Depression, mania, and schizophrenia in patients with HIV

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INTRODUCTION

Neuropsychiatric disorders are common in individuals with the human immunodeficiency virus (HIV), based upon a wide variety of factors that include direct effects of the virus, preexisting psychiatric conditions, personality vulnerabilities, affective disorders, addictions, or responses to the social isolation and disenfranchisement that are frequently associated with the diagnosis of HIV. Adding to the complexity, many persons with HIV have difficulty with treatment adherence due to their behavior patterns as well as specific neuropsychiatric disorders associated with HIV disease progression [1].

However, more recent findings have demonstrated that identification and treatment of psychiatric disorders in AIDS patients increases their likelihood of being prescribed antiretroviral therapy (ART) [2]. As an example, in a cohort of patients (n = 549) with AIDS at an HIV clinic offering onsite psychiatric services, patients receiving treatment for a psychiatric disorder were twice as likely to receive ART for at least six months compared to patients who were not diagnosed with a psychiatric disorder (adjusted odds ratio 2.1, 95% CI 1.2-3.7). Prescription of ART was also associated with a 40 percent reduction in mortality compared to patients without a psychiatric disorder [2].

HIV-associated depression, mania, and schizophrenia will be reviewed here. An overview of the range of neuropsychiatric conditions associated with HIV infection and more detailed reviews of other specific conditions are discussed separately. (See "Overview of the neuropsychiatric

aspects of HIV infection and AIDS" and "HIV-associated neurocognitive disorders: Epidemiology, clinical manifestations, and diagnosis" and "Substance use disorder in patients with HIV".)

MAJOR DEPRESSION

Among patients with HIV, comorbid depression is common and is associated with nonadherence to HIV treatment [3]. Prevalences for major depression (table 1) among patients with HIV and AIDS have been estimated to be between 15 and 40 percent, far exceeding that seen in the general population [4]. Major depression increases the risk of acquiring HIV through intensification of substance abuse and exacerbation of self-destructive behaviors, such as exposure to an increased number of sexual partners and lack of condom use [5]. Patients with major depression are also at increased risk for HIV disease progression and mortality [6]. Depression is underdiagnosed and under-treated in medical clinics, and has thus become a prominent problem in the HIV/AIDS epidemic [7].

The diagnosis of major depression in patients with HIV is complicated by the high frequency of depressive symptoms associated with chronic illness, personal loss and isolation, medical treatments that alter mental function, comorbid neurologic illnesses, and comorbid substance abuse. HIV-associated dementia and other HIV-related central nervous system (CNS) conditions can produce a flat, apathetic state often misdiagnosed as depression. In turn, the differential diagnosis in HIV patients reporting depressive symptoms includes major depression, dysthymia, dementia, delirium, demoralization, intoxication, withdrawal, CNS injury, CNS infection, and acute medical illness.

Epidemiology — Populations at risk for HIV infection already have inherent elevated rates of major depression, and depression is considered to be a risk factor for HIV transmission [4,8].

The prevalence of major depression among patients with HIV is difficult to measure and has ranged from 15 to 40 percent in different studies [8-10]. A meta-analysis of 10 studies comparing HIV-positive and at-risk HIV-negative patients demonstrated a twofold increase in the prevalence of major depression among patients with HIV [11], supporting these earlier findings. However, the results of the meta-analysis continue to be debated due to methodologic difficulties in comparing studies that lack a unified definition of depression.

The risk of major depression also appears to increase with progression of the HIV infection. For example, the Multicenter AIDS Cohort Study demonstrated a 2.5-fold increase in rates of depression in patients as they develop AIDS [12].

Pathogenesis — Although the cause of major depression in HIV patients is not known, the evidence suggests that several different factors may be involved. Major depression is associated with various risk behaviors (eg, substance abuse) for acquiring HIV infection, and progression of HIV disease is associated with an increased risk for developing depression through direct damage to subcortical brain areas, chronic stress, worsening social isolation, and intense demoralization. In addition, chronic neuroinflammation induced by HIV may cause depression [13].

