Chapter 20
Clinical Significant Interactions with Opioid Analgesics

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This chapter summarizes the pharmacokinetic drug interactions of select opioid agents, focusing on underlying molecular mechanisms (e.g., known metabolic interactions at the enzymatic and transporter levels, such as cytochrome P450 [CYP450], uridine 5'-diphospho-glucuronosyltransferases [UGT], and drug transporters) and drawing a connection to pharmacodynamic interactions in clinical studies. The majority of data has focused on drug metabolism, and there are *in vitro* data to support the *in vivo* observations. Many opioids (e.g., codeine) are metabolized by enzymes that are known to exhibit genetic polymorphism, and this additional (gene-drug interaction) factor must be considered. Most data on opioids have focused on their classical analgesic properties, effects on pain threshold, and adverse effects such as somnolence, nausea/vomiting, gastrointestinal motility, or miosis. Additional atypical adverse effects such QT_C prolongation (e.g., associated with methadone) or serotonin syndrome (e.g., associated with tramadol) must be considered and can be manifested by pharmacokinetic-associated pharmacodynamic interactions. Information on pharmacokinetic-mediated pharmacodynamic interactions is relatively scarce in the literature compared to the available pharmacokinetic data. The available human data for opioids only represent a small fraction of all the possible drug interactions but one may use various *in vitro* or *in silico* approaches to aid the prediction of pharmacokinetic interactions. Evidence that a significant pharmacokinetic interaction is associated with a pharmacodynamic interaction must be appropriately weighted based on limitations in the design of existing studies. This chapter concludes with a proposed clinical decision-making algorithm that may be used to ascertain the clinical significance of pharmacokinetic-mediated pharmacodynamic interactions with opioid analgesics.

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20.1 Background

Opioid analgesics are the cornerstone of pain management therapy in cancer [1], noncancer [2], and postoperative pain management [3]. The utility of opioid drugs in both acute and chronic pain is underscored by their prominent positions on the widely used World Health Organization analgesic ladder for management of moderate and severe pain [4]. The pharmacology of opioid analgesics has been discussed in Chap. 10. The current chapter will summarize the pharmacokinetic drug interactions of select opioid agents, focusing on the underlying molecular mechanisms (e.g., known metabolic interactions at the enzymatic and transporter levels, such as cytochrome P450 [CYP450], uridine 5'-diphospho-glucuronosyltransferases [UGT], and drug transporters) and drawing a connection to pharmacodynamic interactions in clinical studies. Despite the fact that it is impossible to have experimental data on every single drug-drug interaction in humans, our mechanistic approach using the information already known at the molecular/enzymatic level can aid clinicians in predicting potential drug-drug interactions that will likely occur for a given opioid drug. We also propose an algorithm that may allow clinicians to systematically determine the significance of the observed clinical interactions.

Drug interactions mediated by pharmacokinetic changes can occur via absorption, distribution, metabolism, and excretion. The majority of the research on opioid pharmacokinetic interactions has focused on metabolism (and to a lesser degree, on transport) since most of the opioids are biotransformed singularly or in combination by various phase I (e.g., CYP450) and/or phase II (e.g., UGT) enzymes and/or phase III (e.g., p-glycoprotein [pgp]) systems [5, 6] and thus are subjected to drug interactions mediated by and/or genetic polymorphisms [7] associated with these enzymes and/or transporters. In general, phase I or II drug metabolism usually mediates the deactivation reaction (e.g., hydromorphone) but sometimes can lead to bioactivation (e.g., codeine) and the production of pharmacologically more potent metabolites. Interacting drugs can act as either inducers (e.g., rifampin for CYP3A4) or inhibitors (e.g., quinidine for CYP2D6) and, depending on the nature of metabolism (e.g., deactivation or bioactivation), can either enhance or decrease the therapeutic effects or pharmacological side effects of opioid drugs (and vice versa). On the other hand, phase III systems are responsible for the transport of drugs across lipophilic membranes (e.g., pgp transporter at the blood-brain barrier), are primarily responsible for decreasing drug concentrations at the tissue of interest, and, like phase I or II metabolic pathways, are also subjected to induction and inhibition. Phase III transporters

are by convention not classified as metabolism enzymes, but for the purpose of this chapter, the phrases "metabolism" and "biotransformation" will be used to denote all phase I–III processes. Moreover, genetic polymorphisms associated with metabolism enzymes can lead to phenotypic changes that result in increased metabolism (e.g., ultrarapid metabolizer phenotype for CYP2D6) or diminished metabolism (e.g., poor metabolizer status for CYP2D6). Considering all of these elements of drug metabolism and transport, it is not difficult to see that one can potentially encounter several layers of complexity while assessing drug-drug interactions associated with opioids. Therefore, the primary focus of this chapter will be on understanding the molecular basis (i.e., reaction phenotyping of opioid agents, formation of inactive or active metabolites, and known effects of genetic polymorphisms) responsible for the pharmacokinetic drug-drug interactions and the associated pharmacodynamic changes, which will serve as the foundation for interpreting clinical drug interactions. Evidence supporting other modes of drug interactions (e.g., absorption or protein binding displacement) will be summarized as well. Mechanisms of interactions mediated by opioids' pharmacodynamic effects on receptor binding or neurotransmitter release are outlined in Chap. 10, and will not be reviewed further here.

20.2 Methodology

One can classify opioids by chemical class or receptor binding activity (i.e., agonist vs. partial agonist) [8] (see Chap. 10). However, for the purpose of this chapter, only opioids that are commonly used in the clinical setting will be reviewed: morphine, codeine, oxycodone, hydromorphone, methadone, fentanyl, and tramadol as these are often itemized on the World Health Organization analgesic ladder. A search of PubMed, Embase, and Google Scholar was conducted (English and human articles only, no time limit) using various combinations of the following terms: individual opioids listed above, pharmacokinetics, pharmacodynamics, drug-drug interactions, CYP450, UGT, transporters, pharmacogenomics, pharmacogenetics, and polymorphism. Reference lists of selected citations were also manually reviewed and pertinent articles extracted. The chapter will be structured per individual opioid drug, as follows:

I. Metabolism-mediated pharmacokinetic and pharmacodynamic interactions
   (a) Reaction phenotyping and clinical pharmacokinetic and pharmacodynamic interactions
   (b) Genetic polymorphism

II. Assessing the clinical significance of pharmacokinetic and pharmacodynamic interactions
   (a) Clinical decision-making algorithm

20.3 Metabolism/Transport-Mediated Pharmacokinetic and Pharmacodynamic Interactions

20.3.1 Morphine

20.3.1.1 Reaction Phenotyping and Clinical Pharmacokinetic and Pharmacodynamic Interactions

Morphine is primarily metabolized by UGT enzymes and is a substrate of p-glycoprotein [9]. Various UGT enzymes are capable of catalyzing the conjugation of morphine [10], but the principal UGT enzyme appears to be hepatic UGT2B7 [11] by virtue of its higher affinity toward morphine compared to other UGT enzymes [10]. However, a comprehensive reaction phenotyping study, which is needed to determine the relative contribution of specific UGT enzymes toward the conjugation of morphine, is still lacking in the literature. The conjugation of morphine leads to the production of morphine-6-glucuronide (M-6-G) and morphine-3-glucuronide (M-3-G). M-6-G appears to be equipotent compared to morphine [12], whereas M-3-G appears to be therapeutically inert but may be associated with toxic effects [13]. The area under the concentration-time curve (AUC) ratios between M-6-G or M-3-G and morphine is often used in clinical drug interaction studies to delineate the effects of interacting drugs on morphine metabolism. Under normal conditions, more M-3-G is produced compared to M-6-G, and their plasma exposure values far exceed that of morphine [14]. Based on these data, drugs that are capable of inducing or inhibiting UGT2B7 (e.g., Tables 20.1 and 20.2 [10]) can potentially affect the disposition of morphine and hence its pharmacodynamic effects in the clinic.

