Managing Psychotropics in Patients with HIV/AIDS on Highly Active Antiretroviral Therapy (HAART)

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Abstract

Patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) have high rates of psychiatric disorders, including substance and alcohol abuse. The successful management of these disorders can dramatically enhance antiretroviral adherence and improve patients’ quality of life (QoL). Providers must recognize the drug-drug interactions primarily based on cytochrome P450 metabolism and additive side effects that may compromise the treatment of this unique patient population. These interactions can eventually result in either a decrease or increase in the metabolism of HIV and psychotropic medications that sometimes require dosage modifications or replacement and the increased demand to monitor therapy.

This paper reviews and summarizes the drug-drug interactions between some of the common psychotropics and HIV medications, including protease inhibitors (PIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), nucleoside reverse-transcriptase inhibitors (NRTIs), and chemokine receptor (CCR5I) antagonists (inhibitors).

Keywords: Antidepressant; Antiretroviral; Autoimmune; Anxiolytic; Benzodiazepine; Cytochrome P450; Drug Interaction; Inhibitor

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome; BZD: Benzodiazepines; CCR5I: Chemokine Receptor Antagonists (Inhibitor); CPR: NADPH-Cytochrome P450 Reductase; CYP450: Cytochrome P450; ENSN: Enhancers of Noradrenergic and Serotonergic Neurotransmission; HAART: Highly Active Antiretroviral Therapy; HIV: Human Immunodeficiency Virus; MA: Melatonin Agonist; MAO-I: Monoamine Oxidase Inhibitor; NNRTI: Non-Nucleoside Reverse-Transcriptase Inhibitor; NRI: Norepinephrine Reuptake Inhibitor; NRTI: Nucleoside Reverse-Transcriptase Inhibitor; PI: Protease Inhibitor; QoL: Quality of Life; SCRI: Selective Catecholamine Reuptake Inhibitor; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor; TCA: Tricyclic Antidepressant

Introduction

Human immunodeficiency virus-infected patients are at higher risk for mental or psychiatric disorders than the general population [1,2]. Caring for a psychiatric patient who is also infected with HIV requires a precise diagnosis and satisfactory treatment. It also involves

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a long-lasting therapeutic relationship between patients and providers, a collaboration between specialties, patients conforming with recommended treatment plans, and coping with the dysfunction and the possibility of death. In order for the patient to feel supported, there needs to be care coordination with family members on general health care as well [2,3].

Psychotropic medications, antipsychotics, anxiolytics, antidepressants, psychostimulants, and mood stabilizers are frequently prescribed to patients infected with HIV. Most of the medications affirmed above are principally metabolized by the cytochrome P450 (CYP450) isoenzymes [2,4]. Prescribing of these psychotropics concomitantly with antiretroviral medications for AIDS patients require several considerations, including liver clearance of these medications, history of substance dependence or abuse, presence of metabolic, cardiovascular abnormalities, and alterations in brain neurotransmitter pathway system where some psychotropic drugs employ their therapeutic actions [2].

The cytochrome P450 system (drug-drug interaction)

The mechanisms of drug interactions are categorized into either a pharmacodynamic or pharmacokinetic process. Pharmacodynamic interactions describe what the drug does to the body, the correlation between the drug concentration at the site of action and the physiological and biological effects expressed as addictive, synergistic, or antagonistic [4-6]. This process can be modified by other drugs, a disorder or disease, and aging processes [4]. Pharmacokinetics details what the body does to a drug and the study of drug absorption, distribution, metabolism, and excretion [4,5]. Several psychotropic and antiretroviral pharmacokinetic interactions may alter the cytochrome P450 metabolic enzyme system [2].

Cytochrome P450 (CYP450) is a superfamily of enzymatic proteins. CYP450 acquired its name because it is a membrane-associated protein within cells (cyto), containing heme (chrome) pigment (P). When its reduced form couples with carbon monoxide, it can absorb light at a wavelength of 450 nm [9,14,24]. CYP450 enzymes are located in cells throughout the body, but are expressed predominantly within the endoplasmic reticulum and mitochondria of liver cells [5,6].

These enzymes are essential for the metabolism of many medications and several injurious foreign substances. They are also pivotal in the biosynthesis and catabolism of steroid hormones (such as estrogen and testosterone) and sterols [6-8]. Genetic fluctuation within this family of enzymes can significantly affect a patient’s response to prescribed medications, such as psychotropics and HIV medications [6,8]. Also, CYP450 enzyme functions can be activated or inhibited by medications, resulting in drug-drug interactions, adverse effects, and treatment failures. Other factors that can influence the CYP450 functions include diet and smoking [6].

