A Review of the Metabolism and Potential Drug-drug Interactions With Addictive Drugs

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People who use drugs (PWUD) are at increased risk for drug-related harms such as overdose. Additionally, they are also at increased risk of secondary harms from bacterial and other infections such as hepatitis B, hepatitis C, and Human Immunodeficiency Virus. These secondary harms, along with other medical conditions, typically require treatment with prescription medications. When considering treatment options, drug-drug interactions (DDIs) must be considered, unfortunately these interactions are often overlooked with addictive drugs. Although DDIs in PWUD have been reviewed for certain drug classes and specific drugs of abuse, no comprehensive list could be found. The objective of this article is to compile a list of potential DDIs between prescription drugs and addictive drugs to create a list allowing prescribers to make more informed decisions when prescribing a medication to PWUD.

Key Words: drug metabolism, drug-drug interactions, harm reduction

(*J Addict Med* 2022;16: e30–e39)

Illicit drug use is prevalent and on the rise in the United States (US). In 2017, 11% of Americans aged 12 and over reported using an illicit drug within the last 30 days.[1] Although a lot of the attention has been focused on opioids, methamphetamine use has increased precipitously over the last few years as well.[2,3] Along with the increase in drug use there has been a rise in drug-related deaths. This increase has been caused largely by opioids, most notably fentanyl and fentanyl derivatives.[4] Not only are people who use drugs (PWUD) at increased risk for drug-related harms such as overdose, but they are also at increased risk of secondary harms from bacterial and other infections such as hepatitis B, hepatitis C, and Human Immunodeficiency Virus (HIV).[5] Due to the stigma that PWUD face, they are often hesitant to seek medical care. They are afraid of being labeled ''challenging, manipulative, drug-seeking, and demanding'' by medical personnel.[5] Despite these concerns, PWUD often require medications to treat the secondary harms as well as other medical conditions. Addictive drugs (previously referred to as drugs of abuse) are often overlooked when considering potential drug-drug interactions (DDIs). Prescribers should recognize that any new medication may interact with any drug, including drugs of abuse.

There have been cases of interactions between prescription drugs and illicit drugs reported, and likely many more that go unreported. A 2018 case detailed a fatal interaction between quetiapine and kratom.[6] The authors postulated that the death was caused by a synergistic effect between the 2 substances that was likely due to kratom's interference with the metabolism and/or elimination of quetiapine.[6] Several reports have also shown that delta-9-tetrahydrocannabinol (THC), one of the main psychoactive components of cannabis, may cause an elevation in INR and bleeding complications in patients who are taking warfarin.[7] In one of the more well-known cases of DDIs, Libby Zion, an 18-year-old college student died from serotonin syndrome (SS) after receiving multiple serotonergic medications possibly in the context of cocaine use.[8]

There are many reviews of DDIs for other types of medical conditions, including diabetes mellitus, HIV, and epilepsy.[9–11] Although DDIs in PWUD have been reviewed for certain drug classes and specific drugs of abuse, no comprehensive list could be found.[12,13] The objective of this article is to compile a list of potential DDIs between prescription drugs and addictive drugs. This list could allow for prescribers to make more informed decisions when prescribing a medication to PWUD. Our patients' safety should be one of our top priorities, and the use of illicit drugs should not preclude prescribers from using safe prescribing practices, including a full medication review for potential DDIs.

METHODS

Search Strategy

We used a standardized method to search in MEDLINE and PubMed from inception to December 2018 for studies, including case-reports evaluating DDIs involving prescription medications and US Drug Enforcement Administration Schedule I and II drugs, substances, or chemicals. We also

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Received for publication September 9, 2020; accepted December 31, 2020.
The authors report no conflicts of interest.
Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.journaladdictionmedicine.com).

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ISSN: 1932-0620/21/1601-0e30
DOI: 10.1097/ADM.0000000000000824

searched Micromedex, LexiComp, and the first 200 hits of Google Scholar. General search terms and MeSH terms included but were not limited to the following medical subject headings and keywords: ''drug-drug interaction,'' ''drug metabolism,'' with the Boolean operator ''and'' combined with the medication keywords listed in Table 1. We specifically searched for case-reports or case-series that documented the DDI, however, if there were no specific case-reports or case-series published, we then sought articles highlighting potential pharmacokinetic interactions. Micromedex and LexiComp have drug interaction tools that were used to identify interactions. These interactions are cited in their database so we could review and extract the citation for use in creating our review article.

