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Safety Considerations in Drug Treatment of Depression in HIV-Positive Patients

An Updated Review

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Abstract

Major depressive disorder (MDD) is one of the most prevalent illnesses associated with HIV infection, and negatively affects medication adherence, disease progression and mortality in HIV disease. Co-morbid treatment of major depression in HIV disease is the optimal therapeutic approach, but discriminating MDD from normal fluctuations in mood state, personality or physiology is difficult. Definitive diagnosis of MDD is critical for drug safety and for avoiding unnecessary exposure to psychotropic medications. HIV patients respond to antidepressant treatment like the general population, and medication adverse effects and patient adherence are the best predictors of treatment outcome.

This review attempts to assist the medical provider with the diagnosis and treatment of MDD in HIV patients. We outline the initial steps in screening and psychiatric referral, the antidepressants that are particularly useful in HIV-infected patients, and the adverse effects and pharmacological strategies for overcoming potential barriers to medication adherence. Potential interactions

between the various classes of antidepressants and HIV/antiretroviral therapy, as well as management of HIV medication-related psychiatric adverse effects, are also discussed.

1. Importance of Treating Major Depression in HIV Patients

Depending on the subpopulation of HIV seropositive patients studied, prevalence rates of major depressive disorder (MDD) are estimated to be as high as 42%.[1-5] Meta-analysis of studies of HIV-infected patients demonstrates a 2-fold increase in the prevalence of major depression compared with non-infected patients.[6-9] MDD is even more pronounced in late-stage HIV disease,[10] with both retrospective and prospective studies reporting a 2.5-fold increase in rates of depression in patients with CD4 cell counts <200 cells/μL.[11-13] Unfortunately, depression is often unrecognized in patients with HIV infection and AIDS. Although treatment of depression in HIV-infected patients clearly improves psychosocial functioning,[14,15] depressive illness still remains underdiagnosed and undertreated in medical clinics.[16-18] Depression negatively impacts patient adherence, quality of life,[19,20] treatment outcome[21-23] and functionality[22,24,25] in patients with HIV. Although two early studies failed to show a relationship between depression and HIV disease markers,[26,27] longitudinal studies[11,12,28] and those conducted over longer periods[29] found that progression of HIV was related to depression.

In addition to hastening HIV disease progression and mortality, depression further facilitates viral transmission and hinders effective treatment in HIV disease itself.[11,30-32] Increased suicidal thoughts and behaviours have also been associated with lower CD4 counts and higher viral loads,[10,33-37] and a cycle of reinforcement between depression and HIV illness is further exacerbated by self-defeating behaviours often seen in this patient population. The antiretroviral therapies used to treat HIV illness decrease virus production, but may also precipitate or worsen MDD.[30,38-40] Proper diagnosis and treatment of MDD in patients with HIV is essential for effective treatment of their viral illness and mental health. The aim of this review is to update an earlier review of safety considerations in the drug treatment of HIV-positive patients with depression.[41]

2. Diagnosis of Major Depression

A practical and effective approach to evaluating mood changes in HIV-infected patients will ensure appropriate patient treatment, while also minimizing the risk of unnecessary exposure to psychotropic medications with potentially harmful adverse effects. Inherent interactions between psychotropic medications and anti-HIV pharmacological therapies make it particularly important to establish an accurate diagnosis. Diagnosis of depressive complaints is complicated by manifestations of personal grief, dementia, co-morbid brain infection, substance abuse and medical treatments that alter mental function and mimic depression in HIV-infected patients.[42] Depressed HIV-infected patients frequently present to internists and family practitioners with a wide variety of nonspecific somatic complaints of no clear aetiology, such as headache, dizziness, fatigue, weakness, sensory loss/anaesthesia, gastrointestinal discomfort, musculoskeletal or visceral pain and cardiac symptoms;[43-45] therefore, depression screening should be part of the annual physical assessment, in addition to being initiated when symptoms are suspected.[46] Complex somatic complaints of unclear aetiology are often surrogate symptoms for MDD. If the diagnosis of depression is suspected but unclear, patients with HIV should be referred for a comprehensive psychiatric evaluation in order to guide the safe and effective treatment of possible depressive illness.

The differential diagnosis for HIV-infected patients reporting mood symptoms includes major depression, demoralization, dysthymia, dementia, delirium, intoxication, withdrawal from sub-

stances, CNS injury, CNS infection and acute medical illness. Although a complete description of the diagnostic nuances of major depression is beyond the scope of this review, it is important for all treating physicians to understand that major depression produces a constellation of deficits in the domain of affective well being.[16,47,48] The *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR)[49] lists known causes of depression and contains inclusive criteria for making the diagnosis (table I). Although the DSM-IV-TR summarizes the primary functions of affective well being, including mood, vital sense, self-attitude and hedonic responsiveness, understanding the subtle differences between each component is essential for being able to exclude MDD in the differential diagnosis of HIV-infected patients with mood symptoms.