Few studies have examined the effects of coadministered drugs on the disposition of morphine in humans (Table 20.1). Overall, morphine pharmacokinetics is minimally altered in the presence of UGT substrates or inhibitors, as evident by the lack of effects on the clearance or exposure of morphine and/or its glucuronides when propranolol [15], ranitidine [16], or travafloxacin [17] was given concurrently in humans. Despite an apparent morphine-sparing effect and the maintenance of sustained M-6-G concentrations (in the presence of reduced morphine dose) by diclofenac in patients receiving morphine patient-controlled analgesia [18], that particular study was not designed to determine, mechanistically, diclofenac's effects on morphine glucuronidation. Moreover, despite the fact that the clearance and exposure of morphine were increased in the presence of rifampin, a potent UGT inducer [19], the formation of morphine glucuronide also decreased; therefore, the apparently significant pharmacokinetic interaction could not be explained by an effect of rifampin on morphine glucuronidation alone. In addition to hepatic metabolism, studies are also available on the effects of cimetidine, used as a modulator of hepatic blood flow [20] and gabapentin [21], an inhibitor of renal excretion, and neither found a significant effect on the pharmacokinetics of morphine in humans

Table 20.1 *In vivo* pharmacokinetic interactions associated with opioid agents in humans

Interacting drug/gene	Summary effects on opioid pharmacokinetics	Reference
Morphine (drug)		
Cimetidine	No effect on clearance or AUC of morphine. Morphine glucuronide not measured	Mojaverian et al. [20]
Diclofenac	Potentially morphine-sparing effect (same concentration of M-6-G glucuronide despite reduced morphine patient-controlled analgesic dose)	Tighe et al. [18]
Gabapentin	No effect on any measured pharmacokinetic parameters (including AUC and clearance) of morphine and M-3-G	Eckhardt et al. [21]
Propranolol	No effect on plasma or urinary concentrations of morphine or morphine glucuronide	Brunk et al. [15]
Quinidine	Increased plasma morphine concentration and AUC, decreased plasma glucuronide/morphine ratio	Kharasch et al. [9]
Ranitidine	No effect on the serum AUC or urinary M-3-G to M-6-G ratio, but decreased serum M-3-G to M-6-G ratio	Aasmundstad and Storset [16]
Rifampin	Increased clearance, decreased AUC of morphine. Decreased clearance of morphine glucuronides	Fromm et al. [19]
Travafloxacin	No effect on any measured pharmacokinetic parameters (including AUC and half-life) of morphine and M-3-G	Vincent et al. [17]
Valspodar	No effect on any measured pharmacokinetic parameters (including AUC and clearance) of morphine. Increased AUC and maximum concentration of M-3-G	Drewe et al. [22]
Morphine (gene)		
−802A>T (UGT) – UGT2B7*2	No effect on M-3-G/morphine or M-6-G/morphine ratio in cancer patients	Holthe et al. [26] Holthe et al. [25]
−840A>G (UGT)	Decreased M-6-G or M-3-G/morphine ratio	Darbari et al. [27]

(continued)

Table 20.1 (continued)

Interacting drug/gene	Summary effects on opioid pharmacokinetics	Reference
−161C>T (UGT)	Decreased M-6-G/morphine ratio and M-6-G or M-3-G concentrations	Saywer et al. [28]
−842G>A (UGT)	Decreased plasma morphine concentration. No effects on glucuronide concentrations in preterm newborns	Matic et al. [29]
Codeine (drug)		
Diclofenac	No effects on the pharmacokinetics of codeine. No change in the concentrations of codeine-6-glucuronide	Ammon et al. [34]
Quinidine	In extensive metabolizers. Decreased morphine in plasma	Sindrup et al. [36]
Quinidine	Decreased morphine concentration in plasma and cerebrospinal fluid	Sindrup et al. [38]
Quinidine	In extensive metabolizers. Decreased the O-demethylation of codeine. More prominent decrease in Caucasians compared to Chinese. Diminished the formation of morphine or morphine glucuronides	Caraco et al. [39]
Quinidine	Decreased plasma morphine	Kathiramalainathan et al. [37]
Quinidine, fluoxetine	Decreased the O-demethylation of dextromethorphan (maker substrate for CYP2D6)	Fernandes et al. [40]
Rifampin	Increased clearance through glucuronidation (increased glucuronide metabolites and norcodeine), decreased formation of morphine	Caraco et al. [41]
Codeine (gene)		
Extensive vs. poor metabolizer of sparteine (CYP2D6 substrate)	Lack of detection of morphine in plasma in poor metabolizers	Sindrup et al. [49]
Extensive vs. poor metabolizer of debrisoquine (CYP2D6 substrate)	Lower exposure of morphine in plasma in poor metabolizers and reduced clearance through the O-demethylation (i.e., CYP2D6) pathway	Yue et al. [52]
Extensive vs. poor metabolizer of dextromethorphan (CYP2D6 substrate)	Increased partial clearance of codeine to morphine in plasma of extensive metabolizers	Chen et al. [53]
Extensive vs. poor metabolizer of sparteine (substrate for CYP2D6)	Lack of detection of plasma morphine or M-6-G in poor metabolizers	Poulsen et al. [50]
Extensive vs. poor metabolizers of sparteine	Higher plasma concentrations and amount of morphine excreted in urine in extensive metabolizers	Mikus et al. [54]

Table 20.1 (continued)

Interacting drug/gene	Summary effects on opioid pharmacokinetics	Reference
Extensive vs. poor metabolizer of CYP2D6 (genotyped)	Only trace formation of morphine in plasma of poor metabolizers. Percentage of morphine converted from codeine in extensive metabolizers (3.9 %) much greater than poor metabolizers (0.17 %)	Eckhardt et al. [55]
Extensive vs. poor metabolizer of sparteine (CYP2D6 substrate)	Lack of detection of plasma morphine or M-6-G in poor metabolizers	Poulsen et al. [51]
Ultrarapid vs. extensive vs. poor metabolizers (genotyped)	Higher plasma exposure of morphine in ultrarapid compared to extensive and poor metabolizers. Lower ratio of morphine to codeine (and their respective glucuronides) in urine	Kirchheiner et al. [56]
Oxycodone (drug)		
Clarithromycin	Increased plasma exposure of oxycodone and decreased that of noroxycodone (age-independent effect)	Liukas et al. [58]
Grapefruit juice	Increased plasma exposure of oxycodone, decreased noroxycodone/oxycodone ratio. Increased plasma exposure of oxymorphone	Nieminen et al. [59]
Itraconazole	Increased plasma exposure of oxycodone (after oral or intravenous dosing) and noroxymorphone, but decreased that of noroxycodone	Saari et al. [61]
Ketoconazole (as CYP3A4 inhibitor) and quinidine (as CYP2D6 inhibitor)	Quinidine increased plasma exposure of noroxycodone and decreased the exposure of oxymorphone. Ketoconazole had opposite effects	Samer et al. [64]
Ketoconazole (as CYP3A4 inhibitor) and paroxetine (as CYP2D6 inhibitor)	Ketoconazole increased exposure of oxycodone, whereas paroxetine had no effect, compared to placebo	Kummer et al. [60]
Miconazole (oral gel) (as a mixed CYP3A4 and CYP2D6 inhibitor)	Increased plasma exposure of oxycodone and noroxycodone but decreased that of oxymorphone	Gronlund et al. [68]
Paroxetine (as CYP2D6 inhibitor) and/or itraconazole (as CYP3A4 inhibitor) – oral oxycodone	Paroxetine decreased plasma exposure of oxymorphone but not oxycodone. Paroxetine and itraconazole together increased plasma exposure of oxycodone	Gronlund et al. [66]
Paroxetine (as CYP2D6 inhibitor) and/or itraconazole (as CYP3A4 inhibitor) – intravenous oxycodone	Paroxetine did not affect the exposure of oxycodone Paroxetine and itraconazole together increased plasma exposure of oxycodone	Gronlund et al. [67]

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Table 20.1 (continued)

Interacting drug/gene	Summary effects on opioid pharmacokinetics	Reference
Rifampin	Decreased plasma exposure of oxycodone, oxymorphone and increased noroxycodone/oxycodone ratio (both oral and intravenous dosing)	Nieminen et al. [70]
Ritonavir or lopinavir/ritonavir	Increased plasma exposure of oxycodone, decreased plasma exposure of noroxycodone, and increased plasma exposure of oxymorphone (only with lopinavir/ritonavir)	Nieminen et al. [62]
St. John's wort (CYP3A4 inducer)	Decreased plasma exposure of oxycodone	Nieminen et al. [71]
Telithromycin (as inhibitors for both CYP2D6 and CYP3A4)	Increased plasma exposure of oxycodone and decreased plasma exposure of noroxycodone. No effects on the pharmacokinetics of oxymorphone	Gronlund et al. [69]
Voriconazole	Increased plasma exposure of oxycodone. Increased plasma oxymorphone/oxycodone ratio, decreased noroxycodone/oxycodone ratio	Hagelberg et al. [63]
Quinidine	No effect on oxycodone concentrations, increased plasma noroxycodone concentrations, decreased formation (lack of detection) of plasma oxymorphone	Heiskanen et al. [65]
Oxycodone (gene)		
CYP2D6 extensive vs. poor metabolizers	Significantly increased plasma oxymorphone/oxycodone ratio in extensive metabolizers	Zwisler et al. [73]
CYP2D6 extensive vs. poor metabolizers	Significantly increased plasma oxymorphone/oxycodone ratio in extensive metabolizers in postoperative patients (intravenous oxycodone)	Zwisler et al. [74]
CYP2D6 ultrarapid vs. extensive vs. poor metabolizers	Increased oxymorphone and decreased noroxycodone plasma concentration in ultrarapid metabolizers of CYP2D6	Samer et al. [64]
CYP2D6 ultrarapid vs. extensive vs. intermediate vs. poor metabolizers	Increased oxymorphone/oxycodone ratio dependent on CYP2D6 metabolizer phenotype status (ultrarapid > extensive > intermediate > poor)	Stamer et al. [72]
Hydromorphone (gene)		
−802A > T (UGT) – UGT2B7*2	No effect on various pharmacokinetic parameters of hydromorphone, or H3G (including exposure)	Vandenbossche et al. [81]
Fentanyl (drug)		
Itraconazole	No effects on the pharmacokinetics (including clearance) of fentanyl (given intravenously) in plasma	Palkama et al. [85]

