

Perspective

Depression and Adjustment Disorder in Patients With HIV Disease

Depressive symptoms are common in patients with HIV disease, reflecting in part the contribution of preexisting depressive illness to risk behaviors for acquisition of HIV infection. Depression complicates management of HIV disease by increasing the likelihood of nonadherence to antiretroviral treatment regimens. HIV-infected patients with depressive symptoms may also be more likely to engage in behaviors that put others at risk of infection. These issues and approaches to diagnosis and treatment of depression in HIV-infected patients were discussed by Andrew F. Angelino, MD, at the Clinical Pathway of the Ryan White CARE Act 2002 All Grantee Conference held in Washington, DC, in August 2002.

Depressive symptoms are common in HIV-infected patients. In a 1991 survey of patients presenting to the Johns Hopkins HIV clinic for their first medical visit, the AIDS Psychiatry Service found that 54% of patients had Axis I (non-substance abuse) psychiatric disorders, including 20% with major depression and 18% with depressive symptoms associated with adjustment disorder (Lyketsos et al, *Int J Psychiatry Med*, 1994). The epidemic nature of HIV disease in the arena of psychiatric practice is indicated by these and other findings in this survey. In particular, 74% of HIV-infected patients had a substance use disorder, 18% had cognitive impairment, and 27% had a personality disorder.

Practitioners in HIV clinics have long anticipated the need for counseling services at the time of diagnosis and for ongoing mental health support as the disease progressed. At the beginning of the HIV epidemic, when the prognosis of the disease was especially grim and most patients died within 18 months of

their diagnosis, there was a high degree of practitioner burnout since little more than palliative care could be offered. Although the advent of potent antiretroviral therapy has allowed patients a substantial increase in life expectancy, depressive symptoms are still extremely common. Depressive symptoms may lead patients toward higher-risk behavior, such as injection drug use (McDermott et al, *Hosp Community Psychiatry*, 1994), and may contribute to nonadherence to medical therapies (Singh et al, *AIDS Care*, 1996). In effect, depression may lead patients to become HIV-infected, concentrating a high proportion of depressed patients in the HIV clinic, and may then lead those patients to be nonadherent to antiretroviral therapy or therapy for opportunistic infections, resulting in a sicker population of patients at the clinic. Sicker patients are more demoralized by their sickness, which may worsen depression. A vicious cycle is thus perpetuated (Figure 1). Depressed HIV-infected patients may also be more likely to engage in behaviors that put others at risk of HIV infection. Important goals of treating depres-

sion in the HIV-infected patient thus include removing barriers to HIV disease treatment adherence and reducing the risk of transmission of infection, in addition to improving other aspects of function and quality of life for the individual patient.

Diagnosis of Depression: Differentiating Depression and Adjustment Disorder

Despite the knowledge that depression may lead to HIV infection and that HIV infection may worsen depression, depression remains underdiagnosed and undertreated in medical clinics. Lack of correct diagnosis is explained in part by the fact that providers find it difficult to distinguish major depression from depressive symptoms associated with adjustment disorder or demoralization. Undertreatment is explained in part by the inadequate availability of specialty referral (eg, psychiatrists, psychologists) and by the refractory nature of depressive syndromes.

The differential diagnosis of depression includes major depression, adjust-

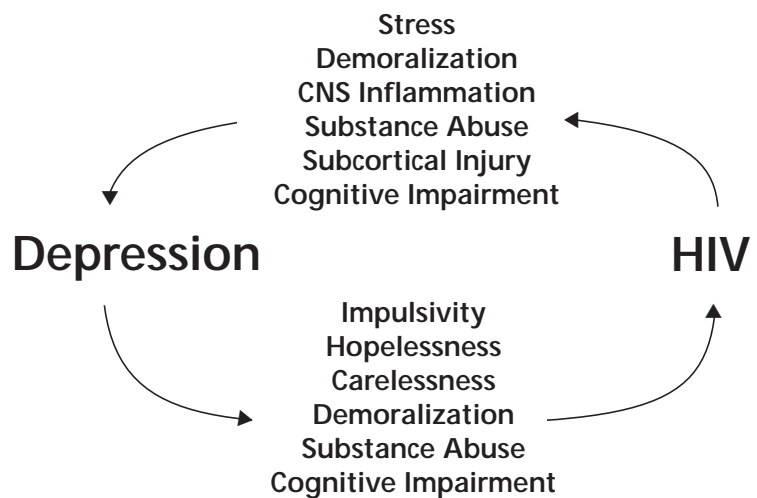


Figure 1. Interrelationship of depressive symptoms and HIV infection. CNS indicates central nervous system.

