Topic: Clinically Relevant Drug Interactions: Buprenorphine or Methadone with Other Frequently Prescribed Drugs

Original Author: Elinore F. McCance-Katz, M.D., Ph.D. (9/24/10)

Last Updated: Derek Blevins, M.D. (6/28/21)

Clinical questions:
1. What drug interactions of clinical significance occur between buprenorphine or methadone and other medications?
2. In thinking about an opioid agonist medication for a patient with opioid use disorder, how can I determine whether to select methadone or buprenorphine?

Background:

Drug interactions are a leading cause of morbidity and mortality. Methadone and buprenorphine are frequently prescribed for the treatment of opioid use disorder. Patients needing treatment with these medications often have co-occurring medical and mental illnesses that require medication treatment. The use of illicit substances is also common in people with opioid use disorders. 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 guidance will summarize that literature in tabular form below (Adapted from Reference 1 below).

HIV Medications	Methadone	Buprenorphine
Zidovudine (AZT)	Increase in AZT concentrations; possible AZT toxicity	No clinically significant interaction
Didanosine (in tablet form)	Significant decrease in didanosine concentrations	No clinically significant interaction
Stavudine	Significant decrease in stavudine concentrations	Not studied in human pharmacokinetics studies
Delavirdine	Increased methadone (and LAAM) concentrations; no cognitive impairment	Increased buprenorphine concentrations; no cognitive impairment
Atazanavir	Not associated with increased levels of methadone	Significant increases in buprenorphine and report of cognitive dysfunction
Darunavir	Opiate withdrawal may occur	No clinically significant interaction
Efavirenz	Opiate withdrawal may occur	No clinically significant interaction
Fosamprenavir	Data suggest that the PK interaction is not clinically relevant; however, patients should be monitored for opiate withdrawal symptoms	No clinically significant interaction
Nelfinavir	Methadone levels are decreased. Opiate withdrawal may occur	No clinically significant interaction
Nevirapine	Opiate withdrawal may occur	No clinically significant interaction
Lopinavir/ritonavir	Opiate withdrawal may occur	No clinically significant interaction
Emtricitabine/tenofovir	Not clinically significant	Not clinically significant
Bictegravir	Unknown	Unknown
Rilpivirine	May induce withdrawal	Unknown
Elvitegravir/cobicistat	Not clinically significant	Not clinically significant
Raltegravir	Not clinically significant	Not clinically significant
Dolutegravir	Not clinically significant	Unknown
Abacavir	May induce withdrawal	Unknown

Tuberculosis Medications		
Rifampin	Opiate withdrawal may occur	Opiate withdrawal may occur
Rifabutin	No clinically significant interaction	Reduction in buprenorphine and rifabutin levels not likely to be clinically significant
Hepatitis C		
Interferon	No clinically significant interaction	Not studied in human pharmacokinetics studies
Ribavirin	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Other Infections		
Fluconazole	Increased methadone plasma concentrations	Not studied in human pharmacokinetics studies
Voriconizole	Increased methadone plasma concentrations	Not studied in human pharmacokinetics studies
Ciprofloxacin	Increased methadone plasma concentrations	Not studied in human pharmacokinetics studies
Clarithromycin	Increased methadone plasma concentrations	Not studied in human pharmacokinetics studies
Antidepressants		
Fluoxetine	Reported association with increased levels of methadone	Not studied in human pharmacokinetics studies
Fluvoxamine	May cause increased methadone plasma levels and discontinuation has been associated with onset of opioid withdrawal	Not studied in human pharmacokinetics studies
Sertraline	No reported adverse drug interaction	No clinically significant interaction
Citalopram	No reported significant interaction	No clinically significant interaction
Mirtazapine	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Duloxetine	May potentially lead to increased duloxetine exposure, but not studied in humans	Not studied in human pharmacokinetics studies
Amitriptyline	Could be associated with increases in plasma methadone concentrations	Not studied in human pharmacokinetics studies

