Interactions between Methadone and Medications Used to Treat HIV Infection:

A Review

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Abstract

Background: It is critical for providers caring for HIV-positive methadone recipients to have accurate information on pharmacologic interactions between methadone and antiretroviral therapy. If providers do not have these data, symptoms of narcotic withdrawal or excess due to medication interactions may be mismanaged, and antiretroviral regimens may be suboptimal in efficacy or associated with increased side effects and toxicities. This review was undertaken to clarify what is known about interactions between pharmacotherapies of opiate dependence and HIV-related medications, to suggest clinically useful approaches to these issues, and to outline areas which need further study.

Methods: A search for relevant published papers and abstracts presented at scientific meetings was conducted using electronic databases. These documents were obtained and reviewed, and additional publications referenced in them were also reviewed.

Results: Pharmacokinetic interactions between methadone and zidovudine, didanosine, stavudine, abacavir, nevirapine, efavirenz and nelfinavir have been documented. The mechanisms, clinical implications and management of these interactions are reviewed.

Conclusions: Interactions between methadone and some HIV-related medications are known to occur, yet their characteristics cannot reliably be predicted based on current understanding of metabolic enzyme induction and inhibition, or through in vitro studies. Only carefully designed and conducted pharmacologic studies involving human subjects can help define the nature of the interactions between methadone (and other pharmacotherapies for opiate dependence) and specific HIV-related medications. Clinicians must be aware of known interactions and be alert to the possibility that interactions which are still undocumented may be present among their patients.

Key Words: Methadone, antiretroviral therapy, interactions, HIV, medications, pharmacotherapies, pharmacodynamics.

Introduction

In the United States, injection drug use is the second most common risk behavior which results in acquired immunodeficiency syndrome (AIDS), and it remains a driving force in the epidemic. Treatment for substance abuse, particularly opiate abuse, is often a critical component of AIDS prevention and treatment. Methadone, an orally administered, long-acting opiate, is an effective and widely accepted pharmacotherapy used in the treatment of heroin dependence (1). According to a survey in 1998 by the American Methadone Treatment Association, of the 179,000 people receiving methadone therapy in the United States, approximately 25–30% are infected with HIV.

Most of the latter group are eligible for treatment with antiretroviral agents and other HIV therapies.

Injection drug users, who have been underrepresented in clinical trials of HIV therapies (2), may be at greater risk for toxicity from antiretroviral medications because of the high prevalence in this population of hepatic, renal, neurologic, pancreatic, and hematologic disease (3). Drug users’ care is further complicated by the fact that so little is known about potentially important interactions between HIV therapies and illicit substances. It is becoming apparent, however, that significant interactions exist between certain HIV therapies and pharmacotherapies used to treat substance abuse. Only recently has attention been directed to the study of potential interactions between HIV-related medications and substances of abuse and their treatments, which can influence the success of either or both treatment.

It is critical for providers caring for HIV-positive methadone recipients to have accurate information on the interactions between methadone and antiretroviral therapy. There are now fourteen antiretroviral medications approved for treat-
ing HIV infection, and others are expected soon. Knowledge of the interactions between these medications and the pharmacotherapies for opiate dependence taken by patients may influence doctors' initial and subsequent choice of antiretroviral regimens. In addition, the interpretation of patients' signs and symptoms, particularly those of narcotic withdrawal ("that HIV pill is eating my meth") or excess ("my meth is feeling too strong on these HIV pills") may be influenced by knowledge of such interactions. Without thoughtful responses by clinicians to such symptoms, patients may implement their own potentially harmful interventions, such as using additional heroin, or avoiding or discontinuing the medication(s) believed to be at fault — thereby risking ineffective treatment and development of antiretroviral resistance (4).

The purpose of this review, therefore, is to examine and discuss what is known about the interactions between methadone and the many medications used to treat HIV infection. Earlier reviews did not provide information on the different classes of antiretroviral medications (5), or were published before the results of several important recent studies had been completed (6). Although this discussion will focus on interactions between methadone and antiretroviral medications, consideration will also be given to interactions with other HIV-related medicines.