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ment disorder or demoralization, dementia, delirium, substance use disorders, and a number of medical mimics, including, but not limited to, hypothyroidism, anemia, drug side effects, malnutrition, and hypotestosteronemia. When other potential causes of depressive symptoms can be ruled out, symptoms of depression due to major depressive disorder and those due to adjustment disorder need to be distinguished. The distinction is much more than one of degree—it concerns

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pathology and etiology. Major depression can be conceptualized as a disease of the brain, affecting those neural systems that control mood. Demoralization or adjustment disorders are disorders that arise from a patient's meaningful reaction to particular life circumstances or events. The symptoms of major depression and demoralization may appear similar, but in fact there are often subtle differences.

Major depression is a syndrome that centers around low mood and anhedonia (Table 1). Anhedonia is the inability to feel pleasure from normally pleasurable experiences. Pleasure can be conceived of as falling into categories of “yeah!” or “ahhhh....” The “yeah!” is the type experienced more as a jolt (eg, when one bowls a strike or hits the jackpot); it is probably a dopaminergic frontal lobe response. The “ahhhh....” is a feeling of calm, relaxation, or satiety (eg, that associated with the experience of a good meal or a good book); it is probably related to endogenous opioid activity. Both types of pleasure typically are missing in major depression. Thus,

depressed patients will sometimes report that they have a decreased amount of excitement or joy from a usually happy circumstance and sometimes will complain that they feel no amount of satiety or comfort after an experience that normally makes them feel at ease. As much as patients with major depression feel sad, they also describe an empty feeling and often feel as if they have the inability to experience good feelings or happiness.

In contrast, patients with demoralization may be able to experience pleasure normally when they are distracted from thoughts of the demoralizing circumstance or event. When they are reminded of the demoralizing circumstance or event, however, they often feel sadness welling up and overcoming them.

Patients with major depression often have a diminished vital sense. They describe this phenomenon as feeling fatigued and having a heavy pressure in their chests, and they often have somatic complaints of aches, pains, and, occasionally, gastrointestinal disturbances. When asked, patients who are depressed frequently will say that they feel sick. In contrast, patients who are demoralized generally feel healthy but can identify external circumstances or events to which their response includes a feeling of physical upset. For example, a patient having a conflict with a spouse may feel upset and have physical symptoms of such distress when at home with the spouse.

Evaluation of patients with depressive symptoms is complicated by the fact that somatic complaints frequently require medical investigation to ensure that they are not related to opportunistic disease. Furthermore, for patients with major depression as well as those with adjustment disorder, anxiety and sadness resulting from hearing bad news, such as being told of a lower-than-expected CD4+ cell count, may worsen feelings of fatigue and somatic symptoms, thus alarming the patient and provider and potentially leading to more investigation for causes, and more anxiety, and so on. A careful balance must be maintained between investigation of symptoms for medical etiology and reassurance that the symptoms are stress-related and no further investigation is warranted.

Table 1. Phenomenology of Major Depression

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- Diminished mood and hedonic responsiveness
 - Decreased vital sense
 - Decreased self-attitude
 - Neurovegetative symptoms
 - Early morning awakening
 - Appetite change
 - Diminished libido
 - Cognitive impairment (“pseudodementia”)
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Many patients with major depression also suffer a diminished self-attitude and believe that they are worthless and that life is hopeless for them. This often leads to despair and thoughts of suicide. In HIV disease patients, suicidal thoughts may be active or can take the form of a passive death wish; patients may act out the death wish, for example, by stopping antiretroviral therapy to allow the disease to progress and end their life. In contrast, very few patients with demoralization suffer from global self-attitude changes. On occasion, however, the demoralized patient may complain of feelings of failure or guilt; this is particularly prominent in patients who have lost a loved one, who may express these feelings in such statements as “I wish I had not argued with him so much,” or “I should have told her I loved her more often.” However, many patients with adjustment disorder can recognize this so-called “survivor guilt” and use it as an impetus to avoid taking things for granted.

