In patients with moderate renal impairment (creatinine clearance of 30-50 ml/min), begin with one 333mg tablet three times daily. Acamprosate is con-
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**Cost Comparison**

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*Average Wholesale Price or Maximum Allowable Cost

References available upon request

**Recreational and Street Drugs in Patients with HIV Infection: What You Need to Know**

Talia Puzantian, PharmD, BCPP

Recreational and street drug use and HIV infection are intimately related issues for many reasons. Substance use can have effects on immune function and effects on high-risk behaviors; it can impact medication adherence and can interact with antiretroviral medications. Unfortunately, very little clinical data exist to help identify these risks. Consequently, this area remains a black hole of scientific knowledge. A survey of 295 gay and bisexual men in the San Francisco area who had attended a circuit party in the previous year was conducted and published in 2001. All respondents reported use of club drugs, 80% reported using MDMA (ecstasy), 66% ketamine, 43% crystal meth, 29% GHB, 14% Viagra, and 12% poppers. 53% used 4 or more drugs. Of interest, 21% of HIV+ and 9% of HIV- individuals had unprotected anal sex with partners of unknown or opposite HIV serostatus. This survey suggested the use of club drugs is rampant and is strongly associated with high-risk sexual behavior.

Not only do substances which decrease social inhibitions promote high-risk sexual behaviors, but they may also have negative immunologic effects in HIV-infected individuals. Drug use has been shown to be an obstacle to antiretroviral medication adherence. Studies have also shown transient immune suppression in the context of drug use. One study showed CD4+/CD8+ cell ratio was decreased in healthy volunteers after MDMA (ecstasy) was administered. Reduced functional responsiveness of lymphocytes and increase in natural killer cell activity were observed. There were even greater reductions in CD4+ cells in those subjects ingesting alcohol in combination with ecstasy.

Perhaps the most challenging aspect of drug use in patients with HIV infection is the management of potential drug interactions with antiretroviral therapy. The following is a summary of such potential interactions.

**Alcohol**

Alcohol use is common in HIV-infected individuals (40-80%); rates of alcoholism are also increased in this population. Alcohol use is associated with disinhibition and increase in high-risk sexual behavior. Alcohol consumption is a risk factor for poor medication adherence. Heavy alcohol users are 4 times less likely to achieve positive virologic response; this is equal to the non-adherence risk of active heroin users. Consumption of greater than 50 g/d (4-5 drinks) is a risk factor for liver disease progression in patients with HIV-Hepatitis C co-infection. Potential drug interactions include:

- Additive/synergistic effects with other CNS depressants (benzodiazepines, opiates, etc.)
- Abacavir levels increased 60% in the presence of 0.1% ethanol
- Alcohol acts as P450 inducer with chronic use
- May decrease some drug effects (e.g., protease inhibitors [PIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs])
- Potentiates cocaine hepatotoxicity
- Increased risk of pancreatitis (didanosine, stavudine, Vinca alkaloids, paclitaxel and zalcitabine)
- Kalter & Antabuse: Kalter oral solution is 42% alcohol

**Marijuana**

Marijuana is metabolized primarily via hepatic metabolism (CYP3A4, 3A3, 2C9, 2C6, 1A2). Most metabolites are active (possibly more so than parent compound). Co-administration of P450 3A4 Inhibitors (PIs, delavirdine, alog antifungals) results in little to no increased pharmacologic activity of marijuana. However, P450 3A4 Inducers (nevirapine, efavirenz, rifampin, rifabutin, anticonvulsants) may cause increased pharmacological activity of marijuana secondary to increased formation of active metabolites. In addition, one study showed smoked marijuana resulted in a 34% decrease in indinavir levels.

**Ecstasy (MDMA)**

Ecstasy was initially developed in 1914 as an appetite suppressant. It was used in the 1970s to improve communication during psychotherapy and started becoming popular in the club scene in 1992.

continued page 2
Amphetaamines and Methamphetamine

Increased levels of amphetaamines have also led to hyperthermia, seizures, hypermetabolic crises, cardiac arrhythmias, and death. Like ecstasy, amphetaamines are metabolized by P450 2D6. Ritonavir, a potent P450 2D6 inhibitor, would be expected to increase amphetaamine levels similar to the ecstasy example above. This combination should be avoided. In vivo data have suggested increased viral replication due to amphetaamines. Most importantly, in many cases, amphetaamines may induce an inpatient with an antiretroviral therapy through discontinuation of medication adherence.