Methods

A search for relevant published papers and abstracts presented at scientific meetings was conducted using the National Library of Medicine's Medline and AIDSLine databases; these documents were obtained and reviewed. Additional references listed in the literature obtained were also reviewed. In addition, responses from the manufacturers of antiretroviral medications to requests for data on the interactions of their products with methadone were received and incorporated into this review.

Overview of Hepatic Metabolism

Metabolism of drugs by the liver may be viewed as occurring in two phases. In Phase I, compounds are chemically altered (e.g., oxidized, reduced, hydrolyzed) by one of the cytochrome P450 enzymes. Fourteen distinct families of cytochrome P450 enzymes have been identified (CYP 1, CYP 2, CYP 3, etc.), each with subfamilies (CYP 3A, CYP 3B, etc.) and specific gene products within subfamilies (CYP 3A3, CYP 3A4, etc.). A medication may affect the Phase I metabolism of another medication in several ways. The first drug may diminish the Phase I metabolism of the second drug by competitively inhibiting the CYP 450 enzyme(s) responsible for the second drug's metabolism. Alternatively, the first drug might accelerate Phase I metabolism of the second drug by inducing additional synthesis of the CYP 450 isoform(s) involved in the second drug's metabolism. In Phase II of hepatic metabolism, a compound is altered by being coupled (e.g., conjugated) with another moiety to yield an inactive metabolite.

Methadone Metabolism

Methadone is dosed orally, once daily. With a half-life of 24–36 hours, it takes approximately 3 days at the same dose to achieve steady state levels. Methadone undergoes hepatic biotransformation by the cytochrome P450 system. Two cytochrome P450 isoenzymes, CYP 3A4 and CYP 2D6, appear to be primarily involved in this process, with CYP 2C possibly playing a minor role as well (7, 8). N-demethylation of methadone results in the formation of metabolites, which are excreted in the urine and bile (9). Some unmetabolized methadone is also excreted in the urine, with a ratio of excreted metabolites to excreted unmetabolized methadone of between 5:1 and 1:1 (9). It is likely that substantial interindividual variation (up to 20-fold) in the amount of CYP 3A4 expressed in the liver accounts, at least in part, for uneven correlations between methadone dose and methadone plasma concentration in different persons. Interactions between methadone and inducers of CYP 3A4 such as rifampin (10) result in more rapid metabolism of methadone (11), whereas CYP 3A4 competitive inhibitors like diazepam (12) or fluvoxamine (13) may potentiate methadone's effect. In addition to being a substrate of the cytochrome P450 system, methadone may also act as a partial inhibitor of the CYP 3A4 and CYP 2D6 isoenzymes (13).

Metabolism of Antiretroviral Medications

Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to be inducers or inhibitors of the cytochrome P450 system (14). Zidovudine (AZT) is glucuronidated, and didanosine (ddI), zalcitabine (ddC), lamivudine (3TC), and abacavir (ABC) primarily undergo renal excretion. Animal studies suggest that renal excretion and cleavage to thymidine are principal routes by which stavudine (d4T) is cleared.
By way of contrast, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) share metabolic pathways with methadone, leading to the possibility that important interactions might occur between methadone and these medications. NNRTIs have complex interactions with the cytochrome P450 system. Nevirapine is an inducer of CYP 3A which then causes diminished levels of medications metabolized by this cytochrome P450 subfamily (15). Nevirapine is also metabolized by CYP 3A4 and CYP 2B6 and, to a far lesser degree, by CYP 2D6. Delavirdine is a moderately potent CYP 3A inhibitor and may therefore raise concentrations of other medications metabolized by this isoenzyme. It is metabolized by CYP 3A4 and CYP 2D6 (14). Efavirenz both induces and inhibits CYP 3A4, and is metabolized in vitro by CYP 3A4 and CYP 2B6 (16).