Table 20.1 (continued)

Interacting drug/gene	Summary effects on opioid pharmacokinetics	Reference
Parecoxib or troleandomycin	No effects on the pharmacokinetics (including exposure) of intravenously administered fentanyl in plasma by parecoxib. Troleandomycin decreased clearance of fentanyl in plasma	Ibrahim et al. [87]
Rifampin, troleandomycin, or grapefruit juice	Rifampin decreased exposure and increased clearance of fentanyl in plasma (given as oral lozenge) whereas troleandomycin had opposite effects. Rifampin increased whereas troleandomycin decreased the exposure of norfentanyl in plasma. Grapefruit juice had no effects	Kharasch et al. [86]
Ritonavir	Decreased clearance and increased exposure in plasma of intravenously administered fentanyl	Olkkola et al. [88]
Voriconazole and fluconazole	Decreased fentanyl (given intravenously) clearance (voriconazole and fluconazole) and increased fentanyl exposure (voriconazole) in plasma. Both voriconazole and fluconazole decreased exposure of norfentanyl in plasma	Saari et al. [89]
Tramadol (drug)		
Escitalopram	Decreased plasma exposure of M1 metabolite	Noehr-Jensen et al. [94]
Methadone (CYP2D6 inhibition) or buprenorphine	Decreased urinary ratio of M1/tramadol from methadone compared to buprenorphine-treated subjects. No difference in M2/tramadol or tramadol concentrations in urine between two treatments	Coller et al. [95]
Paroxetine (CYP2D6 inhibition)	Increased plasma exposure of tramadol. Decreased plasma exposure of M1 metabolite	Laugesen et al. [96]
Paroxetine	Increased urinary tramadol/M1 ratio	Nielsen et al. [97]
Rifampin (CYP3A4 induction)	Decreased plasma exposure of tramadol and M1 metabolite (oral and intravenously administered tramadol)	Saarikoski et al. [98]
Ticlopidine (CYP2D6 inhibitor) and itraconazole (CYP3A4 inhibitor)	Ticlopidine increased plasma exposure of tramadol and decreased exposure of M1 metabolite. Itraconazole had no effects	Hagelberg et al. [99]
Tramadol (gene)		
CYP2D6 extensive vs. poor metabolizers	Increased plasma M1 concentrations in extensive metabolizers (not detectable in poor metabolizers)	Poulsen et al. [100]

(continued)

Table 20.1 (continued)

Interacting drug/gene	Summary effects on opioid pharmacokinetics	Reference
CYP2D6 extensive vs. poor metabolizers	Increased plasma exposure of M1 metabolite and decreased exposure of tramadol in extensive metabolizers	Pedersen et al. [101]
CYP2D6 extensive vs. poor metabolizers	Detectable plasma M1 concentrations only in extensive metabolizers	Enggaard et al. [102]
CYP2D6 ultrarapid vs. extensive vs. intermediate metabolizers	Increased tramadol plasma clearance in ultrarapid and extensive metabolizers vs. intermediate metabolizers	Gan et al. [106]
CYP2D6 extensive vs. poor metabolizers	Increased plasma exposure of M1 metabolite, decreased exposure of tramadol in extensive metabolizers	Garcia-Quetglas et al. [103]
CYP2D6 ultrarapid vs. extensive vs. intermediate vs. poor metabolizers	Plasma exposure of the M1 metabolite dependent on phenotype status (ultrarapid > extensive > intermediate > poor)	Stamer et al. [105]
CYP2D6 extensive vs. poor metabolizers	Increased plasma concentration of M1 metabolite in extensive metabolizers	Halling et al. [104]
CYP2D6 ultrarapid vs. extensive metabolizers	Increased plasma exposure of M1 metabolite but decreased exposure of tramadol in ultrarapid metabolizers	Kirchheiner et al. [107]
Methadone (drug)		
Amprenavir (PI)	Decreased both S- and R-methadone plasma exposure (higher magnitude of decrease in S- compared to R-isoform)	Hendrix et al. [126]
Atazanavir (PI)	No change in S- or R-methadone plasma concentrations	Friedland et al. [135]
Delavirdine (NNRTI)	Increased plasma methadone exposure	McCance-Katz et al. [145]
Dolutegravir (INI)	No effect on R-, S-, or total methadone plasma exposure	Song et al. [140]
Fluconazole (CYP3A4 inhibitor)	Increased methadone exposure in plasma	Cobb et al. [121]
Fosamprenavir-ritonavir (PI)	Decreased plasma exposure of S-methadone > R-methadone	Cao et al. [149]
Indinavir (PI)	No effect on plasma exposure of methadone (despite significant inhibitory effects on CYP3A4 substrate marker exposure)	Kharasch et al. [136]
Lamivudine/zidovudine (NRTI)	No effect on plasma exposure of methadone	Rainey et al. [150]
Lersivirine (NNRTI)	No effect on R- or S-methadone plasma exposure	Vourvahis et al. [146]
Lopinavir-ritonavir vs. ritonavir (PI)	Lopinavir-ritonavir decreased plasma exposure of methadone. No effect by ritonavir	McCance-Katz et al. [127]
Lopinavir-ritonavir (PI)	Decreased plasma exposure of methadone	Clarke et al. [128]

Table 20.1 (continued)

Interacting drug/gene	Summary effects on opioid pharmacokinetics	Reference
Lopinavir-ritonavir (PI)	Decreased plasma concentrations of methadone (despite significant inhibitory effects toward CYP3A4 substrate marker exposure)	Kharasch and Stubbert [129]
Nelfinavir (PI)	Decreased plasma exposure of R- and S-methadone (more reduction with S-isomer), despite significant inhibitory effects on CYP3A4 substrate maker exposure	Kharasch et al. [130]
Nelfinavir (PI)	Decreased plasma exposure of methadone	McCance-Katz et al. [131]
Nelfinavir (PI)	Decreased plasma exposure of R- and S-methadone	Hsyu et al. [132]
Nevirapine (NNRTI)	Decreased plasma exposure of R- and total methadone	Stocker et al. [142]
Nevirapine (NNRTI)	Decreased plasma exposure of methadone	Arroyo et al. [143]
Nevirapine (NNRTI)	Decreased plasma exposure of methadone	Clarke et al. [144]
Paroxetine (CYP2D6 inhibitor)	Increased plasma concentrations of both R- and S-methadone in CYP2D6 extensive metabolizers. Increased plasma concentration of S-methadone in poor CYP2D6 metabolizers	Begre et al. [123]
Quetiapine (CYP2D6 inhibitor)	Increased plasma R-methadone/dose ratio (extensive CYP2D6 metabolizers > intermediate metabolizers > poor metabolizers)	Uehlinger et al. [124]
Rifampin (CYP3A4 inducer), troleandomycin (CYP3A4 inhibitor), grapefruit juice (intestinal CYP3A4 inhibitor)	Rifampin increased clearance of oral and intravenous methadone. Troleandomycin and grapefruit juice had no effects on methadone clearance	Kharasch et al. [114]
Raltegravir (INI)	No effect on plasma methadone exposure	Anderson et al. [141]
Saquinavir/Ritonavir (PI)	Decreased plasma exposure of methadone	Jamois et al. [133]
Saquinavir/ritonavir (PI)	Decreased S- or R-methadone plasma exposure	Gerber et al. [134]
Saquinavir/ritonavir (PI)	No effect on S- or R-methadone plasma exposure	Shelton et al. [137]
Sertraline	Increased plasma methadone/dose ratio in the first 6 weeks of treatment. No difference by week 12	Hamilton et al. [125]
Tenofovir (NRTI)	No effect on plasma exposure of methadone (R-, S-, or total)	Smith et al. [138]

(continued)

Table 20.1 (continued)

Interacting drug/gene	Summary effects on opioid pharmacokinetics	Reference
Voriconazole (CYP3A4 inhibitor)	Increased both R- and S-methadone exposure in plasma	Liu et al. [122]
Zidovudine (NRTI)	No effect on plasma exposure of methadone	Schwartz et al. [139]
Methadone (gene)		
ABCB1 3435TT (reduced pgp activity)	Decreased R-methadone plasma concentration-dose ratio	Uehlinger et al. [124]
CYP2D6 ultrarapid vs. extensive vs. poor metabolizers	Increased concentrations to dose-to-weight ratios of R-methadone in plasma (poor metabolizer > ultrarapid metabolizer)	Eap et al. [147]
CYP3A4 activity CYP2B6*6/*6 CYP2D6 ultrarapid vs. extensive vs. intermediate vs. poor metabolizer ABCB1 3435TT (reduced pgp activity)	Lower CYP3A activity led to increased trough R- and S-methadone plasma concentration CYP2B6*6*6 phenotype led to increased plasma S-methadone concentration CYP2D6 extensive metabolizers had decreased R- and S-methadone plasma concentration vs. extensive and intermediate metabolizers ABCB1 3435TT decreased trough R- and S-methadone plasma concentrations	Crettol et al. [148]

CYP cytochrome P450, *ECG* electrocardiogram, *INI* integrase inhibitors, *NNRTI* non-nucleoside reverse transcriptase inhibitors, *NRTI* nucleoside reverse transcriptase inhibitors, *pgp* p-glycoprotein, *PI* protease inhibitors, *UGT* uridine 5'-diphospho-glucuronosyltransferases

(Table 20.1). On the other hand, inconsistent findings were obtained with pgp inhibitors, valspodar [22] which did not affect morphine pharmacokinetics compared to quinidine [9] which apparently increased the absorption (decreased intestinal efflux) of morphine in humans (Table 20.1).

