



## PCSS Guidance

**Topic:** Methadone and Drug Interactions

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**Last Updated:** 2/6/10

**Clinical questions:**

1. What drug interactions of clinical significance occur between methadone or buprenorphine and other medications?
2. In thinking about opioid therapy for an opioid dependent patient, how can I determine whether to select methadone or buprenorphine as the treatment medication?

**Background:**

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 (1). This guidance will summarize that literature in tabular form below.

	<b>Methadone</b>	<b>Buprenorphine</b>
<b>HIV Medications</b>		
AZT	Increase in AZT concentrations; possible AZT toxicity (2)	No clinically significant interaction (3)
Didanosine (in tablet form)	Significant decrease in didanosine concentrations (4).	Not studied in human pharmacokinetics studies
Stavudine	Significant decrease in stavudine concentrations (4).	Not studied in human pharmacokinetics studies
Delavirdine	Increased methadone (and LAAM) concentrations; no cognitive impairment (5)	Increased buprenorphine concentrations; no cognitive impairment (6)
Atazanavir	Not associated with increased levels of methadone (7)	Significant increases in buprenorphine and report of cognitive dysfunction (8)
Darunavir	Opiate withdrawal may occur (9)	Under study
Efavirenz	Opiate withdrawal may occur (10,11)	No clinically significant interaction (6)
Fosamprenavir	Data suggest that the PK interaction is not clinically relevant; however, patients should be monitored for opiate withdrawal symptoms (12)	Under study
Nelfinavir	Methadone levels are decreased. Opiate withdrawal may occur (13)	No clinically significant interaction (14)
Nevirapine	Opiate withdrawal may occur (15, 11)	No clinically significant interaction (16)
Lopinavir/ritonavir	Opiate withdrawal may occur (17)	No clinically significant interaction (14)

	<b>Methadone</b>	<b>Buprenorphine</b>
<b>Tuberculosis Medications</b>		
Rifampin	Opiate withdrawal may occur (18)	Opiate withdrawal may occur (19)
Rifabutin	No clinically significant interaction (20)	Not studied in human pharmacokinetics studies
<b>Hepatitis C</b>		
Interferon	No clinically significant interaction (21, 22)	Not studied in human pharmacokinetics studies
Ribavirin	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
<b>Other Infections</b>		
Fluconazole	Increased methadone plasma concentrations (23)	Not studied in human pharmacokinetics studies
Voriconazole	Increased methadone plasma concentrations (24)	Not studied in human pharmacokinetics studies
Ciprofloxacin	Increased methadone plasma concentrations (25)	Not studied in human pharmacokinetics studies
Clarithromycin	Increased methadone plasma concentrations (26)	Not studied in human pharmacokinetics studies
<b>Antidepressants</b>		
Fluoxetine	Reported association with increased levels of methadone (27)	Not studied in human pharmacokinetics studies
Fluvoxamine	May cause increased methadone plasma levels and discontinuation has been associated with onset of opioid withdrawal (28)	Not studied in human pharmacokinetics studies
Sertraline	No reported adverse drug interaction (29)	No clinically significant interaction (29)
Citalopram	No reported significant interaction (30)	No clinically significant interaction (30)
Mirtazapine	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Duloxetine	May potentially lead to increased duloxetine exposure (31), but not studied in humans	Not studied in human pharmacokinetics studies
Amitriptyline	Could be associated with increases in plasma methadone concentrations (32)	Not studied in human pharmacokinetics studies
St. John's Wort	Increased metabolism and elimination of methadone (33)	Increased metabolism and elimination of buprenorphine (33)
Desipramine	Associated with increased desipramine levels (34)	Not studied in human pharmacokinetics studies
Dextromethorphan	Associated with delirium (35)	Not studied in human pharmacokinetics studies

	<b>Methadone</b>	<b>Buprenorphine</b>
<b>Antipsychotics</b>		
Quetiapine	Increased plasma methadone concentrations (36)	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
<b>Anxiolytics</b>		
Diazepam	Associated with increased sedation and impaired performance on psychological tests (37,38)	Associated with increased sedation and impaired performance on psychological tests (37, 38)
Alprazolam	Fatalities have been associated with combined use (39)	Fatalities have been associated with combined use (40)
<b>Anticonvulsants</b>		
Carbamazepine	Associated with opiate withdrawal (41)	Not studied in human pharmacokinetics studies
Phenytoin	Associated with opiate withdrawal (41)	Not studied in human pharmacokinetics studies
Phenobarbital	Associated with opiate withdrawal (41)	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
<b>Psychostimulant Medications</b>		
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
<b>Antihistamines</b>		
Promethazine	May have synergistic depressant effect (42)	Not studied in human pharmacokinetics studies
Diphenhydramine	May have synergistic depressant effect (42)	Not studied in human pharmacokinetics studies

	<b>Methadone</b>	<b>Buprenorphine</b>
<b>Cardiac and Pulmonary Disease Medications</b>		
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
<b>Psychostimulants</b>		
Cocaine	Decrease in trough methadone concentrations (43)	Increased metabolism and diminished plasma concentrations (44)
Methamphetamine	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
<b>Alcohol</b>	Severe adverse events including death (45), eliminated more rapidly in methadone-maintained (46)	Not studied in human pharmacokinetics studies

**Patient education:** When a patient is seeking pharmacotherapy for opioid dependence, 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 opiate 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 opiate excess (this has been observed in two clinical situations: 1. when a medication that inhibits opioid metabolism or has a synergistic pharmacodynamic interaction with the opioid is given with either methadone (potential exists for such interactions with several antidepressant and anxiolytic medications (see 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 pharmacokinetics/pharmacodynamics 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 opiate withdrawal or opiate 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 maintenance program (should the patient be methadone-maintained). 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 opiate 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 opiate withdrawal symptoms; the methadone dose should be addressed immediately. In a patient showing evidence of acute onset of opiate withdrawal, the methadone dose can be increased immediately to prevent non-adherence to prescribed medications and/or abuse of illicit/nonprescribed drugs. The methadone dose can be increased by up to 10 mg every 2-3 days until the patient is restabilized. 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 (47). 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) (48).

- 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 opiate 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, opiate abstinence (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 opiate 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 opiate-addicted patient considering opioid 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 opiate use, those who have a history of high-dose methadone maintenance treatment (> 100 mg daily), those with chronic pain conditions which may require opioid therapy with a full mu opioid agonist medication, pregnant women (at this time methadone maintenance remains the standard of care for pregnant, opiate-addicted patients), and those who may benefit from the increased structure of the methadone maintenance program may be better suited to methadone treatment. Those with opioid addiction who have physicians that can provide buprenorphine treatment may be best treated by that physician for both opioid dependence and other medical 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.

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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

*British Medical Journal*, 2004;328;1490-