Different cytochrome (CYP) proteins are present in the human body; however, six of them are involved mainly in the bulk of drug metabolism. Most important among them are CYP3A4 and CYP2D6; the remaining are CYP1A2, CYP2C9, CYP2C19, and CYP3A5 [2,4,6] (Figure 1).

Figure 1: Mechanism of assimilation. Adapted from Xie., et al. (2016) [9].
Antidepressants

Antidepressants are psychotropic medications most commonly prescribed to HIV-positive individuals. They include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAO-Is), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors (NRIs), selective catecholamine reuptake inhibitors (SCRIs), melatonin agonists (MAs), and enhancers of noradrenergic and serotonergic neurotransmission (ENSN) [2].

Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are the most generally prescribed antidepressant medications in HIV-infected patients mainly due to their minimal side effect properties compared to first-generation antidepressants [1,2,4]. SSRIs are indicated for major depression, post-traumatic stress disorder, panic disorder, obsessive-compulsive disorder, bulimia, generalized anxiety disorder, premenstrual dysphoric disorder, and social phobia [1]. Examples include sertraline, fluoxetine, paroxetine citalopram, escitalopram, paroxetine, and fluvoxamine.

Adverse effects common to SSRIs include diarrhea, anxiety, insomnia, sexual problems, dizziness, blurred vision, headache, and dry mouth [1]. Most SSRIs, including paroxetine, fluoxetine, and citalopram, are metabolized by the CYP450 system. Hence, antiretrovirals may alter their plasma concentrations, depending on whether they inhibit or activate this pathway [1,2,4].

A typical example involves ritonavir, a protein inhibitor (PI), which inhibits CYP450 metabolism. Ritonavir may increase SSRIs blood level by inhibiting their metabolism [7]. Fluvoxamine inhibits CYP1A2, while paroxetine and fluoxetine inhibit CYP2D6, leading to increased plasma concentration of HIV medications metabolized through the CYP450 enzyme system and possibly resulting in toxicity [1]. In light of this possible occurrence, a far better alternative is using citalopram, escitalopram, or sertraline if drug-drug interactions with antiretrovirals are to be avoided—since they appear to have little effect on most of the CYP isoenzymes [1,4] (Table 1).

Tricyclic antidepressants (TCAs)

Tricyclic antidepressants (TCAs) are indicated to treat obsessive-compulsive disorder and depression. However, they are not the first choice to treat depression in HIV-positive patients due to their side effects and drug-drug interactions [1,2,7]. Their mechanisms of action are inadequately understood but are deemed to be associated with reuptake inhibition of norepinephrine and serotonin [1]. Examples include amitriptyline, imipramine, desipramine, nortriptyline, doxepin, clomipramine, and desipramine. TCAs' adverse effects constitute sedation, confusion, orthosis, dry mouth, constipation, weight gain, urinary retention, seizures, and cardiac arrhythmias [1,2,4].

TCAs are degraded primarily by the CYP2D6 isoenzyme. Also, antiretrovirals, such as ritonavir, moderately inhibit isoenzyme CPY2D6 [2]. Close therapeutic drug monitoring of TCAs and PIs is highly recommended when used concurrently [1,2]. The general recommendation is to begin the patient on a low dose and titrate upward to a desired therapeutic level while monitoring for symptoms of tricyclic toxicity [4] (Table 1).

Enhancers of noradrenergic and serotonergic neurotransmission (ENSN)

Examples of enhancers of noradrenergic and serotonergic neurotransmission (ENSNs) include trazodone and mirtazapine. These drugs heighten the release of norepinephrine and serotonin 1A receptor (5-HT1A)-mediated serotonergic transmission; however, they block 5-HT2 and 5-HT3 receptors [2,10].

Mirtazapine is commonly used to treat depression in patients experiencing insomnia, weight loss, and decreased appetite, often associated with HIV-positive patients [1,2]. Common side effects of mirtazapine include increased appetite, weight gain, sedation, tiredness,
blurred vision, drowsiness, and constipation [1, 2]. Mirtazapine is primarily metabolized in the liver by the CYP450 isoenzymes CYP1A2, CYP2D6, and CYP3A4—potentially leading to drug interactions with NNRTIs and PIs [2,10].

