HRSA CARE ACTION

MAY 2011

MEDICATION-ASSISTED ADDICTION TREATMENT

We can't just tell people to stop using drugs.... We need to offer them more. As soon as buprenorphine became available, we got certified so that people could get all their care and medications in one place.

—Lynn E. Taylor, HIV/hepatitis C coinfection clinic
Miriam Hospital, Rhode Island

The American Society of Addiction Medicine defines addiction as a primary, chronic disease of brain reward, motivation, memory, and related circuitry. The American Psychiatric Association classifies substance dependence and substance abuse as substance use disorders (SUDs).[1]

SUDs are caused by biological, genetic, psychological, and environmental factors. People may try drugs out of curiosity; from peer pressure; or to help them stay awake to work or study. Drugs and alcohol make people feel good; as a result, people sometimes use them to manage stress, anxiety, and depression (a phenomenon known as self-medication).

Researchers who study images of the human brain report that long-term drug use causes changes in its structure, function, and metabolism; some of the changes persist long after drug use has ceased.[2,3]

DID YOU KNOW?

Dopamine is a neurotransmitter (brain chemical) involved with learning, motivation, pleasure, and reward. Illicit drugs change both the amount and the sensitivity of dopamine receptors. When drug use increases dopamine levels, people feel euphoric; when dopamine levels decrease after drug use, people are driven to using more drugs to restore them.

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U.S. Department of Health and Human Services
Health Resources and Services Administration

DIRECTOR'S LETTER

Addressing co-occurring conditions such as HIV and substance use demands the kind of comprehensive, holistic approach that has long been a hallmark of the Ryan White HIV/AIDS Program. From peer advocates and stakeholders, community partners and outreach workers, we have learned not only to screen patients for substance abuse issues but also to assess whether they are ready for treatment and which therapy is best for them.

As best practices evolve and new treatment modalities become available, we continue to investigate and disseminate this information. Efforts encompass a recent Special Projects of National Significance Program on buprenorphine and the inclusion of outpatient substance abuse treatment services as a core medical service. In this issue of *HRSA CARE Action*, we describe what medication-assisted addiction therapies exist for your patients. We share this information in an effort to help you do what you do best—improve the health of people living with HIV/AIDS.

Deborah Parham Hopson
HRSA Associate Administrator for HIV/AIDS

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U.S. Department of Health and Human Services
Health Resources and Services Administration, HIV/AIDS Bureau
5600 Fishers Lane, Room 7–05
Rockville, MD 20857
Telephone: 301.443.1993

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Photographs
Cover: A Denver, CO HIV client receives an array of health care and support services from Ryan White HIV/AIDS Program providers, including primary care and substance abuse treatment.

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HIV AND CO-OCCURRING PSYCHIATRIC AND SUBSTANCE USE DISORDERS

HIV, mental illness, and SUDs overlap. More than one-third of all AIDS cases in the United States are linked directly—or indirectly—to drug use.[4] More than 60 percent of HIV-positive people experience at least one mental illness after diagnosis, and many struggle with co-occurring SUDs.[5-8]

High prevalence of co-occurring conditions among HIV-positive patients requires a coordinated system of care. The Ryan White HIV/AIDS Program community has long recognized the importance of comprehensive care for people living with HIV/AIDS (PLWHA), including primary along with mental health care and treatment for SUDs. Funds from Parts A-D of the Ryan White HIV/AIDS Program can be used for inpatient and outpatient substance abuse treatment, the latter being a core medical service. Part F supports the development of new delivery models for HIV care and treatment, including the Special Projects of National Significance Program (see http://hab.hrsa.gov/law/1002.htm).

MEDICATION-ASSISTED TREATMENT FOR OPIOID DEPENDENCE

Medication-assisted treatment (MAT) is a holistic, individualized approach to SUD treatment that combines pharmacotherapy with counseling and behavioral therapy. There are no U.S. Food and Drug Administration (FDA) approved pharmacologic treatments for cocaine or methamphetamine dependence. Although there are FDA- approved pharmacologic treatments for alcohol dependence (described later in this article), the primary focus of MAT in HIV research, care, and treatment has been on opioid dependence. Research has demonstrated that MAT reduces illicit opiate use, increases engagement in HIV care and treatment, improves adherence to antiretroviral therapy (ART), and enhances HIV treatment outcomes.[9-13] Methadone, buprenorphine, and vivitrol (an extended-release, injectable form of naltrexone) are FDA-approved for treatment of opioid dependence. "Buprenorphine is facilitating highly active antiretroviral therapy; it stabilizes patients, and we see their HIV RNA decline and their CD4 cell count rise," says Lynn E. Taylor, a physician at

the HIV/hepatitis C coinfection clinic at the Miriam Hospital in Providence, Rhode Island.

