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Drug interactions associated with methadone, buprenorphine, cocaine, and HIV medications: implications for pregnant women

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Abstract

Pregnancy in substance-abusing women with HIV/AIDS presents a complex clinical challenge. Opioid-dependent women need treatment with opioid therapy during pregnancy to protect the health of mother and developing fetus. However, opioid therapies, methadone and buprenorphine, may have drug interactions with some HIV medications that can have adverse effects leading to suboptimal clinical outcomes. Further, many opioid-dependent individuals have problems with other forms of substance abuse, for example, cocaine abuse, that could also contribute to poor clinical outcomes in a pregnant woman. Physiological changes, including increased plasma volume and increased hepatic and renal blood flow, occur in the pregnant woman as the pregnancy progresses and may alter medication needs with the potential to exacerbate drug interactions, although there is sparse literature on this issue. Knowledge of possible drug interactions between opioids, other abused substances such as cocaine, HIV therapeutics, and other frequently required medications such as antibiotics and anticonvulsants is important to assuring the best possible outcomes in the pregnant woman with opioid dependence and HIV/AIDS.

Keywords

pregnancy; substance abuse; HIV disease; cocaine; methadone; buprenorphine; drug interactions

Introduction

The complexities of co-occurring HIV infection/disease and drug abuse in pregnant women

Effective clinical care of pregnant women with HIV/AIDS who also have co-occurring substance abuse presents a challenging problem in medicine. Not only must effective medical interventions be rendered to women with changing physiology, but the needs of the developing fetus must also be a primary consideration. The main goals of treatment in these women are a safe pregnancy with avoidance of teratogenicity or fetal toxicity and delivery of a baby free of HIV infection. To achieve these goals we must determine the highly active antiretroviral therapy (HAART) that will best treat the mother's virus and protect the fetus from infection. We must also actively address substance abuse problems faced by the woman. Pharmacotherapy treatments for substance use disorders are limited. For stimulant

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use disorders, such as cocaine abuse and dependence, there are no FDA approved medications. For opioid (heroin, prescription analgesic) use disorders, there are two FDA-approved, effective, opioid therapies available, methadone (Marsch, 1998) and buprenorphine (McCance-Katz, 2004). However, there are certain caveats of which we must be aware in undertaking treatment of these women. In this review, we will address the issue of drug interactions of clinical significance known to occur between opioid therapies and antiretroviral medications (ARV). This will be considered in light of specific challenges presented in pregnancy. Further, it is unfortunately the case that many individuals with opioid dependence also co-abuse stimulants. In particular, the abuse of cocaine is common and can lead to treatment failure (Neufeld et al. 2008). This review will also include recent literature on drug interactions between cocaine and methadone or buprenorphine. Drug interactions are an important source of morbidity and mortality in all clinical populations (Institute of Medicine, 2000, Lazarou et al. 1998). Understanding the potential for such interactions and knowing how to address interactions will improve the health of pregnant, substance-abusing women and the developing fetus.

Treatment of Pregnant Women with Opioid Dependence and HIV Disease

A woman who is opioid-addicted and pregnant is considered a priority admission to methadone maintenance treatment programs. Women who inject heroin are at high risk for adverse events associated with their drug use. High risk injection practices including sharing of syringes places women at greater risk for infectious diseases including HIV (Alcabes and Friedland 1995) and Hepatitis C (HCV) (Steedman and Younoussi, 2000). To best protect the pregnant woman from potential complications of injection drug use, induction onto methadone is the current standard of care, however buprenorphine appears to have few adverse events in neonates and may be associated with less severe neonatal abstinence syndromes than those with methadone (Jones et al. 2005). Further, pregnant women with HIV/AIDS require aggressive treatment of the HIV to decrease viral load and potential transmission to the fetus as well as to protect the mother from opportunistic infections resulting from immune deficiencies induced by the HIV. These clinical tenets become particularly important in the treatment of pregnant, opioid-addicted women with HIV/AIDS. Fortunately, to date, there are fewer drug interactions of clinical significance between ARV and buprenorphine than between ARV and methadone (McCance-Katz et al. 2009) as will be summarized below.