Trazodone is prescribed to treat depression and is frequently applied as an adjunctive sleeping agent [2]. Side effects of trazodone include lethargy, sedation, dizziness, priapism, blurred vision, gastrointestinal discomfort, and an increased risk of hypotension [1,2]. Trazodone is metabolized by CYP3A4 and CYP2D6, resulting in heightened concentrations when combined with antiretroviral medications that inhibit the enzyme, such as NNRTIs and PIs [1,2] (Table 1).

Selective catecholamine reuptake inhibitor (SCRI)

Bupropion—an example of a selective catecholamine reuptake inhibitor (SCRI)—is an activating antidepressant with a selective inhibitory effect on catecholamine (dopamine and norepinephrine) reuptake [2]. Bupropion is used to treat depression and as an aid in smoking cessation. Common adverse effects of bupropion include anxiety, agitation, insomnia, lower seizure threshold, and headache [1,2]. Bupropion is metabolized by CYP2B6 [1,4].

Studies indicate that some antiretroviral medications, including nelfinavir, efavirenz, and ritonavir, inhibit the hydroxylation of bupropion, resulting in increased plasma concentration of bupropion [1,4,11] (Table 1).

Serotonin-norepinephrine reuptake inhibitors (SNRI)

Duloxetine, venlafaxine, and desvenlafaxine are antidepressant agents in the serotonin-norepinephrine reuptake inhibitors (SNRI) category that selectively inhibit the reuptake of serotonin and norepinephrine [1,4]. Venlafaxine and desvenlafaxine are indicated to treat major depression, social anxiety, and generalized anxiety disorder [1].

Venlafaxine is metabolized by CYP2D6 and also acts as a weak inhibitor of CYP2D6 [1]. Studies have shown that venlafaxine decreases the concentration of indinavir [1,12]. Duloxetine is approved for the treatment of major depression and diabetic neuropathic pain [1,2]. CYP2D6 and CYP1A2 metabolize this agent. PIs, like ritonavir, may potentiate toxicity when combined with other specific pharmaceuticals [1,2,4] (Table 1).

Antipsychotics

Antipsychotic medications include the older first-generation (typical) and the newer second-generation (atypicals), also known as neuroleptics. These drugs are indicated for the treatment of schizophrenia and acute mania. They are also used in combination with other drugs to treat delirium and bipolar disorders [1].

A more significant number of drug-drug interactions between neuroleptic and HIV antiretrovirals involve protease inhibitors [7]. Second-generation antipsychotics, like quetiapine, risperidone, aripiprazole, and olanzapine, are metabolized by CYP3A4 [4]. Thus, there is the potential for toxic accumulation when combined with ritonavir, a potent CYP3A4 inhibitor [4]. Possible toxicity and the degree of toxicity depend on the atypical drug involved. Signs of toxicity can include QT prolongation, central nervous system toxicity, weight gain, confusion, and dizziness [4].

Typical antipsychotics, such as thioridazine, act as a substrate for CYP2D6 and, to a lesser extent, CYP3A4. Also, they inhibit CYP2D6 [13]. When thioridazine and ritonavir (an inhibitor of CYP2D6) are co-administered, plasma levels of thioridazine may become elevated, and a dose reduction may be required (Table 1).
Anxiolytics

Benzodiazepines

Benzodiazepines (BZDs) are commonly used for insomnia and anxiety disorders. Alprazolam, diazepam, estazolam, midazolam, and triazolam are BZDs that are dependent on CYP3A4 for metabolism [1,7]. Ritonavir or other PIs strongly inhibit CYP3A4, causing reduced clearance of benzodiazepine, which can lead to adverse effects, such as respiratory depression, sedation, and possibly death [1,4,14]. Other BZDs, such as lorazepam, temazepam, and oxazepam, metabolized by glucuronidation, are safer alternatives [1] (Table 1).

Non-benzodiazepines

Eszopiclone, zolpidem, and zaleplon are newer non-benzodiazepines anxiolytics generally used as sleep aids instead of BZD to prevent daytime sedation and drug dependence [1]. CYP3A4 extensively metabolizes these newer agents. Hence, dosage adjustment and monitoring are required when used with enzyme inhibitors, such as PIs [1] (Table 1).

Mood stabilizers

Lithium, valproic acid, lamotrigine, and carbamazepine are indicated as mood stabilizers in bipolar disorder. Among the mood stabilizers stated, carbamazepine is both a substrate and a significant inducer of CYP3A4. Thus, CYP3A4 inhibitors, such as ritonavir, should be practiced carefully in HIV-positive patients to avoid carbamazepine toxicity [1,2] (Table 1).

