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Drug Interactions of Clinical Importance among the Opioids, Methadone and Buprenorphine, and other Frequently Prescribed Medications: A Review

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Abstract

Drug interactions are a leading cause of morbidity and mortality. Methadone and buprenorphine are frequently prescribed for the treatment of opioid addiction. Patients needing treatment with these medications often have co-occurring medical and mental illnesses that require medication treatment. The abuse of illicit substances is also common in opioid-addicted individuals. These clinical realities place patients being treated with methadone and buprenorphine at risk for potentially toxic drug interactions. A substantial literature has accumulated on drug interactions between either methadone or buprenorphine with other medications when ingested concomitantly by humans. This review summarizes current literature in this area.

The World Health Organization reports that drug interactions are a leading cause of morbidity and mortality.¹ This finding extends to medications used in the treatment of substance use disorders and pharmacotherapies utilized for treatment of medical or mental illnesses, as well as for abused substances—including alcohol, licit, and illicit substances. Furthermore, there has been a dramatic increase in deaths related to methadone use, both for the treatment of pain and illicit use, in the United States in recent years. Drug interactions have been implicated in many of these deaths.² In this paper, we will review the existing literature on drug interactions principally between opioids used in the treatment of opioid dependence, methadone and buprenorphine, and other medications with a focus on clinically relevant drug interactions in humans. Interactions between cocaine, alcohol, and other substances will also be summarized.

Clinical Pharmacology of Drug Interactions

Drug interactions can occur through several mechanisms. One or more mechanisms may be involved in the expression of a clinically significant drug interaction. The primary mechanisms of drug interactions include effects of drugs on hepatic metabolism of pharmaceuticals including effects on cytochrome P450 (CYP) enzymes or effects on glucuronidation, medication effects on the function of the drug transporter, P-glycoprotein, and effects on absorption of drugs.³ Pharmacodynamic interactions are also important. For

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example, some drugs when taken in combination exhibit synergism that can increase drug effects resulting in toxicity.

The opioid medications, methadone and buprenorphine are extensively metabolized by human liver. Specifically CYP3A4 plays a significant role in the metabolism of methadone, and buprenorphine.⁴⁻⁶ Other CYP enzymes play a role in opioid metabolism including 2B6, CYP2C19, CYP2C9 and CYP2D6⁷ for methadone, and 2C8 for buprenorphine.⁸ Drug interactions mediated by CYP 450 enzymes can be associated with the potential for significant adverse events.

Perhaps the best studied mechanism for drug interactions is seen with medications that inhibit the function of hepatic metabolic enzymes. Laboratory assays are well-developed and provide insights on the inhibitory effect of a specific compound on major liver CYP enzymes, particularly CYP3A4. The Food and Drug Administration (FDA) has classified CYP3A4 inhibitors as strong, moderate or weak, based on the increase in exposure they cause in sensitive CYP3A4 substrates (See Table 1 below). With buprenorphine, a CYP3A4 substrate, systemic exposure increase is noted following concomitant administration with ketoconazole, a strong CYP3A4 inhibitor. Drug interactions with other CYP3A4 inhibitors, listed in the Table 1, below may cause an increase in systemic levels or pharmacodynamic effects of buprenorphine.

Although assays that can reliably show induction of CYP enzymes exist, these assays are unable to predict drug interactions when the compounds inhibit some CYP enzymes while inducing other CYP enzymes. In such situations, we often learn of inducing properties of a drug through clinical observations. For example, HIV antiretroviral (ARV) medications such as ritonavir, nelfinavir, and nevirapine, are known to inhibit CYP3A4; however, they are shown to reduce the plasma levels of methadone, possibly due to induction of other CYP enzymes involved in its metabolic clearance.^{9,10} Glucuronidation of many drugs directly results in their elimination. Glucuronidation can also be a late step in the metabolism of drugs which undergo a series of metabolic steps with intermediates produced as a result of metabolism by CYP enzymes. Glucuronidation renders a metabolite water soluble so that it can then be excreted. An example of a clinically significant drug interaction mediated by inhibition of glucuronidation is that of the effect of methadone on zidovudine elimination. Methadone can inhibit zidovudine glucuronidation resulting in increased concentrations that, in some cases, may produce zidovudine toxicity.¹¹

Some drug interactions occur as a result of the production of a pharmacologically active metabolite as in the case of simultaneous cocaine and alcohol consumption which results in the formation of cocaethylene, a cocaine-like compound that can contribute to toxicities associated with the abuse of these substances.¹² Altered absorption can also produce clinically significant drug interactions as when an opioid such as methadone slows gastrointestinal mobility exposing a drug sensitive to acidic pH to prolonged time in the stomach resulting in increased degradation. This has been observed when methadone-maintained patients were administered the ARV medication, stavudine, resulting in sub-therapeutic stavudine concentrations.¹³ This could result in ineffective treatment of HIV disease in patients receiving both medications.