Methadone

Methadone is a synthetic opiate that has been used for more than 30 years to treat opioid dependence. Methadone is a full opioid agonist, which means that it binds to and activates opioid receptors. Low-dose methadone (30–60 mg/day) stops withdrawal symptoms. Higher doses (80–120 mg/day) also reduce drug cravings and discourage opiate use by preventing people from feeling the effects of opiates.

Methadone is taken orally, once daily. Methadone overdose is possible, particularly when it is combined with antidepressants, alcohol, or cocaine.

Methadone has significant drug–drug interactions with some antiretroviral agents (see insert, Table 1). It interacts with several psychiatric medications, including amitriptyline (Elavil), fluvoxamine (Luvox), desipramine (Norpramin), risperidone (Risperdal), quetiapine (Seroquel), carbamazepine (Tegretol), diazepam (Valium), and midazolam (Versed).[14] Methadone is available through opioid treatment programs regulated by the Substance Abuse and Mental Health Services Administration (SAMHSA) Center for Substance Abuse Treatment.

Buprenorphine

Buprenorphine is a semisynthetic opioid that prevents withdrawal symptoms. Because it is a partial opioid agonist, buprenorphine does not stimulate the same degree of activity at the brain's opioid receptors as full opioid agonists do (e.g., heroin, morphine, oxycontin, fentanyl, and methadone). As a result, people using buprenorphine may still experience euphoria and become physically dependent, but to a lesser extent than occurs with full agonists. Buprenorphine reduces drug cravings and prevents people from feeling the effects of opiates by first knocking them off the brain's opioid receptors and then tightly binding to and blocking the receptors.

In 2002, the FDA approved two forms of buprenorphine to treat opioid dependence: Subutex (a white, oval-shaped tablet that contains only buprenorphine) and Suboxone (an orange, hexagonal pill containing four parts buprenorphine to one part naloxone). Naloxone is an opioid antagonist; it binds to and blocks opioid receptors. Suboxone was created to discourage buprenorphine diversion, because buprenorphine can produce a "high" when people not dependent on opiods inject it. Naloxone causes withdrawal symptoms when injected but not when taken orally.

Buprenorphine reaches its full effect (known as the "ceiling effect") at 16 to 32 mg. Overdose is less likely with buprenorphine than with full opioid agonists, but it can occur when buprenorphine is used with large amounts of alcohol or benzodiazepines (i.e., medications such as diazepam, which are used to treat insomnia, anxiety, or seizures). Physicians need to evaluate coadministration of buprenorphine and benzodiazepines.

Buprenorphine has fewer drug–drug interactions with antiretroviral agents than does methadone (see Table 1). Interactions between buprenorphine and psychiatric medications have not been studied in humans, except for citalopram (Celexa) and sertraline (Zoloft); neither drug has clinically significant interactions with buprenorphine.[14]

Doctors can obtain a waiver allowing them to prescribe buprenorphine. The Drug Addiction Treatment Act of 2000 (DATA 2000) waiver allows primary care physicians to treat 30 patients (see "Online Resources," p. 7). After a year, approved prescribers can apply for an exemption to treat up to 100 patients. SAMHSA estimates that 19,000 physicians are certified to prescribe buprenorphine in the United States. DATA 2000 waivers allow SUD treatment to become integrated into HIV primary care.

MAT AND HIV PRIMARY CARE

MAT with buprenorphine is an important option for patients who want to stop opioid use without making daily visits to a methadone clinic or going to a drug treatment program. Some people may not be comfortable disclosing their HIV status during drug treatment, or they may require medical or mental health care that is not always

BUPRENORPHINE INITIATIVE

The Ryan White Special Projects of National Significance (SPNS) Program has funded the Buprenorphine Initiative to assess feasibility and effectiveness of integrating buprenorphine treatment for opioid abuse into HIV primary care settings at 10 demonstration sites. HRSA will be releasing a monograph of findings from the Buprenorphine Initiative in Summer 2011. To learn more about the project, visit: http://hab.hrsa.gov/special/bup_index.htm.

