Choosing Antidepressants for HIV and AIDS Patients:
Insights on Safety and Side Effects

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ABSTRACT

Human immunodeficiency virus (HIV) has a high comorbidity with major depression. Symptoms of depression may be attributed to ongoing HIV infection, thereby reducing the likelihood of timely treatment with antidepressants. This may contribute to the morbidity of both illnesses. This review focuses on an evidence-based approach to selecting antidepressants for first-line treatment of major depressive disorder in patients with HIV and acquired immune deficiency syndrome (AIDS). Some antidepressant medications have side effect profiles that may exacerbate the symptoms commonly seen in patients with HIV and AIDS. Others have side effects that, while normally problematic in the general population, may be helpful in counteracting the difficulties seen in HIV and AIDS patients. Other challenges in treatment include an array of possible drug-drug interactions between antidepressants and HIV medications. Clinicians should focus more on capitalizing on the side effects of psychotropic medications in this patient population than on trying to avoid drug-drug interactions.

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INTRODUCTION

Diagnosing and treating major depressive disorder in patients with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) is a critical issue for clinicians as it is common and its effects are significant. Symptoms of both illnesses often overlap and obscure diagnostic and treatment interventions. Depression in HIV is also a significant contributor to the morbidity of HIV itself. It can decrease quality of life for these patients, decrease adherence with HIV medications, and it has shown to decrease positive outcomes overall.[1] A study of over 3,000 patients with HIV started on nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) found the proportion of individuals with adherence of 80 percent or better was 26 percent, and concluded that nonadherence is therefore the biggest cause of failure of these medicines.[2] Furthermore, depression and HIV both negatively impact the course of each other concurrently. It is imperative that clinicians treat both conditions simultaneously with well-coordinated treatment plans.

This review will examine the efficacy, side effects, and drug interactions of antidepressants in this patient population. Clinicians must consider all three concerns simultaneously when selecting a first-line antidepressant medication for a patient with HIV or AIDS.

EFFICACY AND ADVANTAGES

At first glance, there is no reason to think that antidepressants that successfully treat depression in the general population would not be effective in treating depression in people with HIV. However, in the world of evidence-based medicine, inductive reasoning needs to be backed up by data. Hence, there are studies that have shown that similarly to major depression in the general population, antidepressants have efficacy in HIV patients. Selective serotonin reuptake inhibitors (SSRIs) continue to cause less side effects than tricyclic antidepressants (TCAs), but no single SSRI has emerged as clearly more effective than others.[11]

Data like this often shape the practice of treating major depression by persuading psychiatrists to use multiple trials of SSRIs before trying a TCA or other older classes of medicine. However, studies have not been able to show that interclass switching as opposed to switching to a new class has a clear advantage in treating symptoms.[12,29] Often combination treatment and augmentation treatment can be helpful in nonresponders or partial responders.

There are many studies that have looked at the efficacy of particular antidepressants in HIV and AIDS patients specifically. A 20-person, prospective study of sustained-release bupropion suggested it is effective for the treatment of depression in HIV-positive patients, regardless of HIV clinical staging.[19] A 15-person, prospective study of nefazodone showed that depressed HIV outpatients responded as well to nefazodone as other outpatient populations did.[20]

Medications that have shown efficacy in treating depression in patients with HIV include imipramine, desipramine, nortriptyline, amitriptyline, fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine, venlafaxaine, nefazodone, trazodone, bupropion, and mirtazapine.[21] However, only imipramine, fluoxetine, sertraline, and paroxetine have evidence from double-blind trials.[27]

Despite all these studies, no type of antidepressant has emerged as clearly superior. However, just because they all seem to work equally well, does not mean they are equal in every way. Antidepressants have different likelihoods of side effects and causing interactions with other medications. Side effects, the subject of the next section, are often the most helpful factors in making decisions about which antidepressants to use. Negative side effects will impact patient adherence, strongly impacting efficacy of treatment.

