Psychotropic Medications and HIV

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Patients with human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome have high rates of psychiatric illness. The effective management of these psychiatric conditions can improve a patient’s quality of life and may improve antiretroviral adherence. Care providers for patients with HIV infection frequently encounter clinical situations in which psychotropic medications are needed or are being used. Those clinical situations require familiarity with the broad category of medications termed “psychotropic.” That familiarity should include a basic understanding of indications, adverse effects, and drug interactions. In particular, it is very important to recognize the many potential interactions based on cytochrome P450 metabolism, which is common to many psychotropics, the protease inhibitors, and the nonnucleoside reverse-transcriptase inhibitors. In a brief review of the use of psychotropic medications in patients with HIV infection, we discuss indications, adverse effects, and drug interactions for commonly used antidepressants, mood stabilizers, anxiolytics, antipsychotics, psychostimulants, and drugs of abuse.

Patients with AIDS are at higher risk for mental illness than the general population. Prevalences for major depression among patients with HIV infection only and patients with AIDS have been estimated to be between 15% and 40%, far above the prevalence for the general population [1]. Additionally, mental illness places patients at risk for contracting HIV infection. In a study of 671 patients at the Baltimore City Health Department Sexually Transmitted Disease clinic, a diagnosis of depression was associated with behaviors placing one at risk for HIV infection [2]. That 3%–23% of adults with severe mental illness are HIV infected, compared with 0.6% of the population in the United States, is likely related to such high-risk behavior [3]. Mental illness also impacts a patient’s ability to adhere to complicated antiretroviral regimens [4]. Treatment of comorbid mental illness in HIV-infected patients, however, can improve adherence to HAART regimens [5].

Psychiatric disorders are under-recognized and under-treated in patients with chronic medical illness. In 1996, an epidemiologic study examined a representative sample of 2864 patients receiving medical care for HIV infection [6]. In addition to finding a 12-month prevalence of nearly 50% for psychiatric illness, 27.2% of all HIV-infected patients receiving medical care were taking a psychotropic drug. Antidepressants were the most common (20.9% of all patients), followed by anxiolytics (16.7%), antipsychotics (4.7%), and psychostimulants (3%). Over one-half of the patients reporting a major depressive disorder were not treated with antidepressants [7].

We will discuss the indications and uses of psychotropic medications (antidepressants, anxiolytics, mood stabilizers, antipsychotics, psychostimulants, and drugs of abuse) in the HIV clinic. Our goal is to promote the rational treatment of psychiatric disorders in HIV-infected patients. Because these patients are underserved, underinsured, and often have no access to psychiatric care, HIV care providers should be reasonably familiar with psychiatric treatments.

METHODS

Medline searches for specific psychotropics (e.g., fluoxetine and alprazolam), classes of medications (e.g., antidepressants and anxiolytics), psychiatric diagnoses (e.g., major depression), and psychiatric symptoms (e.g., anxiety) with HIV infection or AIDS were performed. Micromedex, a comprehensive, evidence-based pharmacological database, was reviewed for antiretrovirals and psychotropics [8].

PSYCHOTROPIC MEDICATION USE

Medication treatment in psychiatry is made confusing by overlapping terminology for symptoms and conditions. “Depression” may mean the specific syndrome of major depression,
formerly termed “endogenous depression” or “melancholia.” “Depression” may also refer to the mental state or symptom that a patient describes. Anxiety as a symptom may be caused by underlying major depression or by worries about HIV and the burdens of infection. In general, symptomatic treatment is less desirable than diagnostically driven treatment.

After establishing a diagnosis, we must consider the benefit of alleviating symptoms versus the burden of possible treatments. This is accomplished by discussing with patients the risks and benefits of proposed treatments. This is also the opportunity to develop an alliance that may improve medication adherence [9, 10].

The next step is to consider treatment options. In many conditions, >1 treatment has been found to be effective. For instance, all approved antidepressants have efficacy in the treatment of major depression. Therefore, you could start treatment with any approved antidepressant. For panic disorder, the literature suggests that cognitive behavioral treatments and medications may have similar efficacy [11–13]. Combination treatment with cognitive behavioral therapy and medication may have even greater success in primary care settings [14]. The factors guiding decisions include clinical judgment about the patient’s ability to engage in and tolerate treatment, the way the treatment may interfere with other medicines, the availability of a treatment for the patient involved, and the treating physician’s available time commitment (behavioral treatments are more labor-intensive).

