



PCSS Guidance

Topic: Opioid therapies, HIV disease and drug interactions

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Last Updated: 2/28/08

Guideline Coverage: TIP #40, Special Populations: Patients with Medical Comorbidities (pgs. 67-68).

Clinical Questions:

1. Do drug interactions of clinical significance occur between methadone or buprenorphine and HIV medications?
2. How can I determine whether an opiate-addicted patient with HIV disease should be treated with methadone or buprenorphine?

Background:

Injection drug use is a risk factor for HIV infection. Many, if not most injection drug users are addicted to opiates. The treatment of choice for opioid dependence in these patients is opioid maintenance therapy available principally as either methadone or buprenorphine pharmacotherapy (Johnson et al. 2000).

Preclinical studies elucidating the clinical pharmacology of antiretroviral medications and opioids indicate that drug interactions are likely to occur (Kumar et al. 1996, Iribarne et al., 1998). Methadone and buprenorphine are primarily metabolized by hepatic cytochrome P450 enzymes (CYP 450), specifically CYP 450 3A4 (Moody et al., 1997, Iribarne et al, 1996). A number of antiretroviral medications are substrates of and have been shown in preclinical studies to inhibit the activity of CYP 450 3A4 leading to speculation of opioid toxicity and/or toxicity related to increased exposure to the HIV medications in those receiving maintenance therapies. Conversely, if an antiretroviral agent were to induce CYP 450 enzyme production, an opiate abstinence syndrome could result placing the patient at risk for relapse to illicit drug use and/or nonadherence to HIV medication therapies.

To date (February 2008), methadone has been associated with several clinically important, adverse drug interactions with HIV medications. Buprenorphine has been studied in combination with antiretroviral medications more recently. Table 1 summarizes drug interactions that have been identified between antiretroviral

medications and either methadone or buprenorphine. The clinical importance of drug interactions lies in the associated adverse events that occur. Drug interactions that lead to reduced methadone concentrations in the blood have been associated with opiate withdrawal syndromes which themselves have been linked to non-adherence to HIV medications and to increases in illicit drug use including high risk behaviors such as injection drug use. To date, reductions in buprenorphine concentrations resulting from drug interactions have not been associated with opiate withdrawal. Drug interactions that lead to low plasma concentrations of antiretroviral medications may produce subtherapeutic concentrations that may be clinically ineffective and risk the possibility of the development of viral resistance. Similarly, toxicities resulting from drug interactions that might increase plasma concentrations of opioids or antiretroviral medications include the risk of non-adherence or sporadic adherence to HIV regimens that may result in the development of viral resistance. These consequences underscore the need for clinicians to be familiar with the drug interactions of importance between opioids and antiretroviral therapies so that they can monitor patients for adverse events and intervene as needed as well as to educate their patients.

Table 1		
HIV Medication	Interaction with Methadone	Interaction with Buprenorphine (BUP)
Nucleoside Reverse Transcriptase Inhibitors		
Zidovudine (AZT)	↑ AZT AUC by 40%, AZT toxicity observed requiring dose adjustment in several participants, no effect on methadone levels (McCance-Katz <i>et al.</i> , 1998)	Non-clinically significant ↓ AZT concentrations ; no need to adjust AZT dose (McCance-Katz <i>et al.</i> , 2001)
Didanosine (ddI) tablet	↓ ddI AUC by 63%, no effect on methadone levels (Rainey <i>et al.</i> , 2000)	Not studied
Didanosine (ddI) enteric-coated	No significant effect of methadone on ddI (this formulation should be used in patients with HIV/AIDS and who are methadone maintained (Friedland <i>et al.</i> , 2002)	No clinically significant interaction
Zalcitabine (ddC)	None	Not studied
Lamivudine (3TC)	None	No effect of lamivudine on buprenorphine concentrations
Lamivudine/zidovudine	None (Rainey <i>et al.</i> , 2002)	Not studied
Stavudine (d4T)	↓ d4T AUC by 25% (Rainey <i>et al.</i> , 2000)	Not studied