Pharmacodynamic interactions can result when two or more drugs with the capability of producing similar pharmacological effects in an individual are ingested in the same time frame resulting in significant adverse effects. For example, when buprenorphine and benzodiazepines (e.g.: alprazolam) have been injected together, deaths have resulted that are thought to be related to depression of the central nervous system (CNS) with a resulting decrease in respiration.¹⁴ Although buprenorphine when given alone has been shown to

have a ceiling effect at which higher doses do not produce further opioid agonist effects,¹⁵ when injected with benzodiazepines, it is possible that high plasma concentrations of two drugs with sedating and respiratory depression properties occur resulting in a potentially life-threatening drug interaction.¹⁶

It can be difficult to determine what mechanism(s) are responsible for adverse drug interactions. Controlled studies in humans that include simultaneous administration of medications and measurement of plasma drug concentrations are important to understanding the pharmacokinetic and pharmacodynamic drug interactions important in the treatment of common medical and mental disorders. In the following sections, important drug interactions that have been described will be briefly reviewed.

Drug Interactions of Clinical Significance in Substance Use Disorders

Drug Interactions Between Medications Used to Treat Substance Use Disorders and Other Medical Illnesses

HIV Disease—Historically, approximately 25% of new HIV cases in the U.S. have been attributed to injection drug use. The HIV epidemic has had a significant component attributable to injection drug use and high risk practices with 25% of new HIV cases in the U.S. historically being secondary to injection drug use.¹⁷ These high risk practices include the sharing of needles and syringes as well as other paraphernalia used in the preparation of drugs for injection. The majority of injection drug users are addicted to heroin or opium. There are several medical treatments available for opioid dependent patients. These include medical withdrawal from opioids and maintenance treatment with methadone or buprenorphine. Medical withdrawal from opioids has been shown to have a high relapse rate.¹⁸ For those with HIV disease, where relapse places these patients at risk for resumption of injection drug use, its associated high risk practices, and non-adherence to HIV ARV therapy, opioid maintenance therapy is recommended. US FDA-approved therapies for opioid maintenance therapy include methadone, l-acetyl-methadol (not currently manufactured in the U.S.), and buprenorphine, the most recently approved medication for the treatment of opioid dependence. Buprenorphine is co-formulated with naloxone, an opioid antagonist (as buprenorphine/naloxone or Suboxone) for the purposes of decreasing the likelihood of abuse or diversion of the medication.¹⁹ It is important to be aware of clinically significant drug interactions that may occur between opioids and medications used to treat HIV disease because of the high prevalence of HIV in opioid dependent patients. This population represents a significant risk for personal harm and harm to others should they relapse to opioid use and continue high risk injection drug use and sexual practices. For that reason, much research has been devoted to determining the presence of clinically significant drug interactions between opioids and ARV medications.

The first ARV medication to be approved by the FDA for the treatment of HIV infection was zidovudine (AZT).²⁰ At that time, as currently, most opioid-dependent patients with HIV disease were maintained on methadone. Some methadone-maintained patients with HIV disease who were started on AZT therapy for HIV infection were noted to develop symptoms that appeared to be consistent with opioid withdrawal including muscle and joint pain, dysphoria, insomnia, and depression.²¹ In a human laboratory study which examined the direct interaction of methadone and AZT, it was found that methadone treatment was associated with a 41% increase in exposure to AZT in opioid-dependent patients with HIV disease which was attributed to inhibition of AZT glucuronidation and a general opioid effect of slowed gastrointestinal transit that could result in increased absorption of AZT.¹¹

The results of this study led to another question: did interactions between methadone and AZT characterize interactions between AZT and other opioid therapies? To test this

question, another study was conducted in which the interaction of AZT with either buprenorphine, LAAM, or naltrexone was examined.²² The hypothesis for this study, based on the findings of the interactions between methadone and AZT was that medications that are antagonists at the mu opioid receptor, such as naltrexone, would have no effect on AZT concentrations, while mu opioid agonists such as buprenorphine or LAAM would increase AZT concentrations. In fact, what was observed were non-clinically significant decreases in AZT concentrations in patients treated with buprenorphine or LAAM; the opposite of that observed with methadone. These findings indicated that the observation for methadone was not representative of what would occur in the context of other opioids in combination with ARV therapies.

To date, a number of frequently utilized ARV therapies have been examined in combination with methadone and other opioid therapies. These drug interactions are summarized in Table 2. Selected important drug interactions are summarized below.

Interactions between methadone and several HIV therapies demonstrate the potential for adverse drug effects that can occur when absorption of a drug is altered. Methadone is a full mu opioid receptor agonist. A general effect of such drugs is to slow gastrointestinal mobility. Methadone has been associated with significant decreases in HIV medications that are sensitive to the acidic environment of the stomach. Didanosine (DDI or Videx) (in tablet formulation) and stavudine (d4T) are two non-nucleoside reverse transcriptase inhibitors (NRTIs) that may produce sub-therapeutic plasma concentrations of methadone when administered to methadone-maintained individuals.¹³ Didanosine is now available in an enteric-coated formulation to prevent excess degradation in the stomach. This formulation has been shown to be associated with therapeutic plasma concentrations in both methadone-maintained²³ and buprenorphine-maintained individuals.²⁴