Protease inhibitors (PIs) are metabolized primarily by the 3A4 isoform of the cytochrome P450 system (17). In addition, the PIs inhibit CYP 3A4: ritonavir most potently; indinavir, nelfinavir and amprenavir all somewhat less intensely; and saquinavir the least of all (17, 18). Each PI has a unique profile of induction and inhibition of, and metabolism by, specific cytochrome P450 isoforms.

Interactions between Methadone and Anti-retroviral Medications

1. NRTIs

Researchers have performed detailed pharmacokinetic studies of the interaction between AZT and methadone in human subjects (19, 20). Methadone administration increased the area under the AZT concentration-time curve (AUC) by approximately 40%. Methadone appeared to exert this effect by means of inhibition of AZT glucuronidation and, to a lesser extent, by decreasing renal clearance of AZT. Although AZT side effects are dose related, the clinical significance of the increase in AZT AUC in patients receiving methadone is unclear. Formal study of AZT-related toxicities in this population has not been performed and would be difficult. Persons receiving both methadone and AZT may experience symptoms that are characteristic of opiate withdrawal, such as headache, muscle aches, fatigue, and irritability, and may attribute these symptoms to reduced methadone levels (“this AZT is eating my meth”). It is noteworthy, however, that the AZT and methadone pharmacokinetic interaction studies determined that AZT has no effect on plasma methadone levels. It is, therefore, more likely that such symptoms are side effects of AZT — perhaps occurring more frequently and with greater severity as a result of the patient’s increased AZT exposure — rather than indications of AZT-induced methadone withdrawal.

Results from studies with d4T and ddi were reported at the Sixth Conference on Retroviruses and Opportunistic Infections in 1999 (21). Fifteen patients receiving long-term methadone treatment alternatively received ddI (200-mg tablet BID), and d4T (40 mg BID). Pharmacokinetic parameters were compared with a matched control group of 10 patients who were not on methadone but who received the same NRTIs. Neither ddI nor d4T affected methadone levels. However, methadone appeared to alter the disposition of both NRTIs. Methadone decreased the AUC for d4T by 18% and the maximum concentration (Cmax) by 39%. These values are unlikely to be of clinical significance. However, methadone decreased the AUC for ddI by 60% and the Cmax by 64%. These results suggest that an increase in ddI dosage may be indicated in patients who are also treated with methadone. The likely mechanism is decreased absorption of the tablet formulation resulting from methadone-induced delay in gastric motility. Further study is needed to determine if this effect is confined to the tablet formulation or if similar effects will be seen with other ddI preparations. This issue is particularly important because of evidence that ddI can be dosed once daily, making it an excellent candidate for inclusion in a regimen of directly observed antiretroviral therapy in methadone programs (22).

Pharmacokinetic data regarding the interaction between methadone and abacavir, which like zidovudine is metabolized by glucuronidation, were presented recently by Sellers and colleagues (23). Nineteen patients entering methadone treatment were given a single dose of abacavir (600 mg) on day 1, begun on methadone and brought to a “steady state” dose on days 2–14, and then co-administered abacavir and methadone on days 15–28. Pharmacokinetic sampling was performed on days 1 and 15 (for abacavir) and on days 14 and 28 (for methadone). Seven patients did not complete the study. The authors report a statistically significant increase (23%) in the rate of clearance of methadone from day 14 to day 28, but no changes in the time to peak concentration, half-life (t1/2) or renal clearance of methadone. In addition, they observed a significant decrease (34%) in the peak concentration and increase (67%) in the time to peak concentration of abacavir from day 1 to 15, but no changes in the
overall clearance, renal clearance, or $t_{1/2}$ of abacavir. The clinical relevance of these findings is unclear. While the delay in time to peak concentration of abacavir could plausibly be due to the inhibiting effect of methadone on gastric motility, it is not clear whether the changes observed were in fact due to methadone-abacavir interactions or to other factors, such as other medications participants may have been taking. Confirmation of these findings with data regarding patient symptomatology is needed before clinically grounded conclusions can be drawn from these data.

