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A Review of Pharmacological Interactions Between HIV or HCV Medications and Opioid Agonist Therapy: Implications and Management for Clinical Practice

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Abstract

Global access to opioid agonist therapy and HIV/HCV treatment is expanding but when used concurrently, problematic pharmacokinetic and pharmacodynamic interactions may occur. Review of articles from 1966 into 2012 in Medline using the following keywords: HIV, AIDS, HIV therapy, HCV, HCV therapy, antiretroviral therapy, HAART, drug interactions, methadone, and buprenorphine. Additionally, abstracts from national and international meetings and a review of conference proceedings were conducted; selected reports were reviewed as well. The metabolism of both opioid and antiretroviral therapies, description of their known interactions, and clinical implications and management of these interactions are reviewed. Important pharmacokinetic and pharmacodynamic drug interactions affecting either methadone or HIV medications have been demonstrated within each class of antiretroviral agents. Drug interactions between methadone, buprenorphine and HIV medications are known and may have important clinical consequences. Clinicians must be alert to these interactions and have a basic knowledge regarding their management.

Keywords

HIV/AIDS; Hepatitis C; methadone; buprenorphine; pharmacokinetics; pharmacodynamics; drug metabolism; drug interactions; antiretroviral therapy

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Introduction

Opioid dependence, particularly the injection of heroin, and infections with HIV and hepatitis C (HCV) are explosive, intertwined epidemics that adversely impact tens of millions of people globally [1–6]. Approximately 5% of the global population, or 230 million people have used drugs[7]. An estimated 15.9 million individuals in 148 countries inject drugs of abuse; 3 million of these are estimated to be HIV-infected and 9 million HCV-infected [8]. The link between drug use, particularly drug injection, and HIV/HCV has been well described since the beginning of the HIV pandemic and the recognition of HCV [9]. With the advent of medication-assisted treatment (MAT) for opioid dependence, these inter-related epidemics can now be addressed. Methadone and buprenorphine are effective for the treatment of opioid dependence, including people who inject drugs (PWID) [10–13]. Similarly, HIV therapy has revolutionized the clinical course of HIV, while recent developments in HCV treatment promise to bring the possibility of cure to those chronically infected with HCV [14–16]. Efforts to expand access to and use of both MAT and antiviral therapies continue to advance, especially in the wake of the HPTN 052 trial validating HIV treatment as effective HIV prevention [17].

Pharmacological interactions between MAT and antiviral therapies remain a critical issue in the clinical care and treatment of HIV/HCV infected patients with opioid dependence [18]. We have previously reviewed key interactions between HIV therapeutics and opioid dependence treatments [19]. The last 6 years, however, have seen the approval of several new HIV medications, as well as a new class of direct-acting antiviral medications for the treatment of HCV. These new medications will often be prescribed to individuals who are receiving opioid pharmacotherapy; therefore, we reviewed the pharmacological data between methadone/buprenorphine and HIV/HCV therapies with an emphasis on the clinical implications of these interactions and methods to manage possible interactions. Naltrexone, due to its primary metabolic pathway of carbonyl reduction and lack of data regarding interactions with HIV or HCV therapeutics, is not reviewed here.

Methods

We reviewed relevant English language articles identified through Medline, Google Scholar, and Web of Science since our last review in 2006 through December 2012. Articles were retrieved using the following keywords: HIV, AIDS, HIV therapy, antiretroviral therapy, HAART, drug interactions, pharmacokinetics, methadone, buprenorphine, as well as all currently FDA approved HIV and HCV medications and select compounds that have advanced to Phase III are included where data is available. Where appropriate, references from key papers were reviewed as well as were abstracts from selected national and international meetings 2006 to 2012.

Overview of Drug Disposition

Cytochrome P450 (CYP), through metabolism, and P-glycoprotein (P-gp), through active cellular transport, perform key roles in drug disposition [20]. To understand the

pharmacological interactions under review, a basic understanding of these systems is necessary.

The metabolism of a medication occurs in two phases. In Phase I, medications are altered chemically, customarily by one or more CYPs. In Phase I, inhibition and induction are of greatest clinical significance. Specifically, if medication A impedes the CYP enzyme(s) responsible for the metabolism of medication B, medication A is said to inhibit that CYP(s) and is an inhibitor of medication B's metabolism (e.g., ritonavir inhibiting CYP3A4 and increasing atazanavir plasma levels). Conversely, medication A could stimulate the synthesis of additional CYP enzyme(s) there by accelerating the metabolism of medication B. Medication A is then said to be an inducer of the metabolism of mediation B (e.g., rifampin at inducing 3A4 and lowering atazanavir plasma levels). Phase II metabolism sees a medication undergo coupling (e.g., conjugation) with another moiety to typically yield an inactive metabolite. Inhibition and induction of Phase II enzymes can occur; however, this is a less common documented mechanism of drug interactions.

Many membrane transporters are now known; however, P-gp remains the most studied active membrane transporter to-date and impacts medication disposition, including certain classes of antiviral therapies. Methadone and buprenorphine are not significant substrates of P-gp; however, norbuprenorphine, an active metabolite of buprenorphine, is a substrate of P-gp [21–23]. HIV therapeutics which influence P-gp could thereby impact the disposition of norbuprenorphine and may thereby impact its therapeutic effect [21]. P-gp has been described as a significant determinant of norbuprenorphine brain exposure and antinocicpetion [21]. Efflux of norbuprenorphine via P-gp may be important to prevent respiratory sedation caused by norbuprenorphine [21,24–26]. One recent study has shown that buprenorphine, due to its higher binding affinity and prolonged receptor occupancy, has a protective effect on the respiratory depressive effect of norbuprenorphine [26]. Medications that impact norbuprenorphine access to the mu opioid receptor could therefore potentially impact the degree of respiratory depression experienced.

Although incompletely understood, gender impacts the metabolism of various medications. Women, for example, have a higher AUC of buprenorphine than men, possibly due to differences in body composition, as well as potential differences in CYP 3A4 [27].

Overview of Metabolism of Methadone

Methadone is an orally administered, rapidly absorbed, full mu-opioid agonist used for the treatment of opioid dependence [28]. A chiral drug, methadone is administered as a racemic of R (d) and S (l) enantiomers with R-methadone having the greater potency at the mu-opioid receptor [29]. This greater mu-opioid activity of R-methadone was first demonstrated in animal models [29,30] as was the inactivity of methadone's primary metabolite, 2-ethylidine-1,5dimethyl-3,3-diphenylpyrrolidine (EDDP), and 2-ethyl-5-methyl-3, 3-diphenylpyrroline (EMDP) [31]. These findings are supported by *in vitro* ligand binding assays [30,32–34]. S-methadone is a more potent inhibitor of the human ether-a-go-go-related gene (hERG) K^+ gated channels that are important for QTc prolongation [35,36].