Several antiviral medications that are used to treat HIV are associated with depression. As an example, the nucleoside/nucleotide reverse transcriptase inhibitors efavirenz and rilpivirine may be associated with depression [14]; however, the association is clouded by CNS-related side effects such as fatigue and cognitive impairment. In addition, integrase inhibitors (eg, dolutegravir) may be associated with depression as well [15].

HIV-related infections or malignancy (eg, CNS toxoplasmosis, cryptococcal meningitis, lymphoma, or syphilis) may also cause depressive symptoms, and several of these conditions have been associated with the development of major depression. Significant rates of depressive symptoms among male patients with HIV may also be associated with low testosterone levels. (See "Pituitary and adrenal gland dysfunction in patients with HIV".)

Many of the medications used in HIV patients to treat conditions other than HIV may produce major depression or depressive syndromes. These include: interferon, metoclopramide, clonidine, propranolol, sulfonamides, anabolic steroids, corticosteroids and muscle-relaxants. In these cases depression often responds to withdrawal of the offending drug.

Clinical features — Cardinal features of depression in patients with HIV include:

- Decrease in mood, vital sense, and self-attitude
- Anhedonia (decrease in pleasure, satiation, satisfaction, or enjoyment from activities)
- Neurovegetative features (changes in sleep, appetite, or somatic body functions)

HIV patients with major depression may present with sadness and low mood, but may also present with anxiety, irritability, or feeling “flat” or emotionless. Although the key finding is a change in baseline mood, the patient may be unaware that they are different from their usual state, and someone else who knows the patient may be required to provide a description of the change. Patients with strong emotional reactions at baseline may not be able to see changes in their mood because of the variability of their emotional states. A “diurnal” variation of mood, with certain times of the day worse and certain times better (the most common pattern is worse in the morning and best in the afternoon) is a common finding. Another helpful sign of depression is anhedonia, which is defined as a reduction or loss of the sense of pleasure or

reward that is normally associated with many life behaviors. In anhedonia, normal responsiveness to enjoyment or positive reinforcement related to activities and experiences of life is blunted or absent. Behaviors that are less rewarding include those driven by appetite (eg, sleeping, eating, and sex) or those associated with functioning (eg, work, hobbies, dress, or social activity). Vital sense, a subjective perception of well-being, is usually diminished in patients with major depression. Afflicted individuals may report that they are sick, feel a sense of heavy pressure in their chest, have low energy, or are even dying. Patients may feel guilty or concerned that they are bad or evil, that they do not deserve the things they have, or that they have failed those whom they care about.

Another cardinal feature of major depression is neurovegetative symptoms, such as difficulties with sleep, appetite, concentration, and memory. Sleep disturbances may include insomnia or hypersomnia, and patients usually experience early morning awakening with difficulty falling back to sleep. Appetite may be either increased or decreased, and patients often complain that food has lost its flavor. Impairments in concentration and short-term memory may manifest as slowed thought processes or generalized confusion. Major depression is a leading cause of suicide, and every patient must be carefully evaluated for suicidal thoughts or feelings [16,17].

Patients with HIV and depression often present initially to internists and family practitioners with multiple nonspecific somatic symptoms, such as headache, gastrointestinal (GI) disturbances, inexplicable musculoskeletal or visceral pain, cardiac symptoms, light-headedness, vertigo, tinnitus, weakness, and anesthesia. Fatigue is associated with depression rather than HIV disease progression, as worsening fatigue and insomnia at six-month follow-up is highly correlated with worsening depression but not CD4 count, change in CD4 count, or HIV disease progression. Thus, multiple nonspecific somatic symptoms in HIV patients should prompt a full psychiatric evaluation.

Additional information about the clinical features of depression is discussed separately. (See "Unipolar depression in adults: Clinical features".)