Abacavir (ABC)	↑ Methadone clearance, but no withdrawal, no clinically significant effect on ABC concentrations (Sellers <i>et al.</i> , 1999),	Not studied
Tenofovir	No significant interaction	No significant interaction
Non-Nucleoside Reverse Transcriptase Inhibitors		
Nevirapine	Withdrawal symptoms, need for increased methadone dose (Altice <i>et al.</i> , 1999), 40% decrease in methadone (Stocker <i>et al.</i> 2004)	Under study
Delavirdine (DLV)	↑ Methadone levels without toxicity (McCance-Katz, <i>et al.</i> 2006), no effect on DLV	↑ BUP concentrations without toxicity, no effect on DLV (McCance-Katz <i>et al.</i> 2006)
Efavirenz (EFV)	↓ Methadone levels, withdrawal symptoms, ↑ methadone dose necessary (up to 50%) (Clarke <i>et al.</i> , 2001, McCance-Katz <i>et al.</i> 2002)	↓ BUP levels, no withdrawal, no dose change needed, no effect on EFV levels (McCance-Katz, <i>et al.</i> 2006)
Protease Inhibitors		
Nelfinavir (NLF)	↓ Methadone levels, but no withdrawal symptoms observed (McCance-Katz <i>et al.</i> , 2004), increased NLF, decreased M8 metabolite, no clinically significant change in NLF exposure	No effect on BUP (McCance-Katz <i>et al.</i> , 2006), no significant effect of BUP on NLF
Indinavir	Not studied	Not studied
Ritonavir (RTV)	↑ Methadone levels, not clinically significant (McCance-Katz <i>et al.</i> 2003)	↑ BUP levels, not clinically significant, no effect of BUP on RTV
Saquinavir	↓ Methadone levels (S enantiomer), no withdrawal (Gerber <i>et al.</i> 2002)	Not studied
Amprenavir	↓ methadone, no withdrawal	Under study
Lopinavir/ritonavir (L/R)	↓ methadone, withdrawal may occur, methadone may need to be increased (McCance-Katz <i>et al.</i> , 2003)	No significant effect on BUP, no effect of BUP on L/R (McCance-Katz, 2006)
Atazanavir (ATZ) or Atazanavir/ritonavir (ATV/r)	No effect of ATZ on methadone, no effect of methadone on ATZ (Friedland <i>et al.</i> , 2005)	Significant increase in BUP and norbuprenorphine; sedation may occur (McCance-Katz <i>et al.</i> , 2007); clinical observation of sedation and cognitive impairment with ATV/r (Bruce, 2005)

Patient Education:

When a patient with HIV disease 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 only been observed with certain antiretroviral medications and methadone) or opiate excess (this has been recently observed in several patients receiving the protease inhibitor combination atazanavir/ritonavir and buprenorphine).

Buprenorphine has fewer adverse drug interactions with HIV medications than does methadone. Buprenorphine treatment may also be preferable to methadone for many patients in that physicians with appropriate training and qualifications can prescribe buprenorphine for opioid addiction; thus one physician may be able to provide both HIV care and treatment for opioid dependence. Demonstration projects of this model of care are currently underway (see www.bhives.org).

Recommendations:

Level of evidence: **High – Clinical observation and controlled pharmacokinetics/pharmacodynamics studies**

1. For the patient with HIV disease who is methadone-maintained and requires initiation of highly active antiretroviral therapy (HAART):