In general, studies that have characterized the pharmacodynamic effects of morphine have shown little influence by the interacting drug, whereas those that have demonstrated an apparent pharmacological effect were potentially confounded by other factors (Table 20.2). All of these negative findings should be interpreted with caution, however, as these studies had relatively small sample sizes and except for diclofenac, which is a known potent inhibitor of UGT2B7 [10], the potency or specificity of other putative UGT modulators has not been well characterized. As well, the case of rifampin further highlights the complexity of all combined metabolic processes in humans: that one should also consider other metabolic pathways being affected by the modulator rather than only taking into consideration a single process (i.e., glucuronidation) by itself. Alternatively, one might hypothesize that morphine, being a high extraction drug, may be relatively insensitive to changes in its intrinsic clearance (i.e., as a result of enzyme modulation) than hepatic blood flow, which may explain the general lack of pharmacokinetic interactions reported for morphine in the literature.

20.3.1.2 Genetic Polymorphism

As morphine is primarily conjugated by UGT2B7, polymorphism in this specific metabolizing enzyme that results in altered phenotype can potentially result in significant pharmacokinetic alterations. The available literature illustrates a mixed picture, however, where only certain genetic polymorphisms are associated with altered glucuronide to morphine ratios in humans (Table 20.1). *In vitro* studies using microsomes containing polymorphic -802A>T variant (UGT2B7*2) show little difference in the formation of morphine glucuronide compared to the wild type [23, 24]. These *in vitro* observations are supported by the lack of an effect by UGT2B7*2 variants in the glucuronide/morphine plasma ratios in cancer patients [25, 26]. On the other hand, patients with sickle cell disease possessing the -840A>G allele as a hetero- or homozygote had a significantly reduced morphine glucuronide/morphine ratio [27], subjects with the -161C>T allele (which is also in complete linkage disequilibrium with UGT2B7*2) had decreased M-6-G/morphine ratios and reduced morphine glucuronide concentrations compared to the wild type [28], and preterm newborns with the -842G>A allele showed decreased morphine concentrations and increased M-3-G/morphine ratios [29]. It has to be noted, however, that these genetic studies are of relatively small sample sizes and only association in nature; and it remains to be clarified whether these pharmacokinetic variations are translated to clinically relevant pharmacodynamic effects.

20.3.2 Codeine

20.3.2.1 Reaction Phenotyping and Clinical Pharmacokinetic and Pharmacodynamic Interactions

Codeine is a weak analgesic that requires further activation to morphine to exert its pharmacological effects. The hepatic enzyme responsible for the activation of codeine is CYP2D6 [30], although this pathway constitutes only a small portion of codeine clearance as most of codeine is deactivated by UGT2B7, UGT2B4 [24] and CYP3A4 [31] in the formation of inactive glucuronide metabolites and norcodeine, respectively. Given the influence of concurrent bioactivation and deactivation pathways, pharmacokinetic drug-drug interactions involving codeine are dependent on the combined effects of the modulators toward all of these enzyme pathways. For example, a CYP3A4 modulator, although not directly responsible for the bioactivation of codeine, can also affect the CYP2D6 bioactivation pathway indirectly by enhancing or reducing the availability of codeine. This scenario was demonstrated in a case report where an individual with ultrarapid CYP2D6 genotype (i.e., enhanced codeine activation) taking CYP3A4 inhibitors (i.e., reduced codeine deactivation) exhibited codeine intoxication, presumably a result of additive effects of two concurrent drug-drug interactions on two separate codeine metabolic pathways [32]. The complexity of codeine metabolism highlighting the interplay between

Table 20.2 *In vivo* pharmacodynamic interactions (mediated by pharmacokinetic changes) associated with opioid agents in humans

Interacting drug/gene	Summary effects on opioid pharmacodynamics	Reference
Morphine (drug)		
Cimetidine	No effects on the duration of miosis associated with morphine	Mojaverian et al. [20]
Diclofenac	Morphine-sparing effect, although the analgesic effect from diclofenac itself was difficult to control	Tighe et al. [18]
Gabapentin	Increased analgesic effect of morphine (cold pressor test, although the analgesic effect of gabapentin itself was difficult to control)	Eckhardt et al. [21]
Quinidine	Increased morphine-induced miosis	Kharasch et al. [9]
Rifampin	Significantly decreased the analgesic effects of morphine (cold pressor test)	Fromm et al. [19]
Travafloxacin	No change on adverse effects associated with morphine	Vincent et al. [17]
Valspodar	No effects on adverse events associated with morphine	Drewe et al. [22]
Codeine (drug)		
Diclofenac	No change in the findings from cold pressor test	Ammon et al. [34]
Quinidine	In extensive metabolizers. No difference in pin-prick or tolerance pain thresholds	Sindrup et al. [36]
Quinidine	In extensive metabolizers. Decreases in codeine therapeutic effects only observed in Caucasians but not in the Chinese	Caraco et al. [39]
Quinidine, fluoxetine	No effect on codeine dependence	Fernandes et al. [40]
Quinidine	Decreased positive (“high”) and negative (“nausea”) effects	Kathiramalainathan et al. [37]
Rifampin	Decreased respiratory and psychomotor but no change in miotic effects in extensive metabolizers. Opposite effects in poor metabolizers	Caraco et al. [41]
Codeine (gene)		
Extensive vs. poor metabolizer of sparteine (CYP2D6 substrate)	Increased pricking pain threshold only in extensive metabolizers	Sindrup et al. [49]

Table 20.2 (continued)

Interacting drug/gene	Summary effects on opioid pharmacodynamics	Reference
Extensive vs. poor metabolizer of sparteine (CYP2D6 substrate)	Extensive metabolizers responded to codeine (pain reduction and tolerance threshold), whereas codeine had no effects in poor metabolizers	Poulsen et al. [50]
Extensive vs. poor metabolizers of sparteine	Reduced gastric motility only in extensive metabolizers	Mikus et al. [54]
Extensive vs. poor metabolizer of CYP2D6 (genotyped)	Analgesic effect only evident (cold pressor test) in extensive metabolizers. Incidence of side effects (from visual analogue scale) comparable between the two phenotypes	Eckhardt et al. [55]
Extensive vs. poor metabolizer of sparteine (CYP2D6 substrate)	No difference between the two CYP2D6 phenotypes with respect to postoperative pain	Poulsen et al. [51]
Ultrarapid vs. extensive vs. poor metabolizers (genotyped)	Higher incidence of sedation in ultrarapid compared to extensive metabolizers	Kirchheiner et al. [56]
Oxycodone (drug)		
Clarithromycin	No difference in behavioral/ ocular/or analgesic pharmacodynamic effects	Liukas et al. [58]
Grapefruit juice	No effects on analgesia. Increased deteriorating effect and self-rated performance	Nieminen et al. [59]
Itraconazole	Increased alertness, and deterioration of performance, but no change in heat pain or cold pain threshold	Saari et al. [61]
Ketoconazole (as CYP3A4 inhibitor) and paroxetine (as CYP2D6 inhibitor)	Ketoconazole increased analgesic efficacy, pupil dilation, nausea, drowsiness, and pruritus. Paroxetine had no effect	Kummer et al. [60]
Ketoconazole (as CYP3A4 inhibitor) and quinidine (as CYP2D6 inhibitor)	Quinidine decreased whereas ketoconazole increased pain threshold. Ketoconazole treatment also increased side effect measures of oxycodone	Samer et al. [64]
Miconazole (oral gel)	No pharmacodynamics interaction observed (analgesia, drowsiness, pleasantness, pupil size, cold pain threshold, and the digit symbol substitution test (a psychomotor measure))	Gronlund et al. [68]

(continued)

Table 20.2 (continued)