**DRUG-DRUG INTERACTIONS**

Many unknowns exist regarding the clinical relevance of the numerous potential cytochrome P450 (CYP) interactions described for antiretrovirals. HIV-infected patients, like other patients with chronic medical conditions taking many medications, are at high risk for drug interactions. They often require smaller doses of medication, and their medication can become toxic quickly.

All protease inhibitors and nonnucleoside (or nucleotide) reverse-transcriptase inhibitors (NNRTIs) are metabolized by the P450 system and possess enzyme-inhibiting or enzyme-inducing properties. Ritonavir (metabolized by CYP3A4 and 2D6) may be associated with the most significant interactions because of its potent inhibition of CYP3A, 2D6, 2C9, and CYP2C19 isoenzymes. Amprenavir, indinavir, and nelfinavir are all metabolized by CYP3A4 and are moderately potent CYP3A4 inhibitors. Nevirapine and efavirenz are potent inducers of CYP3A4, whereas delavirdine and efavirenz may inhibit CYP3A4, CYP2C9, and CYP2C19 [15]. The nucleoside reverse-transcriptase inhibitors (NRTIs) and the fusion inhibitor enfuvirtide are not metabolized significantly by the P450 system, making them less vulnerable to interactions with psychotropic medications. Zidovudine plasma levels, however, can be increased by concurrent use of methadone or valproic acid [8].

It is not clear how often psychotropics adversely impact antiretroviral blood levels (causing either toxicity or failure). The assumption we are making, however, is that better antiretroviral adherence through improved mental health will outweigh the negative impact psychotropics might have on antiretroviral blood levels. Although there is some evidence to support this stance [16], this area needs intense research.

**ANTIDEPRESSANTS**

Antidepressants are the most commonly prescribed psychotropic drugs for HIV-infected patients. Antidepressants include selective serotonin reuptake inhibitors, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors, and other new atypical drugs. The advent of the newer antidepressants has increased the number of people being treated for depression, because these antidepressants are effective, have fewer adverse effects, and are safer with respect to overdose.

**SELECTIVE SEROTONIN REUPTAKE INHIBITORS**

Selective serotonin reuptake inhibitors are indicated for major depression (fluoxetine, sertraline, paroxetine, citalopram, and escitalopram), bulimia (fluoxetine), panic disorder (fluoxetine, sertraline, and paroxetine), obsessive compulsive disorder (fluoxetine, fluvoxamine, sertraline, and paroxetine), generalized anxiety disorder (paroxetine and escitalopram), post-traumatic stress disorder (sertraline and paroxetine), social phobia (sertraline and paroxetine), and premenstrual dysphoric disorder (fluoxetine, sertraline, and paroxetine). Common adverse effects include anxiety, diarrhea, insomnia, and sexual dysfunction.

Through randomized clinical trials, fluoxetine has been shown to be the most effective of the selective serotonin reuptake inhibitors in the treatment of major depression in HIV-infected patients. Paroxetine, sertraline, and citalopram have also demonstrated efficacy [17].

The combination of fluoxetine and ritonavir has been shown to increase the concentration of ritonavir [18]. In a series of 5 cases of serotonin syndrome in patients taking fluoxetine and antiretrovirals, the most common culprit was ritonavir, which was believed to increase fluoxetine levels by inhibition of CYP2D6 [19]. One study has indicated no apparent interaction between ritonavir and escitalopram [20].

Interactions with antiretrovirals are possible with all selective serotonin reuptake inhibitors by means of their potential to inhibit cytochrome P450 enzymes [21, 22]. Because they are all metabolized by CYP isoenzymes, there is the potential for increased levels of selective serotonin reuptake inhibitors when used in combination with enzyme inhibitors. Fluoxetine and
paroxetine, potent inhibitors of CYP2D6, may cause toxicity by increasing levels of protease inhibitors. Fluvoxamine, a potent inhibitor of CYP1A2, may also create toxicity through increased levels of protease inhibitors. Sertraline, citalopram, and escitalopram, however, appear to have little effect on the major CYP isoforms.