Treatment — While the mainstay of treatment is pharmacologic, psychotherapy also plays a critical role in effective treatment of major depression [18].

Pharmacologic — Patients with HIV and major depression respond to antidepressant medication similarly to other patients with major depression. A meta-analysis of five randomized trials (425 patients) found that response (50 percent or greater decrease in baseline depression rating scale score) occurred in more patients who received an antidepressant, compared with placebo (62 versus 37 percent) [19]. It does not appear that any particular antidepressant is superior for patients with HIV. However, both the side effect profile of the

antidepressant and possible interactions with antiretroviral drugs need to be considered in the selection of an agent for treatment of depression [20].

The most important component of drug treatment is patient adherence, which is highly influenced by side effects experienced during treatment. The best strategy is to start at low medication doses and slowly titrate up to a therapeutic dose in order to minimize early side effects that may act as obstacles to adherence. After achieving a therapeutic dosage or serum level, patients should be encouraged to wait as long as six to eight weeks for therapeutic effect.

Adherence to antiretroviral treatment has also been demonstrated to be higher in depressed patients who are prescribed and adherent to antidepressant medication, compared to patients who are neither prescribed nor adherent to these medications [21-23]. Thus routine assessment for depression and prompt pharmacologic treatment is essential to optimize treatment of HIV patients.

Dose and side effects — The doses of antidepressants that are used for patients with HIV disease and the side effects that can occur are described in the tables (table 2 and table 3). Agents whose side-effect profiles are least likely to exacerbate a patient's HIV clinical status should be used first. For example, medications associated with increased GI motility should be avoided as much as possible in patients suffering from chronic diarrhea. Side effects should be assessed at every visit and treated aggressively. Insomnia, a common side effect of selective serotonin reuptake inhibitors (SSRIs), often responds well to low doses of trazodone (25 to 150 mg) at bedtime. Constipation from tricyclic antidepressants can be addressed by increased water and fiber intake.

Sexual side effects from SSRIs are common; male impotence may be treated with phosphodiesterase-5 (PDE-5) inhibitors (eg, sildenafil, tadalafil, and vardenafil), and other approaches are available for decreased libido and delayed orgasm. (See "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management".)

Drug interactions — Significant drug-drug interactions can occur between antidepressant medications and drugs used in antiretroviral therapy (ART). Specific interactions of antidepressants or antipsychotics with antiretroviral drugs may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate. Information about ART is discussed elsewhere. (See "Overview of antiretroviral agents used to treat HIV".)

While the clinical significance of interactions between antidepressants and ART remains unclear in many cases, these interactions can increase or decrease serum concentrations of either the antidepressant or the antiretroviral drug, thereby heightening side effects or decreasing the efficacy of either agent [20]. Clinicians should determine potential drug interactions when

selecting an antidepressant or antipsychotic agent for patients receiving ART. As an example, a low dose of ritonavir, a potent inhibitor of CYP3A4 metabolism, can be used to boost serum concentrations of the HIV protease inhibitors, such as darunavir. Ritonavir can thereby increase levels of trazodone and most tricyclic antidepressants, and thus increase side effects of these drugs. When trazodone or a tricyclic antidepressant is used in combination with a ritonavir-boosted protease inhibitor regimen, the lowest dose of antidepressant should be used initially and adjusted based on clinical assessment and serum drug concentrations, where available [14].

However, depression is associated with nonadherence to ART; thus, untreated depression may be even more detrimental to progression of HIV than medication interactions.

Augmentation strategy — Patients who show only partial response to antidepressant medication should be offered an augmentation strategy. The best-studied agent for antidepressant augmentation is lithium, but its side-effect profile often prevents its use in medically ill patients with HIV.

A number of other agents may be used to augment antidepressants. (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Initial approach'.) As an example, thyroid preparations, especially triiodothyronine, may benefit patients complaining of fatigue [24-27]. Other augmentation agents include other antidepressants or mood stabilizers, trazodone, methylphenidate, benzodiazepines, sleep deprivation, and bright light therapy.

