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Psychopharmacological Treatments in HIV Patients under Antiretroviral Therapy

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Abstract

Human immunodeficiency virus-infected patients have high rates of psychiatric disorders, including substance and alcohol abuse. Prompt identification and effective management of mental disorders can improve the quality of life and antiretroviral adherence in HIV patients. Additive side effects and drug interactions may complicate the psychopharmacological treatment in this population. This article reviews the indications and precautions needed when prescribing psychoactive drugs to HIV patients with mental disorders. **(AIDS Rev. 2012;14:101-11)**

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Introduction

Patients with HIV infection have high rates of psychiatric disorders. Effective management of these conditions can improve the quality of life of patients and increase adherence to antiretroviral therapy[1-3]. Psychiatric care of HIV-infected patients, besides adequate diagnosis and treatment of mental disorders, also includes: (i) a durable therapeutic relationship, (ii) coordinated care with other specialists, (iii) compliance with the treatment plan, (iv) health education on mental disorders, (v) prevention of risky behaviors, (vi) psychological and social adaptive functioning, (vii) integration of spirituality, (viii) coping with disability, death and dying, and (ix) advice to relatives and significant others on health care and support[4].

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Psychopharmacological interventions

Psychotropic medications are commonly used by HIV-positive patients receiving medical care[5]. Prescription of psychoactive drugs to HIV patients requires considering the following:

- The concomitant use of other therapeutic substances, mainly antiretrovirals. Drug interactions may occur at different levels: (i) by competition in plasma protein binding, which is especially evident in the case of hypoproteinemia (i.e. in malnutrition or liver disease), and (ii) changes in the hepatic metabolism of drugs. Most psychoactive drugs are metabolized at the cytochrome P450 (CYP450) isoenzymes, especially subgroups 3A4 and 2D6, where some also have an inhibitory effect. Protease and nonnucleoside reverse transcriptase HIV inhibitors (PI and NNRTI, respectively) are also metabolized at CYP450, where the former have inhibitor and the latter inductor effects[6].
- Information regarding the tolerance of psychotropic drugs in HIV patients receiving antiretroviral medications is very scarce[7]. In the case of patients with concomitant liver disease, adverse effects may be more common or atypical due to reduced liver clearance of drugs, substance abuse, or psychiatric comorbidity. In particular, patients at

advanced stages of liver or HIV disease have physical and cognitive impairment that increase sensitivity to the adverse effects of psychotropic drugs. Lower drug doses should be employed in this setting.

– Prolonged use of antiretrovirals may induce metabolic (hyperlipemia, hyperglycemia, insulin resistance) and cardiovascular (hypertension, atherosclerosis) abnormalities, forming the so called metabolic syndrome[8-11]. This appears to increase the risk for cardiovascular and cerebrovascular disease[12-14]. Psychotropic medications that induce similar abnormalities should be avoided in HIV patients[15-17].
– Patients with a current or past history of substance dependence or abuse have greater risk of abuse of many psychotropic drugs[18].
– HIV patients have proven alterations in brain neurotransmitter systems, such as dopamine and serotonin pathways, where common psychotropic drugs exert therapeutic effects. This coincidence may explain atypical clinical pictures, fluctuation of psychiatric symptoms, and unexpected responses to psychoactive drugs in HIV patients[18,19].

General guidelines for the prescription of psychotropic medication to HIV patients include: (i) start with lower therapeutic doses and gradually increase according to tolerance and response, (ii) decide on the simplest possible regimen, (iii) use drugs with a side effect profile that can be used as a therapeutic advantage, and (iv) consider drug pharmacokinetics to minimize interactions.