Cocaine

Cocaine, another stimulant which can be dangerous at in- creased levels (hyperthermia, psychosis, cardiac arrest, seizures, and death), is considered a Schedule II controlled substance. In the 1980s, it became a Schedule I controlled substance in 1985. Increased levels of amphetamine have also led to hyperthermia, seizures, hypermetabolic crises, cardiac arrhythmias, and death. Like ecstasy, amphetaamines are metabolized by P450 2D6. Ritonavir, a potent P450 2D6 inhibitor, would be expected to increase amphetaamine levels similar to the ecstasy example above. This combination should be avoided. In vivo data have suggested increased viral replication due to amphetaamines. Most importantly, in many cases, amphetaamines may induce an inpatient with an antiretroviral therapy through discontinuation of medication adherence.

Ketamine

Ketamine is a derivative of PCP introduced in the 1960s as a dissociative anesthetic. It is still being used in veterinary medicine and has limited human clinical use. At lower doses, ketamine exerts sedative effects; at higher doses, amnesic effects, loss of motor skills, euphoria, altered perceptions, dissociative effects (“trips to Kland” or “k-holos”) and increased blood pressure occur. In overdose, respiratory depression may occur; however, ketamine has a large therapeutic window and death is rare. Metabolism of ket-amine occurs via P450 3A4 (major), 2B6 (minor) and 2C9 (minor). 3A4 Inhibitors (nelfinavir, saquinavir, amprenavir, ritonavir, and dapsone) increase ketamine levels. 3A4 inducers (rifampin, etravirine, phenytoin, carbamazepine, phenobarbitone) reduce ketamine levels. Patients on 3A4 inducers often require 33-100% higher methadone. Patients on 3A4 inhibitors often require 33-100% lower methadone. Treatment of ketamine overdose requires supportive care. Management of severely intoxicated patients includes rapid stabilization, airway protection, and early intubation. Ketamine is metabolized by hydroxylation with a small yield of N-desmethylketamine. N-desmethylketamine is oxidized by cytochrome P-450 3A4. The N-desmethyl metabolite is further oxidized to an inactive metabolite. An increase in ketamine levels, coma, seizures, anxiety, confusion, agitation, loss of consciousness, bradycardia, hypotension, hyperthermia, respiratory arrest, or death may occur. The metabolism of ketamine is not well defined. The primary route of metabolism is the lungs with P450 2D6 involvement likely. A near-na- tural effect in patients on ritonavir and saquinavir was reported. One induction agent (etoricoxib, nevirapine, carmustine, carbamazepine, phenobarbitone) is likely to induce opioid intake in patients taking methadone. Patients on 3A4 inducers often require 33-100% higher than initial methadone dose. Surprisingly, ritonavir also decreases methadone levels. Amnesteem, benzodiazepines, and other CNS depressants should be avoided. The drug should be used as part of a comprehensive therapy program. The combination should be avoided. In vivo data have suggested increased viral replication due to amphetaamines. Most importantly, in many cases, amphetaamines may induce an inpatient with an antiretroviral therapy through discontinuation of medication adherence.

Erectile Dysfunction Agents

Sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) are used recreationally to overcome drug-induced impotence or to ex- ercise. Significant drug interactions with sildenafil, tadalafil, and vardenafil (Levitra) are likely to cause a prolonged half-life of sildenafil, tadalafil, and vardenafil and increased effects (49-fold increase bioavailability of vardenafil in presence of ritonavir). CYP3A4 inducers (nevirap-ine, efavirenz, rifampin, rifabutin, anticonvulsants) are likely to decrease sildenafil, tadalafil, and vardenafil induced effects. Nitrates (“Poppers,” Amyl or butyl nitrate) should never be used with these erectile dys- function agents due to possibility of cardiac arrest, syncope and strokes.