Mood describes the prevailing emotional tone of one's personal experiences, and depressed patients may describe feeling blue, low, sad, flat, devoid of emotion, empty, miserable, anxious, worried, upset, irritable or angry. HIV-infected patients with MDD may not say they are sad, but instead experience anxiety, apathy or irritability as a result of their low mood.[50] Depressed HIV-infected patients may also sometimes appear apathetic and describe their mood state as an uneasy or uncomfortable feeling, commonly worse in the morning and better in the afternoon.[51,52] Vital sense is a subjective sense of healthy energy and contentment. Depressed patients may report a physical feeling of heavy pressure in their chest accompanied by a sense of low energy and occasional feeling of impending demise.[53] Self-attitude describes feelings directed at one's self. Depressed patients often feel guilty and consider themselves undeserving of good things in their life. They also frequently report a sense that they have failed their loved ones.[54]

Anhedonia in depressed patients typically manifests as suppression of the sense of pleasure or reward that would normally be associated with various activities. The most common activities are those driven by sleep, appetite and sex, as well as those associated with daily functioning, such as work, hobbies, dress, social activity and artistic expression. In the anhedonic state, normal responsiveness to personal enjoyment or positive reinforcement related to these activities is blunted or absent. The presence of pervasive anhedonia strongly predicts major depression in HIV-infected patients.[55] Demoralized patients, on the other hand, can often be distracted from their sadness. For example, hospitalized demoralized patients

Table I. Diagnostic criteria for a single episode of major depressive disorder summarized from the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV TR)[49]

A. Five (or more) of the following symptoms have been present during the same 2-wk period and represent a change from previous functioning; at least one of the symptoms is either (i) depressed mood; or (ii) loss of interest Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful) Note: In children and adolescents, can be irritable mood
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3. Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of bodyweight in 1 month), or decrease or increase in appetite nearly every day Note: In children, consider failure to make expected weight gains
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings or restlessness or being slowed down)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either subjective account or as observed by others)
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms do not meet criteria for a mixed episode
C. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning
D. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism)
E. The symptoms are not better accounted for by bereavement, i.e. after the loss of a loved one; the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

may enjoy family visits but then return to a demoralized state afterwards, whereas depressed patients typically report that they are unable to enjoy this experience and may even desire their family to leave so that they can be alone with their grief.

Neurovegetative symptoms, such as difficulties with sleep, appetite, concentration and memory are other cardinal features of MDD. Sleep disturbances may include insomnia or hypersomnia. Patients usually experience early morning awakening and report difficulty falling back asleep. Appetite may be either increased or decreased, and patients often complain that food has lost its flavour. Impairments in concentration and short-term memory may manifest as slowed thought processes or generalized confusion. Subjective reports of fatigue and insomnia may also be uniquely associated with depression in HIV-infected patients as studies have shown that worsening fatigue and insomnia at 6-month follow-up is highly correlated with worsening depression and not with absolute CD4 count, change in CD4 count or disease progression by CD4 criteria.[56,57]

In addition to careful clinical assessment as outlined above, routine psychiatric screening tools can be effective in diagnosing MDD in the primary care setting. The combination of two brief psychiatric questionnaires, the Beck Depression Inventory (BDI)[58] and the General Health Questionnaire (GHQ)[59] are reliable indicators of MDD. These instruments have been validated in a series of patients with a comprehensive psychiatric evaluation to show that a score of >14 on the BDI or a score of >6 on the GHQ prospectively predicts a psychiatric disorder other than substance abuse with a sensitivity of 81%, specificity of 61% and positive predictive value of 71%.[18] Numerous other screening questionnaires are available and have similar value in screening for depression. Patients who score above the screening threshold should be referred to a psychiatrist for further diagnosis and treatment.

3. Pharmacological Treatment of Major Depression in HIV Disease

Pharmacotherapy is the mainstay of treatment for major depression, and HIV-infected patients with this disorder respond similarly to antidepressants, as do other patients with major depression. Given that no particular antidepressant medication has been shown to be superior for treatment of depressed HIV-infected patients in controlled clinical trials, medication options should be directed by other properties of the drug. For example, antidepressants that cause weight gain are useful in patients with anorexia and weight loss, and antidepressants useful in chronic neuropathic pain may provide a secondary benefit based on this property.[50] Studies have shown that HIV-infected patients with major depression can be effectively treated with typical antidepressant medications,[60] including fluoxetine,[61] paroxetine[62] and tricyclic antidepressants (TCAs).[63] Trazodone, although a poor antidepressant at low doses, has been shown to improve sleep in patients who are demoralized but not necessarily clinically depressed.[64] While there are few studies that examine whether antidepressants directly alter the HIV virus, notably, derivatives of the antidepressants paroxetine and femoxetine, such as cis(Z)- and trans(E)-flupentixol, have been shown to directly inhibit HIV replication.[65]