available through drug treatment programs. PLWHA who are lesbian, gay, bisexual, or transgender (LGBT) may prefer being treated for opiate dependence at their HIV clinic, because less than 10 percent of drug treatment facilities offer programming for LGBT clients, and counselors often lack formal training on LGBT-specific issues.[15,16]

When MAT is integrated into HIV primary care settings, "Buprenorphine can be picked up along with HIV and psychiatric medications, so the patient has control. This is important, because so many patients lose control of housing and other things in their lives," says Jeff Watts, the psychiatric medical director at Chicago's CORE Center. "Our patients are required to go to 12-step meetings or meetings in our clinic, where we have harm reduction meetings, individual therapy, and intensive 28- or 60-day outpatient treatment programs," he adds. "We had a group of people on MAT; it was a great advertisement. The group helped us to recruit more patients, and we were able to work on HIV adherence, nutrition, and other issues."

Research supports integrating MAT into HIV primary care. A recent study funded by the Health Resources and Services Administration compared outcomes among 93 HIV-positive, opioid-dependent patients, who were assigned either to clinic-based buprenorphine and individual counseling or to case management with referral to drug treatment. People in the buprenorphine group were significantly more likely to participate in treatment for opiate dependence (74 percent vs. 41 percent), less likely to use opioids and cocaine, and more likely to attend their HIV primary care visits than were people in the group referred to drug treatment.[17] In another study, 16 HIV-positive patients were given buprenorphine and counseling along with clinical care; their HIV RNA (viral load) and opioid use decreased significantly.[18]

INCORPORATING MAT: OFFICE-BASED CARE

Buprenorphine precipitates acute withdrawal if opioids are in the bloodstream; they should be discontinued 12-24 hours before buprenorphine initiation. Buprenorphine is then administered during early withdrawal, under medical supervision (a process known as induction). "We induce patients in the office as part of care for the whole person," says Taylor. Taylor's colleague, Cindy MacLeod, Miriam Hospital's AIDS and addictions–certified nursing clinical coordinator, plans inductions in advance. She says,

I take a complete history: their drug use, what kind of treatment they have tried—including past experience with buprenorphine—and what they are willing to do. I explain to patients that buprenorphine can cause sudden and intense withdrawal in people who have used recently. With short-acting opioids (like heroin and Vicodin), people can take their last dose at midnight and come in the next day, but they need to wait 2 or 3 days if they are using longer-acting opioids (like methadone and fentanyl) or if they have serious liver damage, because drugs take longer to leave their system.

MacLeod stays in close contact with patients beforehand. "I treat inductions like going into labor—'How far has your withdrawal progressed?'"

MacLeod uses a short, standardized questionnaire to assess patients before inductions and keeps an eye on people for 1 to 2 hours afterward. "Within 30 minutes, people go from being very anxious, sweating, and having diarrhea to feeling normal. Patients have said that they forget what feeling normal is like," she says. Watts adds, "It is amazing to see how bad patients look when they come in—and how a little pill can abate their symptoms but not knock them out like methadone or heroin."

Buprenorphine is not a magic bullet, however. "Addiction is not fixed just by picking up methadone or buprenorphine," says Watts. "People need counseling and 12-step programs. Some people may start using cocaine or methamphetamine. The natural course of addiction and mental illness is relapse; it is rare to lick it on the first go." MacLeod agrees. "Patients and providers think that this is going to be a quick fix—just take a pill—but recovery is work. Some people who are doing well on buprenorphine may need help with their cocaine and alcohol use. Our patients have been using drugs for decades, and polypharmacy is the signature of our population. Start looking at all of your patients and getting into conversations with them about drug use."

METHADONE OR BUPRENORPHINE?

It is important for patients to have the option of both buprenorphine and methadone. "Buprenorphine hasn't caught on yet [at the CORE Center]—but it has changed so many patient's lives that we wanted to offer it. We also have patients [who] aren't doing well with buprenorphine, so we refer them to the methadone clinic," says Watts.

Some of Taylor's patients prefer buprenorphine. "Some individuals cycle in and out of correctional facilities, unfortunately often due to addiction, and are scared of methadone withdrawal. Boom, they end up in jail and are immediately taken off of methadone. Withdrawal

"Some people prefer to receive treatment in the privacy of their doctor's office rather than running into people they used to do drugs with at a methadone clinic."

from buprenorphine is not as bad," she says. Taylor adds, "Some patients prefer to receive treatment in the privacy of their doctor's office rather than running into people they used to do drugs with at a methadone clinic."