Psychostimulants

Psychostimulants, such as methylphenidate and dextroamphetamine, are applied frequently to treat chronic fatigue, narcolepsy, refractory obesity, attention-deficit hyperactive disorder, and as an adjunct for treating depression. Prior experiments with methylphenidate and dextroamphetamine in HIV-infected patients demonstrated improved energy level, lessened depression, and enhanced mood [1,4,15–17].

The cytochrome P450 system also metabolizes this class of psychotropics. Thus, there is the potential for adverse drug-drug interactions when they are combined with antiretrovirals [1,4]. CYP450 inhibitors, such as ritonavir and lopinavir-ritonavir, may elevate psychostimulant blood levels; alternatively, nevirapine (a P450 inducer), may reduce these levels [1,18]. Adverse effects commonly associated with psychostimulants include weight loss, insomnia, appetite suppression, mania, irritability, and headaches [1] (Table 1).

St. John’s Wort

St John’s Wort is an ancient herbal product used widely to treat depression, but has resulted in clinical drug interactions. St. John’s Wort is a significant CYP3A4 inducer. Thus, combining it with NNRTIs and PIs (which are metabolized by the CYP3A4 isoenzyme) would most likely lead to reduced blood concentrations of antiretroviral medications, resulting in therapy failure [4,19,20] (Table 1).

Antiretrovirals

There are approximately six significant categories of antiretrovirals available for use in highly active antiretroviral therapy (HAART): NRTIs, NNRTIs, PIs, integrase strand transfer inhibitors, fusion inhibitors, and chemokine receptor (CCR5) antagonists (inhibitors) [21].

Among these types, fusion inhibitors, NRTIs, and integrase strand transfer inhibitors are not extensively metabolized by the CYP450 system. Thus, they have fewer drug-drug interactions with psychotropic medications [1,21]. NRTIs are predominantly excreted and eliminated by the renal system. Subsequently, drug interactions with psychotropics are minimal [2]. NRTIs’ (such as zidovudine) plasma concentrations can be elevated when combined with valproic acid [1].

Conversely, PIs, NNRTIs, and chemokine receptor antagonists (such as maraviroc) are significantly metabolized by CYP450 isoenzymes, making them more vulnerable to adverse psychotropic drug interactions [1,21]. Unlike maraviroc (which exerts a minimal effect on the CYP450 system), PIs and NNRTIs can induce or inhibit some of the CYP450 isoforms [21–23].

Ritonavir (a PI) is metabolized by CYP3A4 and CYP2D6 and seems to be the most potent inhibitor of CYP3A4, CYP2D6, CYP2C9, and CYP2C19 isoenzymes, causing the most extensive drug interactions when they are co-administered with psychotropics [1,2].

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Other PIs, like nelfinavir, indinavir, and amprenavir, are relatively potent CYP3A4 inhibitors and are metabolized by CYP3A4 [1]. Of the NNRTIs, nevirapine and efavirenz are inducers of CYP3A4. Efavirenz and delavirdine may inhibit CYP3A4, CYP2C9, and CYP2C19; nevertheless, the CYP3A4-inducing characteristics of efavirenz dominate [1,18,21–23] (Table 1).

Table 1: Drug-drug interactions of some HIV medications.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Protease Inhibitors</th>
<th>NNRTIs</th>
<th>NRTIs</th>
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Key to symbols:
- Δ: clinically significant interaction occurs
- ▲: Potential interaction - may require close monitoring, alteration of dose, or timing of administration
- ▼: Contraindicated

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Conclusion

The treatment of HIV-infected patients requires more elaborate drug cocktails due to the presentation of individuals highly susceptible to psychiatric illness or disorders. Drug-drug interactions with combined antiretroviral therapy frequently complicate the management of HIV-positive patients with concomitant psychiatric illnesses. Among the antiretroviral medications used to treat HIV patients, NNRTIs and PIs are implicated in most adverse drug interactions. The cytochrome P450 system, especially isoenzyme CYP3A4, facilitates most of these interactions. Recognizing and understanding the mechanisms of these possible drug interactions, their clinical repercussions, and interventions to avoid or diminish these adverse interactions are crucial for enhancing the effective treatment and management of HIV-infected patients also taking psychotropics.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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