Figure 1 outlines a general algorithm for pharmacological treatment of major depression, which should be followed on an individual patient basis, and which takes into account important adverse effects and pharmacological interactions. Thus, 'first-line' pharmacological therapy is patient-specific and cannot be generalized to any particular class of antidepressant. The most important component of treatment of major depression in HIV-disease is patient adherence, which is highly influenced by antidepressant adverse effects.[42,62,63,66-69] The first week of treatment with a drug usually determines whether a patient will be able to tolerate it. An optimal treatment strategy is to start with low doses of medication and slowly titrate up to a therapeutic dose in order to minimize early adverse effects that may act as obstacles to adherence. Once a therapeutic dosage is achieved, patients should be encouraged to anticipate a 4–8 week interval before experiencing a therapeutic effect.

Table II outlines dosages and potential advantages of antidepressants that are important

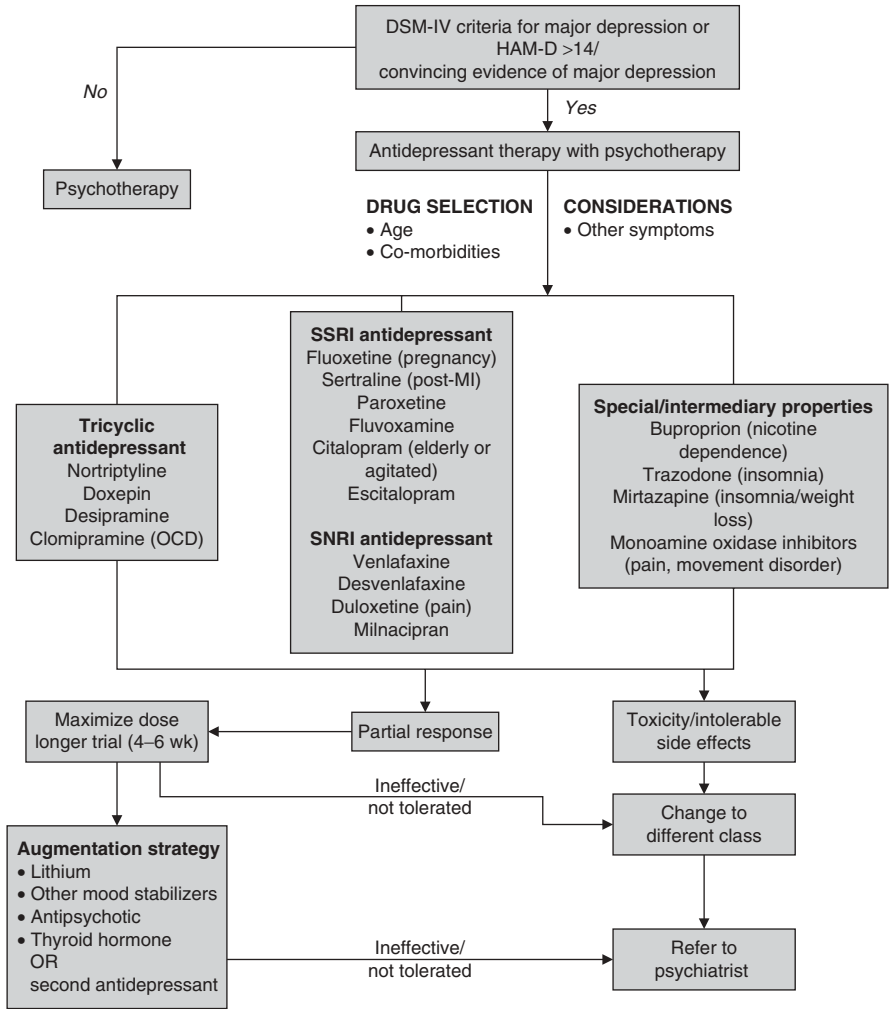

Fig. 1. Algorithm for pharmacological treatment of depression (reproduced from Pieper and Treisman,[41] with permission from Adis, a Wolters Kluwer business. © Adis Data Information BV 2005. All rights reserved). **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; **HAM-D** = Hamilton Depression Rating Scale; **MI** = myocardial infarction; **OCD** = obsessive compulsive disorder; **SNRI** = selective norepinephrine (noradrenaline) reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor.

in HIV disease. Individual agents or classes of antidepressants with adverse effect profiles least likely to exacerbate a patient's syndrome should be used first. For example, medications associated with increased gastrointestinal motility should be avoided as much as possible in a patient suffering from frequent bouts of diarrhoea.[70] Adverse effects should be assessed at every visit and treated aggressively. Insomnia, a common adverse effect of selective serotonin reuptake inhibitors (SSRIs), can often be addressed effectively with low-dose trazodone (25–150 mg) at bedtime.[71,72] Constipation from TCAs can be addressed by increased water and fibre intake.