Methadone undergoes N-demethylation to inactive metabolites by a variety of cytochromes (CYP). In vitro CYPs, primarily 2B6, and 3A4, but also 2C19, 2D6, and 2C8 are involved in the metabolism of methadone with various studies assigning different degrees of activity to each CYP [37–48]. Metabolism at CYP 2B6 (S>R), 2D6 (S>R) and 2C19 (R>S) are stereoselective [39,41,42] and this may help illuminate the variable R/S methadone ratios reported in the interactions that follow. *In vivo* studies that phenotyped for CYP3A activity demonstrated an association between the measured CYP3A activity and methadone or metabolite concentrations [49–51]. The *in vivo* role for CYP2B6 has been demonstrated with genotyping for poor metabolizing (PM) alleles 6*6 and 6*11, which are associated with significantly higher S-methadone concentrations [52–54]. In addition, the CYP2B6 PMs required lower doses of methadone [55–57]. Higher S-methadone concentrations, via inhibition of (hERG) K^+ gated channels, could also result in QTc prolongation and *torsades de pointes* and may help explain a post mortem analysis linking the 2B6*6 allele to methadone-associated deaths [36,58,59]. Although potentially of clinical importance, a commercial test for this allele is not currently available. Comparison of PM and extensive metabolizers (EM) of 2B6 revealed that 2B6*5 was overrepresented in subjects with lower methadone levels suggesting increased 2B6 activity [54]. Comparison of CYP2C9 and 2C19 EMs and PMs did not reveal involvement of these enzymes, however, the numbers for PMs were relatively small [53]. Comparison of CYP2D6 EMs and PMs also did not reveal significant involvement in CYP2D6 ultra-metabolizers; however, increased metabolism was noted [51,60]. These studies suggest that CYPs that had *in vitro* methadone metabolizing activity, but did not appear quantitatively important, may contribute *in vivo* if they are induced. This may explain why *in vivo* methadone metabolism is induced by ritonavir and nelfinavir when CYP3A activity is significantly inhibited by these protease inhibitors [61,62], as both induce CYPs 1A2, 2B6 and 2C9 [63].

Plasma concentrations of methadone follow a bi-exponential curve: the transition of medication from blood to tissue corresponds to the rapid α-phase, while the slower elimination corresponds to the β-phase [64]. Inactive metabolites and some unmetabolized methadone are excreted in the bile and urine [64]. Although not normally thought of as an inhibitor, a recent *in vivo* study suggests that methadone is associated with inhibition of CYP 2D6 and UDP-glucuronosyl transferase (UGT) 2B4 and 2B7 [65]. The clinical significance of this inhibition is currently unknown. Methadone is both a substrate and a mechanism-based inhibitor of CYP 19 (aromatase), which normally converts testosterone to estradiol [66].

Substantial inter-individual variation exists in methadone's metabolism as evidence by a half-life range of 5 to 130 hours. Based on an average half-life of 22 hours, steady state is achieved after roughly 5 days [20,67]. Changes in plasma concentrations of methadone, however, do not necessarily predict the pharmacodynamic response. A similar change in plasma concentrations may produce withdrawal symptoms in one patient and none in another. Such unpredictability is multi-factorial and may be the result of varying protein displacement, stereospecific binding, metabolism and transporters (e.g., P-gp or genetic expression of CYP isoenzymes) [42,68]. The clinical consequences of this variability is that

patients require ongoing observation once a new medication is started for possible alterations in the effect of methadone as the predicted effects may or may not occur.

Overview of Metabolism of Buprenorphine

Buprenorphine is extensively metabolized through the *N*-dealkylation of its *N*-cyclopropylmethyl group to norbuprenorphine and both are glucuronidated [69]. The N-demethylation was first shown to be carried out by CYP3A4 [70,71]. The involvement of CYP2C8 was subsequently established [72,73]. Hydroxylation of the ring and alkoxy side chain are also performed by CYP 3A4 and 2C8 [73,74]. While these hydroxyl-metabolites are responsive to inducers and inhibitors of metabolism [75], they do not appear to be of quantitative importance to the clearance of buprenorphine [73,74]. The glucuronidation of buprenorphine is primarily performed by UGT 1A1 and 2B7 with contributions from 1A3 and 2B17; that of norbuprenorphine is performed by 1A1 and 1A3 [76,77]. Buprenorphine and metabolites are mainly excreted into the bile; here they may undergo enterohepatic circulation [69]. About 10% of the daily dose of buprenorphine is excreted in the urine, with high concentrations of the norbuprenorphine glucuronide, lower concentrations of buprenorphine glucuronide and norbuprenorphine and very low concentrations of buprenorphine [78]. *In vitro* data suggest that buprenorphine and norbuprenorphine may inhibit CYP2D6 and 3A4; however, they are not predicted to cause significant interactions at therapeutic concentrations [79,80].

In animal models, an intravenous dose of norbuprenorphine had only 1/72nd the effect of buprenorphine in the rat tail-flick test; equimolar norbuprenorphine was slightly more potent after intraventricular injection [81]. In mice, intravenous norbuprenorphine was 1/3rd as potent as buprenorphine in the writhing suppression test, a measure of peripheral activity [82]. A recent study found both norbuprenorphine and buprenorphine-3-glucuronide (B3G) were about 1/5th as potent as a 1/3rd lower dose of buprenorphine in the mouse tail-flick model a measure of central activity; norbuprenorphine-3-glucuronide (N3G) had much less activity [83]. Buprenorphine and norbuprenorphine displacement of ligands from opioid receptors were first compared using expressed rat mu, rat delta, human kappa and human nociception receptors. Norbuprenorphine was equipotent for mu, but approximately one-tenth as potent with delta and kappa with all IC_{50}s in the (sub)nanomolar range. The IC_{50} for nociception ligand displacement was in the micromolar range for both. The IC_{50} for downstream ^{35}S-GTP subunit binding was 20-, 180- and 40-fold lower for buprenorphine with MOP mu-, kappa and nociception-receptors; only norbuprenorphine had activity at the delta receptor [82]. Displacement by buprenorphine, norbuprenorphine, B3G and N3G were subsequently compared using expressed human mu, delta, kappa and nociception receptors [83]. The relationship between buprenorphine and norbuprenorphine was generally similar to the previous findings [82]. B3G also caused displacement with a reported mu-receptor K_i close to buprenorphine's. The B3G displacement curve, however, was biphasic so the Cheng-Prusoff correction used was not appropriate [83]. The *in vitro* and *in vivo* differences between buprenorphine and metabolites suggest access to the CNS may play an important role in buprenorphine metabolite activity. The role that P-gp may play in CNS mediated effects, such as respiratory depression, was discussed earlier.

Interaction of Antiviral Medications with Drug Metabolizing Enzymes

Before considering specific interactions with opioids, it is necessary to first understand the metabolism of specific HIV therapies and their interactions with drug metabolizing enzymes. Because of similarities within groups, the following discussion is grouped according to the class of medication discussed.

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)

The antiviral effectiveness of this class is associated with the intracellular concentration of the activated form of the medication (e.g., zidovudine-TP). The measurement of intracellular concentrations is costly and most studies prefer to calculate the area under the curve (AUC) of the parent compound which correlates satisfactorily with intracellular concentrations [84]. Current data suggests that NRTIs are not inducers or inhibitors of hepatic cytochromes [85]. While zidovudine and abacavir are hepatically metabolized, didanosine, lamivudine, stavudine, tenofovir, and zalcitabine are primarily excreted renally [86–88]. Zidovudine and lamivudine are both substrates of P-gp [89] and abacavir and tenofovir are both inhibitors of P-gp, but to a lesser extent than the NNRTIs and PIs [90].