Changing drugs — If augmentation fails or the treatment must be abandoned due to intolerable side effects, treatment should be initiated with an entirely new agent. It is important to remember that although medications within the same class may produce similar side effects, a therapeutic response may be seen with one drug even when no response is seen with another drug in the same class.

Psychotherapeutic — Treatment with medication plus psychotherapy is likely to be more effective than either modality alone. Psychotherapy also provides a framework for the provider-patient relationship by enabling patients to take control of their lives, which is crucial to successful treatment. Among the individual psychotherapies, interpersonal psychotherapy and cognitive-behavioral psychotherapy have the best evidence to support their efficacy in the treatment of major depression. (See "Unipolar major depression in adults: Choosing initial treatment".)

Supportive psychotherapy often helps patients with HIV disease and major depression that have interpreted their suffering as a reaction to the diagnosis or morbidity of HIV infection. Because these individuals may believe that they should be able to pull themselves out of

depression without psychiatric treatment, they can become frustrated and further demoralized as they expend significant effort with little benefit. These patients may benefit from education about the disease nature of their depression, encouragement to continue treatment, and therapeutic optimism that psychiatric treatment will ultimately be beneficial.

MANIA

Mania (table 4) occurs in patients with HIV both as a component of bipolar illness and as a unique entity known as AIDS mania. Manic episodes are associated with increased substance abuse and impulsive behavior, and one retrospective study of patients with HIV (n = 196) found that the incidence of sex with commercial partners, sex outside the primary relationship, and substance use disorders was greater in patients with bipolar disorder than patients without bipolar disorder [28]. This suggests that bipolar disorder may possibly increase the risk for acquiring HIV infections.

Bipolar illness is broad in spectrum, ranging from a severely crippling and chronic mental illness to a mild disorder with alternating experiences of elevated and depressed mood. It is thus difficult to accurately measure the prevalence and incidence of bipolar disorder, which would be necessary for exploring its relationship with HIV. Over the years it has also been difficult to distinguish severe bipolar illness from schizophrenia, and investigators looking at the relationship between HIV and mental illness have often simply employed the term "chronically mentally ill" for patients with severe disability from either schizophrenia or bipolar disorder. (See "Bipolar disorder in adults: Epidemiology and pathogenesis".)

Clinical course of bipolar illness — Patients with bipolar illness classically present with extended episodes of low mood similar to major depression alternating with manic episodes characterized by elevated mood, increased energy, increased confidence and sense of well-being, and grandiose ideas about themselves and their circumstances. Elevated mood states form a continuum that ranges from hypomania (characterized by increased energy and elevated mood) to mania (characterized in its most severe state by hallucinations, delusions, disordered thinking and sometimes violently agitated behavior). These individuals report feeling elated and energized as if they are functioning better than normal. Their thoughts become more rapid and their horizons expand, such that they may feel that many brilliant ideas are presenting themselves in rapid succession.

Hypomanic patients may be harder to diagnose and may present with irritability rather than euphoria. There is often a noticeable increase in the amount and speed of speech and interrupting these patients can be difficult. With increased energy, these patients feel a

decreased need for sleep and sometimes do not sleep at all. Elevated mood states transition into mania when symptoms impair judgment and function. In addition to pressured speech, manic patients often demonstrate flight of ideas, in which ideas come so quickly that it is impossible for the observer to make connections between them. Grandiose delusions, paranoid delusional thoughts, and hallucinations may also occur.

Although patients most frequently cycle from one mood state to another with interspersed periods of normal mood, some patients may manifest features of both depressive and elevated mood states simultaneously (mixed state) or in very rapid successions (rapid cycling). The current literature describes bipolar illness type II, characterized by a milder form of mania.

