancer pain control: a chart review. *Anesth Analg*. 2000;90(4):933-937.
- Duragesic (fentanyl transdermal system) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2008.
- OxyContin (oxycodone HCl controlled-release tablets) [package insert]. Stamford, CT: Purdue Pharma LP; 2007.
- Coffman BL, King CD, Rios GR, Tephly TR. The glucuronidation of opioids, other xenobiotics, and androgens by human UGT2B7Y(268) and UGT2B7H(268). *Drug Metab Dispos*. 1998;26(1):73-77.
- Codeine Contin (codeine controlled-release tablets) [product monograph]. Pickering, Ontario, Canada: Purdue Pharma; 2006.
- Hydrocodone [package insert]. Corona, CA: Watson Laboratories; 2004.
- Methadone hydrochloride tablets [package insert]. Hazelwood, MO: Mallinckrodt, Inc; 2004.
- Ultram ER (tramadol hydrochloride) [package insert]. Raritan, NJ: Ortho-McNeil; 2008.
- Dilaudid-HP injection 10 mg (hydromorphone hydrochloride) full prescribing information. North Chicago, IL: Abbott Laboratories; 2008.
- OPANA ER (oxymorphone hydrochloride extended-release tablets) [package insert]. Chadds Ford, PA: Endo Pharmaceuticals Inc; 2008.
- Foster DJ, Somogyi AA, Bochner F. Methadone N-demethylation in human liver microsomes: lack of stereoselectivity and involvement of CYP3A4. *Br J Clin Pharmacol*. 1999;47(4):403-412.
- Totah RA, Allen KE, Sheffels P, Whittington D, Kharasch ED. Enantiomeric metabolic interactions and stereoselective human methadone metabolism. *J Pharmacol Exp Ther*. 2007 Apr;321(1):389-399. Epub 2007 Jan 26.
- Wang JS, DeVane CL. Involvement of CYP3A4, CYP2C8, and CYP2D6 in the metabolism of (R)- and (S)-methadone in vitro. *Drug Metab Dispos*. 2003;31(6):742-747.
- Li Y, Kantelip JP, Gerritsen-van Schieveen P, Davani S. Interindividual variability of methadone response: impact of genetic polymorphism. *Mol Diagn Ther*. 2008;12(2):109-124.
- Crettol S, Déglon JJ, Besson J, et al. ABCB1 and cytochrome P450 genotypes and phenotypes: influence on methadone plasma levels and response to treatment. *Clin Pharmacol Ther*. 2006;80(6):668-681.
- Zhou SF, Xue CC, Yu XQ, Li C, Wang G. Clinically important drug interactions potentially involving mechanism-based inhibition of cytochrome P450 3A4 and the role of therapeutic drug monitoring. *Ther Drug Monit*. 2007;29(6):687-710.
- Zhou SF. Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. *Curr Drug Metab*. 2008;9(4):310-322.
- Girennavar B, Jayaprakasha GK, Patil BS. Potent inhibition of human cytochrome P450 3A4, 2D6, and 2C9 isoenzymes by grapefruit juice and its furocoumarins. *J Food Sci*. 2007;72(8):C417-C421.
- Huber WW, Rossmannith W, Grusch M, et al. Effects of coffee and its chemopreventive components kahweol and cafestol on cytochrome P450 and sulfotransferase in rat liver. *Food Chem Toxicol*. 2008;46(4):1230-1238.
- Flockhart DA. Drug interactions: cytochrome P450 drug interaction table. Indiana University School of Medicine. <http://medicine.iupui.edu/flockhart/table.htm>. Accessed March 5, 2009.
- Evans DA, Mahgoub A, Sloan TP, Idle JR, Smith RL. A family and population study of the genetic polymorphism of debrisoquine oxidation in a white British population. *J Med Genet*. 1980;17(2):102-105.
- Heiskanen T, Olkkola KT, Kalso E. Effects of blocking CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. *Clin Pharmacol Ther*. 1998;64(6):603-611.
- Bertilsson L, Lou YQ, Du YL, et al. Pronounced differences between native Chinese and Swedish populations in the polymorphic hydroxylations of debrisoquine and S-mephenytoin [published correction appears in *Clin Pharmacol Ther*. 1994;55(6):648]. *Clin Pharmacol Ther*. 1992;51(4):388-397.
- Bathum L, Johansson I, Ingelman-Sundberg M, Hørdler M, Brosen K. Ultrarapid metabolism of sparteine: frequency of alleles with duplicated CYP2D6 genes in a Danish population as determined by restriction fragment length polymorphism and long polymerase chain reaction. *Pharmacogenetics*. 1998;8(2):119-123.