Interacting drug/gene	Summary effects on opioid pharmacodynamics	Reference
Paroxetine (as CYP2D6 inhibitor) and/or itraconazole (as CYP3A4 inhibitor)	Paroxetine alone had no effects on subjective drug effects, drowsiness, or deterioration of performance. Paroxetine and itraconazole together significantly increased these effects	Gronlund et al. [66]
Paroxetine (as CYP2D6 inhibitor) and/or itraconazole (as CYP3A4 inhibitor) – intravenous oxycodone	No change in pharmacodynamic effects by paroxetine alone or in combination with itraconazole	Gronlund et al. [67]
Rifampin	Decreased self-reported drowsiness, drug effect, deterioration of performance, miosis (intravenous), and heterotropia (oral). Decreased the analgesic effects of oral oxycodone only	Nieminen et al. [70]
Ritonavir or lopinavir/ritonavir	Increased self-reported drug effect, nausea/vomiting. No effects on analgesia	Nieminen et al. [62]
St. John's wort (CYP3A4 inducer)	Decreased self-reported drug effect. No effects on analgesia	Nieminen et al. [71]
Telithromycin (as inhibitors for both CYP2D6 and CYP3A4)	Increased self-rated drug effect but decreased self-rated performance and pupil size. Increased heat pain threshold and cold pain analgesia. No effects on heat pain analgesia or tactile sensitivity	Gronlund et al. [69]
Voriconazole	Increased subjective drug effects, heterophoria, and miosis. No effects on analgesia. Effects on adverse events not quantifiable	Hagelberg et al. [63]
Quinidine	No effects on psychomotor or subjective drug effects. No effects on adverse events	Heiskanen et al. [65]
Oxycodone (gene)		
CYP2D6 extensive vs. poor metabolizers	Increased pain tolerance thresholds and pain reduction (cold pressor test) in extensive metabolizers	Zwisler et al. [73]
CYP2D6 extensive vs. poor metabolizers	No difference between metabolizer phenotypes on intravenous oxycodone analgesic effects in postoperative patients	Zwisler et al. [74]

Table 20.2 (continued)

Interacting drug/gene	Summary effects on opioid pharmacodynamics	Reference
CYP2D6 ultrarapid vs. extensive vs. poor metabolizers	Greater effects of oxycodone on cold pressor test, subjective pain threshold, and pupil size in ultrarapid versus extensive or the poor metabolizers of CYP2D6. Side effect measures more likely observed in ultrarapid metabolizers	Samer et al. [64]
CYP2D6 ultrarapid vs. extensive vs. intermediate vs. poor metabolizers	Ultrarapid and extensive metabolizers required reduced oxycodone consumption but only compared to poor metabolizers. No difference in pain scores	Stamer et al. [72]
Hydromorphone (gene)		
−802A>T (UGT) – UGT2B7*2	No effect on adverse events	Vandenbossche et al. [81]
Fentanyl (drug)		
Parecoxib or troleandomycin	Troleandomycin, but not parecoxib, had an effect on pupil diameter on intravenously administered fentanyl	Ibrahim et al. [87]
Itraconazole	No change in pharmacodynamic effects (therapeutic effect, drowsiness, nausea, itching – via visual analogue scale)	Palkama et al. [85]
Tramadol (drug)		
Escitalopram (CYP2D6 inhibition)	No change in response to cold pressor test	Noehr-Jensen et al. [94]
Paroxetine (CYP2D6 inhibition)	Decreased analgesic effects of tramadol compared to tramadol alone	Laugesen et al. [96]
Tramadol (gene)		
CYP2D6 extensive vs. poor metabolizers	Increased pain thresholds and analgesic effects (cold pressor test) in extensive metabolizers	Poulsen et al. [100]
CYP2D6 extensive vs. poor metabolizers	Decreased analgesia response rate in poor metabolizers	Stamer et al. [101]
CYP2D6 extensive vs. poor metabolizers	Increased analgesic effects (cold pressor test) in extensive metabolizers. Increased pain tolerance thresholds to nerve stimulation in poor metabolizers	Enggaard et al. [102]
CYP2D6 ultrarapid vs. extensive vs. intermediate metabolizers	More adverse events observed in intermediate metabolizers	Gan et al. [106]

(continued)

Table 20.2 (continued)

Interacting drug/gene	Summary effects on opioid pharmacodynamics	Reference
CYP2D6 ultrarapid vs. extensive metabolizers	Increased pain threshold and pain tolerance in ultrarapid metabolizers. Increased miotic effects and higher incidence of nausea in ultrarapid metabolizers	Kirchheiner et al. [107]
Methadone (drug)		
Amprenavir (PI)	No effect on analgesia, withdrawal, or dose change	Hendrix et al. [126]
Atazanavir (PI)	No effect on methadone withdrawal	Friedland et al. [135]
Delavirdine (NNRTI)	No effect on cognitive deficits, opioid withdrawal, or adverse effects	McCance-Katz et al. [145]
Dolutegravir (INI)	No effect on adverse events, ECG, vital signs	Song et al. [140]
Fluconazole	No effect on opioid overdose	Cobb et al. [121]
Fosamprenavir-ritonavir (PI)	No effect on withdrawal, adverse events, or dosage change	Cao et al. [149]
Lersivirine (NNRTI)	No effect on methadone withdrawal	Vourvahis et al. [146]
Lopinavir-ritonavir (PI)	No effect on methadone withdrawal or dose adjustment	Clarke et al. [128]
Nelfinavir (PI)	No effect on methadone-induced miosis	Kharasch et al. [130]
Nelfinavir (PI)	No effect on methadone withdrawal	McCance-Katz et al. [131]
Nelfinavir (PI)	No effect on withdrawal or adverse event rate	Hsyu et al. [132]
Nevirapine (NNRTI)	Induced withdrawal symptoms in 90 % of subjects	Arroyo et al. [143]
Nevirapine (NNRTI)	Induced withdrawal symptoms in 6 out of 8 subjects	Clarke et al. [144]
Raltegravir (INI)	No change in adverse events	Anderson et al. [141]
Saquinavir/Ritonavir (PI)	No effect on adverse events, ECG, vital signs	Jamois et al. [133]
Saquinavir/ritonavir (PI)	No effect on withdrawal or dose requirement	Gerber et al. [134]
Saquinavir/ritonavir (PI)	No effect on sedation or dose requirement	Shelton et al. [137]
Sertraline (CYP2B6, CYP2D6, and CYP3A4 inhibitor)	No effect on adverse events associated with methadone. Methadone dose adjustment not required	Hamilton et al. [125]

Table 20.2 (continued)

Interacting drug/gene	Summary effects on opioid pharmacodynamics	Reference
Tenofovir (NRTI)	No change in opioid withdrawal effects and miotic effects	Smith et al. [138]
Voriconazole	No effect on opioid withdrawal or overdose	Liu et al. [122]
Methadone (gene)		
CYP2D6 ultrarapid vs. extensive vs. poor metabolizers	No difference in treatment outcome	Eap et al. [151]

CYP cytochrome P450, *ECG* electrocardiogram, *INI* integrase inhibitors, *NNRTI* non-nucleoside reverse transcriptase inhibitors, *NRTI* nucleoside reverse transcriptase inhibitors, *PI* protease inhibitors

various metabolic pathways is also demonstrated in a model-based simulation clinical study [33]. With respect to real clinical drug interaction data, few studies are available in the literature and most have focused on drug modulators that affect known enzymatic pathways (i.e., CYP2D6, UGT2B7, UGT2B4, and CYP3A4) associated with codeine metabolism. For the glucuronidation pathway, diclofenac, a potent UGT2B7 inhibitor [10], did not affect the pharmacokinetics of codeine in human subjects as evident by similar elimination rates or maximum concentration of codeine-6-glucuronide in the experimental versus the control group [34] (Table 20.1). The lack of pharmacokinetic drug interaction also did not translate to altered pharmacodynamic effect because the addition of diclofenac to codeine did not change the results of a cold pressor test (although it was difficult to tease out diclofenac's own analgesic effects) in these human subjects (Table 20.2). Of interest is that the lack of an observed pharmacokinetic interaction was in contradiction to the *in vitro* observation in liver tissue homogenates where diclofenac inhibited the formation of codeine-6-glucuronide in a potent manner ($Ki = 7.9\ \mu M$), suggesting that *in vitro* findings do not always correlate with the *in vivo* situation [35].

With respect to the CYP2D6 bioactivation pathway, studies conducted with quinidine or fluoxetine, putative inhibitors of CYP2D6, reported decreased plasma morphine concentrations in extensive metabolizers [36–39], decreased morphine concentrations in cerebrospinal fluid [38], reduced O-demethylation of codeine with corresponding reduction in plasma morphine glucuronide concentrations (an effect more prominent in Caucasians than in Chinese) [39], and decreased O-demethylation of dextromethorphan (a marker substrate for CYP2D6) [40] in human subjects coadministered codeine and quinidine/fluoxetine compared to controls taking codeine alone. These data strongly suggest that the functional inhibition of CYP2D6 activity will translate to significant pharmacokinetic interactions with codeine, resulting in reduced formation of morphine and morphine-6-glucuronide. In light of this knowledge, irrespective of the lack of available human data, one

could still predict that potent and selective inhibitors of CYP2D6 will likely interact with codeine bioactivation if administered concurrently. Various lists of CYP2D6 inhibitors have been compiled by many authors, and readers are directed to these references for further details (e.g., http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm). CYP2D6 is not subjected to enzyme induction. However, other metabolic pathways of codeine (e.g., CYP3A4 and UGT2B7) can be subjected to enzyme induction, which can indirectly affect the metabolism of codeine through the CYP2D6 pathway. This was demonstrated in a study by Caraco et al. (1997) where subjects treated with rifampin showed increased formation of both codeine glucuronide and norcodeine (inactive metabolites), while the formation of morphine was significantly decreased presumably due to the shunting of codeine metabolism through these inactivation pathways [41].