Drug interactions through the cytochrome P450 system

Modifications in the liver clearance of antiretrovirals may be a risk factor for adverse events or viral failure with selection of viral resistance. Practitioners need to consider pharmacokinetic, pharmacologic, therapeutic, and adherence factors when managing interactions between antiretrovirals and other drugs[7]. Nucleoside reverse transcriptase inhibitors (NRTI) are predominantly excreted at the kidney, so that interactions with psychotropic drugs are uncommon. The NNRTI are extensively metabolized at the CYP450 system. Besides substrates, nevirapine, efavirenz, and etravirine are also inducers of CYP3A4. In addition, *in vitro* studies showed that efavirenz inhibits CYP2C9 and CYP2C19. Etravirine also is an inhibitor of CYP2C9 and CYP2C19. Therefore, drug interactions can be anticipated if the NNRTI are coadministered with other drugs that are metabolized by the same CYP450 isoenzyme[20,21]. Protease inhibitors (PI) are metabolized at CYP450 and may inhibit or induce multiple isoenzymes. Ritonavir is the most potent inhibitor among PI, with the greatest impact on CYP3A4, and to a lesser extent CYP2D6[22,23]. The CCR5 blocker maraviroc is metabolized by CYP3A4, but this antiretroviral has no effect on the activity of the isoenzyme. Plasma levels of maraviroc may change when combined with CYP450 inducers or inhibitors, but maraviroc does not significantly affect the pharmacokinetics of other drugs. The fusion inhibitor enfuvirtide is cleared at the kidney and has no effect on CYP450 isoenzymes. The integrase inhibitor raltegravir is cleared at the liver via glucuronidation, with null effect on the CYP450 system. Thus, these drugs have no significant impact on blood levels of psychiatric medications or other antiretrovirals[24].

Despite the described risks for drug-drug interactions, to date no clinical data have revealed serious side effects among the majority of patients on antiretroviral therapy in combination with psychotropic drugs. In any case, it is important for psychiatrists to remain in contact with other medical providers, maintain updated lists of all medications and substances of abuse, and frequently consult updated web-based information sites regarding potential drug-drug interactions. Table 1 provides the most up-to-date information about specific drug-drug interactions.

Table 1. Selected web sites for drug interactions with HIV therapy

Clinical Care Options *www.clinicaloptions.com*
School of Medicine, Indiana University *www.medicine.iupui.edu/clinpharm/DDIs/table.asp*
Toronto General Hospital Immunodeficiency Clinic *www.hivclinic.ca/main/drugs_interact.html*
University of California, San Francisco *www.hivinsite.com*
University of Liverpool *www.hiv-druginteractions.org*

Anxiolytics

Two-thirds of medications prescribed for anxiety among HIV-infected individuals are benzodiazepines (BZD)[5]. Patients with HIV infection are particularly sensitive to the side effects of BZD, such as amnesia and paradoxical reactions (disinhibition, confusion, etc.). Among patients

Table 2. Most commonly used anxiolytics in HIV patients

	Dose (mg/day)	Half-life	Active metabolites	Interactions
Alprazolam	0.75-3	Intermediate (5-24 h)	Yes	↑ toxicity by PI
Bentazepam	25-100	Short (< 5 h)	No	–
Bromazepam	3-12	Intermediate	No	–
Clonazepam	1-4	Long (> 24 h)	No	↑ toxicity by PI
Clorazepate	5-45	Long	Yes	↑ toxicity by PI
Chlordiazepoxide	30	Long	Yes	No
Diazepam	5-20	Long	Yes	↑ toxicity by PI
Lorazepam	2.0-7.5	Intermediate	No	↑ toxicity by zidovudine
Flurazepam	15-30	Long	Yes	↑ toxicity by PI
Lormetazepam	0.5-2	Intermediate	No	–
Midazolam	7.5-15	Short	Yes	Contraindicated with PI or efavirenz
Oxacepam	15-60	Intermediate	No	↑ zidovudine toxicity
Temazepam	15	Intermediate	No	↑ zidovudine toxicity
Triazolam	0.125-0.25	Short	Yes	Contraindicated with PI
Zoplicone	7.5-15	Intermediate	Yes	↑ PI levels and ↓ NNRTI levels
Zolpidem	10-20	Short	Yes	↑ PI levels and ↓ NNRTI levels

PI: protease inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor.

at risk of habituation, tolerance development, and abuse, BZD are only indicated for short periods of time. Studies examining the efficacy of BZD for the treatment of anxiety in HIV-infected individuals are lacking[25].

Intermediate-acting BZD without active metabolites such as oxazepam and lorazepam are preferable in HIV patients due to their low risk of neurotoxicity. Long-acting agents are not recommended for patients with cognitive compromise, disinhibition, delirium, or frontal lobe dysfunction[26].