Adverse events related to inhibition of the clearance of opioid medications have the potential to produce opioid toxicity including altered cognition and decreased respiration. Delavirdine is a non-nucleoside reverse transcriptase inhibitor that inhibits the function of CYP 450 3A4.²⁵ Administration of delavirdine to methadone or LAAM-maintained patients results in significantly elevated opioid concentrations and delayed clearance, although in a drug interaction study, no clinically significant adverse events were observed.²⁶ This finding might be related to the short period of time in which the medications were co-administered, with greater risk for those who taking such medications on a long-term basis. Buprenorphine has been associated with cognitive dysfunction in patients with HIV who received treatment with the protease inhibitors, atazanavir (Reyataz)/ritonavir.²⁷ A subsequent study to determine if a drug interaction could have been responsible for the observed cognitive dysfunction showed that atazanavir alone and in combination with ritonavir was associated with substantial increases in buprenorphine exposure and delayed clearance.²⁸ While no cognitive dysfunction was observed during the drug interaction study, several participants complained of increased drowsiness that abated after cessation of atazanavir/ritonavir.

Of equal concern are the drug interactions that result in diminished concentrations of opioid therapies. For example, co-administration of a medication that induces methadone metabolism could result in a reduction of plasma methadone concentrations in a methadone-maintained patient leading to the potential development of opiate withdrawal symptoms. The onset of opiate withdrawal may be associated with abuse of opioids or other illicit substances and resumption of high risk behaviors related to drug abuse with risk for HIV transmission. HIV ARV medications producing the induction of CYP 450 3A4 associated with opiate withdrawal have been reported. The NNRTIs efavirenz and nevirapine, as well as the protease inhibitor combination drug lopinavir/ritonavir, have been linked to opiate withdrawal in methadone-maintained patients.²⁹⁻³³ Interestingly, these medications when

given to buprenorphine-maintained individuals were not associated with the onset of opiate withdrawal despite marked reductions in buprenorphine plasma concentrations.³⁴⁻³⁶ Buprenorphine has a metabolite, norbuprenorphine, that is formed when buprenorphine undergoes dealkylation by CYP 3A4.³⁷ Norbuprenorphine is also a mu opioid agonist. This may be one reason that withdrawal does not occur even with induction of buprenorphine metabolism. Further, buprenorphine is a partial mu opioid agonist with a high affinity for and slow dissociation from the mu opioid receptor which may protect buprenorphine-maintained individuals from opiate withdrawal.¹⁹

The use of ARV medications in those who also require opioid therapy for treatment of opioid addiction can be challenging with methadone. However, to date, none of the adverse drug interactions that have been observed between methadone and ARVs have been observed in buprenorphine-maintained individuals. With the exception of atazanavir/ritonavir which substantially increases buprenorphine and norbuprenorphine plasma concentrations with possible cognitive effects, there have been no other reports of toxic interactions between buprenorphine and ARVs. Further, buprenorphine has not been shown to significantly alter plasma concentrations of ARVs and therefore, buprenorphine/naloxone treatment appears to be less likely to be associated with adverse drug effects in combination with ARVs. These findings may be useful to clinicians who must treat both HIV disease and opioid dependence in the same patient.

What are the practical implications of drug interactions between opioid therapies and HIV medications? If a patient with co-occurring HIV/AIDS and opioid dependence is already methadone-maintained and on a stable, therapeutic dose, it is not recommended that the patient be converted to buprenorphine treatment. The necessary tapering of methadone to achieve buprenorphine induction could potentially destabilize the patient. Rather, clinicians with such patients should be aware of major drug interactions that may occur between ARV and methadone and adjust medication doses accordingly. If a patient is new to opioid therapy or wishes to be readmitted to opioid therapy and HIV/AIDS is a consideration, buprenorphine may be preferable as appears that it will have fewer clinically significant interactions with ARV.

Tuberculosis—Tuberculosis is a common opportunistic infection often seen in those with immunosuppressed states such as HIV/AIDS. Tuberculosis can also occur independently and is seen more frequently in individuals addicted to heroin. Medications used to treat tuberculosis can have significant interactions with methadone. The best known of these interactions is that of the effect of rifampin, a first-line agent used in combination with isoniazid for the treatment of tuberculosis infection, to induce methadone metabolism.³⁸ Rifampin has been associated with significant opiate withdrawal symptoms in methadone-maintained patients. Some patients receiving buprenorphine also develop opiate withdrawal symptoms when treated with rifampin, however at this time, the final data is still pending.³⁹ Rifabutin can be substituted for rifampin in those requiring tuberculosis treatment who are also receiving methadone treatment. This same finding is likely to be true for buprenorphine-treated patients, although this has not yet been examined. While rifabutin can also induce CYP 3A4, it appears not to produce the withdrawal symptoms rifampin does.⁴⁰ Rifampin is also used as a treatment for methicillin-resistant staphylococcus aureus (MRSA). This increasingly common infection also occurs in methadone-treated patients who will similarly require substitution of rifampin with rifabutin in this clinical circumstance. Isoniazid is a CYP 3A4 inhibitor,⁴¹ but has not been associated with adverse events in opioid-maintained patients to date, perhaps because any effect to inhibit opioid metabolism is opposed by the concomitantly administered rifampin in patients with tuberculosis and receiving chronic opioid therapy.