TOLERABILITY AND SIDE EFFECTS

TCAs have been shown to be equally effective to the newer antidepressant medications. Many psychiatrists have removed them from first-line treatment for depression because they feel their side effect profiles are less tolerable. However, while the side effects are different than those of SSRIs, in certain patients the side effects may actually be more tolerable. Other older antidepressants like monoamine oxidase inhibitors (MAOIs) have generally fallen below both SSRIs and TCAs in the treatment line, mainly because of concerns about strict dietary precautions that must be maintained when using these medications.

TCAs have anticholinergic side effects that include dry mouth, blurred vision, decreased gastrointestinal (GI) motility (promoting constipation and decreasing diarrhea), and urinary retention. Other side effects include drowsiness, confusion, dizziness, weight gain, hypotension, and tachycardia. However, some of these side effects can be taken advantage of when treating HIV and AIDS patients, specifically weight gain, increased sleep, and decreased diarrhea. By starting at low doses and increasing slowly, the clinician may see a favorable ratio of the positive and negative effects of the medicine being reached in the patient.

SSRIs can be activating, sedating, or neutral. These medications also commonly affect patients gastrointestinally and sexually in a negative manner. However, bupropion is one medicine in this group that does not show sexual side effects. Sustained-release bupropion appears to be well tolerated in patients with AIDS-related medical conditions.[22] Other newer medicines have also been studied for tolerability. Depressed HIV

outpatients taking nefazodone had few adverse effects.[20]

USING SIDE EFFECTS TO TREAT SYMPTOMS OF HIV

Knowledge of individual side effects associated with the various antidepressants and antidepressant classes can be helpful when deciding which to use with any depressed patient. However, HIV patients present specific challenges because of their medical problems and diverse symptoms. Ideally, a well-informed selection of antidepressant treatment a patient with HIV or AIDS involves broad consideration of all of the patient's symptoms. Side effect profiles of antidepressants may be exploited in that they can be beneficial in some circumstances.

Fatigue. One study showed that the prevalence of clinical fatigue in men with CD4 counts less than 500 was 14 percent. This was significantly higher than HIV- men and HIV+ men with CD4 counts greater than 500. The study showed that the fatigue was not directly correlated with CD4 count or HIV ribonucleic acid (RNA). It was thought to be associated with depression in HIV patients, but did not seem to be merely a symptom of depression.[22] If a patient complains of fatigue, the clinician would not want to worsen that symptom by prescribing an antidepressant that would cause sedation, and the clinician may want to offer an antidepressant that has been shown to be more stimulating.

Studies comparing antidepressants specifically treating symptoms of fatigue are rare. It is usually expected that the fatigue will decrease as the depression improves. Buproprion is known to be stimulating, but has shown a slight increase in risk of seizures.[26] Of the SSRIs, we believe fluoxetine, anecdotally, is the most stimulating.

Insomnia. Many HIV patients may experience insomnia as part of their depression. These patients may benefit from sedating antidepressants and may have worsened insomnia by stimulating antidepressants.

All of the TCAs can be sedating. One study suggests that stimulation of serotonin 5-HT2 receptors as seen in SSRIs can worsen insomnia, but that antidepressant drugs with 5-HT2 blocking properties are a good option for treating depressed patients with insomnia. These include medicines such as trazodone, nefazodone, and mirtazapine.[25] Paroxetine is an SSRI that has sedative effects in some people.

Treating weight loss. A two-year, prospective, HIV study showed that 58 (31%) of 187 enrolled HIV+ men had significant body mass depletion at some point during the study, and many of them showed consistent weight loss during the study. The additional weight loss correlated with 'increased fatigue, global distress and depressive symptomatology, and reduced life satisfaction.'[23]

Many antidepressants are associated with weight gain. All MAOIs and TCAs have been shown to have associated weight gain. Within the SSRI group, paroxetine has shown the most association with weight gain, but sertraline, mirtazapine, and fluvoxamine also have associations. Venlafaxine and nefazadone have no weight changes, and patients on bupropion have been shown to lose weight.[24]

Treating diarrhea. The anticholinergic side effects of TCAs that normally cause constipation may be helpful when patients have diarrhea. Mirtazapine can also be constipating.