Drug-Drug Interaction Studies between ARV and Opioids

Treatment Issues Related to Drug-Drug Interactions Between Opioids and ARV

The shared metabolic pathways, both of methadone and buprenorphine, as well as a number of widely prescribed ARV would predict the occurrence of drug interactions when opioids are used in combination with HIV therapeutics. Buprenorphine is mainly metabolized by CYP 450 3A4 and 2C8 (Chang et al. 2006) and methadone is metabolized by several CYP 450 enzymes including CYP 450 3A4, 2D6, and 2B6 (Iribarne et al. 1996, Kharasch et al. 2009, Gerber et al. 2001). Similarly, many of the ARVs are not only substrates of these enzymes, but some may inhibit or induce activity of the drug metabolizing enzymes resulting in the potential for opioid and/or ARV toxicity or, alternatively, opioid withdrawal or subtherapeutic ARV concentrations, respectively.

The consequences of opioid toxicity include cognitive impairment, sedation, possible respiratory depression, or cardiac arrhythmias (the latter two more likely to occur with methadone) (McCance-Katz et al. 2009). Some of these adverse events could result in significant morbidity and even mortality. Alternatively, the onset of opiate withdrawal as a result of administration of medications that induce opioid metabolism may be associated

with non-adherence to prescribed HAART, increased abuse of street drugs including opioids and stimulants and risk of failure of both substance abuse treatment and HIV treatment. The induction of enzymes that produce more rapid metabolism of ARV could also result in the production of HIV resistant to current ARV. Any of these consequences are of sufficient clinical importance that an understanding of potential drug interactions between opioids and ARV is essential to the care of those with these co-occurring disorders. Furthermore, the occurrence of any of these clinical consequences could result in adverse events in pregnancy. For example, opioid withdrawal and illicit drug use is associated with fetal distress and premature birth (SAMHSA, 1993). In the following sections, drug interactions between opioids and ARV of clinical significance will be reviewed.

Early Studies in Human Opioid-Dependent Volunteers Show that Opioid Therapy Selection May Be Helpful in Decreasing Adverse Drug Interactions in those with HIV/AIDS

The first drug interaction study undertaken by our research group was in response to clinical observations that methadone-maintained patients with HIV starting treatment with what was at that time the only treatment for HIV, zidovudine, experienced symptoms that appeared to be consistent with opiate withdrawal. A study was undertaken in which individuals with HIV disease and opioid dependence were medically withdrawn from opioids. They then began zidovudine therapy and underwent a study of zidovudine pharmacokinetics. Methadone maintenance therapy was initiated and the drug interaction study repeated once these individuals who remained on treatment with zidovudine reached steady state for methadone. This study showed that zidovudine concentrations were significantly higher once methadone therapy was initiated with an area under the time-concentration (AUC) curve increase of approximately 41%. However, methadone plasma concentrations remained in the therapeutic range (McCance-Katz et al. 1998). This increase in zidovudine exposure is sufficient, in some patients, to produce zidovudine toxicity which has symptom overlap with opiate withdrawal. An important question generated from these results was whether what occurred between methadone and zidovudine also occurred when other opioid therapies were given simultaneously with zidovudine. In a similarly designed study, the interaction of zidovudine with l-acetyl-methadol (a long-acting opioid which is FDA approved for the treatment of opioid dependence but is no longer produced in the United States), naltrexone, or buprenorphine was undertaken. Interestingly, unlike the results for the interaction between methadone and zidovudine, neither the opioid agonist medication l-acetyl-methadol nor buprenorphine nor the opioid antagonist medication naltrexone were associated with increased zidovudine exposure (McCance-Katz et al. 2001). The clinical implications of these studies were that opioid dependent patients with HIV disease could potentially be matched to an opioid therapy (or HIV therapy) that would be less likely to be associated with adverse drug interactions, thus improving clinical outcomes in this population.