2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

The antiviral effectiveness of this class is associated with intracellular concentrations that are in equilibrium with their plasma concentration (e.g., C_{min}). Nevirapine induces metabolism of substrates at CYP 3A4 and 2B6, [91,92] is metabolized by these same CYPs and, to a far lesser degree, by 2D6 [93,94]. Similarly, efavirenz induces CYP 3A4 [95] and 2B6, [96] and *in vitro* undergoes metabolism by 3A4 and 2B6. [97] Although inhibition is rapid, induction is slower because it requires the synthesis of new enzymes and is influenced by the potency of the inducer and its half-life [98]. Unlike nevirapine, however, under *in vitro* conditions efavirenz inhibits 3A4 [99]. Although infrequently used, delavirdine requires mention because it is a significant inhibitor of 3A4 [100]. Etravirine is metabolized by CYP 3A4, 2C9 and 2C19 followed by glucuronidation. *In vitro*, etravirine is an inhibitor of CYP 2C9 and P-gp while *in vivo* it is an inducer of CYP 3A4 and an inhibitor of the CYP 2C subfamily, including CYP 2C9 [101–103]. Rilpivirine is a substrate and inducer of CYP 34A *in vitro*; however, based on *in vivo* data mild induction of CYP 3A was reported at 300 mg once daily and a clinically relevant affect on CYP 3A is not considered likely at the chosen doses of 25mg and 75mg once daily [104]. Lersivirine is predominantly cleared via glucuronidation by UGT 2B7 with oxidation by CYP 3A4 being of additional importance [105]. Lersivirine is a modest inducer of CYP 3A4 *in vivo* though it is considered unlikely to induce metabolism of other substrates cleared by CYP 3A4 at clinical doses [106].

The NNRTIs inhibit P-gp, in order of decreasing intensity as follows: delavirdine > efavirenz > nevirapine [90]. The clinical significance of this inhibition, which could affect methadone is doubtful since both efavirenz and nevirapine typically result in opioid withdrawal with methadone [107,108] suggesting P-gp inhibition was not clinically meaningful. Similarly, efavirenz decreases [109] and nevirapine has no effect [110] on norbuprenorphine concentrations, suggesting that P-gp inhibition by efavirenz and nevirapine is not clinically significant.

3. Protease Inhibitors (PI)

The effectiveness of this class correlates with their minimum plasma concentration (i.e., C_{min}) [111]. Most medications in this class are principally metabolized by CYP 3A4 [112]. Interestingly, they inhibit 3A4 to varying degrees and are listed, in order of decreasing intensity as follows: ritonavir > indinavir = nelfinavir = amprenavir > saquinavir [113]. Darunavir, like ritonavir, is a substrate and inhibitor of CYP 3A4; a clinical study of darunavir combined with ritonavir observed induction of CYP 2C9 and CYP 2C19 and inhibition of CYP 2D6; this was potentially attributable to ritonavir [114]. Tipranavir predominately induces CYP 3A4 [115]. Although CYP 3A4 is a common site of interactions in this class, many of these medications interact at other sites. Ritonavir is a good example as it both inhibits CYP 2D6 and induces CYP 1A2. These additional interactions further complicate predictions of drug-drug interactions [116].

The following PIs inhibit P-gp: nelfinavir, ritonavir, tipranavir, saquinavir, amprenavir, atazanavir, and lopinavir [90,117]. Each of these inhibit P-gp to a greater extent than efavirenz and nevirapine. Recent *in vitro* work suggests that darunavir may induce P-gp synthesis that could further influence drug disposition [118].

4. Integrase Inhibitors (INIs)

Although it is unlikely that raltegravir will influence the pharmacokinetics of other therapeutics given its unique metabolic pathway, drug–drug interactions are expected to occur with co-administration of medications that modulate the UGT1A1-mediated metabolism of raltegravir [119]. Atazanavir, for example, inhibits UTG1A1 and increases raltegravir plasma concentrations [120]. The major route of elvitegravir metabolism is CYP3A4/5, allowing for boosting with ritonavir or cobicistat, with UGT1A1/3 being a minor route of metabolism [121].

5. CCR5 Antagonists

Maraviroc is an inhibitor of the chemokine receptor, CCR5, and is primarily metabolized through CYP3A4 and is a substrate of P-gp [122]. It does not inhibit the metabolism of midazolam, a 3A4 probe, when co-administered suggesting that it is not an inhibitor of 3A4 [123]. Rifampin, a known inducer of 3A4, however, reduces the AUC of maraviroc by 70% [124]. Potent inhibitors of 3A4, such as ritonavir, increase maraviroc plasma concentrations and half-dosing of maraviroc to 100 mg bid may be necessary [125].

6. Pharmacoenhancers

Both ritonavir and cobicistat function as pharmacoenhancers; that is, they are both potent inhibitors of drug metabolism thereby increasing plasma concentrations of other medications of interest. Ritonavir, an HIV protease inhibitor, is a potent inhibitor of CYP3A4 [126]. Cobicistat, a structural analogue of ritonavir, is a potent mechanism-based inhibitor of CYP3A4/5 without activity against HIV [127]. Cobicistat is a moderate inhibitor of CYP2D6 and recent data also suggest a lack of inductive effects of cobicistat on CYP2C19 and CYP2B6 [128]. Although cobicistat is currently only co-formulated with elvitegravir, emtricitabine and tenofovir, there are ongoing studies examining co-formulation with

atazanavir and darunavir. Most protease inhibitors are now dosed with a pharmacoenhancer, chiefly by ritonavir, as these boosted PIs have greater efficacy and, typically, simpler dosing than when non-boosted. As a result of their frequent use, these CYP3A4 inhibitors often complicate the metabolism of other medications.

Interaction of Antiviral Medications with Opioid Agonist Therapies

There are currently six FDA-approved classes of medications for the treatment of HIV with other classes under development, and one FDA-approved class of antiviral agents targeting HCV viral replication (i.e., HCV protease inhibitors). Interactions with opioid agonist therapies have been studied and documented in four ARV classes: NRTIs, NNRTIs, PIs, and INIs. In addition, the HCV protease inhibitors and pegylated interferon alfa 2a and 2b have been examined with opioid agonists.

Interactions between Methadone and Specific Antiretroviral Medications (Table 1)

1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Detailed pharmacokinetic studies of the interaction between methadone and zidovudine alone [129–131] or zidovudine in combination with lamivudine [132] have been performed in human subjects. Despite patient complaints of opioid withdrawal, zidovudine did not affect methadone concentrations; however, methadone increased zidovudine AUC by roughly 40%. The authors speculated that methadone impacted zidovudine glucuronidation and, to a lesser extent, decreased renal excretion of zidovudine. Although the clinical significance of this remains uncertain, healthcare providers should observe patients for zidovudine-associated effects (e.g., headache, and anemia), especially those that patients may mistake for opioid withdrawal (e.g., abdominal pain and irritability).

The fixed dose co-formulation of lamivudine/zidovudine (Combivir®) was assessed in 16 subjects and it did not appreciably alter the AUC of methadone [132]. Although not specifically examined, methadone is unlikely to impact lamivudine metabolism since 70% of lamivudine is excreted unchanged in the urine.