Treating chronic pain. Many HIV-infected patients have chronic pain from relating medical issues or comorbidity with opioid dependence. Some antidepressants have a role in decreasing chronic pain.

Trazodone does not appear to be effective for treating chronic pain. Bupropion, venlafaxine, and duloxetine have been shown to relieve different kinds of chronic pain. Other antidepressants do not have clear data on this matter.[28]

CONCERNS OF DRUG INTERACTIONS

The HIV drug ritonavir is a protease inhibitor that can be given at a small dose as a synergistic enhancer, reducing the liver metabolism of other antiretroviral drugs. It is often given in combination with the protease inhibitor lopinavir (in a form called kaletra) in a 1:5 ratio. It also enhances other protease inhibitors (saquinavir, atazanavir). Ritonavir has been a main focus of study when looking at interactions between antidepressants and HIV medicines.

TCAs. TCAs, including nortriptyline, desipramine, imipramine, amitriptyline, clomipramine, and doxepin, have all been shown to have increased levels in plasma by ritonavir and ritonavir combinations. However, these increases have often been shown to be problematic even to the point of needing dose adjustments. Furthermore, TCA blood levels can and should be checked even in patients not on other medications with possible interactions.

Desipramine, in the setting of ritonavir, was shown to have clearance decreased by 59 percent. In the setting of nelfinavir, desipramine was shown to have increased blood levels. Both ritonavir and nelfinavir independently showed potential to increase TCA side effects.[13,14] Despite possible increased

Ideally, a well-informed selection of antidepressant treatment in a patient with HIV or AIDS involves broad consideration of all of the patient's symptoms. Side effect profiles of antidepressants may be exploited in that they can be beneficial in some circumstances.

TABLE 1. Theoretical CYP inhibitions and actual effects of SSRIs and other antidepressants in the setting of retroviruses

SSRI OR OTHER NEW ANTIDEPRESSANTS	CYP INHIBITIONS	ACTUAL EFFECTS TO RETROVIRAL LEVLS	ACTUAL EFFECTS TO ANTIDEPRESSANT LEVELS
Fluoxetine and metabolite norfluoxetine	Strong: CYP2D6 Weak: CYP3A4	Increased	None
Paroxetine	Strong: CYP2D6	None	Decreased
Sertroline	Weak: CYP2D6	None	Decreased
Citalopram	None	None	None
Fluvoxamine	Strong: CYP1A2, CYP2C19 Weak: CYP2C9, CYP2D6, CYP3A4	Unknown	Unknown
Nefazadone	Strong: CYP3A4	Unknown	Unknown
Trazodone	Unknown	None	Increased
Venlafaxine	Some weak	Unknown	Unknown
Mirtazapine	Some weak	Unknown	Unknown
Reboxetine	Some weak	Unknown	Unknown
Escitalopram	Unclear	Unknown	Unknown

desipramine levels in the setting of antiretrovirals, it is not thought that desipramine would require dose adjustments.[6] Amitriptyline in the setting of ritonavir showed increased levels and potential for increased TCA side effects.

There have also been studies that show that some antifungals, such as terbinafine, can inhibit the metabolism of TCAs, specifically nortriptyline and desipramine.[7]

SSRIs. SSRIs that have been shown to have decreased metabolism in the setting of ritonavir include sertraline and citalopram. Paroxetine and escitalopram have no data on this. Fluoxetine and fluvoxamine are both decreased by nevirapine, and they both increase the levels of the following HIV medications: amprenavir, delarvidine, efavirenz, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, and saquinavir.[4]

Escitalopram. Escitalopram in the setting of ritonavir showed no effect on levels or side effects.[13,16]

Fluoxetine. Fluoxetine in the setting of delavirdine showed that the delavirdine C_{min} increased by 50 percent, and there were some increased delavirdine effects. Fluoxetine in the setting of ritonavir had a ritonavir AUC increased by 19 percent, no change to C_{max}, and increased ritonavir effects. There was no effect on fluoxetine levels or side effects.[13,15]