**Mirtazapine**

This novel antidepressant is indicated by the US Food and Drug Administration (FDA) for treatment of major depression and has been shown to be effective in treating depression in HIV-infected patients [23]. Common adverse effects include sedation, weight gain, and constipation. One of the most valuable aspects of mirtazapine in HIV-infected patients is its tendency to promote appetite and sleep. It is metabolized by CYP isoenzymes, leaving the potential for interactions with CYP inhibitors like ritonavir.

**Nefaqzodone and Trazodone**

Nefazodone and trazodone are chemically similar antidepressants, and both are indicated by the FDA for treatment of depression. One open trial of nefazodone found it to be effective in the treatment of depression in HIV-infected patients [24]. Nefazodone, however, has a black box warning because of its associations with liver failure and has been removed from the market in many countries.

Trazodone is used often as an adjunctive sleeping agent. Common adverse effects include sedation, lethargy, dry mouth, dizziness, and gastrointestinal discomfort, as well as increased risk of hypotension and priapism. Trazodone is metabolized by CYP3A4 and CYP2D6, leaving the potential for increased levels of trazodone when it is combined with enzyme-inhibiting protease inhibitors or NNRTIs. In a blinded study of healthy individuals taking trazodone, the addition of ritonavir slowed clearance of trazodone and resulted in nausea, dizziness, and hypotension, and caused 1 subject to pass out [25].

**Venlafaxine**

Venlafaxine selectively inhibits the reuptake of serotonin, norepinephrine, and dopamine. It is indicated for treatment of major depression, generalized anxiety disorder, and social anxiety disorder and has clinical utility in chronic pain conditions [26]. It is metabolized and is a weak inhibitor of CYP 2D6. One drug-interaction study found that venlafaxine decreased the plasma concentration of indinavir [27].

**Duloxetine**

Duloxetine inhibits the reuptake of both serotonin and norepinephrine. No specific clinical data exist to discuss the use of this medicine in HIV-infected patients. It is indicated by the FDA for treatment of major depression and diabetic neuropathic pain. Because it is metabolized by CYP2D6 and 1A2, combining duloxetine with a potent CYP2D6 inhibitor like ritonavir can increase the severity of adverse effects.

**Bupropion**

Bupropion is indicated for treatment of depression and smoking cessation. A major strength of bupropion is the infrequency of sexual adverse effects associated with it. One open study of bupropion in HIV-infected patients found it to be effective against depression [28]. Clinically, bupropion is an activating antidepressant with common adverse effects, including agitation, anxiety, insomnia, and headache, and it has the potential to cause seizures. The drug is primarily metabolized by CYP2B6. One in vitro study indicated that ritonavir, nelfinavir, and efavirenz inhibited bupropion hydroxylation, suggesting the potential for increased levels of bupropion [29]. One case series (10 patients) examined in vivo experience with the combination of bupropion and ritonavir, efavirenz, or nelfinavir and found no increase in the number of seizures (no seizures were reported) [30].

**Tricyclic Antidepressants**

TCAs are indicated for treatment of depression (amitriptyline, imipramine, desipramine, doxepin, nortriptyline, protriptyline, and trimipramine) and obsessive compulsive disorder (clomipramine). The mechanism of action of TCAs is not well understood but is believed to be related to reuptake inhibition of norepinephrine and serotonin. These drugs cause anticholinergic adverse effects, orthostasis, sedation, and weight gain. In overdose, conduction abnormalities (prolonged QT) can be deadly.

The role of TCAs in treating HIV-infected patients is based on our long-term experience with them and the potential for capitalizing on their side effects. For instance, a patient with AIDS who has stomach distress from HAART, chronic diarrhea, and depression may benefit from treatment with a TCA.

In patients infected with HIV, data indicate that TCAs are as effective as other antidepressants. One trial examined paroxetine and imipramine versus placebo. Both were equivalently effective, but imipramine was less well tolerated because of anticholinergic adverse effects [31]. Another study found that imipramine was equally effective in depressed HIV-infected and medically healthy patients [32].