One of the most discussed adverse effects of antidepressants is weight gain. Although many antidepressants are associated with weight gain, factors other than the medication, such as overeating, lack of exercise and regaining weight after

Table II. Dosages and potential advantages of antidepressants in HIV disease (adapted from Pieper and Treisman,[41] with permission from Adis, a Wolters Kluwer business. © Adis Data Information BV 2005. All rights reserved)

Drug	Start dose	Usual therapeutic dose	Therapeutic serum level	Advantages	Interactions with HIV medications
Fluoxetine	10 mg qam	20–40 mg qam	Unclear	Activating	Levels decreased by nevirapine. Fluoxetine also increases levels of amprenavir, delavirdine, efavirenz, indinavir, nelfinavir, ritonavir, saquinavir
Sertraline	25–50 mg qam	50–200 mg qam	Unclear	Insufficient data	Levels increased by ritonavir Levels decreased by darunavir
Citalopram	20 mg qam	20–60 mg qam	Unclear	Indicated in older adults and anxiety	Levels increased by ritonavir
Escitalopram	10 mg qam	20–30 mg qam	Unclear		No data
Paroxetine	10 mg qhs	20–60 mg qhs	Unclear	Somewhat sedating	Levels increased by ritonavir Levels decreased by darunavir, fosamprenavir
Fluvoxamine	50 mg qhs	150–250 mq qhs	Unclear	Somewhat sedating	Levels are decreased by nevirapine. Fluvoxamine increases levels of amprenavir, delavirdine, efavirenz, indinavir, nelfinavir, ritonavir, saquinavir
Venlafaxine	37.5 mg qam	75–300 mg qam	Unclear	Indicated for anxiety and depression	Levels increased by ritonavir
Desvenlafaxine	50 mg qam	100 mg qam	Unclear	Active metabolite of venlafaxine Mildly activating Helpful in chronic pain	Insufficient data
Duloxetine	30 mg qam	60–120 mg qam	Unclear	Helpful in chronic pain	Insufficient data
Milnacipran	25 mg qam	100–200 mg q day	Unclear	Indicated for fibromyalgia not depression Useful for chronic pain	Insufficient data
Mirtazepine	7.5–15 mg qhs	15–45 mg qhs	Unclear	Promotes sleep and weight gain	Insufficient data
Nefazodone	50 mg bid	300–400 mg/d in divided dose (bid or tid)	Unclear	Somewhat sedating	Nefazodone increases levels of efavirenz, indinavir
Trazodone	50–100 mg qhs	50–150 mg qhs for sleep 200–600 mg qhs for depression	Unclear	Promotes sleep	Levels increased by ritonavir, lopinavir/ritonavir, darunavir, indinavir
Nortriptyline	10–25 mg qhs	50–150 mg qhs	70–125 ng/dL	Promotes sleep Promotes weight gain Decreases diarrhoea	Levels increased by fluconazole, ritonavir.
Desipramine	10–25 mg qhs	50–200 mg qhs	>125 ng/dL	Promotes sleep Promotes weight gain Decreases diarrhoea	Levels increased by ritonavir, nelfinavir

Continued next page

Table II. Contd

Drug	Start dose	Usual therapeutic dose	Therapeutic serum level	Advantages	Interactions with HIV medications
Imipramine	10–25 mg qhs	100–300 mg qhs	>225 ng/dL	Promotes sleep Promotes weight gain Decreases diarrhoea	Levels increased by ritonavir
Amitriptyline	10–25 mg qhs	100–300 mg qhs	200–250 ng/dL	Promotes sleep Promotes weight gain Decreases diarrhoea	Levels increased by ritonavir
Clomipramine	25 mg qhs	100–200 mg qhs	150–400 ng/dL	Promotes sleep Promotes weight gain Decreases diarrhoea	Levels increased by ritonavir
Doxepin	10–25 mg qhs	150–250 mg qhs	100–250 ng/dL	Promotes sleep Promotes weight gain Decreases diarrhoea	Levels increased by ritonavir
Bupropion	100 mg SR bid 150 mg XL qam	150–450 mg SR/d in divided dose (bid or tid) 300–450 mg XL qam	Unclear	Activating No sexual adverse effects	Levels decreased by tipranavir and efavirenz

bid = twice daily; **q** = every; **qam** = every morning; **qhs** = every night at bedtime; **SR** = sustained release; **tid** = three times daily; **XL** = extended release.

losing it because of depression, may be the primary cause of weight gain. The TCA and monoamine oxidase inhibitor (MAOI) classes of drugs have been shown to contribute to weight gain.[73] Individually, mirtazapine, paroxetine and trazodone have been associated with changes in weight; however, there are few studies that have examined the influence of SSRIs and serotonin-norepinephrine (noradrenaline) reuptake inhibitors (SNRIs) on weight after extended use. A recent meta-analysis[74] demonstrated that SSRIs, SNRIs and bupropion used for 4- to 12-weeks correlated with weight loss. When prescribed for longer than 4 months, only paroxetine and the TCA amitriptyline were associated with a 5–6 lb (2.3–2.7 kg) weight gain, with bupropion linked to the most significant weight loss (about 4 lbs [1.8 kg]).