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, opiate excess (sleepiness, impaired thinking), or symptoms of antiretroviral toxicity (such symptoms are specific to the medications being prescribed; thus far the only antiretroviral medication that has been associated with toxicity is zidovudine (AZT) and this appears to be a rare event). Patients should be encouraged to immediately report any adverse symptoms to their HIV treatment provider and to clinical staff at the methadone maintenance program. It should be recognized that patients receiving HAART and methadone may require methadone dose adjustments. A trough methadone level prior to initiation of HAART and when a patient experiences symptoms thought to be opiate withdrawal/excess may be helpful. A significant decrease or increase in trough methadone concentration with antiretroviral treatment would indicate a need for increasing/decreasing the methadone dose. In patients experiencing acute, severe symptoms; the methadone dose should be addressed immediately. In a patient showing evidence of acute onset of opiate withdrawal, the methadone dose will need to be increased immediately to prevent non-adherence to HIV medications and/or abuse of illicit drugs. The methadone dose can be increased by up to 10 mg every 2-3 days until the patient is restabilized. An additional challenge for patients with HIV/AIDS and who are methadone-maintained can occur when the patient requires a change in antiretroviral medication necessitating discontinuation of the inducing HIV therapeutic. 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 complication is cardiac arrhythmia due to increased methadone exposure when an antiretroviral medication that can induce methadone metabolism is discontinued resulting in increased methadone exposure (Krantz et al. 2003). Once the medication that is inducing CYP 450 3A enzymes 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 with HIV disease who is buprenorphine-maintained and requires initiation of highly active antiretroviral therapy (HAART):** Patients should continue on their current buprenorphine/naloxone dose. Patients should be informed of the potential for drug interactions with HIV medicines that may cause them to experience symptoms of opiate excess (sleepiness, impaired thinking) (this has been observed only with atazanavir/ritonavir to date) or potentially, opiate abstinence (this has not been observed between buprenorphine and any antiretroviral medication studied to date). Patients should be encouraged to report any adverse events experienced which should be clinically evaluated and if necessary, buprenorphine dose adjustment should be made.
- 3. For the opiate-addicted patient with HIV disease 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 antiretroviral medications than does methadone. However, patients 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, 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 HIV physicians who can provide buprenorphine treatment may be best treated by that physician for both disorders. Patients needing HAART may benefit from a trial of buprenorphine treatment due to the reduced likelihood of adverse drug interactions as compared to methadone. Any patient treated with HAART and initiating opioid therapy warrants clinical observation to determine whether adverse interactions occur and, if so, how to address these interactions.

References:

Altice FL, Friedland GH, Cooney EL: Nevirapine induced opiate withdrawal among injection drug users with HIV infection receiving methadone. AIDS 13:957-62, 1999.

Bruce RD, Altice FL: Three case reports of a clinical pharmacokinetic interaction with buprenorphine and atazanavir plus ritonavir. *AIDS* 21: 783-784, 2005.

Clarke SM, Mulcahy FL, Tjia J, Reynolds NE, Gibbons SE, Barry MG, Back DJ: Pharmacokinetic interactions of nevirapine and methadone and guidelines for the use of nevirapine to treat injection drug users. *Clin Infect Dis* 33: 1595-1597, 2001.

Friedland G, Rainey P, Jatlow P, Andrews L, Damle B, McCance-Katz E: Pharmacokinetics of didanosine from encapsulated enteric coated bead formulation versus chewable tablet formulation in patients on chronic methadone therapy. 14th International AIDS Conference, Abstract number: TuPeB4496, Barcelona, Spain, 2002

Friedland G, Andrews L, Schreibman T, Agarwala S, Daley L, Child M, Shi J, Wang Y, O'Mara E: Lack of an effect of atazanavir on steady-state pharmacokinetics of methadone in patients chronically treated for opiate addiction. *AIDS* 14: 1835-184, 2005.

Gerber JG, Rosenkranz S, Segal Y, et al. Effect of ritonavir/saquinavir on stereoselective pharmacokinetics of methadone: results of AIDS Clinical Trials Group (ACTG) 401. *J Acquir Immune Defic Syndr* 27:153-60, 2001.

Iribarne C, Berthou F, Baird S, et al. Involvement of cytochrome P450 3A4 enzyme in the n-demethylation of methadone in human liver microsomes. *Chem Res Toxicol* 9:365-373, 1996

Iribarne C, Berthou F, Carlhant D, et al. Inhibition of methadone and buprenorphine n-dealkylations by three HIV-1 protease inhibitors. *Drug Metab Dispos* 26: 257-260, 1998

Johnson, RE, Chutuape, MA, Strain, EC, Walsh, SL, Stitzer, ML, Bigelow, GE: A comparison of levomethadyl acetate, buprenorphine and methadone for opioid dependence. *New England Journal of Medicine*, 343, 1290-1297, 2000.

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.

Kumar GN, Rodrigues AD, Buko AM, Denissen JF: Cytochrome P450-mediated metabolism of the HIV-1 protease inhibitor ritonavir (ABT-538) in human liver microsomes. *J Pharm Exp Ther* 277: 423-431, 1996.

McCance-Katz EF, Jatlow P, Rainey P, Friedland G: Methadone effects on zidovudine (AZT) disposition (ACTG 262). *J Acquir Immune Defic Syn Hum Retrovirol*, 18: 435-443, 1998.