AIDS mania — AIDS mania is uniquely associated with late-stage HIV infection. AIDS mania is characterized by typical mania and additional cognitive impairment in the setting of a lack of previous personal or family history of bipolar illness. AIDS mania has less euphoria and more irritability than idiopathic bipolar mania, and is also far more chronic. AIDS mania also does not appear to remit if left untreated. The prevalence of AIDS mania has greatly diminished now due to the advent of potent ART.

Epidemiology — Manic syndromes in HIV patients occur with higher frequency after the onset of AIDS and at rates greater than observed in the general population. In one series, 8 percent of all AIDS patients seen at an HIV clinic over 17 months exhibited mania, which is more than 10 times the six-month general population prevalence [29]. This study grouped manic patients into those whose first manic episode came early with a CD4 count >200 cells/microL and those whose first manic episode came late with a CD4 count <200/microL. Late-onset mania patients were less likely to have a personal history of mania or mood disorder, which presumably indicates that they were less likely to have bipolar disorder or a genetic predisposition to mania. These same individuals were also more likely to have dementia or other cognitive impairment.

Clinical course — In contrast to mania in bipolar disorder, AIDS mania is associated with a worse prognosis, greater number of symptoms, more chronic course, and infrequent spontaneous remissions. AIDS mania patients are commonly irritable and infrequently hypertalkative or euphoric. Although it is difficult to ascertain the cognitive state in acute mania, the history is often different in patients with AIDS mania compared to those with bipolar mania. The former is frequently characterized by progressive cognitive decline prior to the onset of mania, typically accompanied by prominent psychomotor slowing. In contrast, a history of hyperactivity is common in bipolar mania [29].

A frequent manifestation of AIDS mania, either early or late, is the delusional belief that the patient has either been cured of HIV or has discovered the cure. This dangerous delusion often

results in resumption of high-risk behavior and medication nonadherence. With cessation of treatment, AIDS mania usually relapses. Unfortunately these patients usually have cognitive deficits that render them less able to pursue treatment independently or consistently.

Treatment

Bipolar illness — Treatment of mania in early stage HIV is similar to standard treatment of mania in bipolar disorder: neuroleptics, lithium salts or anticonvulsants such as valproic acid or carbamazepine. (See "Bipolar disorder in adults: Epidemiology and pathogenesis".)

AIDS mania — AIDS mania patients frequently respond to treatment with neuroleptic agents alone. Because of their more favorable side effect profile relative to older "typical neuroleptics", newer "atypical neuroleptics", such as risperidone, olanzapine quetiapine, and ziprasidone, are often considered first-line therapy. However, superior efficacy of atypical neuroleptics has not been demonstrated in clinical trials.

Different treatment strategies are mandated as HIV disease progresses due to more accompanying medical illnesses, greater CNS involvement, and greater overall physiologic vulnerability. In late stage HIV disease the therapeutic dose of neuroleptics may be much lower due to greater sensitivity of these patients to both therapeutic and toxic neuroleptic effects.

Lithium use in AIDS mania patients is often complicated by delirium, GI symptoms, or polyuria, which can lead to dehydration, sudden unpredictable changes in lithium levels, and arginine vasopressin resistance (previously called nephrogenic diabetes insipidus).

Valproic acid may be beneficial in AIDS mania patients when titrated to the usual therapeutic serum level of 50 to 100 ng/dL. AIDS patients usually tolerate enteric-coated tablets (Depakote) better due to a lower incidence of GI side effects. Treatment with valproic acid can be limited by possible hepatotoxicity, especially in patients with chronic viral hepatitis. The drug should probably be avoided in patients with substantial preexisting liver dysfunction due to infection (eg, hepatitis C or Mycobacterium avium complex [MAC] infection involving the liver) or cirrhosis (eg, portal hypertension).

Because carbamazepine and valproic acid can diminish hematopoiesis, white blood cell and platelet counts should be monitored during treatment. Data are limited for the newer anticonvulsants, such as gabapentin (neurontin) and lamotrigine (lamictal) in the treatment of AIDS mania.