Alprazolam, midazolam, and triazolam are dependent on CYP3A4 for metabolism, which is strongly inhibited by ritonavir or other PI, resulting in decreased clearance of the BZD, which could cause excessive sedation and respiratory depression[27-29]. Oxazepam, lorazepam, and temazepam are metabolized by glucuronidation, which activity is enhanced by ritonavir decreasing plasma levels of the BZD[30,31]. Clonazepam and lorezepam, both lacking active metabolites and safe in terms of drug-drug interactions, are possibly the BZD of choice for HIV patients receiving antiretrovirals[32,33]. Newer non-BZD hypnotic agents (i.e. eszopiclone, zopiclone, zolpidem and zaleplon) avoid drug dependence and daytime sedation that may result from use of BZD, but have extensive CYP3A4 metabolism[29,33], so they should be used with caution in HIV patients under PI (Table 2).

Other therapeutic options for anxiety include buspirone, which functions as a serotonin 5-HT1A receptor partial agonist, but is also metabolized by CYP3A4. Unlike BZD, buspirone shows no potential for addiction or dependence, and tolerance, sexual dysfunction or weight gain are rare[34]. Sedative antidepressants, such as trazodone, mirtazapine, or nefazodone, may be used as anxiolytics in patients also suffering from agitation or insomnia. Antipsychotics like olanzapine or quetiapine are good options when anxiety is associated with delirium, panic states, or early stages of AIDS dementia. Finally, pregabalin is indicated for generalized anxiety disorder.

Antidepressants

These drugs are the psychotropic medications most commonly prescribed to HIV patients, but there are scarce studies of specific antidepressants in this population.

Table 3. Effect of antidepressants on activity of CYP450 isoenzymes, and interaction with antiretrovirals

	1A2	2C9	2C19	2D6	3A4
Fluoxetine	↓	↓↓	↓↓	↓↓↓	↓
Fluvoxamine	↓↓↓	↓↓	↓↓	↓	↓↓↓
Paroxetine	↓↓	↓↓	↓↓	↓↓↓	↓↓
Sertraline	↓	↓	↓	↓↓	↓
Citalopram	–	–	↓	↓	0
Escitalopram	–	–	0	0	0
Venlafaxine	–	–	–	↓	0
Duloxetine	0	–	–	↓↓	–
Nefazodone	0	–	–	↓	↓↓↓
Mirtazapine	0	–	–	0	0
Trazodone	–	–	–	0	0
Reboxetine	–	–	–	↓	↓
Bupropion	0	0	–	↓↓	0
Agomelatine	0	0	0	–	–
Substrate antiretrovirals and effect on isoenzyme activity	Ritonavir ↓	Ritonavir ↓↓ Amprenavir ↓ Efavirenz ↓↓ Etravirine ↓↓	Ritonavir ↓↓ Amprenavir ↓ Efavirenz ↓↓ Etravirine ↓↓	Ritonavir ↓↓↓ Lopinavir ↓↓ Amprenavir ↓ Nevirapine ↑↑	Ritonavir ↓↓↓ Lopinavir ↓↓↓ Amprenavir ↓↓ Atazanavir ↓ Darunavir ↓↓ Nevirapine ↑↑↑ Efavirenz ↑↑↓ Etravirine ↑↑↑

(0) no induction or metabolic inhibition, but step through this pathway; (–) not passing through this metabolic pathway; (↑↑↑) potent inducer; (↑↓) inducer and inhibitor; (↓) mild inhibitor; (↓↓) moderate inhibitor; (↓↓↓) potent inhibitor.

Antidepressants include tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAO-I), and other new drugs like selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), norepinephrine reuptake inhibitors (NRI), selective catecholamine reuptake inhibitors (SCRI), enhancers of noradrenergic and serotonergic neurotransmission (ENSN), and melatonin agonists (MA). Within this last generation of antidepressants, the choice of a particular agent depends on its pharmacokinetic profile, tolerability, and potential drug interactions. Major characteristics of these drugs for the treatment of patients infected with HIV are following (Table 3)[35-38].

Tricyclic antidepressants

These drugs are not the first choice in the treatment of depression in HIV settings due to potential drug interactions and their adverse effect profile. Starting with half the usual dose and slowly increasing, with close monitoring, is recommended, including liver enzymes.

As TCA may cause constipation, sedation, and neuropathic analgesia, these side effects may benefit patients with chronic diarrhea, anxiety, or painful neuropathy. Non "beneficial" side effects are impairment of cardiac conduction, orthostatic hypotension, blurred vision, and dry mouth, which may predispose immune-depressed patients to the appearance of oropharyngeal candidiasis[39].

Tricyclic antidepressants are primarily metabolized by CYP2D6, an isoenzyme moderately inhibited by ritonavir. Therapeutic drug monitoring of TCA and PI is recommended[1,36-37].