Both stavudine and didanosine have been examined with methadone; however, both compounds are minimally prescribed due to their propensity for adverse events. In summary, neither significantly altered methadone concentrations or resulted in opioid withdrawal [133]. Although methadone lowered stavudine concentrations, this reduction is not believed to be clinically relevant. While the buffered formulation of didanosine is contraindicated with methadone due to a significant reduction in didanosine concentrations (see Table 1 for details), the capsule lacks a significant interaction [134].

Unlike other NRTIs, abacavir is principally metabolized by alcohol dehydrogenase and glucuronidation [135,136]. No significant changes in pharmacokinetic parameters were reported and no dose adjustments are required when co-administered with methadone [137].

Tenofovir did not significantly impact the pharmacokinetics of methadone in 13 patients on methadone for a minimum of 2 weeks [138]. Because tenofovir is not a CYP substrate and is predominately excreted in the urine, it was speculated that methadone would have little impact upon tenofovir concentrations and tenofovir concentrations were therefore not obtained [139].

2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Several clinical reports have demonstrated that nevirapine can precipitate opioid withdrawal in methadone patients [140–144]. To investigate these clinical reports, 8 HIV infected methadone patients were formally studied upon the initiation of nevirapine based HIV therapy (NRTIs used included stavudine, didanosine, zidovudine, lamivudine and abacavir). Patients were dosed with 200 mg of nevirapine for the first two weeks of HIV therapy as recommended by guidelines, and pharmacokinetic assessments were repeated at day 14 before the dose was increased to 400 mg. Between days 8–10, 6 patients experienced opioid withdrawal and required a mean increase in methadone of 16% while methadone AUC decreased by 47% [108]. Stocker and colleagues provided similar pharmacokinetic data for the induction of methadone metabolism whether it was administered as the racemic mixture or R-enantiomer [145].

About the same time period, methadone patients started on efavirenz also began to report withdrawal symptoms [107,146,147]. To investigate these clinical reports, 11 HIV infected methadone patients were formally studied upon the initiation of efavirenz based HIV therapy (NRTIs used were not reported). Between days 8–10, 9 patients experienced opioid withdrawal and required a mean increase in methadone of 22% while methadone AUC decreased by 43% [107]. Recent work to elucidate the mechanism of this interaction pointed to efavirenz induction of hepatic CYP 2B6. This study also found that efavirenz induced hepatic CYP 3A4, gastrointestinal 3A4/5 and efflux transporters [46]. Not surprisingly, the development of opioid withdrawal can prompt methadone patients to resume heroin use and possibly discontinue HIV therapy [148]. Recognizing and addressing such interactions is a clear safety concern.

Delavirdine co-administration with methadone for 7 days resulted in a 19% increase in methadone AUC without clinical consequences, possibly due inhibition of CYP3A4. Methadone has a long half-life and it is unclear if prolonged co-administration of delavirdine and methadone would result in larger increases in AUC and the development of clinical symptoms; therefore, the co-administration of these medications should be undertaken judiciously and with close oversight [149]. A separate study demonstrated that methadone does not significantly effect delavirdine’s pharmacokinetics [150].

Etravirine was studied at a lower dose (100 mg BID) than the currently approved dosing (200 mg BID) in an effort to prevent the development of severe opioid withdrawal symptoms caused by the anticipated induction of CYP3A4. Surprisingly, the authors observed an 8% increase in the AUC of the pharmacologically active R-methadone isomer. At this modified etravirine dose, no methadone or etravirine dose adjustments were necessary [151].

Rilpivirine resulted in a 22% reduction in R-methadone AUC when studied in 13 HIV negative subjects receiving methadone maintenance. Although no withdrawal symptoms were seen in this small cohort, the authors caution that patients should be monitored for opioid withdrawal as some patients may require dose adjustments [152].

Lersivirine was studied in 13 HIV-negative subjects receiving methadone maintenance. No clinically relevant change in R/S-methadone exposure resulted from co-administration. No opioid withdrawal symptoms were observed when lersivirine was co-administered with methadone [153].

3. Protease Inhibitors (PIs)

Most PIs do not appear to have clinically meaningful effects upon methadone levels. Ritonavir [154], indinavir [45,155], nelfinavir [156], amprenavir [157], atazanavir [158], fosamprenavir [159], and the combination of saquinavir/ritonavir (400/400 mg b.i.d.) [160] and (1600 mg/100 mg) [161] have been studied and changes in dosing of methadone do not appear to be needed with any of these agents. A case report of nelfinavir resulting in opioid withdrawal, however, is an important example that the short duration of these studies and very select patient population does not rule out the possibility that opioid-related effects might develop over time or in other populations [162].

Lopinavir/ritonavir requires a more detailed examination due to varying reports in the literature. Clarke and colleagues enrolled 8 HIV/hepatitis C co-infected methadone patients who were starting lopinavir/ritonavir based HIV therapy (NRTIs used included stavudine, didanosine, zidovudine, and lamivudine). Despite a significant reduction in methadone AUC and C_{max} of 36% and 44%, respectively, none of the patients experienced opioid withdrawal during the study and during the six week follow-up period [163]. Stevens and colleagues prospectively followed 18 HIV-infected methadone patients upon initiation of lopinavir/ritonavir as part of HIV therapy and found that none of these individuals experienced opioid withdrawal [164]. McCance-Katz and colleagues, however, examined lopinavir/ritonavir and ritonavir alone in 15 HIV-negative methadone patients. Reductions in AUC and C_{max} were reported at 26% and 28%, respectively. Despite lower reductions than Clarke and colleagues, 4 patients (27%) experienced symptoms consistent with opioid withdrawal on the Objective Opioid Withdrawal Scale (OOWS). Interestingly, all 4 had sub-therapeutic methadone troughs (less than 200 μg/L). To delineate the etiology of the reduction in methadone levels, patients underwent a second examination with ritonavir alone at 100 mg twice daily (the dose used in the lopinavir study). No significant reductions in methadone AUC occurred with ritonavir alone leading the authors to conclude that lopinavir was responsible for the reductions and the symptoms of withdrawal reported in the lopinavir/ritonavir study [154]. Importantly, the side effects of lopinavir/ritonavir are similar to opioid withdrawal (e.g., abdominal cramping, diarrhea, nausea, and body aches) [165]. The two studies that did not reveal opioid withdrawal were populated with HIV infected subjects with prior experiences taking HIV therapy. It is possible that differences in the assessments of opioid withdrawal symptoms and/or differences in how they were perceived by subjects (e.g., differential attribution of symptoms to HIV therapy versus methadone) between the studies may have contributed to the differences in symptoms reported. Ongoing clinical

studies have supported the lack of withdrawal symptoms in methadone patients who receive lopinavir/ritonavir [166]. It is important to note, however, that in the McCance-Katz and colleagues study, the subjects that experienced withdrawal did have lower methadone troughs suggesting that their symptoms may indeed be due to opioid withdrawal. Clinicians must listen carefully to patients who report symptoms consistent with opioid withdrawal and strive to define the etiology and frequency, and work with the patient to appropriately manage them.