TCAs are metabolized by P450 enzymes, and antiretrovirals that inhibit these enzymes can increase serum concentrations. Close observation for signs and symptoms of tricyclic toxicity is necessary when combining TCAs with CYP inhibitors. In addition, a case report of fluconazole showed an increased serum concentration of nortriptyline [33].
ANXIOLYTICS

Anxiolytics, such as benzodiazepines, are effective at stopping anxiety and promoting sleep. Pharmacologically similar to ethanol (through γ-aminobutyric acid potentiation), these drugs are potentially habit forming. They are indicated by the FDA for treatment of anxiety, panic disorder, and alcohol withdrawal. In a patient population for which substance abuse is a serious problem, the use of these drugs for symptomatic relief should be critically examined before prescriptions are given. In the epidemiologic study described above, one-half of the patients reported illicit substance use in the previous year, and 12% screened positive for dependence [6].

Of the benzodiazepines, alprazolam, midazolam, and triazolam are dependent on CYP 3A4 for metabolism. Potent inhibitors of this CYP isoform, such as ritonavir, can decrease clearance of these drugs and result in oversedation and possibly death [34]. The benzodiazepines oxazepam, lorazepam, and temazepam are metabolized by glucuronidation. Drugs that increase the activity of glucuronidation, such as ritonavir or nelfinavir, may lower the levels of these drugs. Additionally, the use of midazolam, along with delavirdine (as well as protease inhibitors) may increase its effect and lead to oversedation [35].

Newer hypnotic agents—eszopiclone, zolpidem, and zaleplon—are nonbenzodiazepine sleeping aids designed to avoid drug dependence and daytime sedation that may result from use of benzodiazepines. Eszopiclone is the first drug to be FDA approved for long-term use. Both eszopiclone and zaleplon are metabolized by CYP3A4, leaving them vulnerable to interactions with enzyme inhibitors [8].

MOOD STABILIZERS

Lithium, valproic acid, and carbamazepine have been shown to be effective mood stabilizers and are indicated treatments in patients with bipolar affective illness. Lithium (excreted unchanged in the urine) is the least likely to have specific drug interactions with antiretrovirals. However, it has a narrow therapeutic index and can be a potent deliriant in a patient taking multiple medications who has underlying cognitive limitations. In HIV-infected patients, lithium has the potential to cause nausea, vomiting, diarrhea, tremor, thyroid dysfunction, and kidney problems at therapeutic doses [8].

Valproic acid does not appear to exhibit significant CYP-based drug interactions with antiretrovirals. Valproic acid may impair zidovudine metabolism through inhibition of glucuronidation, but there is no evidence of clinical importance [36]. Because VPA can cause elevated transaminase levels and severe hepatitis, it is important to observe liver enzymes periodically. VPA can also cause thrombocytopenia, weight gain, tremor, nystagmus, and ataxia.

Carbamazepine is metabolized via CYP3A4 and induces its own metabolism. Such autoinduction and the potential for bone-marrow suppression make its use complicated. There is clinical evidence of carbamazepine toxicity resulting from its use in combination with CYP3A4 inhibitors, such as ritonavir. One report showed virologic failure caused by the CYP-induction effects of carbamazepine [37].

Lamotrigine has shown promise in the treatment of mood disorders and is indicated for treatment of bipolar disorder. It is not metabolized through the CYP system, but its concentration has been shown to decrease when used in combination with ritonavir (without any clinical implications) [36]. Lamotrigine can cause life-threatening rashes, such as Stevens-Johnson syndrome, when the dose size is increased too quickly.