Selective serotonin reuptake inhibitors

The main components of this class are fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram. The SSRI are slightly less effective than TCA

but better tolerated[40], which makes them more suitable for long-term therapy. Controlled trials comparing different SSRI are lacking, so no preferred drug may be suggested. It appears that most SSRI may be used in HIV-positive adults[41,42], considering that the most common side effects include anxiety, agitation, akathisia, weight loss, and sexual dysfunction. All SSRI are metabolized at CYP450 isoenzymes[43] so antiretrovirals may change their plasma levels according to their potential to induce or inhibit this pathway. Fluoxetine and paroxetine, inhibitors of CYP2D6, and fluvoxamine, inhibitor of CYP1A2, may cause greater PI plasma levels[44]. Sertraline, citalopram, and escitalopram are better options if interactions with antiretrovirals are to be avoided[45,46].

Serotonin-norepinephrine reuptake inhibitors

Within this group is venlafaxine, which lacks the blocking properties of alpha-1, muscarinic, or histamine receptors of the classic TCA, but retains effectiveness for the treatment of melancholic depression. Extended-release formulation improves compliance and does not affect the bioavailability. It is metabolized by CYP2D6, also acting as weak inhibitor. Duloxetine is indicated for treatment of major depressive disorder and diabetic peripheral neuropathic pain. This SNRI is metabolized by CYP2D6 and CYP1A2, so that PI may enhance toxicity. Patients with pre-existing liver disease are at greater risk for hepatotoxicity by duloxetine[47]. Desvenlafaxine, the active metabolite of venlafaxine, is the most recently approved medication for the treatment of major depressive disorder. Although evidence supports its safety and efficacy, there is no published experience in the HIV population[48].

Norepinephrine reuptake inhibitors

These drugs, with reboxetine being the most popular, have no significant effects on histaminergic, cholinergic, or adrenergic receptors. The most frequent adverse effects are insomnia, sweating, and shivering. There is a small report showing good tolerance of reboxetine in HIV patients[49].

Selective catecholamine reuptake inhibitors

There is only one drug, bupropion, with a selective inhibitory effect on the neuronal reuptake of catecholamines (norepinephrine and dopamine). This compound is an activating antidepressant with common adverse effects, including agitation, anxiety, insomnia, and headache, besides lowering seizure thresholds. As an advantage, bupropion does not cause weight gain or sexual dysfunction and is indicated for treating nicotine dependence, given its effect as a nicotinic acetylcholine receptor antagonist. One open study demonstrated that bupropion is effective for depression in HIV patients. The drug is primarily metabolized by CYP2D6 and has a potent inhibitory effect on this isoenzyme. One *in vitro* study indicated that ritonavir and efavirenz inhibit the hydroxylation of bupropion[50,51].

Enhancers of noradrenergic and serotonergic neurotransmission

These drugs (i.e. nefazodone, trazodone, mirtazapine) increase noradrenergic and 5-HT1 serotoninergic neurotransmission but block 5-HT2 and 5-HT3 serotoninergic receptors. Nefazodone, shown to be effective in the treatment of depression in HIV patients[52], has been removed from the market due to the risk of severe hepatotoxicity. 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. This drug is metabolized by CYP3A4 and CYP2D6, leaving the potential for PI or NNRTI interactions[53]. Mirtazapine is also effective in treating depression in HIV patients[54]. The most commonly reported side effects are sedation, drowsiness, blurred vision, muscle pain, tiredness, increased appetite, and weight gain. The last two can be used as a therapeutic advantage in HIV patients with wasting syndrome. It is metabolized by CYP450 isoenzymes, so that interaction with PI or NNRTI is expected.

Melatonin agonists

Agomelatine is a MT1 and MT2 agonist and 5-HT2C antagonist. It has no effect on monoamine reuptake and no affinity for adrenergic, histaminergic, cholinergic, dopaminergic, or GABAergic receptors. Agomelatine has a reduced level of sexual side effects as well as discontinuation effects compared to some other antidepressants, and may also have positive effects on sleep. Agomelatine is generally well tolerated, but is contraindicated in patients with impaired liver function and in patients taking drugs that potently inhibit CYP1A2. Regular monitoring of liver function tests is recommended. There are no specific data on the use of MA in HIV patients[55,56].