A formal drug-drug interaction study between tipranavir boosted with ritonavir and methadone has not been published. The package insert, however, reports that 500 mg of tipranavir boosted with 200 mg of ritonavir can result in a 50% decrease in methadone plasma concentrations and, as a result, methadone dose adjustments may be required [167]. Reductions of 20% or less are unlikely to result in clinically relevant interactions. It is important to note that this study occurred in opioid-naïve volunteers who were initially started on tipranavir with ritonavir until steady state and were then given a single 5 mg dose of methadone [168]. The generalizability of this study for methadone maintenance patients remains unclear and until more experience is obtained with methadone patients taking tipranavir, healthcare providers should closely monitor these patients for opioid withdrawal.

Darunavir and methadone were co-administered in 16 subjects where a reduction in C_{min}, C_{max}, and AUC were observed by 15%, 24%, and 16%, respectively. Although methadone doses were not increased in subjects, the authors suggest that these reductions could potentially lead to symptoms of opioid withdrawal and patients should be observed accordingly [169].

4. Integrase Inhibitors (INIs)

Raltegravir has been studied in methadone-maintained patients and had no significant effect on the pharmacokinetic parameters of methadone [170]. Raltegravir's absorption is diminished by an acidic stomach environment [171]. Despite prior reports showing that methadone's slowing of GI transit time could affect acid labile medications, as classically demonstrated with buffered didanosine [133], methadone did not have any significant effect on the pharmacokinetic parameters of raltegravir.

Elvitegravir boosted with cobicistat was studied in 11 methadone maintained subjects and no significant differences were found in the AUC, C_{max}, and C_{min} of both R- and S-methadone. Methadone did not have any significant effect on the pharmacokinetic parameters of elvitegravir boosted with cobicistat. No dosage adjustments are required when elvitegravir/cobicsistat is co-administered with methadone [128].

5. CCR5 Antagonists

Maraviroc has not been studied with methadone. Maraviroc is primarily metabolized by CYP3A4 and does not inhibit or induce 3A4 [123]. As a result, significant pharmacological interactions were felt to be improbable and to-date there have not been any case reports in the literature to suggested otherwise. No dosage adjustments are suggested when maraviroc is co-administered with methadone.

Interactions between Buprenorphine and Specific Antiretroviral Medications

Buprenorphine, unlike the full agonist methadone, is a partial μ-opioid receptor agonist that appropriately credentialed physicians may prescibe for opioid dependence in primary care settings. This has allowed for the integration of buprenorphine within HIV clinical settings [15,172,173] and the need for a broader understanding of pharmacological interactions between buprenorphine and HIV medications.

1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Fewer NRTIs have been studied with buprenorphine. Didanosine, lamivudine and tenofovir have no significant effect on the pharmacokinetics and pharmacodynamics of buprenorphine, and buprenorphine does not effect their pharmacokinetics [174]. Buprenorphine does not significantly alter the pharmacokinetics and pharmacodynamics of zidovudine, and none of the patients reported symptoms consistent with opioid withdrawal [131]. Of note, buprenorphine plasma concentrations were not obtained in the zidovudine study.

2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Nevirapine did not have a significant effect on the pharmacokinetics and pharmacodynamics of buprenorphine [110]. Efavirenz, however, significantly reduced the AUC of buprenorphine by approximately 50% without precipitating symptoms of opioid withdrawal [109]. The higher binding affinity of buprenorphine at the mu-opioid receptor may be the etiology of this pharmacodynamic response. Methadone, which has a lower binding affinity, saw a similar reduction in AUC with efavirenz, but 80% of patients had precipitated withdrawal (see earlier discussion above). Buprenorphine may have remained bound to opioid receptors despite a reduction in buprenorphine plasma levels due to its higher binding affinity, thereby preventing opioid withdrawal [175]. This data from the efavirenz interaction is encouraging and suggests buprenorphine may be more ‘forgiving’ with reductions in plasma concentrations and have fewer occurrences of opioid withdrawal than methadone. In contrast, delavirdine, increased buprenorphine AUC by 400%. This increased exposure to buprenorphine was not, however, associated with any adverse effects; however, the authors caution on the co-administration of buprenorphine and delavirdine as effects beyond the 7 days of the study are unknown [109].

3. Protease Inhibitors (PIs)

Buprenorphine appears to have a potential interaction with atazanavir that can lead to oversedation in some individuals [176,177]. Buprenorphine can be used with atazanavir, however slower upward titration of dosing is advised with monitoring. In a recent study, however, a lack of oversedation was seen in a prospective cohort of HIV-infected opioid dependent patients on buprenorphine [178]. This study, however, occurred after the previous publications cautioning providers on the rate of build-up and it is unclear if the lack of oversedation was the result of a slower upward titration or a lack of effect [179]. The package insert for atazanavir states that buprenorphine should not be co-administered with

unboosted atazanavir due to concerns that buprenorphine may decrease atazanavir plasma concentrations [180]. The only published examination of buprenorphine and unboosted atazanavir, however, did not reveal a statistically significant difference between atazanavir concentrations before and after the addition of buprenorphine [177].

The protease inhibitors darunavir/ritonavir [169,181], fos-amprenavir/ritonavir [181], lopinavir/ritonavir [182,183], and nelfinavir [183] have been studied with buprenorphine and found to be without clinically meaningful pharmacokinetic and pharmacodynamic interactions. Ritonavir by itself caused a 1.57-fold increase in buprenorphine AUC, but this was without any significant pharmacodynamic changes [183]. Buprenorphine reduced tipranavir AUC by 19% when compared to historical controls; however, the clinical significance of this is unknown. Tipranavir significantly altered the disposition of norbuprenorphine without producing a pharmacodynamic effect [184]. This reduction in norbuprenorphine concentrations is suggestive of a combined inhibition of the UGT 1A family and CYP 3A4 that spares UGT 2B7 leading to a shunting of buprenorphine away from the production of norbuprenorphine and towards buprenorphine-3-glucuronide [185].

4. Integrase Inhibitors (INIs)

The interaction of buprenorphine with raltegravir was studied in 12 individuals who had been on a stable buprenorphine dose for at least 3 weeks. Patients were administered raltegravir 400 mg twice daily for a minimum of 4 days and then underwent pharmacokinetic and pharmacodynamic assessment. Raltegravir did not significantly change the AUC, C_{min} and C_{max} of buprenorphine or norbuprenorphine, and buprenorphine did not significantly impact upon the pharmacokinetic parameters of raltegravir. No dosage modifications are required for buprenorphine or raltegravir when co-administered [186].

Elvitegravir with cobicistat was studied in 17 individuals on chronic buprenorphine/naloxone treatment. The AUCs of buprenorphine and norbuprenorphine increased by 35% and 42%, respectively. This increase in AUC was not clinically meaningful and patients did not have evidence of opioid withdrawal or excess [128].

5. CCR5 Antagonists

Maraviroc has not been studied with buprenorphine. Maraviroc is primarily metabolized by CYP3A4 and does not inhibit or induce 3A4 [123]. As a result, significant pharmacological interactions were felt to be improbable as buprenorphine is also primarily metabolized by 3A4 and to-date there has not been any case reports in the literature to suggested otherwise. No dosage adjustments are suggested when maraviroc is co-administered with buprenorphine.