- Løvlie R, Daly AK, Molven A, Idle JR, Steen VM. Ultrarapid metabolizers of debrisoquine: characterization and PCR-based detection of alleles with duplication of the CYP2D6 gene. *FEBS Lett*. 1996;392(1):30-34.
- Sohn DR, Shin SG, Park CW, Kusaka M, Chiba K, Ishizaki T. Metoprolol oxidation polymorphism in a Korean population: comparison with native Japanese and Chinese populations. *Br J Clin Pharmacol*. 1991;32(4):504-507.
- Akhillu E, Persson I, Bertilsson L, Johansson I, Rodrigues F, Ingelman-Sundberg M. Frequent distribution of ultrarapid metabolizers of debrisoquine

- in an Ethiopian population carrying duplicated and multiduplicated functional CYP2D6 alleles. *J Pharmacol Exp Ther.* 1996;278(1):441-446.
36. Bathum L, Skjelbo E, Mutabingwa TK, Madsen H, Hørder M, Brøsen K. Phenotypes and genotypes for CYP2D6 and CYP2C19 in a black Tanzanian population. *Br J Clin Pharmacol.* 1999;48(3):395-401.
37. Relling MV, Cherrie J, Schell MJ, Petros WP, Meyer WH, Evans WE. Lower prevalence of the debrisoquin oxidative poor metabolizer phenotype in American black versus white subjects. *Clin Pharmacol Ther.* 1991;50(3):308-313.
38. Masimirembwa C, Persson I, Bertilsson L, Hasler J, Ingelman-Sundberg M. A novel mutant variant of the CYP2D6 gene (CYP2D6\*17) common in a black African population: association with diminished debrisoquine hydroxylase activity. *Br J Clin Pharmacol.* 1996;42(6):713-719.
39. Mbanefo C, Bababunmi EA, Mahgoub A, Sloan TP, Idle JR, Smith RL. A study of the debrisoquine hydroxylation polymorphism in a Nigerian population. *Xenobiotica.* 1980;10(11):811-818.
40. Lötsch J, Skarke C, Liefhold J, Geisslinger G. Genetic predictors of the clinical response to opioid analgesics: clinical utility and future perspectives. *Clin Pharmacokinet.* 2004;43(14):983-1013.
41. Foster A, Mobley E, Wang Z. Complicated pain management in a CYP450 2D6 poor metabolizer. *Pain Pract.* 2007 Dec;7(4):352-356. Epub 2007 Nov 6.
42. Susce MT, Murray-Carmichael E, de Leon J. Response to hydrocodone, codeine and oxycodone in a CYP2D6 poor metabolizer. *Prog Neuropsychopharmacol Biol Psychiatry.* 2006 Sep 30;30(7):1356-1358. Epub 2006 Apr 24.
43. Kadian (morphine sulfate extended-release capsules) [package insert]. Piscataway, NJ: Alpharma; 2008.
44. Bhasker CR, McKinnon W, Stone A, et al. Genetic polymorphism of UDP-glucuronosyltransferase 2B7 (UGT2B7) at amino acid 268: ethnic diversity of alleles and potential clinical significance. *Pharmacogenetics.* 2000; 10(8):679-685.
45. Hara Y, Nakajima M, Miyamoto K, Yokoi T. Morphine glucuronosyltransferase activity in human liver microsomes is inhibited by a variety of drugs that are co-administered with morphine. *Drug Metab Pharmacokinet.* 2007;22(2):103-112.
46. Projean D, Morin PE, Tu TM, Ducharme J. Identification of CYP3A4 and CYP2C8 as the major cytochrome P450s responsible for morphine N-demethylation in human liver microsomes. *Xenobiotica.* 2003;33(8):841-854.
47. Takeda S, Ishii Y, Iwanaga M, et al. Modulation of UDP-glucuronosyltransferase function by cytochrome P450: evidence for the alteration of UGT2B7-catalyzed glucuronidation of morphine by CYP3A4. *Mol Pharmacol.* 2005;67(3):665-672. Epub 2004 Dec 20.
48. Takeda S, Ishii Y, Mackenzie PI, et al. Modulation of UDP-glucuronosyltransferase 2B7 function by cytochrome P450s in vitro: differential effects of CYP1A2, CYP2C9 and CYP3A4. *Biol Pharm Bull.* 2005; 28(10):2026-2027.