While clinically significant pharmacokinetic interactions were observed when potent CYP2D6 inhibitors were coadministered with codeine, the corresponding pharmacodynamic effects were not always apparent. For example, despite significantly decreased plasma morphine concentrations [36] or demonstrated reduction in the O-demethylation of dextromethorphan (marker substrate for CYP2D6), the coadministration of quinidine in human subjects taking codeine did not change the results of the pin-prick/tolerance pain threshold tests or have any effects on physical codeine dependence in the test subjects [36, 40]. On the other hand, a significant reduction of morphine or morphine glucuronide concentrations in the presence of quinidine did lead to decreased therapeutic and positive (“high”) or negative (“nausea”) effects of codeine in certain studies [37]. Similarly, in extensive codeine metabolizers, patients administered codeine and rifampin had significantly decreased respiratory and psychomotor, but no change in miotic effects [41], presumably associated with reduced formation of morphine. An interesting observation is that an apparent opposite pharmacodynamic effect (i.e., decreased miotic effect in the absence of attenuated respiratory or psychomotor effects) of codeine in the presence of rifampin was observed in the same study but only in the cohort of poor (codeine) metabolizers [41]. The latter observation seems to suggest a differential pattern of codeine bioactivation/deactivation which may be dependent on an individual’s CYP2D6 phenotype status, a concept that will be discussed further below.

20.3.2.2 Genetic Polymorphism

The importance of CYP2D6 in the bioactivation of codeine has fueled significant interests in understanding the effects of CYP2D6 genetic polymorphism on codeine pharmacokinetics or pharmacodynamics in humans. A survey of the literature finds several alarming reports of codeine-related fatalities or severe adverse events potentially secondary to genetic polymorphism of CYP2D6 leading to a higher conversion rate of codeine to morphine [32, 42–46]. A case report where an infant died of

suspected morphine overdose secondary to the breastfeeding mother (who was later determined to be an ultrarapid metabolizer) ingesting codeine (prescribed within the typical dose limit) highlights the importance of the CYP2D6 gene and codeine pharmacokinetic/pharmacodynamic interaction [47]. Many CYP2D6 alleles are known but the functional status of every single one has not been characterized. In short, alleles can be designated as null functioning (e.g., CYP2D6*4, *5, or *6), reduced functioning (CYP2D6*10 or *41), or full functioning (*CYP2D6*1 or *2). Based on allele combinations, an individual can be categorized into one of several CYP2D6 metabolic activity phenotypes [48]: poor metabolizer (lacking any functioning allele), intermediate metabolizer (one normal and one reduced functioning allele), extensive metabolizer (at least one full- or two reduced-functioning alleles), and ultrarapid metabolizer (duplication of full-functioning alleles) (48). Although the percentage of individuals in each CYP2D6 phenotype category varies between ethnicity, the majority of humans will be classified as either extensive or intermediate metabolizers. Pharmacokinetic or pharmacodynamic interactions will likely be observed on the two ends of the spectrum, where poor metabolizers would not be able to convert codeine to morphine leading to therapy failure, whereas ultrarapid metabolizers will convert a higher percentage of codeine to morphine leading to toxicity.

Clinical data supporting a pharmacokinetic interaction between CYP2D6 phenotype status and codeine metabolism are clearly evident in the literature. Many studies have compared the effects of extensive versus poor metabolizer status in humans and reported either a lack of detection of plasma morphine [49–51], absence of morphine-6-glucuronide [50, 51], or reduced formation or exposure to morphine in plasma and urine [52–55] in poor metabolizers taking codeine compared to extensive metabolizers. Moreover, the effects of ultrarapid metabolizer phenotype on codeine metabolism have also been compared to individuals categorized as extensive or poor metabolizers, where significantly higher morphine exposure in plasma and lower total morphine/codeine ratios in urine were also observed for these patients with duplicate functional CYP2D6 alleles [56] (Table 20.1). These clinically significant pharmacokinetic interactions have also been correlated with significant interactions on the pharmacodynamic level, where only extensive metabolizers are responsive to codeine's analgesic effects (Table 20.2). Likewise, extensive or ultrarapid metabolizers of CYP2D6 are also more prone to adverse pharmacodynamic effects of codeine, as demonstrated by a significant reduction in gastric motility (i.e., constipation effect of the opioid) and increased incidence of sedation [54, 56] On the other hand, a lack of difference in codeine's therapeutic effect on postoperative pain [51] or adverse reactions [55] has also been reported when comparing extensive versus poor metabolizers, but the evidence favoring a significant interaction (presented above) certainly outweighs that of the null effect, and clinical genotyping may be warranted to optimize codeine therapy [48].

20.3.3 Oxycodone

20.3.3.1 Reaction Phenotyping and Clinical Pharmacokinetic and Pharmacodynamic Interactions

Oxycodone exerts its analgesic activity directly (i.e., is not a prodrug), is deactivated by CYP3A4 (N-demethylation) in the formation of the inert noroxycodone, and is bioactivated by CYP2D6 (O-demethylation) in the formation of the relatively more potent oxymorphone in humans [57]. The formation of noroxycodone is the predominant pathway in human liver microsomes and constitutes to a large extent the total intrinsic clearance of oxycodone [57]. Based on this mechanistic information, one can predict drug-drug interactions with CYP3A4, and potentially CYP2D6, modulators.

The available clinical data in the literature support a prominent role of CYP3A4 in mediating pharmacokinetic drug-drug interactions with oxycodone. Various inhibitors of CYP3A4 (i.e., clarithromycin [58], grapefruit juice [59], ketoconazole [60], itraconazole [61], ritonavir or lopinavir/ritonavir [62], voriconazole [63]) have been shown to significantly increase the plasma exposure of oxycodone or reduce the formation of noroxycodone. The data support a shunting effect where the inhibition of CYP3A4-mediated N-demethylation enhances the O-demethylation of oxycodone through the CYP2D6 pathway (i.e., grapefruit juice [59], ritonavir or lopinavir/ritonavir [62], voriconazole [63]). On the other hand, CY2D6 inhibitors, when used alone, are only able to reduce the exposure of noroxymorphone with little effects on that of oxycodone, as demonstrated in studies that have used quinidine [64, 65] and paroxetine [60, 66, 67]. The observation of a relatively minor and possibly insignificant role of CYP2D6 in mediating oxycodone drug-drug interactions is supported by the fact that only the coadministration of both CYP2D6 and CYP3A4 inhibitors can have an effect on the pharmacokinetics of oxycodone, as shown in studies using miconazole [68], paroxetine with itraconazole [66, 67], and telithromycin [69] (Table 20.1). Supporting a major role of CYP3A4 in mediating pharmacokinetic drug interactions with oxycodone, inducers of this enzyme have also been demonstrated to significantly reduce the plasma exposure of oxycodone and increase that of the inactive metabolite, noroxycodone/rifampin [70], and St. John's wort [71] (Table 20.1).

Despite significant clinical pharmacokinetic drug-drug interactions observed with CYP3A4 modulators and oxycodone, the pharmacodynamic effects from the interactions were less apparent. Some CYP3A4 modulators produced pharmacokinetic interactions in the absence of pharmacodynamic effects (e.g., clarithromycin [58] miconazole [68], paroxetine with ketoconazole [67]), whereas others only generated mixed pharmacodynamic effects (e.g., grapefruit juice [59], rifampin [70], ritonavir [62], St. John's wort [71], and telithromycin [69], voriconazole [63] (Table 20.2)). However, the relative importance of CYP3A4 and CYP2D6 in mediating pharmacodynamic drug interactions is consistent with the pattern observed for pharmacokinetic interactions where modulators of CYP3A4 are more likely to be associated with significant pharmacodynamic interactions compared to CYP2D6 modulators (e.g., paroxetine and quinidine; Tables 20.1 and 20.2). It is unclear why there is a

lack of robust pharmacokinetic-pharmacodynamic relationship in oxycodone drug interactions, but one might hypothesize that the small samples used in these studies and/or the semiquantitative nature of some pharmacodynamic tests (e.g., self-rated drug effect) may have contributed to some false-negative findings. Nevertheless, taken together, the overall evidence supports the prediction of significant pharmacokinetic-pharmacodynamic drug interactions of oxycodone with strong CYP3A4 inducers or inhibitors. Many authors have published various lists of CYP3A4 modulators, and readers are directed to these references for further details (e.g., http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm).

20.3.3.2 Genetic Polymorphism

All of the investigations on the pharmacogenetics of oxycodone have focused on the minor, but bioactivating, CYP2D6 pathway because no functional polymorphic phenotypes have yet been identified for oxycodone's major metabolic pathway (CYP3A4). The available data in the literature indicate that the plasma oxymorphone/oxycodone ratio is clearly dependent on CYP2D6 metabolizer status where ultrarapid metabolizers produce more oxymorphone than extensive metabolizers [64, 72], and in turn have higher catalytic activity compared to the poor metabolizers [73, 74] (Table 20.1). However, consistent with the observation made on the CYP2D6 drug modulators, genetic polymorphism of CYP2D6 has little or at best mixed impact on the pharmacodynamics of oxycodone (Table 20.2); thus, more studies are needed to increase this body of knowledge. The clinical significance of CYP2D6 polymorphism on oxycodone drug effects remains to be proven.