Paroxetine. Paroxetine in the setting of darunavir showed a decreased paroxetine AUC by 39 percent, C_{max} by 36 percent, C_{min} by 37 percent, and showed decreased paroxetine effects. In the setting of fosamprenavir, paroxetine had similar results with a decreased AUC by 58 percent, C_{max} by 60 percent, and half-life of 25 percent, with decreased paroxetine effects. The retrovirals did not have affected levels.[13,17]

Sertaline. Sertraline in the setting of darunavir showed decreased AUC by 49 percent, C_{max} by 44 percent, and C_{min} by 49 percent with decreased sertraline effects. There were no effects on the darunavir levels or efficacy.[13]

Citalopram. Citalopram has been shown to have no interactions with ritonavir.[18]

Trazodone. Trazodone has the most studies (darunavir, indinavir, lopinavir/ritonavir, ritonavir [x2]), and all five of these studies showed potential to increase the trazodone side effects of nausea, dizziness, hypotension, and syncope.[13] Additionally, in the setting of darunavir and lopinavir/ritonavir, there were increased trazodone concentrations, and both ritonavir studies showed specifically that trazodone had an increased AUC by 240 percent, C_{max} by 34 percent, and a half-life by 220 percent.[13]

Theoretical interactions. Outside of these measured effects, knowledge about the metabolism of other similar antidepressant medications can lead to theoretical effects of combination with antiretroviral medications. Many SSRIs and new multireceptor targeting medications are known to be weak or potent inhibitors on the CYP isoforms.[9,10]

While most studies show no clinical significance of the interactions of antidepressants and HIV medications, one report alerts of five cases of serotonin syndrome that developed after patients who were taking fluoxetine ingested antiretrovirals that were P450 inhibitors.[8]

However, theoretical possibilities or small case reports should not guide treatment in all cases. Until bigger trends can be shown, clearly defined side effects of drugs and drug classes are better suited to serve as a guide for treatment. This is what will determine patient

adherence with treatment plans, and in the real world setting, nothing is more important than getting patients to take their medicines.

See Table 1 for theoretical CYP inhibitions and actual effects of SSRIs and other antidepressants in the setting of retroviruses.

GUIDELINES AND SUMMARY

Patients with HIV and AIDS should be frequently monitored for depressive symptoms, and those that have them should be monitored by one of many available scales of depression symptoms. Education about HIV and mental health is always helpful, and talk therapy of different types can have benefit regardless of psychiatric diagnosis because of the stressors related to having HIV and AIDS.

Major depressive disorder should be diagnosed carefully. However, in many cases, clinicians should have a low threshold for initiating treatment in this patient population. If the syndrome of major depression can be discerned and criteria are met, then treatment is certainly warranted. However, treatment can be justified even without meeting full criteria if certain symptoms are intense or dangerous, such as suicidality, if patients are nonadherent with HIV medications in the setting of low mood or other depressive symptoms, or if there are side effects of antidepressants that can be used for their positive treatment effects.

When it is decided to treat depression with a medication, normal methods of treating depression are applicable. Start slow and taper up. Do not recommend discontinuation of a drug because of side effects during the first week, unless severe. If the medication is tolerable but ineffective, then a full trial should be continued for 4 to 6 weeks at a therapeutic dose. If it is working but causing undesirable side effects, use other medications to fight those side effects to a reasonable degree. If there is partial success, use augmentation or a second agent.

Both TCAs and SSRIs/multireceptor antidepressants are equally effective treatments. Both have theoretical drug interactions with antiretroviral medications, but these effects have not been shown clinically to be strong enough to affect the choice of antiretroviral or antidepressant class of medicine to use first line. SSRIs are considered the safest, particularly in the case of overdose, and they tend to have less side effects. Though there are theoretically different risks of interacting with HIV medicines, it is more practical to choose medicines based on their side effect profiles.

TCAs, while not first line generally, have the advantage in that their levels can be monitored, which helps to prevent toxicity and increase patient adherence. In treating major depression in the general population, it is not unusual to try several antidepressants in the newer classes before initiating a trial of TCAs. In patients with more advanced AIDs or with somatic symptoms that may be amenable to side effects of TCA, such as diarrhea, insomnia, or weight loss, TCAs would be appropriate first-line treatment for depression.

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