Hepatitis C—Hepatitis C virus (HCV) is a frequent infection in opioid-addicted patients with the reported rate of HCV in injection drug users in the United States to be estimated at approximately 33%.⁴² Injection drug use remains the most common cause of HCV in the U.S., with over 60% of all new infections occurring as a result of injection drug use.⁴³ The standard of care for pharmacotherapy of HCV is the use of a combined regimen consisting of pegylated interferon and ribavirin. These medications have a high rate of adverse symptoms and side effects associated with their use including depression, anxiety, malaise, myalgia, fatigue, and anemia (ribavirin).⁴⁴ The documentation of these symptoms being experienced by opioid-dependent patients on methadone therapy as opiate withdrawal symptoms led to studies to examine whether there was a pharmacokinetic drug interaction between methadone and interferon. To date, two studies have been reported in the literature and both have shown no significant drug interactions between methadone and interferon.^{45,46} No studies of drug interactions between ribavirin and methadone have been completed at this time.

Other Infections—There are four antibiotic treatments, specifically antifungal and antibacterial therapies that cause potentially clinically significant drug interactions with methadone as a result of inhibition of CYP 450 3A4 which can increase methadone concentrations. Both the antifungal medications fluconazole⁴⁷ and voriconazole⁴⁸ are inhibitors of this enzyme and might increase methadone plasma concentrations when administered concomitantly. Similarly, ciprofloxacin inhibits CYP450 3A4 and there has been a case report of life-threatening opioid toxicity when this medication was given to a methadone-maintained individual.⁴⁹ Biaxin is also an inhibitor of CYP450 3A4⁵⁰ and may increase methadone concentrations. Because buprenorphine is a substrate of CYP450 3A4, its plasma concentrations would likely be increased in the presence of any of these antibiotics as well. However, the ceiling effect for opioid agonist effects of buprenorphine could diminish any potential opioid toxicity.

Mental Illness—The lifetime rate of co-occurring mental illness in those with opioid dependence has been estimated to be as high as 50%.⁵¹ As a result, many patients with opioid addiction will require treatment with psychotropic medications at some time. While exhaustive work examining drug interactions between opioids and medications commonly used to treat mental illness has not been undertaken, there are some findings that can be summarized in this review.

Antidepressants—Affective disorders, particularly major depression are common in opioid dependent patients. Current rates for depression of up to 25% and lifetime rates of 50% have been reported for this population.⁵² Depressive symptoms will often resolve with methadone or buprenorphine treatment, but a significant minority of patients will require treatment with antidepressant medications.

The serotonin reuptake inhibitors exert a variety of effects on the cytochrome P450 enzyme system. Both fluoxetine and fluvoxamine have been examined in vitro for evidence of potential for drug interactions with methadone and buprenorphine. Both fluoxetine and fluvoxamine (with fluvoxamine being more potent than fluoxetine) inhibit CYP450 3A4 and 2D6. In vitro studies showed both antidepressants to be associated with decreased metabolism of methadone and buprenorphine.⁵³ Fluoxetine has not been associated with clinically important increases in methadone.⁵⁴ Importantly, administration of fluvoxamine has been reported to result in significantly increased methadone plasma concentrations in a series of 5 patients. Further, discontinuation of fluvoxamine was associated with the onset of opiate withdrawal.⁵⁵ Opiate withdrawal is a risk in any patient experiencing increased methadone exposure as a result of concomitant administration of a medication that inhibits

methadone metabolism. Discontinuation of the concomitant medication will result in resumption of normal methadone metabolism which could decrease methadone plasma concentrations to the point that the patient experiences opiate withdrawal. This subsequent opiate withdrawal may lead to non-adherence to the treatment regimen and increased use of illicit substances, underscoring the importance of clinician awareness of the potential for such interactions. Other serotonin reuptake inhibitors including sertraline⁵⁶ and citalopram⁵⁷ have not been associated with adverse drug interactions with methadone or buprenorphine. However, both sertraline and citalopram have been associated with inhibition of CYP450 2D6. Since methadone metabolism is contributed to by CYP450 2D6, it is possible that methadone concentrations could increase in a patient receiving one of these antidepressants in combination with methadone. Although no clinical reports of serotonin syndrome have been reported in conjunction with methadone treatment and treatment with serotonin reuptake inhibitors, it is a consideration should those receiving concomitant therapies develop symptoms of neuromuscular hyperactivity including tremor, clonus, myoclonus, and hyperreflexia. Other symptoms of serotonin syndrome include rigidity, autonomic hyperactivity (diaphoresis, fever, tachycardia and tachypnea) as well as altered mental status characterized by agitation, excitement and confusion.⁵⁸

Other antidepressant medications have not been reported to have significant interactions with methadone or buprenorphine. Mirtazepine has no reported interactions with these opioids. Duloxetine, an antidepressant medication also approved for treatment of neuropathic pain particularly in patients with diabetes, a common co-morbid medical condition in patients with opioid dependence, is a substrate of CYP450 2D6. Methadone has been reported to not only be a substrate of this enzyme, but also has some ability to inhibit its function. As such, methadone could potentially lead to increased duloxetine exposure;⁵⁹ however a formal drug interaction study has not been conducted. Amitriptyline has been shown to inhibit both CYP450 3A4 and 2D6.⁶⁰ As such it could be associated with increases in plasma methadone concentrations, although no clinically important adverse events have been reported. However, the use of amitriptylene as either an antidepressant or for the treatment of pain syndromes warrants clinician awareness of the potential for drug interactions between amitriptylene and methadone.