METABOLISM

To determine the potential risks for DDIs, it is important to understand the metabolism of each medication (illicit and prescription). As discussed below in the ''Limitations'' section, reported cases of these types of interactions are rare, therefore, many of these interactions are theoretical and based on pharmacokinetic interactions. Below we discuss the primary metabolism of the most commonly used addictive drugs to further investigate potential for pharmacokinetic interactions. A summary of the enzymes involved in the metabolism of the addictive drugs that have been discussed can be found in Table 1. We then go on to discuss potential DDIs with each of the most common addictive drugs.

OPIOID METABOLISM

The majority of opioids undergo extensive first-pass metabolism in the liver before distributing within the systemic circulation.[14] Fentanyl and Oxycodone are primarily metabolized by CYP3A4 with a small portion of oxycodone undergoing CYP2D6 metabolism to oxymorphone (Supplemental Figures 1, http://links.lww.com/JAM/A248 and 2, http://links.lww.com/JAM/A249).[18] CYP2D6 is almost entirely responsible for the metabolism of hydrocodone and codeine (Supplemental Figure 3, http://links.lww.com/JAM/A250). Hydrocodone can further undergo metabolism via CYP3A4 to norhydrocodone (Supplemental Figure 4, http://links.lww.com/JAM/A251).[18] Tramadol is primarily metabolized by both CYP3A4 and CYP2D6 (Supplemental Figure 5, http://links.lww.com/JAM/A252).[14] Methadone primarily interacts with CYP3A4 and CYP2B6 but can also involve CYP2C8, 2C19, 2D6, and 2C9 (Supplemental Figure 6, http://links.lww.com/JAM/A253).[15] Morphine and hydromorphone undergo phase 2 metabolism by UDP-glucuronosyltransferase (UGT) 2B7 (Supplemental Figure 7, http://links.lww.com/JAM/A254).

Heroin is converted to morphine in the liver by carboxylesterases hCE-1 and hCE-2.[16] Morphine is then converted to M3G (inactive) and M6G by UGT1A1, 1A3, 1A6, 1A8, 1A9, 1A10, and 2B7. Morphine also undergoes metabolism to normorphine by CYP3A4 and CYP2C8 (Supplemental Figure 7, http://links.lww.com/JAM/A254).[16]

The major metabolic pathway of loperamide is via oxidative N-demethylation.[17] Loperamide is a major substrate of CYP2C8 and CYP3A4 and a minor substrate of CYP2B6 and CYP2D6 (Supplemental Figure 8, http://links.lww.com/JAM/A255).[17] Loperamide is also a substrate of P-glycoprotein.[18]

Buprenorphine is a partial mu-opioid agonist and undergoes N-dealkylation via CYP 3A4 and 3A5 to norbuprenorphine. Buprenorphine and norbuprenorphine then undergo glucuronidation to inactive metabolites, buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide respectively.[19] Naltrexone is a mu-opioid receptor antagonist and is metabolized in the liver by cystolic dihydrodiol dehydrogenases to 6β-naltrexol, which is an active metabolite.[20]

Mitragynine is the main active chemical found in Kratom. Similar to other opioids, it is primarily metabolized by CYP 3A4 and CYP2D6, but also CYP2C9. Mitragynine is metabolized to another active metabolite, 7-hydroxymitragynine.[21]

Potential Opioid Interactions

Carbamazepine, phenytoin, and phenobarbital are potent inducers of CYP3A4, 2C9, and 1A2 causing a significant decrease in drug concentrations of opioids that are also metabolized by the same enzymes (eg, fentanyl, methadone).[22] Due to significant decrease in drug concentration, patients may need increased opioid doses to achieve pain control. However, if the potent inducer is removed from the therapeutic regimen, this could lead to supratherapeutic concentrations of the induced medication causing severe adverse consequences such as respiratory depression and death. Valproic acid is a potent CYP2C9 and 3A4 inhibitor resulting in drug interactions with opioids as well.[23] Enhanced monitoring

TABLE 1. Enzymes Involved in the Metabolism of Select Addictive Drugs

CYP3A4	CYP2D6	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2E1	UGT2B7	hCE-1 and hCE-2
Fentanyl	Oxycodone	Methadone	Methadone	Methadone	Methadone	Ethanol	Heroin	Heroin
Oxycodone	Hydrocodone		Loperamide	THC	CBD		Morphine	Cocaine
Hydrocodone	Codeine						Hydromorphone	
Tramadol	Tramadol							
Methadone	Methadone							
Morphine	Methamphetamine							
Loperamide								
Cocaine								
THC								
CBD								

and dosage adjustments are recommended if patients are using opioids and valproic acid.[22]