The implications of such a study for a pregnant, opioid-dependent patient would be that buprenorphine would be the better choice of these four opioid dependence pharmacotherapies. L-acetyl-methadol is no longer available as a result of concerns about its effect on cardiac QT interval (Langley et al. 1982). Naltrexone, an opioid antagonist, is often associated with poor adherence; thus the recommendation for opioid replacement therapy for pregnant, opioid –addicted women (CSAT/SAMHSA, 1993). While methadone has been the recommended opioid therapy for pregnant women with opioid addiction (CSAT/SAMHSA, 1993), there is accumulating evidence that buprenorphine is equivalent to or may be a better choice for some of these women (Kakko et al. 2008, Jones et al. 2005, Schindler et al. 2002).

Other Drug Interactions of Clinical Significance Between Opioids and ARVs

To date, a large number of drug interaction studies have been reported for methadone or buprenorphine with ARV medications. The FDA now requires drug interaction studies to be conducted with any new ARV and methadone in order to receive full approval of the ARV medication. There is no similar requirement for buprenorphine to be studied with ARV. However, buprenorphine offers unique advantages for patients with co-occurring opioid dependence and HIV/AIDS. Buprenorphine Is the first opioid to be FDA-approved for the treatment of opioid dependence that is available by prescription from qualified physicians. This means that physicians treating HIV disease may become certified to provide treatment of opioid dependence from their office-based practices upon meeting at least one of the criteria outlined in the Drug Abuse Treatment Act of 2000. Most physicians become eligible for the waiver and revised DEA registration permitting office-based treatment of opioid dependence by taking 8 hours of continuing medical education sanctioned by the Center for Substance Abuse Treatment (CSAT/SAMHSA) (McCance-Katz, 2004). Understanding drug interactions between buprenorphine and ARV then becomes important because were the clinical profile of combined use of buprenorphine with ARV to be more favorable, physicians treating HIV disease could also treat opioid dependence in the same patient when needed. This greatly simplifies the clinical care of such patients and makes it more likely that the patient will receive all needed, clinically-indicated, pharmacotherapy interventions.

Methadone has been shown to have more adverse drug interactions with ARV than does buprenorphine (Table 1). Several ARV have been shown to be associated with decreased plasma methadone concentrations that have also produced opiate withdrawal symptoms in some methadone-maintained patients. The protease inhibitor combination, lopinavir-ritonavir may produce opiate withdrawal, particularly in those with trough methadone concentrations at the lower end of the therapeutic range (McCance-Katz et al, 2003). The non-nucleoside reverse transcriptase inhibitor, efavirenz, has been associated with opiate withdrawal when administered to methadone-maintained patients (McCance-Katz, 2002). Similarly, nevirapine, another non-nucleoside reverse transciptase inhibitor has also been associated with opiate withdrawal symptoms in patients also receiving methadone maintenance therapy (Back et al. 2003).

The consequences of induction of opioid metabolism and associated withdrawal symptoms are of great significance. Those experiencing opiate withdrawal are more likely to stop their ARVs or to resume illicit drug use, which in injection drug users may include resuming high risk behaviors for HIV transmission such as syringe/needle sharing. Those receiving potent inducers of methadone metabolism may require methadone dose increases up to 50% as was shown in a directly observed therapy study where methadone-maintained patients with HIV disease prescribed efavirenz-containing HAART were given ARV in the methadone maintenance program by clinic staff. These patients were closely observed over a 12 week period and several patients required rapid increases in methadone to address moderate to severe opiate withdrawal symptoms (McCance-Katz et al., 2002) underscoring the need to follow patients receiving methadone and medications known to be associated with CYP 450 enzyme induction closely and to offer reassurance that methadone doses will be increased if opiate withdrawal occurs. A concern with the use of such medications concomitantly in a large clinical setting is that patients will not get the individualized attention needed to assure successful treatment with both medications (methadone and the ARV) potentially leading to therapeutic failures. Pregnant women receiving methadone and medications that produce significant methadone metabolism such as efavirenz or nevirapine may require, in addition to increased doses; splitting of the dose to be given in two divided doses daily (discussed in more detail below) in order to prevent the onset of opiate withdrawal.