3.1 Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine (Noradrenaline) Reuptake Inhibitors

SSRIs and SNRIs are the most commonly used drugs for the initial treatment of depression in HIV patients because they pose the least amount of toxicity and greatest likelihood of safety in overdose compared with other antidepressants. SSRIs are relatively safe, have far fewer anticholinergic and α-adrenergic receptor-blocking related adverse effects and need less monitoring than the classic TCA medications. When patients self-discontinue SSRI treatment, it is typically within the first 3 weeks, secondary to complaints of anxiety, agitation or insomnia.[75] SSRIs are also associated with a syndrome of serotonin excess that causes intense agitation, akathisia and subjective distress, particularly when doses are increased rapidly or are added to other pro-serotonin drugs. Common SSRI adverse effects include mild restlessness, mild nausea, delayed orgasm in men and anorgasmia in women. Male impotence from SSRI treatment may be managed with sildenafil,[76,77] and delayed orgasm may be addressed by a drug holiday or addition of bupropion, buspirone, cyproheptadine or gingko biloba.[78,79] SSRIs may also rarely be associated with the development of syndrome of inappropriate antidiuretic hormone secretion.[80,81]

Different SSRIs have subtly different adverse effect profiles and thus should be selected to work for rather than against a particular patient. Paroxetine is the most sedating SSRI and has some utility in sleep promotion as well as a mild increase in appetite. Fluvoxamine may also be useful for its sedating effects. Fluoxetine may be mildly anorectic, particularly in the elderly, and causes almost no sedation in most patients.[82] It also has a long half-life so that a missed dose will have relatively little effect, whereas a missed dose of paroxetine may precipitate withdrawal syndrome due to its short half-life.

We have found sertraline to be a mild gastrointestinal stimulant that is sometimes useful in patients with gastrointestinal slowing or paresis. Citalopram and its *S*-enantiomer, escitalopram, are generally well tolerated; they have intermediate half-lives and favourable pharmacokinetic profiles.[83,84] These agents are relatively non-sedating, and slow-release forms are better tolerated with fewer adverse effects. One study suggests that natural killer cell function in HIV infection and the body's ability to fight HIV may be enhanced by citalopram[84]

Venlafaxine, a selective SNRI, has demonstrated efficacy in neuropathic pain states. We have found this drug to be useful for the treatment of depressed HIV-infected patients with chronic and neuropathic pain syndromes.[85,86] A barrier to its use is occasional elevated blood pressure. Although the sustained-release formulation is often used once daily, it is better tolerated as a twice-daily medication. The active metabolite desvenlafaxine has the advantage of once-daily dosing. Duloxetine is another SNRI with a US FDA indication for the treatment of major depression and neuropathic pain.[83,86] Given that HIV neuropathy is a common manifestation of prolonged HIV infection, even with acceptable T-cell counts, duloxetine is becoming widely used for both pain and depression in HIV disease.[6,86,87] The newest entry into the market is milnacipran, an SNRI indicated for fibromyalgia in the US and indicated for depression elsewhere (not indicated for depression in the US at this time). In general, the SNRI drugs have similar adverse effects to SSRI antidepressants and are well tolerated and easy to use.

3.2 Tricyclic Antidepressants

Like the SSRI drug class, TCAs are highly effective in treating major depression in HIV-infected patients, when properly dosed and monitored.[15,63,88] The TCAs as a class cause antihistaminic, anticholinergic and α-adrenergic receptor blocking properties.[66] While these properties account for significant toxicity and adverse effects, they may also have therapeutic utility in certain patients. TCAs such as desipramine, imipramine and amitriptyline decrease gastrointestinal motility, which may be helpful for treating patients with chronic diarrhoea. These agents are also sedating, therefore they may be useful in treating depression with related insomnia. Other adverse effects of TCAs include erectile impotence, orthostatic hypotension, drying of secretions and weight gain. Dry mouth, one of the most common anticholinergic adverse effects, is also independently one of the most frequent complaints of HIV-infected patients.[89,90] TCAs also diminish chronic pain in a variety of conditions, including neuropathy, which is frequently comorbid with HIV disease.