Gabapentin is used to treat some types of seizures and is often co-prescribed with opioids for chronic pain conditions. Both types of medications can lead to CNS and respiratory depression, however. A study from 2017 showed that concomitant prescription of opioids and gabapentin was associated with a 49% higher risk of dying from an opioid overdose. As gabapentin undergoes minimal metabolism, this life-threatening interaction is due to pharmacodynamic effects as opposed to a pharmacokinetic interaction.[24]

Amiodarone is a Class III antiarrhythmic that is used to prevent lethal arrhythmias. It has an active metabolite and has many metabolic pathways, which are not fully understood.[25] It has shown in vitro inhibition of multiple CYP enzymes, including 1A1, 1A2, 2C9, 2C19, 2D6, 2A6, 2B6, 2C8, and 3A4.[26] This inhibitory effect could potentially increase the toxicity that could be seen with opioids that are metabolized by CYP3A4 (fentanyl, oxycodone, tramadol, methadone, morphine, heroin) and 2D6 (oxycodone, hydrocodone, codeine, tramadol).[25]

Isoniazid (INH) is a commonly prescribed antibiotic for the treatment of tuberculosis and is also an inhibitor of CYP1A2, 2A6, 2C9, 2C19, and 3A4.[27] Opioids such as heroin and methadone require metabolism via CYP3A4 and 2C19.[14,16] Because INH is a potent inhibitor of 3A4 and 2C19, a DDI could lead to significant increases in opioid drug levels, exposing the patient to a higher risk of adverse effects (eg, respiratory depression).[15]

The opposite effect (ie, opioid withdrawal) may occur in patients who receive rifampin. Rifampin is categorized as a potent CYP2D6, 2C19, and 3A4 inducer leading to rapid decreases in opioid drug levels.[28,29]

Several commonly prescribed anti-infective agents (eg, ciprofloxacin, azithromycin, fluconazole) are associated with significant cardiac adverse effects associated with QT interval prolongation.[30] Methadone has been associated with cardiac conduction delays and QT interval prolongation which can lead to Torsades de Pointes (TdP).[31] These effects are dose-related, therefore, as the plasma concentration increases the risk of cardiac arrhythmia increases.[31] Ciprofloxacin and fluconazole increase methadone plasma concentrations via inhibition of CYP3A4 which also puts patients at increased risk for respiratory depression and arrhythmias.[15,30] Many antidepressant medications can also prolong the QT interval, increasing the risk for TdP in a patient taking methadone. This includes all the selective serotonin-reuptake inhibitor's (SSRI), most notably citalopram and escitalopram, as well as TCAs.[31,32] Some first (eg, haloperidol) and second generation (eg, ziprasidone, quetiapine, risperidone) antipsychotics are associated with QT interval prolongation leading to TdP.[33–35] Haloperidol is one of the most commonly reported drugs associated with TdP with some cases leading to death.[36–38] Class III antiarrhythmics, including amiodarone, also prolong the QT interval and increase the risk of TdP.[25]

The major enzymes involved in omeprazole metabolism is CYP2C19 and 3A4. The other 3A isoforms involved in omeprazole metabolism do not have any interactions with other drugs.[39] Because of the metabolism by CYP2C19, it is possible that methadone levels may be increased with omeprazole use.

Linezolid is an antimicrobial agent with weak, nonspecific inhibition of monoamine oxidase enzymes.[40] Some opioids share SSRI properties (eg, meperidine, tramadol, methadone, dextromethorphan) that may precipitate SS when combined with linezolid.[40,41]

Other commonly used anti-infectives with significant CYP substrate inhibition include trimethoprim-sulfamethoxazole (2C9) and metronidazole (2C9).[42] While this is a metabolic pathway listed for methadone, it has been determined to be a minor pathway so drug interactions are likely to be minor.[42]

The metabolism of some opioids may be impaired by fluoxetine and paroxetine via inhibition of CYP2C9, which could lead to increased opioid effect.[15]

Metoclopramide and promethazine are CYP2D6 inhibitors.[43,44] Administering these drugs with certain opioids (eg, codeine, hydrocodone, oxycodone, tramadol) could lead to increases in opioid drug levels.