49. Darbari DS, van Schaik RH, Capparelli EV, Rana S, McCarter R, van den Anker J. UGT2B7 promoter variant -840G>A contributes to the variability in hepatic clearance of morphine in patients with sickle cell disease. *Am J Hematol.* 2008;83(3):200-202.
50. Duguay Y, Báár C, Skorpen F, Guillemette C. A novel functional polymorphism in the uridine diphosphate-glucuronosyltransferase 2B7 promoter with significant impact on promoter activity. *Clin Pharmacol Ther.* 2004;75(3):223-233.
51. Toide K, Takahashi Y, Yamazaki H, et al. Hepatocyte nuclear factor- $\alpha$  is a causal factor responsible for interindividual differences in the expression of UDP-glucuronosyltransferase 2B7 mRNA in human livers. *Drug Metab Dispos.* 2002;30(6):613-615.
52. Mercadante S, Casuccio A, Fulfaro F, et al. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. *J Clin Oncol.* 2001;19(11):2898-2904.
53. Cone EJ, Caplan YH, Moser F, Robert T, Black D. Evidence that morphine is metabolized to hydromorphone but not to oxymorphone. *J Anal Toxicol.* 2008;32(4):319-323.
54. Cone EJ, Heit HA, Caplan YH, Gourlay D. Evidence of morphine metabolism to hydromorphone in pain patients chronically treated with morphine. *J Anal Toxicol.* 2006;30(1):1-5.
55. McDonough PC, Levine B, Vorce S, Jufer RA, Fowler D. The detection of hydromorphone in urine specimens with high morphine concentrations. *J Forensic Sci.* 2008;53(3):752-754.
56. Hutchinson MR, Menelau A, Foster DJ, Coller JK, Somogyi AA. CYP2D6 and CYP3A4 involvement in the primary oxidative metabolism of hydrocodone by human liver microsomes. *Br J Clin Pharmacol.* 2004;57(3):287-297.
57. DrugBank Web site. Departments of Computing & Biological Sciences, University of Alberta. <http://drugbank.ca>. Accessed March 5, 2009.
58. Oyler JM, Cone EJ, Joseph RE Jr, Huestis MA. Identification of hydrocodone in human urine following controlled codeine administration. *J Anal Toxicol.* 2000;24(7):530-535.
59. Oda Y, Kharasch ED. Metabolism of methadone and *levo*- $\alpha$ -acetyl-methadol (LAAM) by human intestinal cytochrome P450 3A4 (CYP3A4): potential contribution of intestinal metabolism to presystemic clearance and bioactivation. *J Pharmacol Exp Ther.* 2001;298(3):1021-1032.
60. Reisfield GM, Salazar E, Bertholf RL. Rational use and interpretation of urine drug testing in chronic opioid therapy. *Ann Clin Lab Sci.* 2007;37(4):301-314.
61. Dalén P, Frengell C, Dahl ML, Sjöqvist F. Quick onset of severe abdominal pain after codeine in an ultrarapid metabolizer of debrisoquine. *Ther Drug Monit.* 1997;19(5):543-544.
62. Gasche Y, Daali Y, Fathi M, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism [published correction appears in *N Engl J Med.* 2005;352(6):638]. *N Engl J Med.* 2004;351(27):2827-2831.
63. Eckhardt K, Li S, Ammon S, Schänzel G, Mikus G, Eichelbaum M. Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. *Pain.* 1998;76(1-2):27-33.
64. Barkin RL, Iusco AM, Barkin SJ. Opioids used in primary care for the management of pain: a pharmacologic, pharmacotherapeutic, and pharmacodynamic overview. In: Boswell MV, Cole BE, eds. *Weiner's Pain Management: A Practical Guide for Clinicians.* 7th ed. New York, NY: CRC Press/Taylor & Francis Group; 2006:789-804.
65. Hucks D, Thompson PI, McLoughlin L, et al. Explanation at the opioid receptor level for differing toxicity of morphine and morphine 6-glucuronide. *Br J Cancer.* 1992;65(1):122-126.
66. Cann C, Curran J, Milner T, Ho B. Unwanted effects of morphine-6-glucuronide and morphine. *Anaesthesia.* 2002;57(12):1200-1203.
67. Peñon RT, Joel SP, Baksh K, Clark SJ, Langford RM, Slevin ML. Randomized placebo-controlled trial of the activity of the morphine glucuronides. *Clin Pharmacol Ther.* 2000;68(6):667-676.
68. Smith MT. Neuroexcitatory effects of morphine and hydromorphone: evidence implicating the 3-glucuronide metabolites. *Clin Exp Pharmacol Physiol.* 2000;27(7):524-528.