Interactions between Hepatitis C Antivirals and Methadone or Buprenorphine (Table 2)

Until recently, the treatment for HCV consisted of the combination of ribavirin and pegylated interferon alpha. Due to reports of the symptoms of opioid withdrawal during interferon therapy, three studies were conducted to examine a possible interaction between

methadone and interferon. These studies revealed that both pegylated interferon alpha 2a and 2b had an increase in methadone plasma AUC by 10 to 15%. The symptoms that were misinterpreted by the patient as opioid withdrawal were attributed to the interferon itself [187–189]. A pharmacokinetic interaction study between buprenorphine and interferon alpha has not been conducted. Ribavirin co-administered with either methadone or buprenorphine has not undergone formal pharmacokinetic and pharmacodynamic examination.

Telaprevir and boceprevir are PIs used for the treatment of HCV. Telaprevir is strongly inhibited by ritonavir likely through inhibition at CYP3A4 [190]. Boceprevir is predominantly metabolized by aldo-keto reductases to an inactive, ketone-reduced metabolite; however, boceprevir is a strong reversible inhibitor of CYP3A4 and may interact with substances that use CYP3A4 as their predominant metabolic pathway [191].

Methadone interactions with telaprevir dosed at 750 mg every 8 hours were studied in 16 subjects. After 7 days of co-administration a 29% reduction in R-methadone AUC was observed; however, no opioid withdrawal was observed in this group. The authors speculated that the lack of withdrawal was evidence that the fraction of unbound R-methadone did not change significantly [192]. A similarly designed study in 13 patients over 7 days was conducted to examine interactions with buprenorphine. No significant differences in the AUC of buprenorphine or norbuprenorphine were observed, and opioid withdrawal did not occur. Based on this data, telaprevir can be safely dosed in patients on methadone or buprenorphine [193].

Boceprevir is a potent inhibitor of CYP3A4/5. Boceprevir dosed 800 mg every 8 hours was studied in 10 methadone patients and demonstrated a reduction in the AUC of both R- and S-methadone of 15% and 22%, respectively, without clinical evidence of opioid withdrawal. The slight reduction in methadone cannot be explained based on the inhibition of 3A4/5 by boceprevir. Boceprevir was studied in 11 buprenorphine/naloxone patients and demonstrated an increase in the AUC of buprenorphine and naloxone of 19% and 33%, respectively, which was not statistically significant. Norbuprenorphine was significantly reduced by 65% with the addition of boceprevir [194]. The increase in buprenorphine and the reduction in norbuprenorphine are reminiscent of the tipranavir/ritonavir inhibition of 3A4 and the shunting of buprenorphine metabolism away from norbuprenorphine. [185]. Based on this data, boceprevir can be safely dosed in patients on methadone or buprenorphine.

Sofosbuvir (GS-7977) is an oral uridine nucleotide analog polymerase inhibitor of HCV viral replication. Fourteen subjects on methadone were studied with sofosbuvir 400 mg once daily for 7 days [195]. There were no significant changes in the AUC of both S-methadone and R-methadone. Methadone did not significantly impact the AUC of sofosbuvir and the two can be safely co-administered based on this data. No published data examines this investigational compound with buprenorphine.

TMC435 is an inhibitor of the NS3/4A proteases of HCV. Twelve subjects (11 of which had all time points available) on methadone maintenance were studied with TMC435 once daily for 7 days [196]. No significant differences in methadone plasma concentrations occurred.

Interestingly, a reduction in the AUC of TMC435 was noted compared to historical controls, but did not reach statistical significance. Given the small sample size of the study it is not known if additional subjects would have made the difference reach statistical significance. Methadone and TMC435 can be safely co-administered based on this data. No published data examines this investigational compound with buprenorphine.

HIV/HCV co-infection is a particular challenge for potential drug-drug interactions in patients on methadone or buprenorphine. Studies are lacking on multi-drug interactions such as with HIV and HCV medications in patients on methadone or buprenorphine maintenance therapy. As therapies continue to grow for the treatment of both infections, ongoing pharmacological studies will be important to ascertain possible interactions among multiple medications and the risk of serious adverse events such as QTc prolongation (discussed below).

Clinical Management of Opioid Withdrawal or Excess

Understanding the clinical significance of drug-drug interactions between HIV/HCV medications and pharmacological therapies for opioid dependence, healthcare providers should be able to identify and provide assistance to individuals in opioid withdrawal or excess (Table 3 summarizes symptoms). Several open access questionnaires are available to assist healthcare providers in quantifying symptoms, including the Clinical Opioid Withdrawal Scale (COWS) and the Subjective Opioid Withdrawal Scale (SOWS) [197].

It is first of all important to understand that some changes in plasma concentrations do not incur any clinical symptoms. Indeed, dose changes of methadone up to 20% may result in no clinical symptoms and this may help explain why, though an interaction was predicted to occur, this buffer resulted in a lack of clinical symptoms. Typically changes in plasma concentrations of 25% or more are required for clinical symptoms.

As with all adverse reactions, however, healthcare providers must examine all possible etiologies before assuming causation is related to a change in opioids. Once other etiologies are excluded, however, an adjustment in opioid dose may be required. Although this review has summarized existing data, it must be stressed that these studies have limitations. First, these studies have small numbers of patients and may not be generalizable to all populations. Second, these studies focus on single drug-drug interactions; however, the patient is frequently taking several medications that have not been studied when ingested simultaneously. This is particularly an issue for patients on methadone/buprenorphine given the high prevalence of psychiatric co-morbidity and possible interactions between psychotropic medications and methadone/buprenorphine [14,198]. Third, these studies typically exclude patients with many of the common abnormalities that HIV/HCV patients experience such as hepatic and renal impairments. Finally, healthcare providers must be attentive to patients who may experience an adverse event related to a change in opioid pharmacology that has yet to be described.

Most HIV/HCV care is provided outside of addiction treatment settings; therefore, coordination between the addiction treatment program and the HIV/HCV clinical team will be necessary to address opioid interactions that may occur. Prior to initiating a new

medication, the HIV/HCV clinical providers should be in contact with the addiction treatment program to alert the latter of a possible medication interaction and the kind of interaction to expect (e.g., withdrawal or excess) upon the initiation of a new antiviral medication. The timing of symptom development is variable and depends upon a wide assortment of factors including the strength of the medication's induction or inhibition properties. Inhibition of an enzymatic reaction is rapid; beginning once the inhibitor (e.g., ritonavir) is started. Symptoms resulting from inhibition (typically opioid excess), therefore, appear typically on the day of medication initiation. Fluconazole [199] is a classic example of inhibition and opioid excess in patients on methadone. In addition to the classic symptoms of respiratory depression, inhibitors will impact other dose dependent effects that may be clinically significant, such as prolongation of QTc.

Induction, however, requires the synthesis of new enzymes and will therefore take several days (depending on the strength of the inducer) [20]. The precise timing and quantity of dose adjustments is unknown; however, the following recommendations are consistent with expert opinion. First, the inter-individual pharmacology of opioids, especially methadone, is quite diverse and the need for adjustments and the quantity of those adjustments may vary widely between patients. Second, when interactions are likely to occur (e.g., efavirenz), patients should be assessed clinically on a daily basis. The utilization of an aforementioned scale to assess for withdrawal (e.g., SOWS or COWS) by nursing staff may be an efficient way to accomplish this. Alternatively, healthcare providers can examine patients for signs of withdrawal that are summarized in Table 3). Third, in addition to alerting clinical staff, the patient should be educated on the possibility that the medications may interact and cause withdrawal. Fourth, if symptoms of withdrawal develop and a dose adjustment is required, methadone can be safely increased by 10 mg every 3 days until symptoms subside. Obviously symptoms of opioid withdrawal in a methadone or buprenorphine patient may result in strong urges to relapse to drug use. Healthcare providers and patients must be alert to this possibility and may need to consider alternative medications in certain patients. Fifth, if the medication causing induction of opioid metabolism is removed, enzymatic activity will slowly return to baseline levels and this will require a gradual tapering of the methadone/buprenorphine dose back to pre-treatment levels over several weeks.