St. John's wort is an over-the-counter herbal remedy purported to have antidepressant properties. Its use is widespread and represents a potential for adverse drug interactions. This medication is known to induce both CYP450 3A4 and P-glycoprotein which can result in increased metabolism and elimination of methadone and buprenorphine.⁶¹ The large number of clinically significant adverse events that have been reported between St. John's wort and other medications underscore the need to query patients about the use of over-the-counter remedies, herbal, and nutraceutical use when other medications are prescribed for concomitant medical conditions.

Antipsychotics—There are few reports of antipsychotic medications having adverse drug interactions with opioids. Some of the older neuroleptic medications would not be expected to have clinically significant pharmacokinetic drug interactions with opioids because their major metabolic pathways are not shared by methadone or buprenorphine. Pharmacodynamic interactions might occur, however, as a result of increased sedation or cognitive dysfunction that could be experienced when these medications are given concomitantly. There is a report of increased plasma methadone concentrations in those treated with quetiapine. This interaction results from quetiapine's ability to inhibit CYP450 2D6 as well as to inhibit P-glycoprotein.⁶² There have been no reports of adverse events related to methadone toxicity in the literature resulting from this interaction, however the impact on two mechanisms of methadone clearance could be of potential clinical importance. No clinically significant pharmacokinetic drug interactions have been reported

for methadone or buprenorphine when administered concomitantly with risperidone, clozapine, aripiprazole, olanzepine, or ziprasodone.

Anxiolytics—The use and abuse of anxiolytic medications, benzodiazepines and sedative-hypnotics by those with opioid addiction and being treated with buprenorphine or methadone is common. The anxiolytics share common pharmacological properties of sedation and when abused, altered cognition. In combination with methadone or buprenorphine, these drugs have potential for significant harm. Opioids such as methadone and, to a lesser extent, buprenorphine as a result of its partial agonist effect, can decrease respiration through agonist action at mu receptors in the medullary respiratory center. Benzodiazepines (and alcohol) act synergistically in that these drugs facilitate inhibition at gamma-aminobutyric acid (GABA) receptors and alcohol decreases the excitatory effect of glutamate at N-methyl-D-aspartic acid (NMDA) receptors. These mechanisms may help to explain fatal overdose in the presence of opioids and/or benzodiazepines and alcohol.⁶³ Diazepam has been shown not to be associated with altered methadone plasma concentrations.⁶⁴ However, significant pharmacodynamic interactions have been reported between diazepam and methadone as well as diazepam and buprenorphine.^{65,66} Diazepam has been associated with increased sedation and impaired performance on psychological tests. Fatalities have been reported when methadone and alprazolam were co-ingested.⁶⁷ In these cases, methadone concentrations in blood were not in the toxic range indicating that a pharmacodynamic interaction between methadone and alprazolam played a role in the toxicity. Buprenorphine has also been associated with deaths when ingested by the intravenous route in combination with benzodiazepines.^{68,69} This is also thought to be a pharmacodynamic interaction resulting in fatal respiratory depression. The impairment associated with combined methadone or buprenorphine use with benzodiazepines as well as the morbidity and mortality that has been linked to co-ingestion of these drugs indicates that caution should be used in prescribing benzodiazepines to those receiving methadone or buprenorphine treatment of opioid dependence. Further, clinicians should monitor for evidence of benzodiazepine abuse substance-related disorders resulting from benzodiazepine abuse should be treated in these patients.

Anticonvulsants—Anticonvulsant medications are commonly prescribed to patients treated with methadone or buprenorphine to treat either seizure disorders or mental illnesses including bipolar disorder and schizoaffective disorder. Several anticonvulsants have clinically significant drug interactions with methadone. Carbamazepine, phenytoin, and phenobarbital are all inducers of CYP450 3A4 and have been associated with opiate withdrawal when administered to methadone-maintained patients.⁷⁰ Larger doses of methadone have been required in patients treated with anticonvulsants that induce methadone metabolism. Whether such drug interactions occur in buprenorphine-treated patients has not been evaluated, but induction of buprenorphine metabolism is likely to occur since it is a substrate of CYP450 3A4.

Newer anticonvulsant medications do not have the same broad spectrum effects on CYP450 enzymes or drug interactions with opioids. Oxcarbazepine, lamotrigene, and topiramate have not been reported to have adverse drug interactions with methadone or buprenorphine. These anticonvulsants are likely to be better choices for clinical use in opioid-maintained patients.

Psychostimulant Medications—Psychostimulant medications frequently prescribed for attention deficit hyperactivity disorder, night shift work or narcolepsy include amphetamines, methylphenidate, pemoline, or modafinil. Psychostimulant medications have not been reported to produce adverse drug interactions in methadone or buprenorphine-treated patients.