69. Wright AW, Mather LE, Smith MT. Hydromorphone-3-glucuronide: a more potent neuro-excitant than its structural analogue, morphine-3-glucuronide. *Life Sci.* 2001;69(4):409-420.
70. Wright AW, Nocente ML, Smith MT. Hydromorphone-3-glucuronide: biochemical synthesis and preliminary pharmacological evaluation. *Life Sci.* 1998;63(5):401-411.
71. Klepstad P, Borchgrevink PC, Dale O, et al. Routine drug monitoring of serum concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide do not predict clinical observations in cancer patients. *Palliat Med.* 2003;17:679-687.
72. Quigley C, Joel S, Patel N, Baksh A, Slevin M. Plasma concentrations of morphine, morphine-6-glucuronide and morphine-3-glucuronide and their relationship with analgesia and side effects in patients with cancer-related pain. *Palliat Med.* 2003;17(2):185-190.
73. Angst MS, Bührer M, Lötsch J. Insidious intoxication after morphine treatment in renal failure: delayed onset of morphine-6-glucuronide action. *Anesthesiology.* 2000;92(5):1473-1476.
74. Hagen NA, Foley KM, Cerbone DJ, Portenoy RK, Inturrisi CE. Chronic nausea and morphine-6-glucuronide. *J Pain Symptom Manage.* 1991;6(3):125-128.
75. Osborne R, Joel S, Grebenik K, Trew D, Slevin M. The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther.* 1993;54(2):158-167.
76. Osborne RJ, Joel SP, Slevin ML. Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *Br Med J (Clin Res Ed).* 1986;292(6535):1548-1549.
77. Halling J, Weihe P, Brosen K. CYP2D6 polymorphism in relation to tramadol metabolism: a study of Faroese patients. *Ther Drug Monit.* 2008; 30(3):271-275.
78. Gillen C, Haurand M, Kobelt DJ, Wnendt S. Affinity, potency and efficacy of tramadol and its metabolites at the cloned human  $\mu$ -opioid receptor. *Naunyn-Schmiedeberg's Arch Pharmacol.* 2000;362(2):116-121.
79. Driessen B, Reimann W. Interaction of the central analgesic, tramadol, with the uptake and release of 5-hydroxytryptamine in the rat brain in vitro. *Br J Pharmacol.* 1992;105(1):147-151.

80. Driessen B, Reimann W, Giertz H. Effects of the central analgesic tramadol on the uptake and release of noradrenaline and dopamine in vitro. *Br J Pharmacol*. 1993;108(3):806-811.
81. Lalovic B, Kharasch E, Hoffer C, Risler L, Liu-Chen LY, Shen DD. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. *Clin Pharmacol Ther*. 2006;79(5):461-479.
82. Feierman DE, Lasker JM. Metabolism of fentanyl, a synthetic opioid analgesic, by human liver microsomes: role of CYP3A4. *Drug Metab Dispos*. 1996;24(9):932-939.
83. Inturrisi CE. Pharmacology of methadone and its isomers. *Minerva Anesthesiol*. 2005;71(7-8):435-437.
84. Bush E, Miller C, Friedman I. A case of serotonin syndrome and mutism associated with methadone. *J Palliat Med*. 2006;9(6):1257-1259.
85. Ito S, Liao S. Myoclonus associated with high-dose parenteral methadone. *J Palliat Med*. 2008;11(6):838-841.
86. Sarhill N, Davis MP, Walsh D, Nounch C. Methadone-induced myoclonus in advanced cancer. *Am J Hosp Palliat Care*. 2001;18(1):51-53.
87. He YJ, Brockmüller J, Schmidt H, Roots I, Kirchheiner J. CYP2D6 ultrarapid metabolism and morphine/codeine ratios in blood: was it codeine or heroin? *J Anal Toxicol*. 2008;32(2):178-182.
88. Kirchheiner J, Schmidt H, Tzvetkov M, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J*. 2007 Aug;7(4):257-265. Epub 2006 Jul 4.
89. Cone EJ, Welch P, Paul BD, Mitchell JM. Forensic drug testing for opiates, III: Urinary excretion rates of morphine and codeine following codeine administration. *J Anal Toxicol*. 1991;15(4):161-166.
90. Solomon MD. A study of codeine metabolism. *Clin Toxicol*. 1974;7(3):255-257.
91. Dutt MC, Lo DS, Ng DL, Woo SO. Gas chromatographic study of the urinary codeine-to-morphine ratios in controlled codeine consumption and in mass screening for opiate drugs. *J Chromatogr*. 1983;267(1):117-124.