Glecaprevir and pibrentasvir are inhibitors of P-gp and could increase concentrations of substrates such as loperamide.[18]

Darunavir and ritonavir are part of a class of antiretroviral agents called protease inhibitors. Both drugs are metabolized by CYP3A4 and are substrates and inhibitors of the enzyme.[45–47] Ritonavir is classified as a potent CYP3A4 inhibitor.[48] Because darunavir and ritonavir are inhibitors of this enzyme, the DDI can cause an increase in the concentration of opioids, most notably methadone.[48] Rilpivirine is a non-nucleoside reverse transcriptase inhibitor with weak CYP3A4 induction.[49] Because of induction, rilpivirine has also been associated with decreasing methadone levels.[50]

The integrase strand transfer inhibitors (INSTIs) include agents such as dolutegravir, bictegravir, and raltegravir. The metabolism of these agents involves UGT1A1.[45,51,52] Dolutegravir and bictegravir have further interaction with CYP3A4, whereas raltegravir is not involved with the cytochrome P450 pathway.[45,51,52] Because of the CYP3A4 inhibition by dolutegravir and bictegravir, it is predicted that a DDI resulting in increased concentrations of opioids such as morphine, oxycodone, fentanyl, and methadone is possible. Additionally, the INSTIs increase heroin concentrations due to the inhibition of metabolism via UGT1A1.[45,51,52]

Warfarin is a vitamin K antagonist that is used to prevent and treat thromboembolic disease. It is a mixture of R- and S-enantiomers, each with different metabolic pathways. R-warfarin is metabolized mainly by CYP1A2 and CYP3A4 while S-warfarin is metabolized by CYP2C9. Substrates and inhibitors of these enzymes such as some opioids may decrease the metabolism of warfarin.[14,16,26]

METHAMPHETAMINE METABOLISM

Methamphetamine is metabolized in the liver by CYP2D6 to para-hydroxymethamphetamine (p-OHMA) and amphetamine (Supplemental Figure 9, http://links.lww.com/JAM/A256).[53,54]

Potential Methamphetamine Interactions

If the metabolism of amphetamines is inhibited, the patient could experience a sympathomimetic toxidrome, characterized by hyperthermia, tachycardia, elevated blood pressure, agitation, and diaphoresis. Life-threatening complications of sympathomimetic drugs include severe hyperthermia, seizures, dysrhythmias, and markedly elevated BP which can result in complications such as aortic dissection, myocardial infarctions, and intracranial hemorrhages. These same effects can be seen with cocaine intoxication, discussed below.

As mentioned above, linezolid exhibits inhibition of monoamine oxidase enzymes.[40] This could lead to SS in the setting of methamphetamines, which increase the release of serotonin from the presynaptic neuron.[55]

Many commonly used antidepressants, including SSRI's and TCAs, exert their pharmacologic effect by increasing serotonin activity. The SSRI's Fluoxetine and paroxetine are considered potent CYP2D6 inhibitors and combining them with methamphetamine or cocaine puts the patient at risk for SS.[56] Regardless of a significant drug metabolism interaction, all SSRIs when used in combination with methamphetamine or cocaine, can lead to SS.[57,58]

In addition to the concern for SS when methamphetamine is combined with TCAs, there is also an increased risk of seizures. TCAs lower the seizure threshold and when combined with cocaine or methamphetamine, this threshold may be greatly diminished.[59,60] Other mood stabilizers that are associated with lowering the seizure threshold and should be avoided in patients using cocaine or methamphetamine include bupropion and venlafaxine.[18]

Haloperidol is also a CYP2D6 inhibitor so interactions with methamphetamine could impair the metabolism of methamphetamine and lead to adverse effects.[61] Metoclopramide and promethazine are CYP2D6 inhibitors as well.[43,44] Administering these drugs with methamphetamine could lead to increases in drug levels. Amiodarone is also a CYP2D6 inhibitor and could lead to similar adverse effects.[54]

COCAINE METABOLISM

The majority of cocaine is hydrolyzed to benzoylecgonine by human carboxylesterase 1 (hCE-1) and to ecgonine methylester by pseudocholinesterase and human carboxylesterase 2 (hCE-2), both of which are largely inactive. (Supplemental Figure 10, http://links.lww.com/JAM/A257).[16] Cocaine undergoes N-demethylation involving CYP3A4 to the pharmacologically active norcocaine.[16]