SCHIZOPHRENIA AND PSYCHOTIC EPISODES

The prevalence rates of severe and chronic mental illness in patients with HIV (historically encompassing schizophrenia and bipolar disorder) are estimated to range from 4 to 19 percent [30]. No evidence suggests that HIV causes schizophrenia, but data do suggest that schizophrenia contributes to high-risk behavior associated with HIV infection. As an example, patients with schizophrenia are more likely to engage in unprotected sex with multiple partners, trade sex for money or other goods, and have sex while intoxicated [31]. Despite demonstration of adequate knowledge of HIV risk factors, schizophrenic patients with more positive symptoms (eg, delusions and hallucinations) and impulse control problems are at increased risk for high-risk sexual behavior [32]. Schizophrenia in patients with HIV is managed similarly to schizophrenia in other patients: control of symptoms with medications, psychosocial support, and rehabilitation.

A new episode of psychosis may befall patients with HIV. These episodes typically occur in the context of delirium, schizophrenia, unipolar major depression, or bipolar disorder. In addition, antibodies to the N-methyl-D-aspartate glutamate receptor may be associated with psychosis in HIV patients. One study of new onset psychosis found a patient with vertically transmitted HIV and bipolar disorder, who developed new onset psychosis in the context of antibodies for the N-methyl-D-aspartate receptor [33].

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topic (see "Patient education: HIV-associated neurocognitive disorders (The Basics)")

SUMMARY

- Psychiatric disorders are common in patients with the human immunodeficiency virus (HIV), including major depression, mania, and schizophrenia. (See 'Introduction' above.)

- The prevalence of major depression among patients with HIV ranges from 15 to 40 percent in different studies, and is twice as large in at-risk HIV-negative patients. The risk of major depression also appears to increase with progression of HIV infection. (See 'Epidemiology' above.)

- Among the symptoms of major depression (table 1), the cardinal features in patients with HIV include decreased mood, vital sense, and self-worth; anhedonia; and neurovegetative features. (See 'Clinical features' above.)

- Response to antidepressant medication in patients with HIV and major depression is similar to that of other patients with major depression. No particular antidepressant is superior for patients with HIV. The most important component of antidepressant treatment is patient adherence, which is highly influenced by side effects experienced during treatment. Clinicians should also be aware of potential drug-drug interactions between antidepressants and antiretroviral drugs. Specific interactions of antidepressants with antiretroviral drugs may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate. (See 'Pharmacologic' above.)

- Treatment of major depression with medication plus psychotherapy is likely to be more effective than either modality alone. The individual psychotherapies with the best evidence to support their use are interpersonal psychotherapy and cognitive-behavioral psychotherapy. (See 'Psychotherapeutic' above and "Unipolar major depression in adults: Choosing initial treatment".)

- Mania (table 4) occurs in patients with HIV either as a component of bipolar disorder, or as a unique entity known as AIDS mania caused by late-stage HIV infection. One study found that 8 percent of all AIDS patients seen over 17 months exhibited mania, more than 10 times the six-month general population prevalence. AIDS mania is characterized by typical mania and additional cognitive impairment in the setting of a lack of previous personal or family history of bipolar disorder. AIDS mania has less euphoria and more irritability than idiopathic bipolar mania, and is also more chronic. The prevalence of AIDS mania has greatly diminished now due to the advent of potent ART. (See 'Mania' above.)

- Treatment of mania in early stage HIV is similar to standard treatment of mania in bipolar disorder. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)

- The prevalence of schizophrenia in patients with HIV is not known. No evidence suggests that HIV causes schizophrenia, but data indicate that schizophrenia contributes to high-risk behavior associated with HIV infection. Treatment of schizophrenia in patients with HIV is similar to standard treatment of schizophrenia. (See 'Schizophrenia and psychotic episodes' above and "Schizophrenia in adults: Maintenance therapy and side effect management".)

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