St. John's Wort	Increased metabolism and elimination of methadone	Increased metabolism and elimination of buprenorphine
Desipramine	Associated with increased desipramine levels	Not studied in human pharmacokinetics studies
Dextromethorphan	Associated with delirium	Not studied in human pharmacokinetics studies
Antipsychotics		
Quetiapine	Increased plasma methadone concentrations	Not studied in human pharmacokinetics studies
Risperidone	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Clozapine	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Aripiprazole	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Olanzapine	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Ziprasidone	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Anxiolytics		
Diazepam	Associated with increased sedation and impaired performance on psychological tests	Associated with increased sedation and impaired performance on psychological tests
Alprazolam	Fatalities have been associated with combined use	Fatalities have been associated with combined use
Anticonvulsants		
Carbamazepine	Associated with opiate withdrawal	Not studied in human pharmacokinetics studies
Phenytoin	Associated with opiate withdrawal	Not studied in human pharmacokinetics studies
Phenobarbital	Associated with opiate withdrawal	Not studied in human pharmacokinetics studies
Oxcarbazepine	No clinically significant interaction reported	Not studied in human pharmacokinetics studies
Lamotrigine	No clinically significant interaction reported	Not studied in human pharmacokinetics studies

Topiramate	No clinically significant interaction reported	Not studied in human pharmacokinetics studies
Psychostimulant Medications		
Methylphenidate	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Pemoline	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Modafinil	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Antihistamines		
Promethazine	May have synergistic depressant effect	Not studied in human pharmacokinetics studies
Diphenhydramine	May have synergistic depressant effect	Not studied in human pharmacokinetics studies
Cardiac and Pulmonary Disease Medications		
Digoxin	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Quinidine	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Verapamil	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Heparin	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Theophylline	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Aspirin	No clinically significant interaction reported; but potential for aspirin accumulation	Not studied in human pharmacokinetics studies
Psychostimulants		
Cocaine	Decrease in trough methadone concentrations	Increased buprenorphine metabolism and diminished plasma concentrations
Methamphetamine	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Alcohol	Severe adverse events including death, eliminated more rapidly in methadone maintained	Not studied in human pharmacokinetics studies

Patient education: When a patient is seeking pharmacotherapy for opioid use disorder, they should be informed of the risks and benefits of methadone or buprenorphine therapy including the possibility of adverse drug interactions that might be associated with either symptoms of opioid withdrawal (to date this has been observed with certain antiretroviral medications and methadone, some anticonvulsants and methadone, and tuberculosis medications (i.e. rifampin) and either methadone or buprenorphine) or opioid excess (this has been observed either when (1) a medication inhibits opioid metabolism or has a synergistic pharmacodynamic interaction given with either methadone and this potential exists for such interactions with several antidepressant and anxiolytic medications, as above) or buprenorphine (potential for adverse drug interactions with benzodiazepines) or (2) when methadone has been given with a medication that induces its metabolism resulting in higher doses of methadone needed, then the inducing medication is discontinued without a concomitant reduction in methadone dose leading to methadone toxicity).

Recommendations: Level of evidence: **High – Clinical observation and controlled pharmacokinetic/pharmacodynamic studies**

1. **For the patient who is methadone-maintained and requires initiation of a medication(s) that may alter methadone metabolism or have a pharmacodynamic interaction with methadone:** Patients should continue on their current methadone dose and should be informed of the potential for drug interactions that may cause them to experience either symptoms of opioid withdrawal or opioid excess (sleepiness, impaired thinking). Patients should be encouraged to immediately report any adverse symptoms to their prescribing provider and to clinical staff at the methadone or buprenorphine treatment program. It should be recognized that patients receiving medications that alter methadone exposure may require methadone dose adjustments. For those in methadone maintenance therapy, a trough methadone level prior to initiation of a medication that might alter plasma methadone concentrations, as well as a trough methadone level when a patient experiences symptoms thought to be opioid withdrawal/excess may be helpful. A significant decrease or increase in trough methadone concentration would indicate a need for increasing/decreasing the methadone dose. In patients experiencing acute, severe opioid withdrawal symptoms; the methadone dose should be addressed immediately. In a patient showing evidence of acute onset of opioid withdrawal, the methadone dose can be increased immediately to prevent non-adherence to prescribed medications and/or use of illicit or non-prescribed opioids. The methadone dose can be increased by up to 5-10 mg every 2-3 days until the patient is restabilized.If the patient requires an increase of 20-25% of the starting methadone dose, follow the response for 5-7 days before continuing methadone dose increases unless moderate to severe opioid withdrawal continues. It is suggested that an objective opiate withdrawal scale (either the Objective Opiate Withdrawal Scale (OOWS) or the Clinical Opiate Withdrawal Scale (COWS) be used to determine the severity of opioid withdrawal when a patient is receiving a medication that may induce methadone metabolism. Dose increases should not be based only on subjective report. Another challenge for patients who are receiving methadone therapy can occur when the patient requires a change in a medication necessitating discontinuation of a medication with properties that result in the induction of methadone metabolism. This can result in increased methadone plasma concentrations that