Expert Commentary

Opioid dependence, HIV and HCV are volatile, intertwined epidemics that impact tens of millions of people globally [1–6]. Efforts are underway throughout the world to increase access to and retention on treatment for opioid dependence with methadone or buprenorphine. As a result, many patients find themselves on HIV and/or HCV treatment while also on methadone or buprenorphine.

New data has emerged on the metabolism of methadone and buprenorphine that is of clinical importance. CYP2B6 is one of several CYPs involved in the metabolism of methadone with different alleles (2B6*6 and 6*11) being associated with poor methadone metabolism and higher levels of S-methadone that could increase QTc prolongation and risk of arrhythmia. There is substantial inter-individual variation in the metabolism of methadone and

discoveries such as these allelic variations and others yet to be discovered may help elucidate the etiology of these differences.

Respiratory depression remains a serious concern where opioid treatment is utilized.

Norbuprenorphine clearly causes respiratory depression when administered alone; however, buprenorphine blocks norbuprenorphine's access to the receptor and thereby prevents respiratory depression. Although buprenorphine is not a significant substrate of P-gp, norbuprenorphine is a substrate and medications that impact norbuprenorphine efflux via P-gp may impact on its efficacy. In a setting where norbuprenorphine levels increased while buprenorphine levels declined, patients would be theoretically at greater risk of respiratory depression.

It is critical to recall that the studies described here have small numbers of patients and may not be generalizable to all populations, especially as many of the studies excluded patients with HIV and/or HCV and patients taking multiple medications for various medical problems. As a result, the medical provider must weigh the known evidence in the literature among one population (e.g., the effect of lopinavir/ritonavir among HIV negative patients on methadone) and extrapolate that to a different population (e.g., HIV-infected patients on lopinavir/ritonavir, tenofovir, emtricitabine, methadone, anti-hypertensives, etc.). It is of paramount importance for the medical provider to remain alert to the possibility of a drug-drug interaction even when current existing data may not support such an interaction. A case report of nelfinavir leading to the dramatic increase of methadone in a patient serves as a lesson that all drug-drug interactions cannot be predicted in all patients [162]. The medical provider should therefore listen, observe, communicate, and consider the possibility of drug interactions whenever the clinical signs are suggestive that an interaction is occurring.

The Five-Year View

Ongoing pharmacological studies between therapies for opioid dependence and HIV/HCV remain critical and should continue over the next five years. HIV clinical pharmacology continues to see the development of new classes of medications (e.g., maturation and attachment inhibitors). The development of new compounds to treat HCV infection is a fast growing area of clinical pharmacology with multiple new agents in different classes (e.g., NS5a, NS5b, nucleotide, polymerase, and protease inhibitors) under investigation. As these medications move forward in development, they will all need to be examined for possible pharmacological interactions with methadone and buprenorphine. As zidovudine instructed us years ago, interactions can occur in the most unlikely circumstances, and formal study is required for each compound [129]. Such studies remain critical as impacting a patient's methadone or buprenorphine plasma concentration runs the risk of nonadherence to antiviral treatments and ultimately clinical failure [140].

Although opioid withdrawal may be paramount in the mind of the patient, other clinical parameters may be of equal or greater concern and should be included in formal studies. QTc prolongation, for example, is a growing concern with overlapping medications that increase methadone plasma levels and prolong QTc [200]. The combination of medications with overlapping QTc toxicities requires careful attention. This is a particular problem in

HIV/HCV patients given the high psychiatric co-morbidity in this population and the multiple psychiatric medications that impact QTc [198]. Because S-methadone is an inhibitor hERG K^+ gated channels, future clinical pharmacology studies must include both QTc specific data as well as determinations of both R- and S-methadone plasma concentrations [35,36].

Beyond single drug interaction studies, however, multiple drug-drug interaction studies are required in the age of poly-pharmacy. Many HIV/HCV infected patients on methadone, for example, will take many different medications and a clearer understanding of the clinical pharmacology in the setting of multiple ingested medications on the disposition of methadone and buprenorphine is needed. Although these clinical studies are useful to clinicians and patients, they are often not undertaken. It will remain critical for NIH and other research institutions to continue to support drug-drug interaction studies and fill this needed gap in clinical pharmacology over the next five years and beyond.

Key Issues

- Methadone increases zidovudine plasma concentrations and, as a result, increases zidovudine side effects. Dose reduction of zidovudine may be required.
- Efavirenz and nevirapine frequently result in opioid withdrawal among patients maintained on methadone and dose increases in methadone are frequently required.
- Atazanavir co-administration in patients on buprenorphine may result in sedation in some patients.
- The medical provider should listen, observe, communicate, and consider the possibility of drug interactions whenever the clinical signs are suggestive that an interaction occurred.
- Typically changes in plasma concentrations of 25% or more are required for clinical symptoms.

Conclusions

This review has summarized the known pharmacological interactions between the opioid treatment medications methadone and buprenorphine, with HIV and HCV medications. Healthcare providers must familiarize themselves with the common interactions and be ready to manage possible interactions in this population. Current studies have many limitations and additional pharmacological studies that examine different racial/ethnic groups, patients on multiple medications, and patients with common co-morbidities that could impact drug disposition (e.g., hepatic impairment). A basic understanding of this clinical pharmacology will improve the delivery of clinical services to HIV/HCV infected patients with opioid dependence, thereby helping them to succeed in treatment.