Antihistamines—Antihistamine drugs are commonly prescribed for a variety of medical symptoms. CYP450 2D6 contributes to the metabolism of some of the antihistamine medications promethazine, diphenhydramine and chlorpheniramine. In addition, some antihistamines such as promethazine and diphenhydramine may inhibit CYP450 2D6.⁷¹ Methadone is a substrate of and can also inhibit CYP450 2D6 as well. While clinical reports of adverse events related to pharmacokinetic and pharmacodynamic interactions are not in the literature, these medications have the characteristics that might result in adverse interactions. This could result from direct pharmacokinetic interactions as well as a synergistic effect of use of the opioids in combination with an antihistamine.

Other Potential Drug Interactions Based on Methadone Effect on CYP 2D6—

Methadone can inhibit CYP450 2D6 and has been reported to alter the pharmacokinetics of the antidepressant desipramine, a substrate of CYP 2D6.⁷² Methadone has been reported to be associated with increased desipramine levels.⁷³ Other tricyclic antidepressants (imipramine), antipsychotics (risperidone, other phenothiazines), analgesics (codeine), antiarrhythmics (flecainide) and some beta blockers are also substrates of CYP 2D6 and may have the potential for adverse drug interactions based on increased plasma concentrations.⁷² Dextromethorphan, a substrate of CYP 450 2D6, has been associated with delirium in a patient receiving methadone.⁷⁴ The adverse events abated with cessation of dextromethorphan and were attributed to the effect of methadone on dextromethorphan clearance.

Other Medical Diseases: Cardiac and Pulmonary—Opioid addicted patients often develop co-occurring medical illnesses. Some of the more common medical illnesses seen in opioid-dependent patients are those associated with the cardiovascular and pulmonary systems. A few commonly prescribed medications include digoxin, quinidine, verapamil, cholesterol-lowering statin drugs, heparin, and theophylline. Adverse interactions between these medications and either methadone or buprenorphine are not found in the clinical literature. Aspirin, a very frequently utilized medication for pain and for its anticoagulant properties is metabolized by a serum esterase which is inhibited by methadone.⁷⁵ No adverse drug interactions between methadone and aspirin have been reported, but the possibility of accumulation of aspirin in methadone-maintenance treatment is a possibility that should be considered in the appropriate clinical situation.

Interactions between Opioids and Other Abused Substances

Psychostimulants: Cocaine and Methamphetamine

Recently, it has been found that cocaine can significantly diminish buprenorphine concentrations.⁷⁶ This may be the result of cocaine having an effect on inducing buprenorphine metabolism through induction of CYP450 3A4⁷⁷ or through induction of P-glycoprotein.⁷⁸ Another possibility is that given that buprenorphine is administered via the sublingual route, vasoconstriction produced by cocaine metabolite might reduce buprenorphine absorption.⁷⁹ There is clinical data that supports these findings in that patients enrolled in a clinical trial receiving buprenorphine treatment and using cocaine had fewer opioid-negative urines ($p=.02$) and lower rates of retention in treatment ($p=.04$).⁸⁰ Cocaine use has a similar, but less dramatic effect on methadone concentrations.⁸¹ This lesser effect may be related to the findings that methadone is metabolized by several CYP 450 enzymes, as compared to buprenorphine which is primarily metabolized by CYP 3A4. Methamphetamine has not been associated with adverse drug interactions in combination with either methadone or buprenorphine.

Stimulants used to treat attention deficit hyperactivity disorder (ADHD) include methylphenidate, amphetamine, and pemoline. To date, no clinically important drug

interactions have been reported between methadone or buprenorphine and these medications. It is worth noting, however, that stimulants have been used with opioid medications to obtain a desired euphoria that results from the opposing actions of the opioids (sedation) with stimulant effects of drugs (e.g.: cocaine) resulting in what has been termed a “speedball.”^{82,83} Clinicians should be aware of this and use caution in prescribing stimulant medications in those receiving opioid therapy.

Alcohol

A pharmacodynamic interaction has been reported to occur between alcohol and methadone. Severe adverse events including deaths have occurred in patients who co-ingest these substances,⁸⁴ although a direct effect on pharmacokinetics of methadone has not been found, but alcohol appears to be eliminated more rapidly in those receiving methadone.⁸⁵ Clinical reports of adverse events related to alcohol ingestion in buprenorphine treated patients has not been reported to date, but a pharmacodynamic interaction similar to that which has been reported with benzodiazepines seems likely (see above). Interestingly, no drug interaction of clinical significance has been detected between methadone and disulfiram⁸⁵ These findings highlight the need to treat co-occurring alcohol disorders in opioid addicted patients receiving opioid agonist therapy.

Consequences of Drug Interactions

There are several important consequences of drug interactions that occur between opioids used in the treatment of opioid dependence and other drugs. Drugs that induce the metabolism of opioids or drugs that induce P-glycoprotein resulting in opioid efflux can produce opiate withdrawal symptoms if plasma concentrations become sub-therapeutic. Should this occur, patients may not adhere to the medication to which they attribute the opiate withdrawal symptoms. Non-adherence can have significant consequences in worsening of disease. For HIV disease, non-adherence can result in viral mutations with the development of resistance to currently available antiretroviral medications increasing the likelihood of disease progression in patients and the likelihood of viral transmission to those with whom they are in intimate contact. In addition, the development of opiate withdrawal can contribute to relapse to illicit drug use in order to relieve the adverse symptoms. Illicit drug use and intoxication is associated with an increased risk of overdose and unsafe practices such as injection drug use. These practices can place the patient at risk for the complications of injection drug use such as abscesses, cellulitis, endocarditis, and osteomyelitis.