According to Sharon Stancliff, medical director at the Harm Reduction Coalition in New York City, "There is no way to predict who will do better on methadone than buprenorphine—older predictors have not borne out (such as higher doses of methadone are better for people with heavier heroin habits)." Alexander Tellez, the administrative assistant at the Tarzana Treatment Center in California, adds, "There may be more than one way for someone to get sober … people need to see that there is not just one option for them."

MAT AND PREGNANCY

The benefits of MAT during pregnancy significantly outweigh the risks. In the United States, methadone is the standard of care for pregnant women, although buprenorphine is an acceptable alternative.[19] Infants born to women using methadone or buprenorphine are at risk for neonatal abstinence syndrome (NAS), but occurrence and severity of NAS are not associated with dosing of methadone or buprenorphine during pregnancy.[20]

MAT AND ALCOHOL

Alcohol use is common among people with HIV. A national sample of almost 3,000 PLWHA reported that 15 percent were heavy drinkers, a rate close to twice that of the general population.[21] Alcohol accelerates progression of hepatitis C, a common coinfection among people with HIV (especially current and former drug users). Alcohol also has an impact on HIV disease: Heavy drinking has been linked with poor adherence to antiretroviral therapy.[22,23] A recent study found that daily consumption of two or more drinks was associated with HIV disease progression, even with use of antiretroviral therapy.[24]

Fortunately, clinicians have two relatively new types of pharmacotherapy to offer patients who are alcohol dependent: naltrexone and vivitrol. "We have been using vivitrol for alcohol dependence…it's not for everyone, but it reduces cravings to drink," says Tom Martinez, the director of community programs and services at Tarzana Treatment Center.

Naltrexone

Naltrexone is an opioid antagonist. Opioid antagonists form a tighter bond with opioid receptors than do opioid agonists. Instead of activating opioid receptors, antagonists block them, so people do not feel the effects of opiates (and alcohol). Naltrexone's exact mechanism of action is not known; it may inhibit pleasure from alcohol intake, possibly by working through the brain's mesolimbic pathway (an area involved with craving for and enjoyment of alcohol).[25]

Vivitrol

Vivitrol is an extended-release, injectable naltrexone formulation that is given every 30 days. In 2006, FDA approved it (when used in conjunction with psychosocial support) for treatment of alcohol dependence for people who have already stopped drinking. Studies have found that naltrexone is more effective at reducing the risk of relapse to heavy drinking than for assisting with abstinence from alcohol.[26]

Vivitrol injections are increasingly being used to treat opioid dependence. In October 2010, FDA approved vivitrol for treatment of opiod dependence (after detoxification is completed). Because naltrexone is an opioid antagonist, vivitrol can cause or worsen opioid withdrawal symptoms, and it complicates management of acute and chronic pain. If opioid pain medication is necessary, patients must be closely and carefully monitored. High-dose vivitrol can cause serious liver damage; risks and benefits must be carefully considered in people with serious liver disease.

ADDITIONAL PHARMACOTHERAPY FOR ALCOHOL DEPENDENCE

Although they have not been studied in people with HIV, acamprosate calcium (Campral) and disulfiram (Antabuse) are FDA approved for treating alcohol dependence.

Acamprosate Calcium

Acamprosate calcium (Campral), when taken in combination with psychosocial support, was approved by the FDA in 2004 to treat alcohol dependence in people who have already stopped drinking. Placebo-controlled studies have reported that duration of abstinence was

TABLE 2. STATE AIDS DRUG ASSISTANCE PROGRAM COVERAGE: METHADONE and BUPRENORPHINE

STATE	COVERAGE		
	Methadone	Buprenorphine	Both
California	X		
Maryland		X	
Massachusetts			X
Missouri	X		
New Hampshire			X
New Jersey			X
New York	X		
Washington, DC		X	

Source: Britten Pund, Senior Associate, Care and Treatment, National Alliance of State and Territorial AIDS Directors.

significantly longer among people who received acamprosate than among people who received placebo.[27]

Although the mechanism of action is not fully understood, experts speculate that acamprosate may reduce alcohol craving by balancing neurotransmitters that are disrupted by alcohol dependence. Acamprosate tablets are taken 3 times daily, making adherence challenging, particularly for people taking additional medications with different dosing schedules.