92. Posey BL, Kimble SN. Simultaneous determination of codeine and morphine in urine and blood by HPLC. *J Anal Toxicol*. 1983;7(5):241-245.
93. George S, Braithwaite RA. A pilot study to determine the usefulness of the urinary excretion of methadone and its primary metabolite (EDDP) as potential markers of compliance in methadone detoxification programs. *J Anal Toxicol*. 1999;23(2):81-85.
94. Levine B, ed. *Principles of Forensic Toxicology*. 2nd ed. Washington, DC: AACC Press; 2003:385.
95. Caraco Y, Sheller J, Wood AJ. Impact of ethnic origin and quinidine coadministration on codeine's disposition and pharmacodynamic effects. *J Pharmacol Exp Ther*. 1999;290(1):413-422.
96. Ahdieh H. Regarding CYP450 2D6 poor metabolizers [letter]. *Pain Pract*. 2008;8(4):329.
97. Foster A. In response to Dr. Ahdieh [published online ahead of print May 26, 2008]. *Pain Pract*. doi:10.1111/j.1533-2500.2008.00218\_2.x.
98. Hasselström J, Eriksson S, Persson A, Rane A, Svensson JO, Säwe J. The metabolism and bioavailability of morphine in patients with severe liver cirrhosis. *Br J Clin Pharmacol*. 1990;29(3):289-297.
99. Crotty B, Watson KJ, Desmond PV, et al. Hepatic extraction of morphine is impaired in cirrhosis. *Eur J Clin Pharmacol*. 1989;36(5):501-506.
100. Haberer JP, Schoeffler P, Couderc E, Duvaldestin P. Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. *Br J Anaesth*. 1982;54(12):1267-1270.
101. Novick DM, Kreek MJ, Fanizza AM, Yancovitz SR, Gelb AM, Stenger RJ. Methadone disposition in patients with chronic liver disease. *Clin Pharmacol Ther*. 1981;30(3):353-362.
102. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc*. 1985;33(4):278-285.
103. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. *J Gerontol*. 1976;31(2):155-163.
104. Anderson S, Brenner BM. Effects of aging on the renal glomerulus. *Am J Med*. 1986;80(3):435-442.
105. Milne RW, Nation RL, Somogyi AA, Bochner F, Griggs WM. The influence of renal function on the renal clearance of morphine and its glucuronide metabolites in intensive-care patients. *Br J Clin Pharmacol*. 1992;34(1):53-59.
106. Pauli-Magnus C, Hofmann U, Mikus G, Kuhlmann U, Mettang T. Pharmacokinetics of morphine and its glucuronides following intravenous administration of morphine in patients undergoing continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant*. 1999;14(4):903-909.
107. Wolff J, Bigler D, Christensen CB, Rasmussen SN, Andersen HB, Tønnesen KH. Influence of renal function on the elimination of morphine and morphine glucuronides. *Eur J Clin Pharmacol*. 1988;34(4):353-357.
108. Dubs A, Wiedemeier P, Caduff B. Morphine poisoning in chronic kidney failure: morphine-6-glucuronide as a pharmacologically active morphine metabolite [in German]. *Dtsch Med Wochenschr*. 1999;124(30):896-898.
109. Babul N, Darke AC, Hagen N. Hydromorphone metabolite accumulation in renal failure [letter]. *J Pain Symptom Manage*. 1995;10(3):184-186.
110. Furlan V, Hafi A, Dessalles MC, Bouchez J, Charpentier B, Taburet AM. Methadone is poorly removed by haemodialysis [letter]. *Nephrol Dial Transplant*. 1999;14(1):254-255.
111. Kreek MJ, Schecter AJ, Gutjahr CL, Hecht M. Methadone use in patients with chronic renal disease. *Drug Alcohol Depend*. 1980;5(3):197-205.
112. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage*. 2004;28(5):497-504.
113. Koehntop DE, Rodman JH. Fentanyl pharmacokinetics in patients undergoing renal transplantation. *Pharmacotherapy*. 1997;17(4):746-752.
114. Chauvin M, Sandouk P, Scherrmann JM, Farinotti R, Strumza P, Duvaldestin P. Morphine pharmacokinetics in renal failure. *Anesthesiology*. 1987;66(3):327-331.
115. Sear JW, Hand CW, Moore RA, McQuay HJ. Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites. *Br J Anaesth*. 1989;62(1):28-32.
116. Murtagh FE, Chai MO, Donohoe P, Edmonds PM, Higginson IJ. The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. *J Pain Palliat Care Pharmacother*. 2007;21(2):5-16.

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