Methadone has also been shown to have drug interactions that could potentially lead to either opioid toxicity or to subtherapeutic ARV concentrations. Delavirdine is a non-nucleoside reverse transcriptase inhibitor that has been shown to inhibit methadone metabolism leading to higher methadone plasma concentrations (McCance-Katz et al. 2005). Although no opioid toxicity was observed in participants in the cited study, participants received delavirdine at standard clinical doses for only 5 days. Chronic dosing of this medication, or medications with similar effects on methadone metabolism, might be associated with opiate toxicity. Aside from the reported interaction between methadone and zidovudine, methadone administration has been associated with significant decreases in nucleoside reverse transcriptase inhibitor plasma concentrations for stavudine and the tablet formulation of didanosine (Rainey et al. 2000). Significant decreases in ARV trough concentrations could result in ineffective treatment of HIV, a serious consequence of a drug interaction. Reduction in ARV plasma concentrations in the presence of methadone could require increased doses of the ARV; however selection, when possible, of an ARV that does not have such an interaction will simplify the treatment of HIV/AIDS in such patients. Of note, the tablet form of didanosine has been replaced by the enteric coated formulation in many countries. This modified formulation does not appear to be affected by methadone administration (Friedland et al. 2002). However, the tablet form of didanosine is still being used in some developing nations.

In contrast to findings for multiple ARV with methadone, buprenorphine has been shown to have few clinically significant drug interactions with ARV. For example, although efavirenz has been shown to substantially and significantly reduce buprenorphine and norbuprenorphine concentrations, no opiate withdrawal was observed (McCance-Katz et. al. 2005). In contrast to findings for methadone, nevirapine has little effect on buprenorphine (McCance-Katz et al. 2010). However, buprenorphine in combination with atazanavir or atazanvir-ritonavir administration has been associated with increased plasma concentrations of buprenorphine. The underlying reason for the large increases in both buprenorphine and norbuprenorphine (an active metabolite of buprenorphine) plasma concentrations is postulated to be due to inhibition of CYP 450 3A4 as well as inhibition of UDP-glucuronosyltransferase 1A1 (UGT 1A1) by atazanavir (McCance-Katz et al 2007). Similar to findings for methadone and delavirdine given concomitantly, delavirdine is also associated with increased buprenorphine plasma concentrations, but without cognitive deficits or other symptoms of opioid toxicity observed over the 5 day dosing interval. It is worth noting that delavirdine is no longer widely used in the treatment of HIV disease because of its relatively low potency. However, its potent ability to inhibit opioid metabolism is an important demonstration of the potential such metabolic inhibitors have to alter opioid plasma concentrations underscoring the need to closely follow patients who must receive metabolic inhibitor drugs when also receiving opioid therapy.

Drug-Drug Interaction Studies between Opioids and Cocaine

Although, co-abuse of opioids and cocaine is a frequent occurrence, there is sparse evidence in the published literature to suspect that cocaine might be associated with alteration of therapeutic methadone or buprenorphine concentrations. Cocaine is mainly metabolized by hepatic and serum esterases (Brzezinski et al. 1997) with a small component of cocaine metabolism occurring via CYP 3A4 enzymes (Le Duc et al. 1993). However, recent data analyses from our research have shown that both buprenorphine and methadone plasma concentrations are significantly reduced in those with current, chronic, cocaine abuse (McCance-Katz et al, 2010 b, McCance-Katz et al. 2010 c). Chronic cocaine administration has been reported to induce CYP 450 3A4 in rodents (Pellinen, 1996). P-glycoprotein, an efflux transporter is also increased both in the HIV disease state as well as in chronic cocaine use (Lopez et al. 2005) which could increase elimination of methadone and

buprenorphine. These mechanisms could explain the decreases in methadone and buprenorphine concentrations observed in chronic cocaine users.

These findings have implications for pregnant, cocaine and opioid-abusing women with HIV disease because of the potential for lower exposure to opioids used to treat opioid addiction and because it is possible that ARV concentrations could also be lowered through these mechanisms. Physiological changes that occur in pregnancy could alter dose needs for these medications during pregnancy (described in more detail below). It is important to be aware of the factors that might lead to inadequate therapeutic drug concentrations in pregnant women with HIV disease and to adjust medications during pregnancy as needed to assure the best possible clinical outcomes.