Acamprosate may worsen depression, and it is not recommended for people with kidney disease. No information is available about drug–drug interactions between acamprosate and antiretroviral agents.

Disulfiram

Disulfiram blocks alcohol metabolism, thereby causing rapid accumulation of alcohol metabolites to levels up to 10 times above normal. It induces a severe, unpleasant reaction (including headache, nausea, vomiting, thirst, and vertigo) within moments of alcohol consumption. This reaction usually lasts from 30 to 60 minutes, but it may linger for as long as alcohol remains in the bloodstream. Disulfiram also increases and maintains dopamine levels in the brain.

Disulfiram is taken once daily, but it stays active in the body for up to 14 days after discontinuation. People with serious liver disease cannot use disulfiram. It cannot be used with liquid and capsule formulations of ritonavir—liquid lopinavir/ritonavir (Kaletra) and tipranivir (Aptivus)—because they contain alcohol. The oral solution of amprenavir should not be used with disulfiram, because it contains propylene glycol (which is also used in antifreeze). Products containing alcohol, such as perfume and cologne, should be used cautiously, because they may cause a reaction in people using disulfiram.

An ongoing clinical trial is evaluating potential drug–drug interactions between disulfiram and efavirenz, atazanavir, and ritonavir; no additional information is available on drug–drug interactions between disulfiram and other antiretroviral agents.

MAT AND CHRONIC PAIN

People are suffering from their pain as well as their addictions. We have to thoroughly evaluate the pain; try to find the cause; and tease apart pain, addiction, and suffering, instead of just writing a prescription.

— Lynn E. Taylor

Chronic pain is common among PLWHA. It is even more prevalent—and worse—in people with co-occurring psychiatric and substance use disorders.[28] Opiate and cocaine use complicate pain management because they lower pain tolerance.[29] No treatment guidelines exist for pain management in people with opioid dependence, and provider strategies vary widely.[30]

MAT also may increase pain sensitivity and opioid tolerance, so it complicates management of acute and chronic pain.[31,32] "Buprenorphine is not a great analgesic. It is not nearly as strong as fentanyl or oxycontin; patients need some other form of painkillers, usually nonsteroidal anti-inflammatory drugs," says Watts. Administering methadone or buprenorphine every 24 to 48 hours prevents withdrawal and reduces drug cravings but is not sufficient for pain control, because the analgesic effects of the drugs wear off after 4 to 8 hours.[33] One study of HIV-positive methadone patients (who were also being treated at a pain clinic) reported that increasing the dose of methadone significantly lowered pain without adverse events over a 12-month period, but the authors recommended further studies.[34]

Pain is often undertreated, particularly in people with a history of SUD. A recent study of prescription opiate use and diversion among street drug users in New York City reported that most of the drugs were used for pain management and to prevent withdrawal symptoms; less than 40 percent of users sold opioids that were prescribed to them.[35] "There's a difference between someone who is drug dependent versus an entrepreneur," says Sharon Stancliff, medical director at the Harm Reduction Coalition. She offers a few tips to clinicians to minimize drug diversion:

- Don't leave your prescription pad lying around.
- Prescribe generics, because brand-name medications have higher street value than generics.
- Because sealed bottles of medication have a higher street value, prescribe an odd number of pills so that they are repackaged.

ACCESS TO MAT

The increased need for AIDS Drug Assistance Programs and funding shortfalls have limited coverage of MAT to only a handful of States (Table 2).

Ryan White HIV/AIDS Program funding can be used to cover methadone (policies vary by area); yet industry-funded patient assistance programs (PAPs) do not exist for this medication. A PAP exists for Suboxone, which is made by Reckitt Benckiser; for information, visit www.patientassistance.com/profile/reckittbenckiser-314/. PAPs may also provide access to MAT for alcohol dependence. Information on access to vivtrol and acamprosate is available at www.patientassistance.com.

MOVING FORWARD

HIV care and treatment have evolved greatly over the past 25 years to include the introduction of effective and tolerable antiretroviral agents and sophisticated tests that indicate which drugs are likely to work for individual patients.

In the future, clinicians may also have more pharmacotherapeutic options to offer drug- and alcohol-dependent patients, as new strategies for and approaches to MAT are evaluated. For example, research on disulfiram, bupropion, and dexamphetamine shows promise for treating cocaine dependence.[36-40]

Many patients, however, continue to struggle with addiction and do not fully realize the benefits of pharmacologic advances. MAT allows HIV clinicians to treat patients *for* SUDs instead of treating patients *with* SUDs. "HIV and viral hepatitis are infectious consequences of addiction. We cannot provide care without working on addiction, too," says Taylor.