Potential Cocaine Interactions

Concomitant use of cocaine with linezolid could lead to SS. Cocaine inhibits the reuptake of serotonin while linezolid inhibits monoamine oxidase.[40,55] Cocaine use in the setting of SSRIs or TCAs may also increase the risk of SS due to the multiple mechanisms of serotonin reuptake inhibition.[57,58] Similar to TCA use in the setting of methamphetamines, cocaine also lowers the seizure threshold so this combination may lead to seizures.[59,60] Bupropion and venlafaxine should also be avoided in patients who use cocaine due to their propensity to lower the seizure threshold.[18]

Metoprolol is a commonly prescribed beta-blocker that is metabolized in the liver mainly by CYP2D6.[26] Potential DDIs between addictive drugs and beta-blockers are not related to their effects on the pharmacokinetic profile of each medication, but their pharmacodynamic effect. Potentially with methamphetamine and all sympathomimetic drugs, but especially cocaine, there is a concern for ''unopposed alpha'' adrenergic effect.[62] Studies in animals have shown a fatal interaction between beta-blockers and cocaine.[13] There are also some human case reports that suggest a possible fatal interaction.[63] The theory proposed and shown in the lab is that beta-blockers, by preventing the beta-adrenergic effect of sympathomimetic drugs, allow only the alpha-adrenergic effect of these drugs. This results in significant vasoconstriction causing marked elevations in blood pressure which can lead to tissue ischemia, myocardial infarction, and intracranial hemorrhage, among other effects.[63] There is considerable controversy surrounding the clinical impact of the DDI between beta-blockers and cocaine in patients who are chronically taking a beta-blocker, and the potential harm is likely only in those patients who are acutely intoxicated with cocaine and then receive a beta-blocker.[62,64]

TETRAHYDROCANNABINOL (THC)

THC undergoes hepatic metabolism mainly by hydroxylation. CYP2C9 metabolizes THC to the active metabolite 11-hydroxy-THC (Supplemental Figure 11, http://links.lww.com/JAM/A258).[16,65] This metabolite undergoes further catalyzation to 11-nor-9-carboxy-THC by a member of the CYP2C subfamily. Minor metabolic steps of THC involve CYP3A4.[16,65]

Potential THC Interactions

If the patient is able to metabolize THC and CBD in an efficient manner, intoxication is typically not harmful. However, if the metabolism is inhibited, or the dose is very high. THC intoxication can result in symptoms similar to sedatives such as sedation, slurred speech, and incoordination, but can also result in symptoms more akin to sympathomimetics such as agitation, psychosis, anxiety, and tachycardia. These types of symptoms are often seen with synthetic cannabinoids as well.

The metabolism of THC may be impaired by fluoxetine and paroxetine via inhibition of CYP2C9, and this could lead to prolonged half-life and longer duration of action of THC.[66–68]

The class III antiarrhythmic amiodarone may inhibit CYP2D6 which could lead to increased concentrations of THC and subsequent toxicity.[16]

THC use may lead to supratherapeutic INR and/or bleeding complications as it can inhibit CYP2C9.[7]

CANNABIDIOL

After ingestion, cannabidiol (CBD) undergoes extensive first-pass metabolism by CYP2C19 and CYP3A4 (Supplemental Figure 12, http://links.lww.com/JAM/A259).[69,70]

Potential Cannabidiol Interactions

Carbamazepine, phenytoin, and phenobarbital are potent inducers of CYP3A4, 2C9, and 1A2. This can lead to significant decrease in drug concentrations CBD.[70] Due to significant decrease in drug concentration, patients may need increased doses to achieve the same clinical effects. Removing the potent inducer could lead to supratherapeutic concentrations of CBD, which could cause toxic CBD effects such as hepatotoxicity, diarrhea, vomiting, and somnolence.[71] Valproic acid is a potent CYP2C9 and 3A4 inhibitor which could also in drug interactions with CBD.[23]

CBD and the FDA approved cannabidiol (Epidiolex) are potent inhibitors of CYP2C19, 2D6, and 2C9. Serum concentrations of several commonly used antiepileptics such as clobazam, topiramate, and zonisamide will be significantly increased in those who use CBD.[72]

There is a potential for increased plasma concentration of CBD with the protease inhibitors darunavir and ritonavir. Both of these medications are inhibitors for CYP3A4.[70] The INSTIs dolutegravir, bictegravir also inhibit CYP3A4 inhibition and this may also lead to an increase in CBD concentrations.[45,51]

The major enzymes involved in omeprazole metabolism is CYP2C19 and 3A4. The other 3A isoforms involved in omeprazole metabolism do not have any interactions with other drugs.[39] Because of the metabolism by CYP2C19, it is possible that CBD levels may be increased with concomitant use.