Another concern when drug interactions occur that increase opioid concentrations is that of opioid toxicity. Cognitive dysfunction and decreased respiration can be life threatening. Methadone has been associated with cardiac conduction delays, prolongation of the QT interval, and arrhythmia that can be fatal through its ability to block HERG (human cardiac ether à go-go-related gene) potassium channels.⁸⁶ This effect is dose-related; therefore as methadone plasma concentrations increase, patients are at increased risk for developing arrhythmia.⁸⁷ Patients can also be at risk when they receive medications that induce methadone metabolism resulting in the need for an increase in methadone dose. However, if the medication that is causing induction of metabolism is discontinued, methadone concentrations will rise, possibly to toxic levels, unless the methadone dose is tapered to that on which the patient was stable before starting the medication. A case report describes such a clinical event where a patient developed Torsades de Pointes after stopping lopinavir/ritonavir and failure to reduce the methadone dose which had been increased due to opiate withdrawal associated with administration of the protease inhibitor combination.⁸⁸ Buprenorphine has not been shown to prolong the cardiac QT interval⁸⁹ and may be a better choice for opioid-addicted patients needing medication treatments likely to increase

methadone exposure. Further, patient selection for either methadone or buprenorphine treatment based on identification of cardiac risk factors, family history, medical history of cardiac disease or history of arrhythmia, or the finding of a prolonged QT interval prior to starting opioid therapy can be helpful in diminishing the likelihood of this complication.

Another important aspect of understanding drug interactions between opioids and other medications is that of optimally matching treatments to patients. It can be difficult for patients to adhere to prescribed medication regimens. The occurrence of adverse symptoms when medications are given together contributes to non-adherence. Because patients may not want to divulge their lack of adherence to a regimen associated with adverse effects, there can be consequences related to worsening of the conditions which the medications were meant to improve. Anticipation of adverse events when medications known to have interactions are to be given can improve adherence. Patients should be counseled about the possible interactions including the time to expected adverse effects should they occur and the treating clinician should be prepared to make adjustments to the medication regimen should a drug interaction occur. **Drugs that induce the metabolism of a drug require new enzyme production so that the onset of opiate withdrawal generally occurs after about 7 days. Inhibitors can delay metabolism with onset of drug administration so that increases in opioid exposure can occur soon after initiating the medications.** The same is true for pharmacodynamic interactions that occur at the time of the drug use. While knowledge of drug interactions may be helpful in selecting medications; the fact that a drug interaction may occur should not exclude the use of a medication; nor can opioid doses be adjusted in anticipation of a drug interaction. Not all patients will develop drug interactions. **The occurrence is related to doses of medications (e.g.: those with lower methadone plasma concentrations are more likely to develop opiate withdrawal in the presence of an inducer),** the clinical pharmacology of the drug(s), and individual genetics that determine CYP450 enzyme activity.

Finally, the existence of these interactions between methadone and buprenorphine and myriad other medications they may be receiving, underscores how critical it is for clinicians who are caring for patients receiving opioid agonist treatment to routinely query their patients regarding medications they are receiving for treatment of other medical conditions. In addition, given the potential interactions between methadone and buprenorphine and substances of abuse, in order to optimize treatment outcomes, they must discuss with patients the use or mis-use of other substances that may interact with their methadone or buprenorphine. Providing guidance to clinicians with data on these real or potential drug interactions will allow them to better manage their patients' overall medical care by increasing their general awareness of interactions between opioids and HIV antiretrovirals and other medications thereby improving outcomes (avoiding suboptimal levels of medications) and also minimizing the likelihood of adverse events (avoiding toxicity and overdose).

Future Research Needs

There remains much to be learned about drug interactions between opioids used in the treatment of opioid dependence and other drugs. Most medications in combination with opioids have not been directly studied in humans. In vitro studies indicating the likelihood of drug interactions are not always predictive of what will occur in people. The ongoing study of frequently prescribed medications with opioids will help to enhance clinical outcomes and to increase safety with medication treatments in this high risk and challenging population.

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Table 1
Classification of CYP3A inhibitors*

Strong CYP3A inhibitors (Cause \geq 5-fold increase in AUC of sensitive CYP3A substrate)	Moderate CYP3A inhibitors (Cause \geq 2 but $<$ 5-fold increase in AUC of sensitive CYP3A substrate)	Weak CYP3A inhibitors (Cause \geq 1.25 but $<$ 2-fold increase in AUC of sensitive CYP3A substrate)
atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, lopinavir/ritonavir, saquinavir/ritonavir, telithromycin	aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil	cimetidine

Adapted from source at <http://www.fda.gov/cder/drug/drugInteractions/default.htm>.

* Reference: US Food and Drug Administration. Draft Guidance for Industry: Drug Interaction Studies—Study Design, Data Analysis and Implications for Dosing and Labeling, 2006.