A formal study of a single dose of lamivudine (150 mg) combined with zidovudine (300 mg) demonstrated no effect on methadone levels (24).

2. NNRTIs

A recent case series (25) lends further support to substantial anecdotal evidence that nevirapine appears to precipitate symptoms of narcotic withdrawal in methadone-maintained patients. Seven patients receiving nevirapine experienced methadone withdrawal, which was corrected by either discontinuing nevirapine or increasing the methadone dose. Three of these episodes were documented by low trough methadone levels. A methadone-nevirapine interaction was also suggested by data presented by Staszewski et al. (22) from a study of once-daily antiretroviral therapy among drug users in Germany. Among patients maintained on methadone who started nevirapine, an average 45% increase in methadone dose was required to counter the associated withdrawal symptoms.

The results of investigations presented recently by Clarke and colleagues (26) provide pharmacokinetic data to support the clinical observations detailed above. Ten dose-stabilized methadone maintenance patients were started on antiretroviral therapy with nevirapine and two nucleosides. From baseline to approximately three weeks following nevirapine initiation, the mean methadone AUC decreased by 46%.

A recently presented and similarly retrospective case series offers evidence suggesting that, as with nevirapine, initiation of an efavirenz-containing antiretroviral regimen also necessitated increased methadone doses in most patients (27). In this study, nine methadone-maintained patients were followed after initiation of antiretroviral therapy. Seven of the nine patients were taking efavirenz-containing regimens, and six of these (87%) had a resumption of heroin use that resulted in a methadone dose increase, presumably in response to efavirenz-induced withdrawal symptoms. Such findings underscore the clinical urgency of recognizing interactions of this and other medications with methadone.

Further evidence of an efavirenz-methadone interaction derives from the pharmacokinetic data presented by Clarke and colleagues (26). Fifteen dose-stabilized methadone maintenance patients were started on antiretroviral therapy with efavirenz and two nucleosides. From baseline to three weeks following efavirenz initiation, mean methadone peak plasma concentration and AUC decreased by 48% and 57%, respectively. Of the 25 patients begun on nevirapine or efavirenz-containing regimens presented by Clarke et al., 17 (68%) complained of narcotic withdrawal symptoms, necessitating a mean increase in methadone dose of 21%.

To date, no data have been reported regarding interactions between methadone and delavirdine. One might predict, based on delavirdine’s inhibition of CYP 3A4, that if delavirdine were to affect methadone it might potentiate, rather than attenuate, its effectiveness.

Methadone and Protease Inhibitors

In vitro data support the possibility that PIs might influence methadone metabolism. Using a hepatic microsomal preparation derived from healthy human volunteers, researchers demonstrated that methadone N-demethylation was inhibited by ritonavir, indinavir, and saquinavir. Ritonavir had the greatest effect, followed by indinavir and then saquinavir. These in vitro findings suggest that PIs might retard methadone metabolism, and thus increase methadone levels, in persons taking these medications together (28).

Ritonavir was the first PI investigated and reported in human interaction studies with methadone. In a manufacturer-sponsored study using volunteers who were not addicted to opiates, a dose of 20 mg of methadone was administered on day one (29). After a 14-day “methadone washout” period, ritonavir was administered twice daily on days 15 to 28. On day 25, a single dose of only 5 mg of methadone was administered. The extremely low second dose of methadone was chosen because the nonaddicted volunteers had difficulty tolerating the initial 20 mg dose. Researchers studied the effect of ritonavir on methadone levels by comparing “dose-adjusted” methadone levels after the first (20 mg) and second (5 mg) methadone doses. The authors calculated a 36% decrease in the methadone AUC and a 38% decrease in peak methadone concentration in volunteers on ritonavir, an unexpected result, and given the flaws of the study design, one which is uninterpretable and
initiated and continued for 10 days, at which time a 50-mg dose of meperidine was again administered, and meperidine and ritonavir pharmacokinetics reassessed. Ritonavir administration was associated with a 67% decrease in the meperidine AUC, apparently caused by ritonavir-induced increases in meperidine metabolism. Ritonavir levels were not affected by meperidine administration. These data contrast with the warning in the ritonavir package insert that, because of its CYP 3A4 inhibition, ritonavir might boost meperidine levels and that the two drugs should therefore not be co-administered. Such data further emphasize the need for specifically designed studies to investigate the potential interactions between opiates and HIV-related medications. In this instance, increases in opiates used for pain medication are likely to be required for patients receiving ritonavir.