ETHANOL METABOLISM

The majority of ethanol is broken down to acetaldehyde in the liver by alcohol dehydrogenase (ADH), catalase, and CYP2E1 (Supplemental Figure 13, http://links.lww.com/JAM/A260).[73] Aldehyde dehydrogenase then converts acetaldehyde to acetate. CYP2E1 is also involved in ethanol metabolism in the CNS.[73]

Potential Ethanol Interactions

The consumption of alcohol in a patient who is taking metronidazole has been reported to reduce the desire for ethanol and produce mild disulfiram-like reactions due to increased blood acetaldehyde concentrations.[74] Patients are often warned to avoid ethanol due to this risk. However, there is no pharmacokinetic interaction that would explain for the reported disulfiram-like reaction with one study showing that blood acetaldehyde levels were not different in patients who were taking metronidazole.[75] Additionally, there were zero patients in this study that had subjective or objective signs of disulfiram-like reactions.[75]

Abacavir undergoes hepatic metabolism via ADH and glucuronyl transferase.[76] Because of the metabolism by ADH, there is a potential for an interaction between ethanol and abacavir. One study noted that while abacavir does not influence the concentration of ethanol in the blood, ethanol can cause an increase in abacavir concentrations.[77] The clinical significance of the interaction is questionable as the concentrations of abacavir remained in the normal therapeutic range.[77]

Ethanol intake can interfere with the metabolism of warfarin and this can differ based on the chronicity of alcohol consumption.[78] Large acute ingestions of ethanol may inhibit the metabolism of warfarin, leading to a supratherapeutic INR and potential bleeding complications.[78] Chronic heavy ethanol use may induce the metabolism of warfarin and lead to subtherapeutic INR which could lead to complications from clot formation.[79]

BENZODIAZEPINES

The most commonly prescribed class of anti-anxiety medications are the benzodiazepines. The majority of the benzodiazepines are metabolized via CYP450 pathway with the exception of lorazepam, oxazepam, and temazepam.[80] Metabolism of benzodiazepines relies on the CYP450 system, however, there are many other factors that impact the rate of metabolism (eg, absorption, elimination, protein binding). Significant DDIs have been reported with potent CYP450 2A12, 2C19, 2D6, and 3A4 inhibitors resulting in increases in plasma concentrations.[80] While toxicity has rarely been reported with inhibition of the metabolism of benzodiazepines at therapeutic doses, it is unknown if there would be significant harm in patients who abuse benzodiazepines.[81]

Benzodiazepines have been found to have both pharmacodynamic and pharmacokinetic interactions with opioids. The pharmacodynamic interaction is discussed below, but there have been several studies that have shown that benzodiazepines may alter the pharmacokinetics of opioids. Benzodiazepines may inhibit the metabolism of methadone and buprenorphine which could therefore increase the risk for toxicity.[82] This may not be generalizable to benzodiazepines as a class since not all benzodiazepines had similar interactions.[83]

OTHER COMMONLY USED DRUG CLASSES WITH LOW LIKELIHOOD OF INTERACTIONS

Antiepileptics

Many newer antiepileptic medications (eg, levetiracetam, lamotrigine, zonisamide) are devoid of significant drug interactions. Other antiepileptics with potential DDIs are discussed above.

Antiretroviral agents

Nucleoside reverse transcriptase inhibitors (NRTIs) are commonly prescribed in the treatment of viral infections. Common drugs in the NRTI class include abacavir, tenofovir, lamivudine, and emtricitabine. These anti-retroviral agents are renally cleared and therefore have no interaction with the CYP450 pathway.[51,76]

Oral Anticoagulants

Rivaroxaban and apixaban are direct oral anticoagulants (DOACs) that work through inhibition of Factor Xa. They are metabolized by CYP3A4, CYP2J2, and other CYP-independent mechanisms.[84] As they do not induce or inhibit CYP3A4, they are unlikely to interfere with the metabolism of any addictive drugs.[84]

Dabigatran is an oral direct thrombin inhibitor. It is not metabolized by the CYP450 system but is a substrate for P-gp.

As such, it is unlikely to contribute to any significant interactions with any addictive drugs.[84]

Gastrointestinal (GI) Medications

Ranitidine has a very low level of interaction with the CYP450 pathway and therefore no DDIs are predicted.[85]

Hepatitis drugs

Hepatitis C virus (HCV) is a common infection that affects PWID. Infected needles are responsible for up to 2/3 of all new HCV infections reported annually.[86] The medications elbasvir/grazoprevir, glecaprevir/pibrentasvir, and ledipasvir/sofosbuvir are commonly used to treat hepatitis C.