ONLINE RESOURCES

Buprenorphine
Making Opioid Treatment a Primary Concern:
www.careacttarget.org/library/SPNSBulletin/spnsbulletin.mar08.pdf

Substance Abuse Suboxone Treatment Program:
www.careacttarget.org/2010_rw_grantee_meeting/papers/F-15.pdf

Information on Drugs of Abuse
www.nida.nih.gov/drugpages/

State Drug Treatment Programs
http://findtreatment.samhsa.gov/

Treatment Improvement Protocols
www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=hssamhsatip

Buprenorphine Physician/Treatment Locator
http://buprenorphine.samhsa.gov/bwns_locator/

Physician Clinical Support System
www.pcssmentor.org/

Obtaining a Buprenorphine Waiver
http://buprenorphine.samhsa.gov/waiver_qualifications.html

National Alliance of Advocates for Buprenorphine Treatment
www.naabt.org/

State Methadone Programs
http://dpt2.samhsa.gov/treatment/directory.aspx

Screening Tools
www.hivguidelines.org/resource-materials/screening-tools/substance-use-screening-tools/

www.drugabuse.gov/nidamed/screening/

www.drugabuse.gov/nidamed/quickref/screening_qr.pdf

Acute Pain Management for People on MAT for Opioid Dependence
www.ncbi.nlm.nih.gov/pmc/articles PMC1892816/?tool=pubmed

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TABLE 1. DRUG–DRUG INTERACTIONS: ANTIRETROVIRAL AGENTS, METHADONE, AND BUPRENORPHINE

This chart provides information on drug-drug interactions between individual antiretroviral agents, methadone, and buprenorphine. Potential drug-drug interactions between methadone or buprenorphine and other medications should be evaluated prior to their co-administration.

Antiretroviral Agents	Methadone	Buprenorphine
Nucleoside Reverse Transcriptase Inhibitors		
Abacavir (Ziagen; Trizivir and Epzicom also contain abacavir.)	▸ Abacavir increases methadone clearance; monitor for withdrawal symptoms. ▸ Methadone has no effect on blood levels of abacavir.	Not studied
Didanosine (ddI) tablet or EC	▸ ddI has no effect on methadone. ▸ Methadone decreases the amount of ddI in the bloodstream; enteric-coated capsules are recommended for co-administration with methadone.	ddI has no effect on buprenorphine.
Emtricitabine (FTC; Truvada and Atripla also contain FTC.)	▸ Interaction is not anticipated and has not been studied.	Interaction is not anticipated and has not been studied.
Lamivudine (3TC, Epivir; Combivir, Trizivir and Epzicom also contain 3TC.)	▸ 3TC has no effect on methadone. ▸ Methadone's effect on 3TC has not been studied.	3TC has no effect on buprenorphine.
Stavudine (d4T; Zerit)	▸ d4T has no effect on methadone. ▸ Methadone lowers the amount of d4T in the bloodstream, but the effect is not likely to be clinically significant.	Not studied
Tenofovir (Viread; Truvada and Atripla also contain tenofovir.)	▸ Tenofovir has no effect on methadone. ▸ Methadone's effect on tenofovir has not been studied.	▸ Tenofovir has no effect on buprenorphine. ▸ Buprenorphine's effect on tenofovir has not been studied.
Zidovudine (AZT, Retrovir; Combivir and Trizivir also contain zidovudine.)	▸ AZT has no effect on methadone. ▸ Methadone can increase AZT level. Risk of AZT toxicity exists; patients should be monitored for signs and symptoms.	No significant interactions
Non-Nucleoside Reverse Transcriptase Inhibitors		
Delavirdine (Rescriptor)	▸ Delavirdine increases methadone levels in the bloodstream; methadone dose reduction may be necessary when co-administered with delavirdine. Use with caution. ▸ Methadone has no effect on delavirdine.	Not studied
Efavirenz (Sustiva; Atripla contains Sustiva)	▸ Efavirenz significantly lowers methadone levels; withdrawal may occur. Increase methadone dose. ▸ Methadone's effect on efavirenz has not been studied.	▸ Efavirenz lowers buprenorphine in bloodstream, but no withdrawal symptoms result; no dose adjustment is needed. ▸ Buprenorphine's effect on efavirenz has not been studied.
Etravirine (Intelence)	▸ Low-dose etravirine (100 mg twice daily) resulted in a slight increase in methadone in the bloodstream over 14 days; no dose adjustment is required. ▸ Methadone has no effect on etravirine.	Not studied in humans
Nevirapine (Viramune)	▸ Nevirapine significantly lowers the amount of methadone in the bloodstream, and withdrawal symptoms are common; increase methadone dose. ▸ Methadone has no effect on nevirapine.	▸ Nevirapine has no effect on buprenorphine. ▸ Buprenorphine has no effect on nevirapine.
Protease Inhibitors		
Atazanivir (Reyataz) Atazanavir/r*	▸ Atazanavir has no effect on methadone. ▸ Methadone has no effect on atazanavir levels.	▸ Ritonavir-boosted atazanavir significantly increases the amount of buprenorphine in the bloodstream, and oversedation may occur; titrate buprenorphine dose carefully. ▸ Buprenorphine has no effect on atazanavir.