The most serious complication from TCAs is the development of cardiotoxic blood levels that may precipitate fatal arrhythmias. Even blood levels of TCAs only 4- to 10-fold the therapeutic dose range can be toxic and potentially fatal. A 1-month supply may be adequate for a fatal overdose. Therapeutic monitoring of TCA blood levels ensures that the patient receives a therapeutic dose of medication. On the whole, TCAs are probably underutilized as a therapeutic option in depressed HIV-infected patients when one considers their utility in advanced HIV disease for improving appetite and sleep, promoting weight gain, stopping diarrhoea, treating chronic pain and monitoring compliance. The burden of their use, including interactions with antiretroviral medications, is a barrier for many clinicians.[91]

3.3 Special or Intermediate Property Antidepressants

Mirtazapine and nefazodone have pharmacological properties that are intermediate between SSRIs and TCAs, and may thus be useful when

TCAs are too toxic or dangerous to use. Both mirtazapine and nefazodone have some of the desirable effects of TCAs with much larger margins of safety. Mirtazapine is a useful antidepressant for malnourished HIV patients as it increases appetite, promotes weight gain and reduces nausea.[92,93] It also promotes sleep and has less toxicity than TCAs. The most commonly reported adverse effects are weight gain and sedation, although occasionally patients report serotonin excess-like symptoms such as insomnia, restlessness and akathisia.[94] On the other hand, double-blind, placebo-controlled trials of mirtazapine showed modest improvement of akathisia symptoms induced by antipsychotic medications.[95-97] Mirtazapine may offer some benefit as treatment or prophylaxis for progressive multifocal leukoencephalopathy (PML) in patients with HIV infection. A recent case series showed significant clinical improvement and magnetic resonance imaging-associated changes in response to mirtazapine treatment in HIV-positive patients with PML.[97] Although mirtazapine appears to be safe and well tolerated in HIV-infected patients with PML, more studies are necessary.

Nefazodone has demonstrated efficacy for the treatment of depressed HIV-infected patients.[98] However, due to the high co-morbidity of HIV and viral hepatitis, the risk of nefazodone-induced hepatitis is an important consideration. Nefazodone is also somewhat sleep promoting, but is less sedating than a TCA and may be useful when a TCA is contraindicated. On rare occasions, nefazodone has caused visual distortions such as 'trails' that can be seen with serotonin hallucinogens; however, frank visual hallucinations have not been reported. Concerns over hepatotoxicity with associated liver failure with death or liver transplant have resulted in the removal of nefazodone in some European countries and Canada. Although it is available in the US in only the generic formulation, liability concerns have limited its use since 2004 in countries where it is approved.

Bupropion is an atypical antidepressant as well as a smoking-cessation agent. Although the mechanism of action is unknown, bupropion appears to work by inhibiting noradrenaline and dopamine reuptake and potentially blocking nicotine receptors.[99,100] It may be useful in sedated or fatigued patients as it tends to be somewhat activating. Initially, bupropion was contraindicated in association with ritonavir, a protease inhibitor antiviral drug, because of potential drug-drug interactions,[78,101] but this restriction has been lifted as little clinical evidence supports a significant interaction.[79,102,103] Bupropion lowers seizure threshold in a dose-dependent manner.[104,105] It needs to be used with caution in HIV patients who may suffer from CNS infection, injury, alcohol or benzodiazepine withdrawal, or other conditions that lower seizure threshold.[106] The development of slow-release and extended-release forms of the drug (bupropion SR and bupropion XL) have decreased the likelihood of seizures and enabled primary HIV care providers to feel more comfortable with prescribing this drug.

3.4 Monoamine Oxidase Inhibitors

MAOIs are a potent class of antidepressants that inhibit the enzyme monoamine oxidase and therefore prevent the degradation of serotonin, adrenaline (epinephrine), noradrenaline and melatonin. They have traditionally been reserved for use only after failed treatment with other classes of drugs, mainly because of potentially fatal drug and dietary interactions. With the first FDA-approved transdermal patch, the selegiline transdermal system for the treatment of major depression, primary care providers may feel more comfortable prescribing a low-dose patch because patients do not need to follow the dietary restrictions that are needed for all oral MAOIs.[107] Three MAOIs are currently available for use in the US: phenelzine, selegiline and tranylcypromine. Selegiline, the newer agent, is a selective, irreversible MAO-B inhibitor with relatively few restrictive dietary requirements. Given its antioxidant and neurotrophic properties, selegiline has been studied in clinical trials and found to be useful in Parkinson's disease, HIV-associated cognitive impairment[108-111] and atypical depression, but not specifically HIV-associated depression. In clinical practice, it appears to be less effective as an antidepressant in HIV-infected

patients.[112] Phenelzine and tranylcypromine have both been shown to be effective in major depression, particularly in subpopulations of HIV-infected patients with depression. Of the two, phenelzine is associated with more sedation and weight gain. Tranylcypromine has some amphetamine-like properties and may be activating, and causes little weight gain. A major issue with inhibition of this enzyme is that sudden exposure to increased monoamines can lead to hypertensive crisis as well as other toxicities. Patients therefore need to avoid 'indirect sympathomimetic drugs' (drugs that release stored monoamines) such as noradrenaline, adrenaline and dopamine. Amphetamine, adrenaline, pseudoephedrine and other amphetamine-like agents can provoke fatal toxic reactions. Certain foods contain high levels of tyramine, which has a similar effect. Patients must thus follow a low-tyramine diet while taking these drugs. The stimulant-like (amphetamine-like) effects caused by tranylcypromine make it useful in HIV-infected patients with depression, especially when the depression is confounded by co-morbid medical illness.[87]