can place the patient at risk for opioid toxicity unless the methadone dose is also reduced. Another potential toxicity associated with methadone excess is cardiac arrhythmia due to either increased methadone exposure resulting from concomitant treatment with a medication that inhibits methadone metabolism or when a medication that can induce methadone metabolism is discontinued resulting in increased methadone exposure (2). Once a medication that is inducing CYP 450 enzymes associated with methadone metabolism (CYP 450 3A4, 2B6, 2D6) is stopped, the methadone dose should be tapered over 1-2 weeks to return the patient to their previous therapeutic dose of methadone (i.e. that dose on which the patient was stable before starting the HAART regimen) (McCance-Katz et al. 2000).

2. **For the patient who is buprenorphine-maintained and requires initiation of a medication that may alter its metabolism or be associated with a pharmacodynamic interaction:** Patients should continue on their current buprenorphine/naloxone dose. Patients should be informed of the potential for drug interactions with some medications that may cause them to experience symptoms of opioid excess (sleepiness, impaired thinking) (this has been observed only with atazanavir/ritonavir and some case reports of toxicities with buprenorphine and benzodiazepines in combination to date) or potentially, opioid withdrawal (this has been observed with rifampin). Patients should be encouraged to report any adverse events experienced which should be clinically evaluated and if necessary, buprenorphine dose adjustment should be made. If opioid withdrawal is experienced in a buprenorphine-maintained patient taking a medication that induces buprenorphine metabolism (such as the CYP 450 3A4 inducer, rifampin), a 25-50% increase in buprenorphine dose can be given for 1 week followed by reduction to the former, lower buprenorphine dose on which the patient was stable.
3. **For the patient with opioid use disorder considering opioid agonist therapy:** The choice of opioid therapy should be based on the assessment of patient clinical needs. Thus far, buprenorphine has fewer clinically significant drug interactions with other medications than does methadone. However, patients who are not good candidates for buprenorphine/naloxone therapy or with high amounts of daily opioid use, those who have a history of high-dose methadone maintenance treatment (> 100 mg daily), pregnant women being initiated to opioid agonist treatment, and those who may benefit from the increased structure of the methadone maintenance program may be better suited to methadone treatment. Those with opioid use disorder who have a physician that can provide buprenorphine treatment may be best treated by that physician for both opioid use disorder and other medical or psychiatric disorders. Patients requiring methadone for analgesia and their clinicians should be aware of potential drug interactions as described above and appropriate adjustments in methadone dose made when clinically indicated.

References:

1. McCance-Katz EF, Sullivan LS, Nallani S: Drug interactions of clinical importance between the opioids, methadone and buprenorphine, and frequently prescribed medications: A review. Am J Addictions, 19: 4–16, 2009.

2. Krantz MJ, Kutinsky IB, Robertson AD, Mehler PS: Dose-related effects of methadone on QT prolongation in a series of patients with torsades de pointes. Pharmacotherapy 23: 802-805, 2003.

PCSS Guidances use the following levels of evidence*:
High = Further research is very unlikely to change our confidence in the estimate of effect.
Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low = Any estimate of effect is very uncertain.

Type of evidence:
Randomized trial = **high**
Observational study = **low**
Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations
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