Psychostimulants

Methylphenidate, dextroamphetamine, and pemoline are amphetamine-like medications used in cases of severe apathy in the context of depression. There is a specific indication for these drugs in case of neglect of self-care and nutrition in advanced HIV patients[57,58]. Methylphenidate and pemoline may be used as adjunctive medication in the treatment of persistent and severe fatigue, pain, or neurocognitive disorder in HIV-infected patients. Common adverse effects include appetite suppression, weight loss, insomnia, headaches, edginess, stereotyped movements, and increased pulse rate and blood pressure. The main caveats for psychostimulants are the potential for dependency and lack of information on prolonged treatment. These drugs are metabolized by CYP450[59].

Mood stabilizers

Lithium is most commonly used in HIV patients with primary bipolar disorder[60], with recent evidence suggesting that it may improve neuropsychological functioning in individuals receiving antiretrovirals[61]. Lithium should be used with caution in patients with nephropathy or gastrointestinal disorders. Limitations of lithium are its narrow therapeutic window and frequent toxicity (nausea, vomiting, diarrhea, and tremor). In general, lithium should be avoided in patients with advanced HIV disease. Absence of liver metabolism allows use of lithium along with any antiretroviral[25].

Valproic acid (VPA) may be useful in patients with bipolar disorder, especially patients who develop mania secondary to HIV-related complications or use of psychoactive substances. Concerns have been raised about VPA accelerating the progression of HIV disease by lowering glutathione levels and activating HIV replication[62]. However, a retrospective review in 11 HIV patients treated with VPA found no evidence of increased HIV RNA in those receiving adequate antiretroviral treatment[63]. Because VPA can cause severe hepatitis, it is important to monitor liver enzymes periodically and to avoid its combination with other hepatotoxic drugs (i.e. nevirapine or rifampin). Valproic acid can also cause thrombocytopenia, weight gain, tremor, nystagmus, and ataxia. Divalproex sodium is better tolerated than VPA because it produces fewer gastrointestinal side effects and can be dosed less frequently.

Valproic acid does not appear to exhibit significant CYP450-based drug interactions. It may impair zidovudine metabolism through inhibition of glucuronidation, but there is no evidence of clinical importance[64,65].

Although not absolutely contraindicated, carbamazepine is used less frequently in HIV patients because of the potential to cause bone marrow complications (i.e. leukopenia or aplastic anemia). Carbamazepine is metabolized via CYP3A4 and induces its own metabolism. There is clinical evidence of carbamazepine toxicity resulting from its use in combination with CYP3A4 inhibitors. Conversely, one report showed viral failure caused by the CYP450 induction effects of carbamazepine[64-67].

Lamotrigine has shown efficacy in the treatment of bipolar depression and neuropathic pain. It is not metabolized through the CYP450 system but by glucuronidation. Ritonavir may decrease lamotrigine levels by induction of UDP-glucuronyltransferase[68,69]. Lamotrigine can cause life-threatening rashes, such as Stevens-Johnson syndrome, when the doses are increased rapidly.

Gabapentin has been used successfully to treat HIV patients with peripheral neuropathy[70]. No current data support gabapentin use for mood disorders, and experience for the treatment of anxiety disorders or manifestations of substance abuse is limited. Gabapentin is commonly used as adjunctive medication in multiple psychiatric disorders, where it may offer some advantages over other anticonvulsants. It does not bind to plasma proteins and has no hepatic metabolism so interactions with antiretrovirals are not expected[64,65].

Topiramate is ineffective in bipolar disorders, although widely used in impulse control in multiple psychiatric disorders[71].

Pregabalin is an anticonvulsant drug used for neuropathic pain and as an adjunct therapy for partial seizures, with or without secondary generalization in adults. It is also effective for generalized anxiety disorder and chronic pain in patients with fibromyalgia and spinal cord injury. However, despite pregabalin being well tolerated, it is not superior to placebo in the treatment of painful HIV neuropathy[72]. Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. No pharmacokinetic interactions have been demonstrated *in vivo*[64] (Table 4).