Grazoprevir is a substrate of organic anion transporting polypeptide 1B1 (OATP1B1) drug transporters, CYP3A4, and P-glycoprotein (P-gp). Inhibition of these enzymes/transporters is weak, and is unlikely to affect the levels of other drug substrates.[26] Elbasvir is also a substrate of CYP3A4 and P-gp, but inhibition is weak and would not be expected to affect substrate concentrations.[26]

Glecaprevir and pibrentasvir are both inhibitors of CYP3A4, though this interaction was found to be weak and is unlikely to alter the concentration of other drugs significantly.[26]

Ledipasvir is an in vitro inhibitor of P-gp and may increase the absorption of the P-gp substrate loperamide.[26] It undergoes minimal biotransformation and therefore its metabolism should not affect concentrations of other drugs.[25] Sofosbuvir is unlikely to interact with any addictive drugs.[26]

DISCUSSION

DDIs are categorized as either pharmacodynamic or pharmacokinetic interactions. Pharmacodynamics refers to a drug's effect on the body, and an interaction implies that the clinical effects of one or both of the drugs involved will be altered.[9] Pharmacokinetics refers to the body's effect on the drug, and interaction results in a change in how one or both of the drugs is absorbed, distributed, metabolized, or eliminated.[9] Many of the potential interactions with addictive drugs, as noted above, involve interactions of metabolism. These potential interactions occur mainly through the CYP450 enzyme system, which is responsible for much of the oxidative metabolism of medicines.[87] The main interactions that we discovered and/or hypothesized to be significant are noted in Table 2. This includes any known or reported interactions or any potential severe interactions that we discovered in our research.

The pharmacokinetic DDIs typically involve either the inhibition or induction of metabolism via the CYP450 pathway, both of which could have significant consequences and result in patient harm. For example, if a drug inhibits the metabolism of an opioid (eg, INH) the result will be profound respiratory depression. If the drug induces the CYP450 enzyme (eg, rifampin) resulting in enhanced metabolism, the patient may experience abrupt withdrawal.

Although pharmacokinetic interactions were the focus of our review and can cause significant morbidity and mortality, we want to also note a very common and significant pharmacodynamic interaction. A common DDI in PWUD that leads to death is the use of multiple sedating agents. Many sedative-hypnotic medications such as alcohol and benzodiazepines cause CNS depression, but do not cause a significant amount of respiratory depression, except in large overdoses.[88] However, the risk of respiratory depression and death increase substantially with the co-administration of an opioid.[89] Other drugs that can lead to increased risk of respiratory depression and death in the setting of opioid use include INH and the antiretroviral agents darunavir and ritonavir.[15,48] Heroin specifically may increase in concentration in the presence of INSTIs.[46,51,52]

While Table 2 summarizes our findings, many of the proposed interactions are theoretical, and based on pharmacokinetic interactions between drugs that use the same CYP450 enzymes. Further research needs to be done to assess the validity of these potential interactions. To prevent serious complications, it is important for providers and pharmacists to recognize the potential for DDIs in PWUD.

LIMITATIONS

Many drugs that are substrates of a particular CYP enzyme may also be an inhibitor or inducer of that same enzyme, but there is limited data regarding the effect of addictive drugs on specific CYP enzymes. For example, methamphetamine is primarily metabolized by CYP2D6.[44,77] There is no evidence to tell us whether methamphetamine might induce or inhibit CYP2D6 and how this might affect the metabolism of other drugs. These enzyme effects may be an area for future research for each of these drug classes which could further inform the potential for DDIs.

While the potential for enzyme interactions between addictive drugs and prescription drugs is high based on the enzymes involved, there are limited reports of these interactions in the literature. As with all DDIs, this is likely due to underreporting and maybe be exacerbated by the fact that PWUD do not always disclose their use of illicit drugs.[90] If we prescribe a medication and they have an adverse event, they may be less likely to report that adverse event and this will likely further erode their trust in the medical system.

Our objective was to create a comprehensive review for DDIs between addictive drugs and prescription medications. We used identified accurate MeSH terms, however, DDIs could have been missed due to lack of MeSH terms for certain medications. Additionally, we believe that our literature review was thorough but there is a possibility that medications were not included or discussed. Lack of inclusion of certain medications does not mean that there is lack of a DDI. Also, it should be noted that some DDI from the medication package insert can differ from peer reviewed data (eg, disulfiram-like reaction when combining metronidazole and ethanol).[74,75] We focused our review to include DDI that may be included in the package insert and peer-reviewed literature. It was beyond the scope of our review to evaluate for potential discrepancies between the two.