Examples of Other Drug-Drug Interactions that May be of Clinical Importance in Pregnant, Opioid-Dependent Women with HIV Disease

Example 1. Antimicrobial Medications

HIV infection results in immunodeficiency syndromes which render an individual susceptible to a variety of opportunistic infections. Some of the more common infections in those with HIV/AIDS such as candida, Cryptococcus neoformans, and tuberculosis require treatment with medications known to have adverse interactions with opioids. For example, a common treatment for fungal infections is fluconazole, a medication shown to significantly inhibit metabolism of methadone (Cobb et al. 1998) with potential for opioid toxicity with chronic administration to methadone-maintained patients. The effect of fluconazole on buprenorphine has not been determined. Rifampin, one of the primary medications for the treatment of tuberculosis induces CYP 450 enzymes, particularly CYP 3A4. It is known to induce the metabolism of methadone (Kreek et al. 1976) as well as buprenorphine (McCance-Katz, 2009) with opiate withdrawal symptoms occurring in some patients. An alternative medication, rifabutin, which has a lesser effect on CYP 450 enzyme function is generally used in the treatment of tuberculosis in those requiring methadone maintenance therapy.

Example 2. Anticonvulsant Medications

Another relatively common complication of HIV disease is that of peripheral neuropathy. Usual medications for this condition are anticonvulsants. Carbamazepine is an anticonvulsant medication that may be prescribed for peripheral neuropathy, but should be used with caution in methadone-maintained individuals. Carbamazepine is a potent inducer of CYP 450 enzymes responsible for methadone metabolism and its use in therapeutic doses has been associated with opiate withdrawal in some patients (Perrucca 2006). Drug interactions studies to determine the effect of carbamazepine on buprenophine have not been conducted. The treatment of peripheral neuropathy is challenging often with only modest symptom relief obtained. In methadone-maintained individuals prescribed this medication and who also experience opiate withdrawal, therapeutic benefit of both drugs is diminished and may be associated with a worsening clinical condition in the patient. Other anticonvulsant without effects on the CYP 450 metabolic enzyme system are available and are better choices for methadone-maintained patients requiring such medications.

There are far more antibiotic medications that are commonly used in the treatment of infectious diseases that have not been studied for drug interactions with opioids than have been examined. However, given the high frequency of use of these medications simultaneously in patients with co-occurring disorders, further research in this area seems clearly indicated. At this time, it is important for clinicians to be aware that many medications have the potential to produce adverse effects in patients when administered

concomitantly as a result of the effect of various drugs on drug metabolism and metabolic enzyme systems. Thus, it is important for clinicians to consider the potential for drug interactions and to determine this potential for medications being considered for individual patients.

Consequences of Drug Interactions in Pregnant Women

Why are the types of drug interactions described above of importance in pregnant women with HIV/AIDS? First, drug interactions that lead to adverse events are important in any patient and must be an issue of concern in all clinical settings. The use of prescription drugs is increasing in the United States with about one-fifth (20%) of Americans having had three or more drugs prescribed during survey years 2001–2004 (National Center for Health Statistics, 2008) underscoring the substantial risk for drug interactions in large numbers of patients. Multiple medications are needed by pregnant, opioid-dependent women with HIV disease, including HAART consisting of at least three medications, and opioid therapy requiring the use of methadone or buprenorphine in addition to any other medications required for treatment of HIV/AIDS and its complications and any medications needed for obstetrical care of the pregnant woman. This clinical reality increases the likelihood of adverse drug interactions in this population.