Antipsychotic drugs

Also called neuroleptics, this family includes both older “typical” and newer “atypical” medications. They

Table 4. Main pharmacokinetic parameters of mood stabilizers

	Plasma protein binding (%)	Liver metabolism (%)	CYP450 isoenzyme
Carbamazepine	75	95	Metabolic pathway: 3A4 >> 2C8, 1A2 Induction: 3A4, 2D6, 2C9, 2C19, 1A2 and UGT Active metabolite: epoxidehydrolase
Oxcarbazepine	40	5	Metabolic pathway: 3A4, C19 Induction: 3A4 Inhibition: C19
Valproate	90	20	Metabolic pathway: UGT (50%), mitochondrial oxidation (40%), minor CYP450 dependent Inhibition: UGT, 2C9, 2C19
Lamotrigine	55	90	Metabolic pathway: UGT Induction: UGT
Topiramate	15	20	Excreted unchanged in urine (55-97%) Induction: 3A4 Inhibition: 2C19
Gabapentin	0	0	Excreted unchanged in urine
Pregabalin	0	0	Excreted unchanged in urine

UGT: uridine-5'-diphospho-glucuronosyltransferase.

are mostly indicated for treatment of schizophrenia and acute mania, in addition to adjunctive drugs for other conditions, including delirium. Typical neuroleptics (i.e. chlorpromazine and haloperidol) are specific dopamine (D2) receptor antagonists. Atypical antipsychotics also interact with other receptors such as serotoninergic. The use of atypical antipsychotics has flourished due to their efficacy in treating psychotic conditions and the decreased frequency of extrapyramidal adverse effects.

There are little specific data on the safety or efficacy of antipsychotic medications in asymptomatic HIV patients. Advanced HIV infection may cause damage in basal ganglia, predisposing patients to Parkinson-like symptoms even without the use of antipsychotic medication[73-75].

In late-stage HIV infection, the pattern of response to antipsychotic medications is similar to that seen in the elderly, so the "start low, go slow" should be applied and atypical antipsychotics are preferred[4]. Use of depot formulations of antipsychotics is generally contraindicated in patients with AIDS due to increased risk of extrapyramidal effects. Anticholinergic medications to prevent extrapyramidal effects are not indicated due to increased risk of delirium. Classical neuroleptics, such as chlorpromazine and levomepromazine, may also cause cardiovascular side effects[1,25].

Another issue at the time of electing an antipsychotic in HIV patients is that many of them can trigger significant metabolic adverse effects (i.e. hyperglycemia, hypercholesterolemia, and weight gain), especially some of the newer antipsychotics such as olanzapine or quetiapine[76]. Also, there are special considerations when prescribing antiretroviral medications to patients taking clozapine like the risk for agranulocytosis that limits the use of these drugs in HIV patients[77].

CYP450 inhibitors have the potential to increase the concentration of clozapine and pimozide, which are contraindicated along with ritonavir. Conversely, ritonavir decreases olanzapine plasma levels by enhancing CYP1A2 and UDP-glucoronyltransferase[78]. The potential for toxic increases by CYP450 inhibitors exists for other antipsychotics, including chlorpromazine, haloperidol, quetiapine, and risperidone[79,80] (Tables 5 and 6).

Substance and alcohol abuse treatment

Deleterious consumption of alcohol or toxics remains a serious problem among HIV patients. Successful treatment of substance abuse should include both behavioral therapy and medication-assisted treatment, and may result in normalization of behavior, reduction of medical complications and risk behaviors, and enhancement of adherence to antiretrovirals. Medication-assisted treatment includes management of the following[4].

Table 5. Metabolism and interactions of classic antipsychotics

	Liver metabolism at CYP450 isoenzymes	Interactions
Chlorpromazine	2D6 (↓), 1A2, 3A4	Greater levels with PI
Haloperidol	2D6 (↓)	Greater levels with PI
Trifluoperazine	1A2	Greater levels with PI
Pimozide	3A4	Contraindicated with PI and NNRTI
Fluphenazine	2D6 (↓)	Greater levels with PI
Clozapine	1A2 >> 2D6, 3A4, 2C19	Greater levels with PI

(↓) inhibition of isoenzyme; PI: protease inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor.

Table 6. Metabolism and interactions of atypical antipsychotics

	Liver metabolism at CYP450 isoenzymes	Interactions
Amisulpride	No	No
Olanzapine	UGT >> 1A2 (↓) > 2D6 > 3A4 (↓)	Potential with PI and NNRTI
Quetiapine	3A4	Potential with PI and NNRTI
Risperidone	2D6 (↓) > 3A4	Potential with PI
Ziprasidone	3A4	Greater levels with PI
Aripiprazole	3A4, 2D6	Greater levels with PI
Paliperidone	3A4, 2D6	No
Asenapine	1A2 > 3A4, 2D6 (↓)	Unknown

(↓) inhibition of isoenzyme; UGT: uridine-5'-diphospho-glucuronosyltransferase; PI: protease inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor.