Overall, MAOI inhibitors are well tolerated, with little sedation, weight gain or adverse sexual adverse effects. There are little data on the interactions of MAOIs and HIV medications in human subjects. One group using a primate model of HIV infection showed that selegiline caused marked degenerative CNS changes and accelerated viral infection by increasing plasma dopamine,[112,113] but these results have not been replicated in patient studies. Overall, MAOI drugs are relegated as 'expert' drugs to be prescribed by a psychiatrist, more so because of the dietary restrictions and liability than actual drug toxicity. Compliance and the patient's ability to follow the required diet, and adhere to herbal supplement and other medication restrictions must be strongly considered before recommending these medications.

3.5 Psychostimulants

Psychostimulants, such as methylphenidate,[55] dextroamphetamine[114] and modafinil[115-117] are safe and effective treatments for reducing fatigue, and have possible antidepressant properties for use in HIV-infected patients. We have found these drugs most useful as augmentation agents in association with refractory depression, as well as highly efficacious in patients with AIDS dementia-induced apathy or other apathy states. Psychostimulants are particularly useful in patients reporting significant fatigue or resistance to other more typical antidepressants. A randomized controlled trial of methylphenidate and the psychostimulant pemoline in HIV-infected patients demonstrated them to be equally effective psychostimulants for decreasing fatigue severity with minimal adverse effects.[118] However, pemoline is no longer prescribed in the US because of suspected liver toxicity. Randomized controlled studies of modafinil in HIV patients over 6 months showed that those still taking modafinil had a decline in HIV RNA viral load, more energy and fewer depressive symptoms than patients who were not taking modafinil.[115,119] Although these results are promising and HIV-related fatigue is strongly associated with depression, psychostimulants are not recommended as monotherapy for the treatment of depression or HIV-related mood disorders.[55]

3.6 Augmentation Agents

When patients show only partial response to antidepressant medication under conditions of medication adherence, treatment should be augmented with a second antidepressant with a slightly different neuropharmacological profile.[120] Although there are no published trials examining depression in HIV-infected patients, several studies have shown significant improvement in neurocognition in HIV-infected patients treated with mood stabilizers, such as lithium, or antipsychotics.[121,122] The best-studied antidepressant augmentation agent for all types of patients with depression is lithium,[123-125] although few studies have specifically focused on HIV-infected patients; however, the extensive adverse effect profile of lithium can preclude its use in medically complicated HIV disease. Thyroid preparations, especially triiodothyronine, may benefit patients in need of antidepressant augmentation who are also experiencing excessive fatigue.[126]

Antipsychotic drugs, including olanzapine, risperidone and pindolol, have shown efficacy as augmentation agents.[127-129] Adjunctive aripiprazole also appears to be a well tolerated and efficacious treatment for patients with depression who do not respond adequately to standard antidepressant monotherapy.[130] We have used all of the antipsychotics in our HIV clinics, both typical and atypical (sometimes referred to as first- and second-generation antipsychotics), to augment antidepressant effect, with good outcomes.[42]

Other common augmentation strategies include adding a second antidepressant, mood stabilizer, stimulant, or benzodiazepine, sleep deprivation and/or bright-light therapy. Double-blind, placebo-controlled trials have demonstrated that augmentation with antidepressants and mood stabilizers significantly improve treatment refractory depression in HIV patients.[131,132] The other strategies listed above have been examined as case reports in the literature.[133] If augmentation fails or the treatment must be abandoned because of intolerable adverse effects, treatment should be reinstated with a new agent. Although medications within the same class may produce similar adverse effects, a therapeutic response may be seen with one drug even when no response is seen with another drug of the same class.[79,87]