20.3.4 Hydromorphone

20.3.4.1 Reaction Phenotyping and Clinical Pharmacokinetic and Pharmacodynamic Interactions

Hydromorphone is relatively more potent than morphine and primarily metabolized by UGT enzymes in the formation of therapeutically inactive metabolites. The primary enzymes responsible for the conjugation of hydromorphone have been identified as hepatic UGT1A3 [75] and UGT2B7 [76], and the major metabolite generated is hydromorphone-3-glucuronide (H3G), the plasma concentration of which can be many fold higher than hydromorphone in humans [77]. Like its parent compound, H3G has been demonstrated to be more potent than its counterpart, morphine-3-glucuronide [78], and induce neurotoxic side effects [13] in various animal models. However, the presence of these adverse effects of H3G remains to be determined in humans, and preliminary reports have demonstrated a lack of correlation between plasma H3G concentrations and untoward side effects (e.g., myoclonus) in patients given hydromorphone [79].

Unlike morphine, few or no drug interaction studies associated with hydromorphone metabolism have been reported in the literature. However, various substrates, inhibitors, and inducers of human hepatic UGT1A3 and UGT2B7 have been identified [10] *in vitro*, which can potentially mediate pharmacokinetic interactions with hydromorphone *in vivo*. Despite the lack of human data, the clinical significance of the effects of these putative modulators on hydromorphone metabolism may be predicted using data obtained from *in vitro* models (e.g., human liver microsomal systems or primary cultures of hepatocytes) in an approach that may minimize drug testing in humans yet generate meaningful clinical drug interaction data [80].

20.3.4.2 Genetic Polymorphism

Similar to a general lack of metabolism-mediated pharmacokinetic interaction data for hydromorphone in the literature, little is available on the impact of genetic polymorphism in humans. In a study in Taiwanese patients, individuals with UGT2B7*2 genotype (a -802A>T genetic variant that results in reduced catalytic activity) exhibited similar pharmacokinetic parameters (exposure and maximum concentration) of hydromorphone and H3G in plasma compared to wild-type patients [81]. The H3G/hydromorphone ratio also did not change, supporting a lack of genetic effect on the metabolism of hydromorphone in these subjects. The lack of pharmacokinetic gene-drug interaction also translated to null pharmacodynamic effects, where UGT2B7 genotype did not impact the incidence of adverse events associated with hydromorphone. These negative findings are consistent with those observed for morphine [25, 26] and may suggest that UGT2B7*2 genetic polymorphism has little impact toward opioid metabolism, in general. However, the effects of other polymorphic alleles of UGT2B7 or UGT1A3 (which is also known to exhibit polymorphism [10]) on the metabolism of hydromorphone remain to be determined.

20.3.5 Fentanyl

20.3.5.1 Reaction Phenotyping and Clinical Pharmacokinetic and Pharmacodynamic Interactions

Fentanyl is a versatile opioid as it can be administered by various routes and is often used in the treatment of cancer and non-cancer pain [82]. Fentanyl is extensively metabolized primarily by hepatic CYP3A4 in the production of norfentanyl, as demonstrated in experiments conducted in human liver microsomes [83, 84], and the metabolite is considered therapeutically inert. Because it is catalyzed primarily by CYP3A4, fentanyl may be subjected to various drug-drug interactions known to take place with this isoenzyme. All of the clinical studies in the literature, to the best of our knowledge, have focused on the effects of CYP3A4 modulators on the pharmacokinetics of fentanyl and the findings are somewhat inconsistent: itraconazole (a potent inhibitor) [85],

grapefruit juice [86], and parecoxib [87] (the latter 2 agents are relatively weaker inhibitors of CYP3A4) had little effects on the clearance, whereas troleandomycin, ritonavir, fluconazole, and voriconazole (potent inhibitors of CYP3A4) significantly reduced the plasma exposure and/or clearance of intravenously or orally administered (as a lozenge) fentanyl in human subjects [86, 88, 89]. Consistent with the trend that the significance of interacting effects on fentanyl may be dependent on the potency of the CYP3A4 modulator, rifampin, a strong CYP3A4 inducer, was also shown to clearly increase the clearance and reduce the exposure of fentanyl in plasma [86] (Table 20.1). Not all interaction studies mentioned above have discussed pharmacodynamics effects, but those that have reported such effects are generally in agreement with the pharmacokinetic (or lack of) interactions observed: that troleandomycin, but not parecoxib, modulated the effects of fentanyl on pupil diameter [87], whereas itraconazole had little influence on fentanyl's therapeutic and adverse (drowsiness, nausea, pruritus) effects [85] (Table 20.2). Moreover, case reports are available in the literature that seem to favor a pharmacokinetic-mediated pharmacodynamic interaction, such as the manifestation of delirium after coadministration of diltiazem (a known CYP3A4 inhibitor) and the reduction of fentanyl transdermal patch's therapeutic efficacy when rifampin is given concurrently [90]. The inconsistencies observed in the literature of CYP3A4 modulators might be explained by the fact that these inhibitors or inducers may have also affected other (minor) metabolic pathways known to metabolize fentanyl [91], (e.g., resulting in mixed patterns of drug interactions that can be rationalized only if the investigators had determined the pharmacokinetics of all possible metabolites of fentanyl). Alternatively, fentanyl is considered a relatively high extraction drug; thus, its clearance is more dependent on hepatic blood flow than intrinsic hepatic clearance (i.e., metabolism-mediated clearance). This theory, as suggested by Ibrahim et al [87], might explain our observation that only strong modulators (i.e., those presented above) have an effect on the pharmacokinetics or pharmacodynamic of fentanyl in humans.

20.3.5.2 Genetic Polymorphism

Since no functional genetic polymorphisms have been identified for CYP3A4, the primary isoenzyme responsible for the deactivation of fentanyl, little or no known pharmacogenomic data are available in the literature.

20.3.6 Tramadol

20.3.6.1 Reaction Phenotyping and Clinical Pharmacokinetic and Pharmacodynamic Interactions

Tramadol is marketed as a racemic mixture and exerts its analgesic action via mu-receptor binding and norepinephrine/serotonin reuptake inhibition [8]. Tramadol is primarily metabolized by CYP2D6 (O-demethylation) and CYP3A4

(N-demethylation) in the formation of active M1 and inactive M2 metabolites, respectively, as demonstrated *in vitro* in human liver microsomes and c-DNA-expressed CYP450 enzymes [92]. The M1 metabolite is relatively more potent than tramadol, as evident by its much higher affinity toward mu-receptor binding [93]. The majority of the clinical drug interaction data in the literature have focused on the effects of CYP2D6 modulators on the disposition of tramadol. Relatively weak inhibitors of CYP2D6 such as escitalopram [94] and strong inhibitors such as methadone [95] or paroxetine [96, 97] were capable of decreasing the plasma exposure or urinary recovery of the M1 metabolite while increasing that of tramadol (Table 20.1). Stronger inhibition of M1 metabolite formation was translated to reduced analgesic effects in humans [96], whereas escitalopram did not change the subjects' responses to the cold pressor test [95] (Table 20.2). On the other hand, fewer data were available on the effects of CYP3A4 modulators toward the disposition of tramadol in humans. Rifampin pretreatment was shown to reduce the plasma exposure of both the parent and the active M1 metabolite in patients administered oral or intravenous tramadol [98], supporting the result of enzyme induction and possibly enhanced metabolism through the CYP3A4 pathway (no M2 metabolite data were collected in support of this theory in the study). Itraconazole, as a relatively potent CYP3A4 inhibitor, had no additional effects to tramadol or M1 metabolite plasma exposure when used in combination with ticlopidine, an inhibitor of CYP2D6 [99]. Unfortunately, neither study assessed pharmacodynamic outcomes; thus, a correlation could not be established with (or lack of) changes observed on the pharmacokinetics of tramadol. More data are certainly needed to ascertain the contributions of CYP3A4 and CYP2D6 toward the pharmacokinetic and pharmacodynamic drug-drug interactions associated with tramadol.

20.3.6.2 Genetic Polymorphism

No functional genetic polymorphisms have been identified for CYP3A4; thus, the clinical literature data on tramadol pharmacogenomics have focused only on the role of the polymorphic CYP2D6. Various studies have reported the effects of CYP2D6 metabolizer phenotype on the pharmacokinetics of tramadol and found increased plasma exposure of the M1 metabolite (which corresponded with decreased exposure of the parent drug) in extensive metabolizers compared to poor metabolizers administered tramadol [100–104]. The pharmacokinetic effects were more prominent in ultrarapid metabolizers where further increases in plasma M1 metabolite exposure were observed compared to extensive or intermediate metabolizers [105–107] (Table 20.1). These pharmacokinetic changes also corresponded with pharmacodynamic effects, where the degree of analgesia or level of pain threshold appears to be dependent on the presence of functional CYP2D6 alleles (i.e., ultrarapid > extensive > poor metabolizers) (Table 20.2). On the other hand, the extent of adverse events observed is less apparent, where some studies reported more adverse events with intermediate metabolizers (vs. ultrarapid) [106] and others reported the opposite [107]. One may hypothesize that tramadol and its M1

metabolite may each lead to a range of side effects, and the discrepancy observed with respect to CYP2D6 metabolizer status and adverse events might be attributed to pharmacokinetic changes observed with either the parent or the metabolite. Overall, the literature clearly supports a pharmacokinetic-pharmacodynamic interaction mediated by CYP2D6 genetic polymorphism. This, taken together with drug interaction data using CYP2D6 inhibitors discussed above, suggests that the coadministration of CYP2D6 modulators can be predicted to lead to significant drug interactions in the clinic. Various lists of CYP2D6 inhibitors have been compiled by many authors, and readers are directed to these references for further details (e.g., http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm).