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TABLE 1 (continued)

Antiretroviral Agents	Methadone	Buprenorphine
Protease Inhibitors (cont'd)		
Darunavir/r* (Prezista/r)	▸ Darunavir lowers the amount of methadone in the bloodstream; although dose adjustment may not be necessary in all patients, monitoring for withdrawal symptoms is recommended. ▸ Methadone has no effect on darunavir.	Darunavir does not change buprenorphine levels, but it increases norbuprenorphine; this does not cause symptoms, but clinical monitoring is recommended.
Fosamprenavir/r (Lexiva)	▸ Fosamprenavir lowers levels of S-methadone (associated with potentially life-threatening cardiac toxicity) in the bloodstream, but not R-methadone (which is involved with opioid effect). Although effects are not clinically significant, monitoring for withdrawal symptoms is recommended. ▸ Methadone has no effect on fosamprenavir.	Fosamprenavir/r and buprenorphine have not been studied in human beings.
Indinavir/r (Crixivan)	▸ Indinavir does not significantly change methadone level. ▸ Methadone does not cause clinically significant changes in amount of indinavir in the bloodstream.	Not studied
Lopinavir/r (Kaletra)	Kaletra lowers the amount of methadone in the bloodstream and withdrawal symptoms may occur; it may be necessary to increase methadone dose. Methadone has no significant effect on lopinavir.	▸ Kaletra does not significantly change buprenorphine level. ▸ Buprenorphine does not significantly change kaletra level.
Nelfinavir	▸ Nelfinavir lowers the amount of methadone in the bloodstream. Although there are usually no withdrawal symptoms, methadone dose may need to be increased. ▸ Methadone lowers levels of nelfinavir's active metabolite (M8) in the bloodstream; the effect is unlikely to be clinically significant.	Not studied
Ritonavir (Novir)	▸ Ritonavir may decrease the amount of methadone in the bloodstream. Monitoring for withdrawal and consideration of dose adjustment are recommended. ▸ Methadone has no effect on ritonavir.	Not studied
Saquinavir/r	▸ Saquinavir decreases the amount of methadone in the bloodstream; dose adjustment may be needed. Use with caution, due to additive effects on QT and/or PR interval prolongation that may occur with invirase/ritonavir. ▸ Effect of methadone on saquinavir has not been studied.	Not studied
Tipranavir/r (Aptivus)	▸ Tipranavir decreases the amount of methadone in the bloodstream by 50 percent; methadone dose may need adjustment. ▸ No data on methadone–tipranavir co-administration are available.	▸ Tipranavir has no effect on buprenorphine. ▸ Buprenorphine lowers tipranavir in the bloodstream by 19 to 25 percent; therapeutic drug monitoring may be needed.
Integrase Inhibitor		
Raltegravir (Isentress)	▸ Raltegravir has no effect on methadone. ▸ Methadone has no effect on raltegravir.	▸ Raltegravir interaction with buprenorphine has been studied, but no data have been published. ▸ Buprenorphine has no effect on raltegravir.
Entry/Fusion Inhibitors		
T-20 (Enfuvirtide, Fuzeon)	Interaction is not anticipated and has not been studied.	Interaction is not anticipated and has not been studied.
Mariviroc (Selzentry)	Not studied	Not studied

* "/r" indicates ritonavir boosted.

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