Patients with major depression also suffer from neurovegetative symptoms. Patients complain of decreased sleep, especially waking early in the morning with the inability to fall back to sleep. Further, they have diminished appetite with weight loss. Occasionally, they will say that food does not taste good, exhibiting a lack of hedonic response to the taste of the food they have chosen. They may eat sweets or high-fat foods in an attempt to stimulate pleasure or produce a feeling of satiety, and may eat enough of these foods to gain weight.

Patients with major depression may also exhibit decreased libido, and may express lack of interest in sexual activity, or, similar to eating sweets, may engage in reckless or uninhibited sex in an

attempt to recapture lost excitement. In addition, depressed patients will report slowed thinking and decreased concentration and memory. Although this has been termed “pseudodementia” of depression, the term is misleading; the dementia exhibited is a real but reversible decline in cognitive function associated with slowed brain activity. Patients with demoralization may report some of these neurovegetative symptoms; however, the effect in major depression is often much more striking.

To further differentiate between major depression and demoralization, one may inquire about family history, past experiences, and precipitating events and circumstances. Major depression often runs in families. A clear history of other family members with major depression who responded to antidepressant medication is a clue that the patient giving the history also may have major depression. Care should be taken in interpreting patient-provided histories, however. Many people suffer demoralization in their lifetime that

may be mistakenly identified as depression; also, a family history of depression that went unrecognized or untreated by professionals may be misleading. Major depression is often a recurring illness and patients often describe more than one episode in their lifetime of similar feelings of sadness with the lack of ability to have enjoyment and a diminished self-attitude. Patients with demoralization or adjustment disorder may or may not have recurring episodes. By definition, demoralization and adjustment disorder have a precipitating event or circumstance 100% of the time. In contrast, patients suffering from an episode of major depression will be able to point to a precipitating event or circumstance only about 50% of the time.

Confidence in the diagnosis of major depression can be built by finding a strong family history of depression in which a family member has responded to treatment, a lack of precipitating event, and a recurrence of similar symptoms several times throughout the patient's lifetime. Once the clinician reaches a diagnosis of demoralization or major depression, an appropriate course of treatment should begin.

Table 2. Some Commonly Prescribed Antidepressants*

- Tricyclic Agents
 - Imipramine (Tofranil)
 - Desipramine (Norpramin)
 - Amitriptyline (Elavil, Endep)
 - Nortriptyline (Aventyl, Pamelor)
 - Protriptyline (Vivactil)
 - Doxepin (Sinequan)
 - Trazodone (Desyrel)
- Bupropion (Wellbutrin)
- Selective Serotonin Reuptake Inhibitors
 - Fluoxetine (Prozac)
 - Sertraline (Zoloft)
 - Paroxetine (Paxil)
 - Fluvoxamine (Luvox)
 - Citalopram (Celexa)
- Selective Norepinephrine Reuptake Inhibitors
 - Venlafaxine (Effexor)
 - Nefazodone (Serzone)
- Noradrenergic and Specific Serotonergic Antidepressant
 - Mirtazapine (Remeron)

*The US proprietary name(s) for each drug is listed in parentheses following the generic name.

Table 3. Side Effects of Selected Antidepressants

- Tricyclic Agents
 - Sedation
 - Weight gain
 - Constipation
 - Urinary retention
 - Dry mouth
 - Blurred vision
 - Orthostasis
- Selective Serotonin (5-HT) Reuptake Inhibitors
 - Nausea—5-HT_{2A,2C,3} inhibition
 - Sexual dysfunction—5-HT₂ inhibition
 - Anxiety (fluoxetine > sertraline = citalopram > paroxetine)
 - Insomnia (fluoxetine > sertraline)
 - Sedation (paroxetine > citalopram)
- Bupropion
 - Anxiety
 - Insomnia
 - Nausea
- Selective Norepinephrine Reuptake Inhibitors
 - Activation (venlafaxine)
 - Hypertension (venlafaxine)
 - Sedation (nefazodone)
 - Anxiety (nefazodone)
 - Nausea (nefazodone)
- Noradrenergic and Specific Serotonergic Antidepressants
 - Sedation (mirtazapine)
 - Weight gain (mirtazapine)

Antidepressant Treatment of Major Depression

In most cases, the treatment for depression is antidepressant medication. There are many available medications that have demonstrated efficacy in the treatment of major depression (Table 2). A number of these specifically have been shown to be efficacious in the treatment of major depression affecting patients with HIV disease (Elliott et al, *Semin Clin Neuropsychiatry*, 1998). To date, no single antidepressant medication has been shown to be more efficacious than any other medication for major depression in patients with or without HIV disease. It should be noted that *efficacy* is a property of the medication, that is, it is the ability of the medication to successfully treat the illness for which it is prescribed. This does not mean, however, that a given medication will be *effective* for a particular patient. One reason that a medication may not be effective is that it simply does not correct the underlying metabolic disturbance in the brain of the patient with major depression.