4. Potential Interactions of Medications used to Treat HIV and Depression

Highly-active antiretroviral therapy (HAART) regimens include at least three different antiretroviral drugs, and sometimes up to six different agents (Department of Health and Human Services).[38,134] Potential interactions between antidepressant medications and HAART medications are outlined in table I; however, since depression is associated with non-adherence to HAART, untreated depression may be even more detrimental to disease progression than any effect of medication interactions. There is extensive literature describing potential medication interactions in this unique patient population, primarily based on studies of cytochrome P450 (CYP) activity and related mechanisms of drug metabolism.[87,101,135,136] It has been difficult to demonstrate clinical significance of drug-drug interactions that would warrant dosage adjustments of either antidepressants or HAART medications for successful treatment outcome of either illness.[137,138] There is some evidence, however, to suggest that HIV-infected patients receiving antiretroviral therapy are at heightened risk of developing serotonin syndrome.[139] Ritonavir is a known inhibitor of drugs metabolized through the CYP3A and CYP2D6 pathways, which may result in loss of the drug's therapeutic effect. Short-term, low-dose ritonavir increases the occurrence of adverse adverse effects of trazodone due to impaired oral clearance of trazodone.[41,64] Both therapeutic and supratherapeutic doses of ritonavir appear to have an induction effect on multiple drug-metabolizing enzymes.[140] Although we have limited understanding about the mechanisms involved in these possible drug interactions, medications with significant potential value for managing HIV-associated psychiatric disorders should not be unnecessarily avoided. Carefully controlled studies of sufficient power with larger numbers of subjects are needed to examine the effects of potential drug interactions in HIV-infected patients.

5. Depression as a Complication of HIV Treatment

Because neuropsychiatric complications of HIV disease may be caused by CNS viral infection,[6,72,141] it is believed that the use of HAART to reduce viral load might ameliorate psychiatric symptoms. In some studies, improvements in depression have paralleled improvements in CD4 cell counts.[142] Medications used in the treatment of HIV, however, may also cause neuropsychiatric adverse effects, including affective disorder.[42] These agents include efavirenz, interferon, metoclopramide, clonidine, propanolol, sulfonamides, anabolic steroids, corticosteroids and muscle relaxants. In these cases, depression often responds to withdrawal of the offending drug, and when this is not the case then the patient should be treated pharmacologically for major depression. Our clinical experience has also shown that the depressive syndromes caused by efavirenz and

interferon can be effectively managed with concurrent use of antidepressant medication.[87,143]

Zidovudine was the first pharmacological agent shown to reduce mortality and opportunistic infections significantly in HIV-infected patients.[142] Because of its good penetration of the blood-brain barrier, and research and development of a nasal delivery form,[144] zidovudine is considered an attractive candidate for the treatment of HIV patients with CNS complications. However, there are multiple case reports of serious manic episodes following zidovudine treatment, even in patients with no previous psychiatric history.[128,145,146] The mechanism of zidovudine-induced mania is unknown. Discontinuation of zidovudine appears to facilitate resolution of symptoms, which recur with subsequent reintroduction of zidovudine.[145] Many patients are able to continue treatment with zidovudine along with concurrent treatment for mania.[2,146,147] Incidence of mania with zidovudine treatment has declined somewhat compared with initial reports, perhaps because it is now used in lower doses (total of approximately 600 mg/day) than in the pre-HAART era (up to 2000 mg/day).

Although relatively few CNS adverse effects have been seen in clinical trials of most non-nucleoside reverse transcriptase inhibitors, efavirenz does propagate a wide variety of neuropsychiatric effects in approximately 50% of patients.[148,149] Efavirenz-associated psychiatric effects include anxiety, depression and suicidal ideation.[66,145] Indeed, patients who took efavirenz for a mean of 45 weeks scored higher on psychometric scales of anxiety and hostility than patients taking a protease inhibitor for the same amount of time.[66,101] Our clinical experience is that many patients are able to manage these symptoms within 2–4 weeks of initiating treatment, and that bedtime dosing also makes the symptoms more tolerable. In most patients, effects will diminish within weeks of starting therapy and become clinically insignificant within 4–6 weeks of starting the drug. Because insomnia or disturbingly vivid dreams are common adverse effects with efavirenz, a small dose of a sedative-hypnotic agent can be helpful.[148,149] Efavirenz may also cause a euphoric intoxication in some patients. Because of this, it has developed some 'street value' and may be traded or sold.[102] Although not part of the standard treatment guidelines for HIV infection, some experts in the field advocate close monitoring of plasma efavirenz levels in a subset of patients with a history of depression, substance abuse or other mental health problems,[150,151] given that CNS adverse effects are 3-fold more frequent in patients with high, compared with low, plasma efavirenz.[9,72,102] Provided that depression is treated aggressively by a psychiatrist, however, treatment with efavirenz can usually be continued.

6. Conclusions

HIV infection has become a chronic condition amenable to pharmacological management. Treatment of associated psychiatric disorders, including major depression, is essential. Treatment of depressive illness in association with effective HIV care dramatically improves patient outcome and quality of life. Much research remains to be performed in this important area, and we have proposed pharmacological strategies for safely and effectively managing depression in HIV-infected patients, taking into consideration clinically important adverse effects and pharmacological interactions of antidepressant medications as well as medications used to treat HIV disease.

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