The interactions between methadone and the medications discussed in the preceding sections are summarized in the Table.

**Clinical Comments**

Several points deserve emphasis. It is now known that interactions occur between methadone and some HIV-related medications, yet their characteristics cannot reliably be predicted based on current understanding of enzyme induction and/or inhibition, or through in vitro studies. Carefully designed studies using human subjects are urgently needed. Until more data are available, clinicians are left to rely on their best judgment when selecting regimens and when clinical evidence of possible interactions arises in the course of patient care. As always, much is gained from listening to the patient. If a methadone-maintained patient recently started on HIV-related medication, particularly an NNRTI, describes withdrawal symptoms, and no other reason for such symptoms is evident, an empiric trial of raising the methadone dose may be an appropriate response. Methadone dose increases should be in 10-mg increments. If marked withdrawal is present and attributable to a medication interaction in a previously stable methadone-maintained patient, an incremental increase of 20 mg may be considered. To avoid overdosing, however, methadone should not be increased more frequently than every two to three days. Alternatively, use of a different antiretroviral agent might be warranted. Obtaining a trough methadone level to establish whether withdrawal symptoms are indeed due to increased methadone metabolism may be useful in selected cases, particularly if continuation of an HIV therapeutic regimen is deemed necessary. If a patient on AZT and methadone is experiencing side effects and possible withdrawal symptoms, reduction in AZT dose may be appropriate before the methadone dose is altered. If drowsiness or other symptoms of methadone excess are reported, reduction in methadone dose might be considered, following documentation with a trough methadone level.

Further research is needed to elucidate the clinical significance of the changes in methadone levels observed in the types of pharmacokinetic studies described above. For example, narcotic withdrawal symptoms did not accompany the 40% reduction in methadone level among patients receiving nelfinavir; yet frequent symptoms were reported by patients with decreases of similar magnitude in plasma methadone levels caused by efavirenz. This difference in findings might be explained if these medications had differential influences on the percent of methadone that is protein bound (30). Thus, it is possible that one might have to measure free methadone levels, not the combined free and protein-bound levels measured in most assays, to understand such differences. However, this has not yet been studied. For now, investigators of interactions between opioid pharmacotherapies and antiretroviral medications must perform standardized assessments of narcotic withdrawal symptoms in their subjects to define the clinical significance of the changes in blood levels they report.

The delay in the appearance of symptoms due to medication interactions can be highly variable. Inhibition of cytochrome P450 enzymes can occur as soon as an inhibiting medication is started, with associated symptoms appearing shortly thereafter. Induction and increased production of P450 isozymes follows a more prolonged period, typically ranging from 10 to 21 days. Such dynamics notwithstanding, it is not uncommon for a patient who has been on methadone and a stable antiretroviral regimen for a month or longer to report symptoms of methadone lack or excess. When other reasons for such symptoms cannot be discerned (e.g., thyroid dysfunction, new onset of cocaine use, etc.), an empiric change in the methadone dose may be indicated, with careful follow-up to see if this helps. Clinicians must not be reluctant to attempt such interventions in the absence of definitive data regarding the interactions between the medication in question and methadone. In addition to the direct therapeutic value of such interventions, evidence that the provider takes the patient's complaint seriously often builds valuable trust in the doctor-patient relationship.
### TABLE