GHB (Gamma-Hydroxybutyrate)

GHB is a naturally occurring derivative of GABA which was orig- inally used as an anesthetic agent, then as a dietary supplement by bodybuilders, and most recently, as an anorectic agent. A GHB analogue, was approved by the FDA for narcolepsy-associated cataplexy. Over-the- counter sales of GHB was banned in 1990, and it is now a Schedule I controlled substance. GHB is often taken to counter stimulant ef- fects of other club drugs or is used as a “date rape” drug. At increased levels, coma, seizures, anxiety, confusion, agitation, loss of conscious- ness, bradycardia, hypotension, hyperthermia, respiratory arrest, or death may occur. The metabolism of GHB is not well defined. The primary route of metabolism is the lungs with P450 2D6 involvement likely. A near-na- tural effect in patients on ritonavir and saquinavir was reported. One induction agent (etoricoxib, nevirapine, carmustine, carbamazepine, phenobarbitone) is likely to induce opioid intake in patients taking methadone. Patients on 3A4 inducers often require 33-100% higher than initial methadone dose. Surprisingly, ritonavir also decreases methadone levels. Amnesteem, benzodiazepines, and other CNS depressants should be avoided. The drug should be used as part of a comprehensive therapy program. The combination should be avoided. In vivo data have suggested increased viral replication due to amphetaamines. Most importantly, in many cases, amphetaamines may induce an inpatient with an antiretroviral therapy through discontinuation of medication adherence.

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ANTIPSYCHOTICS

In 2004, 83% of the antipsychotic prescriptions written were for atypical antipsychotics. Nearly 60% of our total medication costs were spent on these newer antipsychotics:

As in previous years, the drug companies medication patient assistance programs (PAPs) have been an effective way to reduce costs for our indigent clients prior to MediCal eligibility. In 2004, we saved approximately $400,000 through these programs. Although fewer patients were enrolled and approved for these programs, we were still able to keep our prescriptions costs lower using these PAPs.

The IVAX clozapine program was both the easiest (no recertification of indigent status) and most efficient (online enrollment) program. Due to these factors, the average prescription saving was ~ $280 per clozapine prescription, resulting in an average cost of $67 per prescription.
Alameda County

Over the past 5 years, with the introduction of both ziprasidone and aripiprazole, there have been changes in the prescribing of these agents at our programs providing services to indigent clients:

**ANTIDEPRESSANTS**

Non-TCA antidepressants represented 95% of all antidepressant prescriptions written in 2004. This includes 57.5% for SSRIs and 36.6% for other antidepressants, including bupropion, venlafaxine, and mirtazapine.

- The most commonly prescribed antidepressant was fluoxetine (21.5%), followed by Wellbutrin/bupropion (18.6%) and paroxetine (16.3%).
- The most costly antidepressant on our formulary that was prescribed was venlafaxine. The average cost/Rx for a 1-month supply was $118.
- Sertraline represented the highest cost savings within the MIA program ($13/Rx). Escitalopram had $5 in average PAP savings. The other antidepressants were associated with either MIA savings within the range of $5-$13, or generic status.

**MOOD STABILIZERS**

Depakote was the most prescribed mood stabilizer in 2004 (57.8%), followed by lithium (21.9%). Agents which were being prescribed for mood stabilization, but which have neither the FDA approval for Bipolar Disorder nor any strong backing in the literature, include Trileptal and Topamax. These made up 12.6% of the market share of mood stabilizing agents.

- The most costly mood stabilizing agent was Lamictal ($186/Rx). Trileptal and Topamax are the second and third most costly agents being prescribed in this manner, at $183 and $179 per 1-month supply, respectively. These figures represent substantial cost increases compared to 2003, and are indicative of a notable drop in participation in the MIA programs for these two medications.
- Topamax currently receives the highest MIA savings ($40/Rx), while lithium and carbamazepine currently have $0/Rx in MIA savings, due to their generic status. Lamictal also currently has $0/Rx in MIA savings, but due to their unworkable PAP requirements.
the 1980s. It became a Schedule I controlled substance in 1985. Increased levels of ecstasy have led to hypertensive crises, convulsions, hyperthermia, cardiovascular collapse and death; therefore the potential for drug interactions must be seriously considered. The metabolism of ecstasy is similar to amphetamines (P450 2D6). The most significant drug interaction risk with antiretrovirals and ecstasy is with ritonavir. Ritonavir is expected to increase the serum levels of antiretroviral agents by inhibiting CYP3A4, CYP2D6, and CYP2C9. The most significant drug interaction risk with antiretrovirals and ecstasy is with ritonavir. Ritonavir is expected to increase the serum levels of antiretroviral agents by inhibiting CYP3A4, CYP2D6, and CYP2C9.