References

Reference annotations

* Of interest

** Of considerable interest

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Table 1

Anti-retroviral interactions with methadone and buprenorphine

Medication	Effect on Methadone (METH)	Effect On Buprenorphine (BUP)	Effect on Anti-Viral (unless BUP or METH specified, both are assumed)	Comments	Ref.
NRTI					
Abacavir (ABC)[a]	↑ clearance of methadone concentration	No PK study	↓ C_{max} by METH	No dose change required for METH	137
Didanosine (ddI)	No PK effect	No PK effect	METH ↓ ddI AUC by 57% for buffered tablet, partially corrected by EC capsule No BUP effect on ddI	No dose adjustments necessary when EC capsule used with METH patients.	133, 134, 174
Emtricitabine (FTC)	No PK study	No PK study	No PK study		N/A
Lamivudine (3TC)	No PK effect	No PK effect	No PK data on effect by METH No effect of BUP on 3TC	AZT/3TC co-formulation studied only with METH. No dose adjustments necessary	132, 174
Stavudine (d4T)	No PK effect	No PK study	↓ d4T AUC_{12h} by 23% and C_{max} by 44%	No dose adjustments necessary	133
Tenofovir (TDF)	No PK effect	No PK effect	No PK data on effect by METH No significant effect on TDF by BUP	No dose adjustments necessary	138, 174
Zalcitabine (ddC)	No PK study	No PK study	No PK study		N/A
Zidovudine (AZT)	No PK effect	No PK data, but patients did not experience opioid withdrawal.	↑ AZT AUC by 40% by METH. No PK effect by BUP	Watch for AZT related toxicity (symptoms and laboratory). Dose reductions of AZT may be required.	129–132
NNRTI					
Delavirdine (DLV)	↑ AUC by 19%; ↑C_{max} by 10%	↑ AUC by 400%, without clinical effect	No PK effect	No dose adjustments necessary; however, should be used with caution as long-term effects (>7 days) unknown.	109, 149, 150,
Efavirenz (EFV)	↓ AUC by 57%	↓ AUC by 50%, without clinical effect	No PK data on effect by METH No PK effect by BUP	Opioid withdrawal form METH common. METH dose increase likely necessary.	107, 109, 146, 147
Etravirine (ETV)	No PK effect (only 100 BID of etravirine studied)	No PK study	No PK effect	No dose adjustments necessary	151
Lersivirine	No PK effect	No PK study	No PK study	No dose adjustments necessary	153
Nevirapine (NVP)	↓ AUC by 41 to 52% (depending on the study)	No PK effect	No PK data on effect by METH No PK effect by BUP	Opioid withdrawal form METH common. METH dose increase likely necessary.	108, 110 140–145
Rilpivirine (TMC278)	↓ AUC of R-METH by 16% %	No PK study	No PK study	Monitoring for symptoms of METH withdrawal is recommended.	152

Medication	Effect on Methadone (METH)	Effect On Buprenorphine (BUP)	Effect on Anti-Viral (unless BUP or METH specified, both are assumed)	Comments	Ref.
	↓ AUC of S-METH by 16%% AUC of S-METH by 16%%				
PI					
Amprenavir (AMP)	↓ AUC of R-METH by 13% and S-METH by 25%	No PK study	↓ AUC by 30% ↓ Cmax by 27% ↓ Cmin by 25%	METH dose adjustments unnecessary. Clinical significance of AUC reduction in AMP unknown.	157
Atazanavir (ATV)	No PK effect	↑ AUC by 167%	No PK effect with METH. Package insert states BUP may lower ATV plasma concentrations	Some individuals may experience oversedation. Slower titration upwards of BUP may be advisable in some patients. ATV should be boosted with ritonavir when co-administered with BUP	158, 177
Darunavir (DRV)	↓ R-METH AUC by 16% ↓ S-METH AUC by 36%	↑ nor BUP AUC by 46%	No PK effect	No ARV dose change when combined with METH or BUP. Four subjects out of 16 in METH study reported mild opioid withdrawal, but no dose adjustments were needed.	169, 181
Fosamprenavir (fAMP)	↓ AUC R-METH by 18% ↓ AUC S-METH by 43%	No PK effect	No PK effect	No dose adjustments necessary	159, 181
Indinavir (IND)	No PK effect	No PK study	↓ C_{max} between 16% and 28% and ↑ C_{min} between 50% and 100%	Differences do not appear to be clinically significant	45, 155
Lopinavir/ritonavir (LPV/r)	↓ AUC by 26–36%	No PK effect	No PK study for METH No PK effect with BUP	↓ AUC of METH caused by LPV. One study reported opioid withdrawal symptoms in 27% of patients. METH dose increase may be necessary in some patients.	154, 163–166, 182, 183
Nelfinavir	↓ AUC by 40%	No PK effect	↓ AUC of active M8 metabolite by 48% by METH	Despite ↓ METH AUC, clinical withdrawal is usually absent and *a priori* dosage adjustments are not needed. Decrease in AUC of M8 unlikely to be clinically significant.	156, 162, 183
Ritonavir (RTV)	↓ AUC by 37% in one study and no effect in another (see text)	↑ AUC by 157%	No PK effect	No dosage adjustments necessary	154, 183
Saquinavir (SQV)	↓ AUC by 20–32%	No PK study	No PK study	Saquinavir boosted with ritonavir studied. Despite ↓ METH AUC, clinical withdrawal was not reported.	160, 161
Tipranavir (TPV)	↓ METH plasma concentration by 50%[a]	↓ Nor-BUP AUC by 80%	No ARV dose change when combined with METH. TPV/r AUC and C_{max} decreased 19% and 25% respectively compared to historical controls in the presence of BUP	METH dose may need to be increased. Clinical significance in the changes in TPV PK parameters in the presence of BUP are unknown. No BUP adjustment necessary.	167, 184, 185
Integrase					

Medication	Effect on Methadone (METH)	Effect On Buprenorphine (BUP)	Effect on Anti-Viral (unless BUP or METH specified, both are assumed)	Comments	Ref.
Elvitegravir (with cobicistat)	No PK effect	↑ AUC by 35%	No PK effect	No clinical effect requiring dosage adjustments. Cobicistat dosed at 150 mg daily.	128
Raltegravir	No PK effect	No PK effect	No PK effect	No clinical effect requiring dosage adjustments	170, 186
CCR5 Antagonists					
Maraviroc	No PK study	No PK study	No PK study		N/A

[a]Decrease in methadone not specified as AUC or C_{max}.

NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitor; AUC, area under curve; METH, methadone; BUP, buprenorphine; norBUP, norbuprenorphine. (Updated with permission from Bruce et al. [18]).

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Table 2

Anti-HCV medication interactions with methadone and buprenorphine

Medication	Effect on methadone	Effect On BUP	Anti-Viral	Comment	Ref
Indirectly Acting Anti-Virals					
Pegylated Interferon 2a and 2b	↑ METH AUC by 10 to 15%	No PK study	No PK study	No dose change required for METH, though many patients request dose increases due to the flu-like symptoms caused by interferon.	187–189
Ribavirin (RBV)	No PK study	No PK study	No PK study	Multiple studies have been conducted with patients on methadone and buprenorphine on HCV treatment and patients have reportedly had no difference in adverse events.	N/A
Directly Acting Anti-Virals					
Boceprevir	↓ R-METH AUC by 15% ↓ S-METH AUC by 22%	↑ BUP AUC by 19%	No PK study	No opioid withdrawal reported and dose adjustments unlikely.	194
Sofosbuvir	No PK effect	No PK study	No PK effect		195
Telaprevir	↓ R-METH AUC by 29% ↓ S-METH AUC by 36%	No PK effect	No PK study	No opioid withdrawal reported and dose adjustments unlikely.	192, 193
TMC435	No PK effect	No PK study	Non statistical reduction in AUC	No dosage adjustments in TMC435 with methadone predicted	196

Table 3

Symptoms of Opioid Withdrawal and Excess [208]

Opioid Withdrawal	**Subjective:** • Craving for opioids • Irritability • Myalgias • GI: nausea, vomiting and diarrhea • Muscle spasms • Flushing • Abdominal pain **Objective**: • Restlessness • Diaphoresis • Lacrimation • Rhinorrhea • Mydriasis (dilated pupils) • Yawning • Piloerection (goose flesh) • Tachycardia • Tremulousness
Opioid Excess	Miosis (pinpoint pupils) Sedation/Lethargy Bradycardia Respiratory depression (shallow and slower respirations) Hypothermia Stupor Coma