CONCLUSIONS

Addictive drugs are a potential source of DDIs and should be taken into consideration when initiating any new medication. By recognizing the reality that some of our

TABLE 2. Potential DDIs with Addictive Drugs

Anti-Anxiety Medication Interactions with Addictive Drugs

	Opioids	Methadone	Heroin	Loperamide	Methamphetamine	Cocaine	THC	CBD	Ethanol
Lorazepam								X+	X

Antimicrobial Medication Interactions with Addictive Drugs

	Opioids	Methadone	Heroin	Loperamide	Methamphetamine	Cocaine	THC	CBD	Ethanol
Isoniazid	X+	X+	X+						
Amoxicillin									
Azithromycin		X							
TMP-SMX							X+		X^
Ciprofloxacin		X							
Cephalexin									
Doxycycline									
Metronidazole							X+		
Clindamycin									
Rifampin	X+	X	X+						
Fluconazole		X							
Linezolid	X	X			X^	X^			

Antidepressant Interactions with Addictive Drugs

	Opioids	Methadone	Heroin	Loperamide	Methamphetamine	Cocaine	THC	CBD	Ethanol
Fluoxetine	X^	X+			X^	X^	X+		
Sertraline									
Citalopram	X+	X^			X+	X^			
Amitriptyline		X+			X^	X^			
Trazodone									
Bupropion					X^	X^			
Venlafaxine					X^	X^			

Anti-Epileptic Medication Interactions With Addictive Drugs

	Opioids	Methadone	Heroin	Loperamide	Methamphetamine	Cocaine	THC	CBD	Ethanol
Carbamazepine	X							X^	
Phenytoin	X							X^	
Phenobarbital	X							X^	
Valproic Acid	X							X^	
Topiramate								X+	

Antipsychotic Medication Interactions With Addictive Drugs

	Opioids	Methadone	Heroin	Loperamide	Methamphetamine	Cocaine	THC	CBD	Ethanol
Quetiapine		X^							
Haloperidol	X+	X^			X+	X+			
Prochlorperazine		X^							
Risperidone		X^							

Anti-retroviral Medication Interactions with Addictive Drugs

	Opioids	Methadone	Heroin	Loperamide	Methamphetamine	Cocaine	THC	CBD	Ethanol
Dolutegravir	X+	X+	X+					X+	
Tenofovir									
Abacavir									X
Lamivudine									
Emtricitabine									
Bictegravir	X+	X+	X+					X+	
Darunavir	X+	X+	X+					X+	
Ritonavir	X+	X+	X+					X+	
Raltegravir									
Rilpivirine		X+							

Cardiac Medication Interactions with Addictive Drugs

	Opioids	Methadone	Heroin	Loperamide	Methamphetamine	Cocaine	THC	CBD	Ethanol
Lisinopril					X^	X^			
Atorvastatin									
Simvastatin									
Amlodipine									
Diltiazem									
Hydrochlorothiazide									
Furosemide									
Amiodarone	X+	X^			X+		X+		
Warfarin	X+						X+		X
Rivaroxaban									
Metoprolol					X^	X*			

GI Medication Interactions With Addictive Drugs

	Opioids	Methadone	Heroin	Loperamide	Methamphetamine	Cocaine	THC	CBD	Ethanol
Omeprazole		X^						X+	
Ranitidine									
Metoclopramide	X+	X^			X+			X+	
Promethazine	X+	X^			X+			X+	

Hepatitis Medication Interactions With Addictive Drugs

	Opioids	Methadone	Heroin	Loperamide	Methamphetamine	Cocaine	THC	CBD	Ethanol
Elbasvir									
Glecaprevir				X+					
Ledipasvir				X^					
Grazoprevir									
Pibrentasvir				X+					

X - known interactions in humans.
X^ - in vitro evidence of interaction.
X+ - theoretical interaction based on pharmacokinetics.

patients use drugs and will continue to use drugs we can minimize the possible risks of adverse drug events due to a new medication and improve our patients' safety.

ACKNOWLEDGMENTS

The authors would like to acknowledge Parya Seif (University of Iowa Graduate Student) for her diligent work creating each metabolism pathway.

Parya Seif, Urban and Regional Planning student, University of Iowa Graduate College.

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