Amphetamines and Methamphetamine

Increased levels of amphetamine have also led to hyperthermia, seizures, hypertension, arrhythmias, stroke, cardiac arrest and death. Like ecstasy, amphetamines are metabolized by P450 2D6. Ritonavir, a potent P450 2D6 inhibitor, would be expected to increase amphetamine levels similar to the ecstasy example above. This combination should be avoided. In vivo data have suggested increased viral replication due to amphetamines. Most importantly, in many cases, amphetamines use is an antiretroviral therapy through disruption of medication adherence.

Cocaine

Cocaine, another stimulant which can be dangerous at all concentrations (hypertensive crises, cardiovascular collapse, respiratory arrest), is metabolized by hydroxylation with a very small amount via 3A4. Therefore, the risk of a pharmacokinetic interaction between the antiretroviral agents and cocaine is increased. In fact, the 3A4 and 2B6 enzymes metabolize cocaine; therefore, the primary route of metabolism is the lungs with P450 2D6 involvement likely. A near-fatal reaction in a patient on ritonavir and saquinavir was reported. One may also consider the risk for synergistic CNS depression with cocaine, amphetamines, and ecstasy. Increased levels of cocaine may be seen with these drugs due to possibilities of cardiac arrest, syncope and strokes.

GHBA (gamma-hydroxybutyrate)

GHBA is a naturally occurring derivative of GABA which was originally used as an anesthetic agent, then as a dietary supplement by bodybuilders, and most recently, eutroxy sodium, a GHB analogue, was approved by the FDA for narcolepsy-associated cataplexy. Over-the-counter sales of GHBA were banned in 1999, and it is now a Schedule I controlled substance. GHBA is often taken to counteract stimulant effects of other club drugs or is used as a “date rape” drug. At increased levels, coma, seizures, anxiety, confusion, agitation, loss of consciousness, bradycardia, hypotension, respiratory arrest, or death may occur. The metabolism of GHB is not well defined. The primary route of metabolism is the lungs with P450 2D6 involvement likely. A near-fatal reaction in a patient on ritonavir and saquinavir was reported. One patient died due to cardiac arrest. In addition, increased levels of cocaine may be seen with these drugs due to possibilities of cardiac arrest, syncope and strokes.

In a German study, a combination of naltrexone and acamprosate was compared to each drug alone, and also to placebo, in a double-blind, placebo-controlled, parallel-group trial. There was no significant difference observed between the two drugs. The combined treatment was more effective than acamprosate alone, but not more effective than naltrexone alone. A large study is ongoing at National Institute of Alcohol Abuse and Alcoholism comparing naltrexone, acamprosate, and the combination of these agents, with different degrees of behavioral therapy. The investigators plan to enroll approximately 1300-1400 patients. (COMBINE [Combining Medications and Behavioral Interventions] study).

Adverse Effects:

The most frequent side effect with acamprosate is diarrhea (10-17%); it appears to be dose-related and transient. Other infrequent adverse effects include anemia, headache, hypotension, tachycardia, and gastrointestinal side effects. Acute renal failure has been reported to be temporally associated with acamprosate in at least 3 patients. Incidents of suicidal ideation, suicide attempts and completed suicides were infrequent; they were more common with the drug than with placebo (2.4% vs. 0.8% in year-long studies). There was no association between the incidence of suicide events and naltrexone treatment. Patients on acamprosate include abdominal pain, constipation, nausea and vomiting, Anxiety, nervousness, difficulty in sleeping, fatigue, confusion, and irritability have also been reported.

Adverse effects of disulfiram include thrombocytopenia, psychiatric reactions, disorientation, agitation, seizures, sleepiness, catatonia, hypotension, tachycardia, palpitations, chest pain, hypertension, chest pain, rhinorrhea, head, seizures, weakness, irritability, anaphylaxis, hallucinations, contact dermatitis, and arthritic symptoms. Drug interactions can be significant. Hepatic toxicity including hepatic failure has been reported.