20.3.7 Methadone

20.3.7.1 Reaction Phenotyping and Clinical Pharmacokinetic and Pharmacodynamic Interactions

Methadone is a racemic mixture of R- and S-enantiomers that exhibit differential activity toward mu-receptor binding. The R-form exhibits a higher affinity toward the opioid receptor [108] and hence exhibits greater analgesic effects. The S-enantiomer has antagonistic activity toward N-methyl-D-aspartate receptors and is an uptake inhibitor of norepinephrine and serotonin neurotransmitters [109, 110], which are responsible for pharmacological drug-drug interactions with other serotonin modulators such as the selective serotonin reuptake inhibitor class of antidepressants. Methadone is unique in that it has an extremely long half-life [111] and is one of the principal therapies in opioid withdrawal/maintenance regimens widely used to manage heroin addictions [112]. Methadone is extensively metabolized in the liver to inactive N-demethylated metabolites, and *in vitro* reaction phenotyping studies have determined CYP2B6 [113–115] and CYP3A4 [116–118] to be the principal enzymes. Other CYP450 enzymes (e.g., CYP2D6 and CYP2C9) have also been identified but the relative contributions of these isoenzymes to the overall metabolism of methadone still remain to be determined [113, 119, 120]. Moreover, CYP2B6, but not CYP3A4, catalyzes methadone in a regioselective manner [115, 119], an effect that can potentially result in different concentrations of R- or S-methadone and complicates the interpretation of results from drug interaction studies.

Methadone is subjected to potential clinically significant drug-drug interactions, primarily mediated by CYP2D6 and CYP3A4 modulators. Clinical studies have described mixed effects of classical CYP3A4 inhibitors on the pharmacokinetics of methadone, where fluconazole [121] and voriconazole [122] both increased methadone exposure in plasma, but troleandomycin [114] and grapefruit juice [114] had little effects (Table 20.1). However, significant pharmacokinetic interactions from fluconazole or voriconazole did not translate to pharmacodynamic effects because the coadministration of either drug was not associated with signs of methadone overdose or withdrawal in test subjects (Table 20.2). Confirming a role of CYP3A4 in

methadone metabolism, rifampin, a potent CYP3A4 inducer, was shown to increase the clearance of methadone [114] (Table 20.1), but correlation to pharmacodynamic effects was not established in that particular study. Moreover, studies with CYP2D6 inhibitors or mixed CYP2D6/CYP3A4 inhibitors have also reported significant drug-drug interactions, where paroxetine [123] increased the plasma concentrations of both racemic forms of methadone in patients genotyped as CYP2D6 extensive metabolizers, quetiapine [124] elevated the plasma R-methadone/dose ratio in a finding that was also dependent on CYP2D6 metabolizer phenotype, and sertraline, a mixed CYP2D6/3A4 inhibitor [125], also elevated methadone concentration/dose ratio in the plasma (Table 20.1). Other than a lack of correlation between sertraline's pharmacokinetic effects and adverse events associated with methadone, the other studies did not attempt to correlate pharmacokinetic interactions with pharmacodynamic changes (Table 20.2).

Clinical drug interactions between methadone and HIV antiviral agents have received significant interest because of the overlapping patient populations that would require the two types of therapies. Overall, most of the literature focuses on protease inhibitors (PIs) (Table 20.1), where mixed findings toward the pharmacokinetics of methadone have been reported. In general, PIs are substrates for CYP3A4 and theoretically should compete with the metabolism competitively and elevate the plasma concentrations of methadone. The opposite effects, however, were observed in clinical studies where amprenavir [126], lopinavir-ritonavir [127–129], nelfinavir [130–132], and saquinavir/ritonavir [133, 134] have all been shown to decrease plasma exposure of total, R-, or S-methadone in human subjects (Table 20.1). On the other hand, a lack of effect on the pharmacokinetics of methadone has also been demonstrated for several protease inhibitors, despite control experiments demonstrating significant inhibition toward CYP3A4 in situ: atazanavir [135], indinavir [136], and saquinavir/ritonavir [137]. These observations support a drug interaction pattern that is unlikely mediated by CYP3A4 inhibition, but rather induction by PI toward other metabolic pathways of methadone (e.g., CYP2D6 or CYP2B6) in humans. Molecular studies (e.g., using *in vitro* experimental models that can be subjected to drug induction experiments such as cultured human hepatocytes) are still needed to support this theory. The majority of pharmacokinetic changes mediated by PI are not correlated with altered pharmacodynamic effects of methadone (e.g., withdrawal, adverse events, requirement for dose adjustment, laboratory testing, electrocardiogram (ECG) readings) (Table 20.2).

Data are also available on the nucleoside reverse transcriptase inhibitors (NRTIs) where neither tenofovir nor zidovudine affected the plasma exposure of the two enantiomers of methadone [138, 139] (Table 20.1). Likewise, integrase inhibitors (INIs) dolutegravir [140] and raltegravir [141] also had little effects on the plasma exposure of methadone. With respect to pharmacodynamic effects, none of these antiviral agents were associated with altered withdrawal, miosis, or abnormal laboratory values (e.g., ECG readings) when coadministered with methadone. These observations are consistent with the general lack of metabolism-mediated drug interactions associated with the NRTIs and INIs in the literature. On the other hand, significant pharmacokinetic changes were observed for non-nucleoside reverse

transcriptase inhibitors (NNRTIs) which were consistent with their metabolic properties: that the inductive effects of nevirapine toward CYP3A4 may have resulted in decreased plasma exposure [142–144], the inhibitory effects of delavirdine toward CYP3A4 contributed to increased plasma exposure [145], and a general lack of metabolic-interaction effects of lersivirine resulted in no change [146] in the plasma exposure of methadone in humans (Table 20.1). The coadministration of nevirapine should be cautioned since two studies have demonstrated increased withdrawal symptoms when combined with methadone (Table 20.2).

20.3.7.2 Genetic Polymorphism

Only a few studies are available in the literature examining the effects of genetic polymorphisms on methadone metabolism (Table 20.1) and there appear to be significant interacting effects by CYP2D6 metabolizer status [147, 148], CYP2B6 polymorphism [148], or ABCB1 polymorphism [124, 148]. However, more pharmacokinetic studies are needed to support these observations and to correlate with pharmacodynamic effects, where information is still fairly sparse (Table 20.2).

20.4 Assessing the Clinical Significance of Pharmacokinetic and Pharmacodynamic Interactions: Clinical Decision-Making Algorithm

We have provided an extensive overview on the pharmacokinetic-pharmacodynamic drug-drug interactions associated with a selection of opioid drugs that are commonly used in the clinic today. We propose that the following clinical decision-making algorithm, modified from what we have developed previously [152], can be used to ascertain the clinical significance of pharmacokinetic-mediated pharmacodynamic interactions with opioid analgesics:

1. Does the effector drug and its metabolites possess pharmacokinetic properties (i.e., absorption, distribution, metabolism, elimination) that can be subjected to drug interaction? *The majority of data on opioids has focused on drug metabolism, and there are in vitro data to support the in vivo observations. Moreover, many opioids (*e.g., *codeine) are metabolized by enzymes that are known to exhibit genetic polymorphism and this additional (gene-drug interaction) factor must be considered.*
2. Does the effector drug and its metabolites possess pharmacodynamic properties that can be subjected to drug interaction? *The majority of data on opioids has focused on their classical analgesic properties, effects on pain threshold, and adverse effects such as somnolence, nausea/vomiting, gastrointestinal motility, or miosis. Additional atypical adverse effects such* QT_C *prolongation (*e.g., *associated with methadone) or serotonin syndrome (*e.g., *associated with tramadol)*

must be considered and can be manifested by pharmacokinetic-associated pharmacodynamic interactions.

3. Does the interacting drug possess pharmacokinetic or pharmacodynamic properties that can subject an opioid agent to drug interactions? *The same considerations discussed for points 1) and 2) above also apply here.*
4. Is there evidence that the combination has caused statistically significant changes in drug pharmacokinetics in humans? *The evidence must be appropriately weighted based on limitations in study design (*e.g., *nature of experimental model, generalizability of the data to the real clinical situation, etc.). The available human data for opioids only represent a small fraction of all the possible drug interactions but one may use various in vitro or in silico approaches to aid the prediction of pharmacokinetic interactions.*
5. Is there evidence that a significant pharmacokinetic interaction is associated with a pharmacodynamic interaction? *The evidence must be appropriately weighted based on limitations in study design. Information on pharmacokinetic-mediated pharmacodynamic interactions is relatively scarce in the literature compared to the available pharmacokinetic data.*

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