Although the mechanism of action in antidepressant medicines is known, the specific neurochemical disturbance in a given patient with major depression has yet to be demonstrable in a clinically relevant way. If a particular drug that corrects a certain neurochemical disturbance is prescribed, but the patient's neurochemical disturbance is not corrected by the drug's action, that medication will not be effective.

In a large proportion of patients, antidepressant medications fail because of nonadherence to the medications prescribed. Any medication that has a potential positive effect also has a potential for side effects. Antidepressant side effects are listed in Table 3. A good rule of thumb to increase adherence to antidepressant medicines is to prescribe antidepressants with side effect profiles that either treat patient symptoms or do not worsen patient symptoms. An example of this would be prescribing a medication that is sedating for a patient who

has trouble sleeping, or prescribing a medication that slows gastrointestinal motility for a patient who has diarrhea. In general, prescribing a drug that may cause diarrhea to a patient who already suffers from diarrhea will result in the patient's nonadherence to the medication.

Once patients initiate treatment with antidepressant medications, their progress should be monitored for the alleviation of symptoms and the development of new side effects. It is generally thought to be a good idea to begin with low doses of antidepressant medications and titrate slowly to full doses, using therapeutic serum drug level monitoring for those drugs for which such levels have been established. While it is good practice to start low and go slow, it is likewise important to persist in increasing doses to full doses or therapeutic serum levels and to add additional agents if necessary until a response is achieved. Augmenting agents include lithium, triiodothyronine, and antipsychotic drugs. Although lithium has pronounced toxicity, it is the best studied augmenting agent and has well-defined therapeutic serum levels. If response is not observed at therapeutic serum levels after a few weeks, it is not likely to occur, and the drug can be discontinued.

Another augmenting strategy is to combine antidepressants with different

mechanisms of action. For example, a selective serotonin reuptake inhibitor can be combined with a serotonin-norepinephrine reuptake inhibitor, or either or both can be combined with bupropion, which has a predominantly dopaminergic effect. Although none of these approaches can assure a response in every patient with major depression, the Johns Hopkins AIDS Psychiatry Service has found that partial or full response can be achieved in approximately 85% of patients overall and in greater than 90% of patients who adhere to therapy (Figure 2; Treisman et al, *HIV, AIDS and the Brain*, 1994).

There are no data to support the use of antidepressant medications as a key element of treatment for adjustment disorders. There is opportunity for research into the role of neurochemical changes in patients suffering reactive sadness from life circumstances, however, and thus into the role of antidepressants as adjunctive treatments.

Psychotherapy for Adjustment Disorders and Major Depression

Patients with mild adjustment disorders centering around bad news (eg, the worsening of HIV disease status) and patients with major depression benefit from supportive psychotherapy. Supportive psychotherapy includes educa-

tion regarding the psychiatric illness and the practice of therapeutic optimism, which encourages and sustains the belief that therapeutic response can occur with continued treatment. Regular meetings with a provider to discuss feelings and to urge patients to keep going in treatment are often of great benefit. Support groups and informal counseling sessions can be added as needed. A patient with a more severe adjustment disorder should be referred to a professional counselor for any of the various forms of psychotherapy appropriate to his or her condition.

A general principle in many cases for psychotherapy is to identify those elements of the patient's condition or circumstances that may be under the patient's control to change. With encouragement from the therapist for the patient to practice those changes, the sense of empowerment or mastery that ensues often alleviates the patient's demoralized state. Cognitive-behavioral therapy is one form of psychotherapy that focuses on altering feelings by first changing thoughts and actions. Many patients state that they will be able to make important life changes when they are free from their bad feelings; in cognitive-behavioral therapy, the patient is encouraged to learn that first one must *do* better and then one will *feel* better. The many other forms and goals of psychotherapy that can be employed are beyond the scope of this discussion.