ANTIPSYCHOTICS

Antipsychotic drugs (also called neuroleptics) include both older “typical” drugs and the newer “atypical” (second generation) medications. They are indicated by the FDA for treatment of schizophrenia and acute mania, in addition to being adjunctive treatments for other conditions, including delirium. The typical neuroleptics (characterized by chlorpromazine and haloperidol) are specific dopamine receptor (D2) antagonists. Newer antipsychotics also interact with other receptor families, such as serotonin. The use of newer antipsychotics has flourished because of their efficacy in treating psychotic conditions and the decreased frequency of extrapyramidal adverse effects associated with their use. As more experience is gained, however, significant metabolic adverse effects (such as hyperglycemia, weight gain, and hypercholesterolemia) often make newer neuroleptics less appealing. Clozapine, a very effective neuroleptic, has the potential to cause agranulocytosis, necessitating weekly blood count measurements for the first 6 months. In addition, this medicine can cause significant weight gain, orthostasis, salorrhea, and seizures [8].

CYP inhibitors have the potential to increase the concentration of the antipsychotics, clozapine, and pimozide. For this reason, these drugs have been contraindicated with antiretrovirals with CYP inhibition, such as ritonavir. In addition, the potential for toxic increases by CYP inhibitors exists in other antipsychotics, including chlorpromazine, haloperidol, olanzapine, and risperidone [15].

PSYCHOSTIMULANTS

Psychostimulants, such as methylphenidate, dextroamphetamine, and pemoline, are amphetamine-like medications used for the treatment of narcolepsy, chronic fatigue, refractory obesity, attention deficit hyperactivity disorder, and depression. Common adverse effects include appetite suppression, weight loss, insomnia, headaches, edginess, stereotyped movements, and increased pulse rate and blood pressure. Cases of acute and chronic amphetamine psychosis, mania, and depression
have been repeatedly reported. Psychostimulants are potential drugs of abuse, and their use should be discouraged in patients with a history of substance abuse. Atomoxetine is a nonamphetamine-like stimulant being used for the treatment of attention deficit hyperactivity disorder and investigated for the treatment of depression.

In placebo-controlled trials, methylphenidate and dextroamphetamine have been shown to improve depression, energy level, and mood in HIV-infected patients [38–40]. Methylphenidate and pemoline have been effective in the treatment of persistent, severe fatigue in HIV-infected patients, compared with placebo [41].

Psychostimulants are metabolized by the cytochrome P450 system, although the exact mechanisms remain unknown. Theoretically, cytochrome P450 inhibitors (saquinavir, ritonavir, and lopinavir-ritonavir) may increase amphetamine blood levels, whereas enzyme inducers (nevirapine) may decrease levels [15].

DRUGS OF ABUSE

Amphetamine, methylenedioxymethamphetamine ("ecstasy"), ketamine, phencyclidine, and methadone are metabolized by the CYP system and have the potential to interact with antiretrovirals. Methadone is metabolized primarily by CYP 3A4. Efavirenz, nevirapine, ritonavir, and lopinavir-ritonavir have been reported to cause opiate withdrawal by induction of metabolizing enzymes. There is no good evidence showing significant interactions between heroin and cocaine and antiretroviral agents [34, 35]. The primary method of tetrahydrocannabinol metabolism is through CYP3A4. Two clinical trials, however, have not shown significant interactions between tetrahydrocannabinol and antiretrovirals.

Although alcohol is active in the CYP system (acute ingestion inhibits 2D6 and 2C19, whereas chronic use induces 2E1 and 3A4), evidence has not demonstrated clinically significant interactions. Abacavir is metabolized via alcohol dehydrogenase, but the interaction is not clinically significant [34]. Despite this, patients with HIV disease must be discouraged from regular or heavy alcohol use and must be screened for alcohol use disorders. Regular consumption of low doses of alcohol uniquely affects HIV-infected patients by escalating the risk of liver disease progression in patients coinfected with hepatitis C and by decreasing adherence to medication in a temporally and dose-dependent fashion [42, 43].

CONCLUSION

Working with HIV-infected patients brings you in contact with individuals vulnerable to psychiatric illness. Likewise, working with the mentally ill brings you face-to-face with patients at risk for becoming infected. The education and treatment of mentally ill patients is needed to lower their risk of HIV infection. Likewise, the effective treatment of patients with HIV infection often requires the educated use of psychotropics. Although the potential for trouble is present when combining psychotropics and antiretrovirals, the possibility of an improved quality of life and better HAART adherence makes the risk worthwhile.

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References