Opioid dependence

Pharmacological treatments for addiction to opiates is made up of two groups of substances that act on specific brain receptors, some blocking (antagonists) and other mimicking (agonists) the effect of opioids. Depending on whether the goal is total abstinence or replacement, respective use of one or the other is indicated.

The main opioid agonists used in maintenance treatment are methadone and buprenorphine. On the other hand, the most widely used opioid antagonist in heroin dependence is naltrexone. Interactions between methadone or buprenorphine and antiretrovirals can result in suboptimal or excessive levels of the opiate therapy or of the other medication[81-83].

Methadone is metabolized via CYP2D6 and CYP2C19, with mixed results in the literature on the involvement of CYP3A4, and with minor involvement of CYP2C8 and CYP2D6 pathways[84]. Buprenorphine is primarily converted to an active metabolite, norbuprenorphine, via CYP3A4 and to a lesser extent by CYP2C8[85-87]. Buprenorphine and its metabolite norbuprenorphine are further metabolized by glucuronidation, reducing the potential of competing with other drugs in the CYP450 system, and therefore reducing the likelihood of clinically significant drug interactions when compared to methadone[88]. Neither methadone nor buprenorphine are major inducers or inhibitors of CYP450 enzymes; however, they could compete with other medications metabolized by these same pathways. Tables 7 and 8 summarize the main interactions between antiretroviral drugs and methadone or buprenorphine[89,90].

A once-monthly, extended-release, intramuscular formulation of naltrexone was recently approved for prevention of relapse in patients who have undergone an opioid detoxification program. Naltrexone is also

Table 7. Interactions between methadone and antiretroviral medications

Increases levels of methadone	**No interaction with methadone**
Maraviroc Etravirine	Atazanavir Raltegravir Enfuvirtide
Decreases levels of methadone	**Interactions with methadone**
Efavirenz Nevirapine Darunavir Fosamprenavir Lopinavir Saquinavir Ritonavir	Increase of zidovudine levels (40%)

Table 8. Interactions between buprenorphine and antiretroviral medications

Increases levels of buprenorphine	**No interaction with buprenorphine**
Ritonavir Atazanavir	Lopinavir Darunavir
Decreases levels of buprenorphine	**Unknown interactions with buprenorphine**
Efavirenz Nevirapine	Etravirine

indicated for treatment of alcohol dependency. Naltrexone is not metabolized via the CYP450 and is not expected to interact with antiretrovirals (Food and Drug Administration, FDA; Vivitrolhttp://www.ashm.org.au/projects/arvguidelines/Default.asp?PublicationID=4&ParentSectionID=449&SectionID=491).

Alcohol dependence

Some drugs may be used to prevent alcohol abuse in heavy drinkers. Naltrexone may reduce craving, the reward effect, and the amount of alcohol consumed at relapse. Acamprosate may reduce craving by normalizing glutamatergic neurotransmission and may attenuate relapse. It does not have any known drug interactions. Disulfiram requires the patient´s motivation as it has the potential to produce noxious responses (severe flushing, palpitations, nausea, and vomiting) if alcohol is ingested by interference with the enzyme alcohol dehydrogenase. Although disulfiram is also extensively metabolized in the liver, the CYP450 system is not involved. Certain antiretroviral medications are manufactured as liquid preparations that contain alcohol (e.g. amprenavir oral solution, lopinavir/ritonavir, and ritonavir). Although the amount of alcohol may be minimal, a disulfiram reaction can occur if patients take these liquid formulations with concurrent disulfiram therapy[4].

There are no approved medications for other stimulant use disorders (i.e. cocaine, methamphetamine), cannabis, or sedative/hypnotic use disorders. Effective pharmacotherapies for these addictions are an ongoing focus of research.

Conclusions

In general, psychotropic drugs are effective and well tolerated, although controlled studies are lacking in the HIV infected population. Appropriate psychiatric care of HIV-positive patients is likely to decrease the incidence of medical complications and improve quality of life. Unfortunately, access to mental health services specialized in treating HIV-infected patients is frequently limited or not available. The HIV healthcare providers should be aware of the indications, pharmacokinetics, adverse effects, and potential interactions of psychotropic medications with antiretroviral therapy.

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