McCance-Katz EF, Selwyn P, Farber S, O'Connor AH: The protease inhibitor nelfinavir decreases methadone levels. *Am J Psychiatry*, 157: 481, 2000.

- McCance-Katz EF, Rainey PM, Friedland G, Kosten TR, Jatlow P: Effect of opioid dependence pharmacotherapies on zidovudine disposition. *Am J Addictions*, 10: 296-307, 2001.
- McCance-Katz EF, Gourevitch MN, Arnsten J, Sarlo J, Rainey P, Jatlow P: Modified Directly Observed Therapy (MDOT) For Injection Drug Users With HIV Disease. *Am J Addictions*, 11: 271-278, 2002.
- McCance-Katz EF, Rainey P, Friedland G, Jatlow P: The protease inhibitor lopinavir/ritonavir may produce opiate withdrawal in methadone-maintained patients. *Clin Infect Dis* 37: 476-482, 2003.
- McCance-Katz EF, Rainey P, Smith P, Morse G, Friedland G, Gourevitch M, Jatlow P: Drug interactions between opioid and antiretroviral medications: Interaction between methadone, LAAM, and nelfinavir. *Am J Addictions* 13:163-180, 2004.
- McCance-Katz EF, Rainey P, Smith P, Morse GD, Friedland G, Boyarsky B, Gourevitch M, Jatlow P: Drug interactions between opioids and antiretroviral medications: interaction between methadone, LAAM, and delavirdine. *Am J Addictions*, 15: 23-34, 2006.
- McCance-Katz EF, Moody DE, Morse G, Pade P, Friedland G, Baker J, Alvanzo A, Smith P, Abayomi O, Jatlow P, Rainey PM: Interactions Between Buprenorphine and antiretrovirals I: Non-Nucleoside Reverse Transcriptase Inhibitors I: Efavirenz and Delavirdine, *Clin Infect Dis*, 43 Suppl 4:S224-34, 2006..
- McCance-Katz EF, Moody DE, Morse G, Pade P, Friedland G, Baker J, Alvanzo A, Smith P, Jatlow P, Rainey PM: Interactions between buprenorphine and antiretrovirals II: Protease inhibitors, nelfinavir, lopinavir/ritonavir, or ritonavir. *Clin Inf Dis*, 43 Suppl 4:S235-46, 2006.
- McCance-Katz EF, Moody DE, Morse GD, Ma Q, DiFrancesco R, Friedland G, Pade P, Rainey PM: Interaction Between Buprenorphine and Atazanavir or Atazanavir/Ritonavir. *Drug Alc Dependence*, 91:269-78, 2007.
- Moody DE, Alburges ME, Parker RJ, Collins JM, Strong JM. The involvement of cytochrome P 450 3A4 in the n-demethylation of l-alpha-acetylmethadol (LAAM), norLAAM, and methadone. *Drug Metab Dispos* 25: 1347-1353, 1997.
- Rainey PM, Friedland G, McCance-Katz EF, Andrews L, Mitchell SM, Charles C, Jatlow P: Interaction of methadone with didanosine (ddl) and stavudine (d4T), *J Acquir Immune Defic Syn Hum Retrovirol*, 24: 241-248, 2000.
- Rainey PM, Friedland GH, Snidow JW, McCance-Katz EF, Mitchell SM, Andrews L, Lane B, Jatlow P: The pharmacokinetics of methadone following co-administration with a lamivudine/zidovudine combination tablet in opiate dependent subjects (NZTA4003). *Am J Addictions*, 11: 66-74, 2002.

Sellers E, Lam R, McDowell J, Corrigan B, Hedayetullah N, Somer G, Kirby L, Kersey K, Yuen G: The pharmacokinetics of abacavir and methadone following co-administration: CNA1012. American Society for Microbiology ICAAC, Poster 305, San Francisco, 1999

Stocker H, Kruse G, Kreckel P, Herzmann C, Arasteh K, Claus J, Jessen H, Cordes C, Hintsche B, Schlote F, Schneider L, Kurowski M: Nevirapine significantly reduces the levels of racemic methadone and (R)-methadone in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 48: 4148-4153, 2004.

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-

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