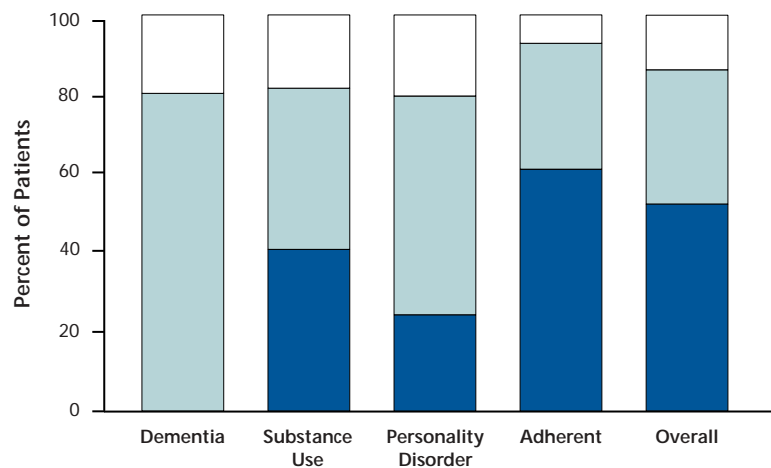


Figure 2. Full (in blue), partial (green), or no (white) response to antidepressant therapy in HIV-infected patients with major depression according to complicating factors (dementia, substance use disorder, personality disorder), and in those adherent to antidepressant treatment, and overall. Adapted from Treisman et al, *HIV, AIDS and the Brain*, 1994.

Addressing Substance Use Disorders

Substance abuse and depressive symptoms are connected in a number of ways. Major depression increases the likelihood of substance use and abuse; many individuals resort to alcohol or drug use in the attempt to replace the lost "yeah!" and "ahhhh..." pleasures. Depressive symptoms can be caused by substance intoxication or withdrawal (substance-induced mood disorder). Patients may also experience adjustment disorder or demoralization as a result of losses experienced through substance use (eg, partners, savings, jobs, homes). Patients with substance-induced mood disorder usually are free from depressive symptoms after the first several weeks of abstinence, whereas

substance-using patients with major depression frequently have episodes of depression during their abstinence.

In the experience of the Johns Hopkins AIDS Psychiatry Service, it is virtually impossible to effectively treat depression in a patient with ongoing substance abuse. Thus, the first step in treating depressive symptoms in all patients with substance use disorders is to stop the substance use. A general behavioral approach that can be used in this setting is to: (1) stop the behavior; (2) identify comorbidities and sustaining factors for the behavior and eliminate them; (3) repeat steps 1 and 2 as necessary; and (4) identify initiating factors and address them (if necessary). Sustaining factors for behaviors can be conceptualized as mutable stimuli and immutable stimuli; the former are those that can be changed or avoided, and the latter are those that cannot be avoided and the responses to which must be directly extinguished. Part of the therapy for patients in this arena is determining which stimuli for substance use are avoidable or changeable and which are inevitable. Patients may be assisted in making a list of "triggers" and examining each item on the list with an eye toward change or avoidance. For example, a man with alcoholism who reports he buys liquor only at a liquor store can be instructed to avoid the street on which the liquor store is located. One immutable stimulus for the substance-abusing HIV-infected patient might be the patient's feelings regarding HIV infection, such as the above-mentioned

demoralization. Since the feelings may be present continually or recurrently because the infection is not yet curable, the patient's response to these feelings should be directly addressed in counseling or psychotherapy, with a prescription of new, non-substance use behaviors to replace those behaviors that maintained the addiction.

Conclusion

In summary, major depression and adjustment disorder or demoralization are 2 major forms of psychiatric disturbance associated with depressive symptoms. Patients with depressive symptoms may be at increased risk for transmission of HIV infection due to increased likelihood of engaging in high-risk behaviors; similarly, HIV-infected patients with depressive symptoms may be at increased risk of transmitting HIV to others through risk behaviors. In addition, patients with depressive symptoms who have HIV infection may have increased risk for nonadherence to medical therapies and worsening of illness. Major depression and demoralization can often be differentiated on the basis of symptoms, family history, pattern of recurrence of illness, and the presence or absence of precipitating circumstances or events. Both major depression and demoralization are treatable conditions, and their identification and treatment lead to improved function and quality of life and may result in reduced risk of transmission of HIV to uninfected individuals.

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Suggested Reading

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