*Interactions between HIV-Related Medications and Methadone — An Overview*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Formally Studied?</th>
<th>Effect on Methadone</th>
<th>Effect on HIV-Related Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (AZT)</td>
<td>Yes</td>
<td>None</td>
<td>↑ AZT AUC by 40%</td>
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<tr>
<td>Didanosine (ddI)</td>
<td>Yes</td>
<td>None</td>
<td>↓ ddI AUC by 60%</td>
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<td>Zalcitabine (ddC)</td>
<td>No</td>
<td>Not studied or reported</td>
<td>Not studied or reported</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Yes</td>
<td>None</td>
<td>↓ d4T AUC by 18%</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Yes</td>
<td>None</td>
<td>Not studied</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>Yes</td>
<td>↑ Methadone clearance</td>
<td>↑ Time to peak concentration</td>
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<td></td>
<td></td>
<td></td>
<td>↓ Peak concentration.</td>
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<tr>
<td>Nevirapine</td>
<td>Yes</td>
<td>Withdrawal symptoms</td>
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<td></td>
<td></td>
<td>↓ Methadone levels by 46%</td>
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<td>Need for ↑ methadone dose observed</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>↑ Methadone levels predicted</td>
<td>Not studied or reported</td>
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<td></td>
<td></td>
<td>↓ Methadone levels by 48%</td>
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<td></td>
<td></td>
<td>Heroin use relapse</td>
<td>Not studied or reported</td>
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<td></td>
<td></td>
<td>Need for ↑ methadone dose observed</td>
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<tr>
<td>Indinavir</td>
<td>No</td>
<td>Not reported</td>
<td>Not studied or reported</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Yes</td>
<td>↓ Methadone levels</td>
<td>No effect reported ↑</td>
</tr>
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<td></td>
<td></td>
<td>reported ↑</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>↓ Meperidine levels</td>
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</tr>
<tr>
<td>Nelfinavir</td>
<td>Yes</td>
<td>↓ Methadone levels, but no withdrawal symptoms observed</td>
<td>No</td>
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<tr>
<td>Saquinavir</td>
<td>Planned</td>
<td>Not studied or reported</td>
<td>Not studied or reported</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>In progress</td>
<td>Not yet available</td>
<td>Not yet available</td>
</tr>
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</table>

**Other medications used in the treatment of HIV-infected persons**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Formally Studied?</th>
<th>Effect on Methadone</th>
<th>Effect on HIV-Related Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>Yes</td>
<td>↓ Methadone levels, often sharply</td>
<td>None reported</td>
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<tr>
<td>Rifabutin</td>
<td>Yes</td>
<td>No change in methadone levels</td>
<td>None reported</td>
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<td></td>
<td></td>
<td>Mild narcotic withdrawal symptoms</td>
<td>None reported</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Yes</td>
<td>↑ Methadone levels by approximately 30%, clinical significance unknown</td>
<td>None reported</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Yes</td>
<td>↓ Methadone levels, often sharply</td>
<td>None reported</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Yes</td>
<td>↓ Methadone levels, often sharply</td>
<td>None reported</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Yes</td>
<td>↓ Methadone levels</td>
<td>None reported</td>
</tr>
</tbody>
</table>

NRTI = nucleoside reverse transcriptase inhibitors
NNRTI = non-nucleoside reverse transcriptase inhibitors
PI = protease inhibitor
AUC = area under curve
* See text for references.
† Study design limits clinical utility of results.

### Conclusions

Only carefully designed and conducted pharmacologic studies of human subjects can help define the nature of the interactions between methadone (and other pharmacotherapies for opiate dependence) and specific HIV-related medications. Clinicians must be informed of those interactions documented thus far, and remain alert to the possibility that other interactions, which are still undocumented, may be present among their patients. Where not already initiated, studies must be promptly undertaken to generate clinically useful data to help clinicians provide optimal care to HIV-infected persons receiving pharmacotherapies for opiate dependence.

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References