Second, physiological changes occur during pregnancy that may alter medication needs including increased plasma volume and increased hepatic and renal blood flow as the pregnancy progresses. These changes may result in a need for higher doses of some medications. For example, pregnant, methadone-maintained women often need increases in methadone dose and/or split dosing as the pregnancy progresses (CSAT/SAMHSA, 1993). Administration of medications shown to induce metabolic enzymes responsible for metabolism of methadone or buprenorphine may have a greater effect in producing withdrawal syndromes in pregnant, opioid-maintained women. This could represent a significant risk to the woman and her fetus since the adverse events observed in participants in pharmacokinetic drug interaction studies could occur in pregnant, opioid-dependent women with HIV/AIDS. Given the physiological changes that occur in women during pregnancy and the relative lack of adverse drug interactions associated with co-administration of medications that induce buprenorphine metabolism relative to methadone, it may be advisable to preferentially treat pregnant women with HIV disease and opioid dependence with buprenorphine maintenance therapy for opioid addiction, unless there is another compelling reason to prescribe methadone to the woman. It is important to note that current guidelines (from 1993 and prior to the approval of buprenorphine for the treatment of opioid dependence) recommend the use of methadone maintenance in pregnant, opioid-dependent women (CSAT/SAMHSA, 1993). A review and updating of these guidelines would be a contribution to the clinical community providing medical care to these patients. It is also important to be mindful of the potential for more rapid ARV metabolism in pregnancy related to physiological changes that occur and to consider the potential effect of these physiological changes on ARV plasma concentrations. Use of methadone could contribute to lower plasma concentrations of some ARV as described above. However, improvement in drug formulations and evolution of newer ARV not affected by methadone are important additions to the armamentarium of ARV and should be preferentially used in pregnant women to treat HIV/AIDS.

There is remarkably little literature on the course of HIV/AIDS in pregnancy. It would be of interest to know if the HIV in a pregnant woman changes over the course of the pregnancy. Does the virus remain susceptible to the ARV used in treatment over the course of the pregnancy? Does viral load and CD4 cell count change as pregnancy progresses? What are the effects on clinical outcomes in pregnant, opioid-dependent women with HIV disease?

Does substance use change over the course of the pregnancy? Pregnancy in HIV-infected, opioid-dependent women would be a reason to consider use of therapeutic drug monitoring to assure adequate plasma concentrations of ARV and opioids, as clinically indicated.

Conclusions

Research on the metabolism of drugs in pregnant women as well as potential drug interactions of clinical significance that have the potential for adverse clinical outcomes is sparse. There are special complexities in the effective treatment of pregnant women with substance use disorders and HIV/AIDS that underline the importance of exploring these issues. In particular, the medical needs of this population as well as their medication needs are likely to change as pregnancy progresses, but there is a lack of data available to guide clinical care.

Given the relative lack of drug interactions of clinical importance between buprenorphine for treatment of opioid dependence and ARVs to date, the use of this medication in the pregnant opioid-dependent woman with HIV disease should be considered. Further, there is accumulating literature (noted above) indicating that buprenorphine does not confer adverse effects on the newborn in terms of severity of neonatal abstinence syndrome. A complete review of this literature and revised recommendations regarding the treatment of pregnant, opioid-dependent women is needed at this time. Another advantage of buprenorphine treatment is the potential for office-based treatment of opioid dependence which allows a qualified obstetrician or physician treating the HIV disease to prescribe buprenorphine for treatment of opioid dependence. This would benefit the patient in simplifying her medical care and eliminating the requirement of daily attendance at a methadone maintenance program.

Finally, the drug interaction studies reported to date underscore the need to treat all substance use disorders in those abusing multiple substances. The effect of cocaine on opioid concentrations has the potential to negatively impact response to opioid therapy. Any patient entering drug abuse treatment should have a full assessment of their substance abuse problems and treatment needs to address all of these issues. This is particularly important for pregnant women with HIV/AIDS because of the need to aggressively HIV to prevent transmission to the developing fetus and to protect the health of the mother. Avoidance of drug interactions resulting from treatment of opioid dependence or drug interactions that may occur when other substances are abused is important to obtaining the best possible clinical outcomes in opioid-dependent women with HIV disease.

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Table 1

Drug Interactions of Clinical Significance: Opioids and HIV Medications

Methadone		**Buprenorphine**	
Zidovudine	↑ zidovudine concentrations	Atazanavir/ritonavir	↑buprenorphine concentrations
Didanosine (tablets)	↓didanosine concentrations		
Stavudine	↓stavudine concentrations		
Lopinavir/ritonavir	↓ methadone concentrations		
Nevirapine	↓ methadone concentrations		
Efavirenz	↓ methadone concentrations		