Table 2
Drug Interactions Between Methadone or Buprenorphine and other Medications

HIV Medications	Methadone	Buprenorphine
AZT	Increase in AZT concentrations; possible AZT toxicity ¹¹	No clinically significant interaction ²²
Didanosine (in tablet form)	Significant decrease in didanosine concentrations. ¹³	
Stavudine	Significant decrease in stavudine concentrations. ¹³	
Delavirdine	Increased methadone (and LAAM) concentrations; no cognitive impairment ²⁶	Increased buprenorphine concentrations; no cognitive impairment
Atazanavir	Not associated with increased levels of methadone ⁹⁰	Significant increases in buprenorphine and report of cognitive dysfunction ²⁵
Darunavir	Opiate withdrawal may occur ⁹¹	
Efavirenz	Opiate withdrawal may occur ²⁹⁻³³	No clinically significant interaction ³⁴⁻³⁶
Fosamprenavir	Data suggest that the PK interaction is not clinically relevant; however, patients should be monitored for opiate withdrawal symptoms ⁹²	
Nelfinavir	Methadone levels are decreased. Opiate withdrawal may occur ⁹³	
Nevirapine	Opiate withdrawal may occur ²⁹⁻³³	No clinically significant interaction ³⁴⁻³⁶
Lopinavir/ritonavir	Opiate withdrawal may occur ²⁹⁻³³	No clinically significant interaction ³⁴⁻³⁶
Tuberculosis Medications		
Rifampin	Opiate withdrawal may occur ³⁹	Opiate withdrawal may occur ³⁹
Rifabutin	No clinically significant interaction ⁴⁰	Not studied
Hepatitis C		
Interferon	No clinically significant interaction ^{45,46}	
Ribavirin	Not studied	
Other Infections		
Fluconazole	Increased methadone plasma concentrations ⁴⁷	
Voriconazole	Increased methadone plasma concentrations ⁴⁸	
Ciprofloxacin	Increased methadone plasma concentrations ⁴⁹	
Biaxin	Increased methadone plasma concentrations ⁵⁰	
Antidepressants		
Fluoxetine	Not associated with increased levels of methadone ⁵⁴	
Fluvoxamine	May cause increased methadone plasma levels and discontinuation has been associated with onset of opioid withdrawal ⁵⁵	
Sertraline	No associated adverse drug interaction ⁵⁶	No clinically significant interaction ⁵⁶
Citalopram	No clinically significant interaction ⁵⁸	No clinically significant interaction ⁵⁸
Mirtazepine	No clinically significant interaction	

HIV Medications	Methadone	Buprenorphine
Duloxetine	Potentially lead to increased duloxetine exposure ⁵⁹	
Amitriptylene	Could be associated with increases in plasma methadone concentrations ⁶⁰	
St. John's Wort	Increased metabolism and elimination of methadone ⁶¹	Increased metabolism and elimination of buprenorphine ⁶¹
Desipramine	Associated with increased desipramine levels ⁷³	
Dextromethorphan	Associated with delirium ⁷⁴	
Antipsychotics		
Quetiapine	Increased plasma methadone concentrations ⁶²	
Risperidone	No clinically significant interaction	No clinically significant interaction
Clozapine	No clinically significant interaction	No clinically significant interaction
Aripiprazole	No clinically significant interaction	No clinically significant interaction
Olanzapine	No clinically significant interaction	No clinically significant interaction
Ziprasodone	No clinically significant interaction	No clinically significant interaction
Anxiolytics		
Diazepam	Associated with increased sedation and impaired performance on psychological tests ^{65,66}	
Alprazolam	Fatalities have been associated ⁶⁷	
Anticonvulsants		
Carbamazepine	Associated with opiate withdrawal ⁷⁰	Not studied
Phenytoin	Associated with opiate withdrawal ⁷⁰	Not studied
Phenobarbital	Associated with opiate withdrawal ⁷⁰	Not studied
Oxcarbazepine	No clinically significant interaction	No clinically significant interaction
Lamotrigene	No clinically significant interaction	No clinically significant interaction
Topiramate	No clinically significant interaction	No clinically significant interaction
Psychostimulant Medications		
Methylphenidate	No clinically significant interaction	No clinically significant interaction
Pemoline	No clinically significant interaction	No clinically significant interaction
Modafinil	No clinically significant interaction	No clinically significant interaction
Antihistamines		
Promethazine	May have synergistic depressant effect ⁷¹	
Diphenhydramine	May have synergistic depressant effect ⁷¹	
Cardiac and Pulmonary Disease Medications		
Digoxin	Not studied	Not studied

HIV Medications	Methodone	Buprenorphine
Quinidine	Not studied	Not studied
Verapamil	Not studied	Not studied
Heparin	Not studied	Not studied
Theophylline	Not studied	Not studied
Aspirin	No clinically significant interaction	
Psychostimulants		
Cocaine	Decrease in trough methadone concentrations ⁸¹	Increased metabolism and diminished plasma concentrations ⁷⁶⁻⁷⁹
Methamphetamine	No clinically significant interaction	
Alcohol	Severe adverse events including death (84), Alcohol appears to be eliminated more frequently ⁸⁵	Not studied