DOSAGE AND ADMINISTRATION

The recommended dosage of acamprosate is 666 mg (two 333 mg tablets) taken three times daily, beginning as soon as possible after the patient has been admitted to a treatment program. Lower doses may be effective in some patients.
In patients with moderate renal impairment (creatinine clearance of 30-50 ml/min), begin with one 333mg tablet three times daily. Acamprosate is contraindicated in patients with severe renal impairment. Acamprosate has minimal drug interactions involving cytochrome P450 enzymes. However, co-administration of acamprosate with naltrexone produces a 33% increase in acamprosate Cmax and 25% increase in AUC of acamprosate. No dosage adjustment is recommended. Naltrexone is dosed 50mg once a day, after patient is opioid-free for 7 to 10 days. Disulfiram is dosed between 125mg to 500mg daily after a minimum of 12 hours of alcohol abstinence. Both Naltrexone and Disulfiram have been associated with hepatocellular injury, and should be used with caution in liver disease.

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**INSIDETHIS ISSUE**

**What You Need to Know**

Talia Puantian, PharmD, BCPP

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Not only do substances which decrease social inhibitions promote high-risk sexual behaviors, but they may also have negative immunologic effects in HIV-infected individuals. Drug use has been shown to be an obstacle to antiretroviral medication adherence. Studies have also shown transient immune suppression in the context of drug use. One study showed CD4+CD8+ cell ratio was decreased in healthy volunteers after MDMA (ecstasy) was administered. Reduced functional responsiveness of lymphocytes and increase in natural killer cell activity were observed. There were even greater reductions in CD4+ cells in those subjects ingesting alcohol in combination with ecstasy.

Perhaps the most challenging aspect of drug use in patients with HIV infection is the management of potential drug interactions with antiretroviral therapy. The following is a summary of such potential interactions.

**Alcohol**

Alcohol use is common in HIV-infected individuals (40-80%); rates of alcoholism are also increased in this population. Alcohol use is associated with disinhibition and increase in high-risk sexual behavior. Alcohol consumption is a risk factor for poor medication adherence. Heavy alcohol users are 4 times less likely to achieve positive virologic response; this is equal to the non-adherence risk of active heroin users. Consumption of greater than 50 g/d (4-5 drinks) is a risk factor for liver disease progression in patients with HIV-Hepatitis C co-infection. Potential drug interactions include:

- Additive/synergistic effects with other CNS depressants (benzodiazepines, opiates, etc.)
- Alcohols (levels increased 60% in the presence of 0.1% ethanol)
- Alcohol acts as P450 inducer with chronic use
- May decrease some drug levels (e.g., protease inhibitors [PIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs])
- Potentiates cocaine hepatotoxicity
- Increased risk of pancreatitis (didanosine, stavudine, Vinca alkaloids, paclitaxel and zalcitabine)
- Kaletra & Antabuse: Kaletra oral solution is 42% alcohol

**MARIJUANA**

Marijuana is metabolized primarily via hepatic metabolism (CYP3A4, 3A3, 2C9, 2C6, 1A2). Most metabolites are active (possibly more so than parent compound). Co-administration of P450 3A4 Inhibitors (PIs, delavirdine, azaconazole) results in little to no increased pharmacologic activity of marijuana. However, P450 3A4 Inducers (nevirapine, efavirenz, rifampin, rifabutin, anticonvulsants) may cause increased pharmacological activity of marijuana secondary to increased formation of active metabolites. In addition, one study showed smoked marijuana resulted in a 34% decrease in indinavir levels.

**ECSTASY (MDMA)**

Ecstasy was initially developed in 1914 as an appetite suppressant. It was used in the 1970s to improve communication during psychotherapy and started becoming popular in the club scene in

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**THE BAY AREA PSYCHOPHARMACOLOGY NEWSLETTER**

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The Bay Area Psychopharmacology Newsletter is now available on the Alameda County Behavioral Health Care Services website: http://bhcs.co.alameda.ca.us/ at the top of the page in the list of Quick Links.