Depression and HIV/AIDS

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HIV/AIDS continues to be a significant public health problem. Millions of people worldwide are infected with this virus daily, and thousands die yearly of AIDS-related illnesses. Despite rapid advances in our knowledge about HIV and its mode of transmission, we have been unable to find a cure or prevent new infections. Psychiatric comorbidity is associated with HIV/AIDS: as a risk factor for HIV infection, a comorbidity of HIV infection, sequelae of HIV/AIDS, and a potential mediator for progression to AIDS. In this article, we focus on depression, which is prevalent in HIV/AIDS. We review the evidence associating depression with HIV, the challenges in recognizing depression in HIV-positive individuals, and the psychopharmacologic strategies known to be effective in the treatment of HIV-positive individuals with depression.

Introduction

HIV continues to be a growing public health problem. Despite significant advances in our understanding of HIV, its modes of transmission, its physiology, and remarkable developments of effective treatments, we have been unable to prevent new infections.

Highly active antiretroviral therapy (HAART) has significantly prolonged the lives of individuals living with HIV and has transformed HIV/AIDS from a life-threatening illness to a chronic condition. Despite our progress, HIV remains an international problem, with new cases occurring daily.

The most recent statistics reported by the Joint United Nations Programme on HIV/AIDS highlight this illness' impact. Recent estimates of HIV/AIDS prevalence worldwide suggest that as many as 40 million people are living with HIV virus type 1, and approximately 4.9 million individuals (adults and children) are newly infected with cases. More than 3 million of those individuals infected with HIV died of AIDS-related complications in 2004 [1].

At the end of 2003, 1 to 1.2 million people in the United States were living with HIV/AIDS, with 24% to 27% undiagnosed or unaware of their infection [2].

The demographics of this illness have shifted significantly since the virus was identified more than 20 years ago. HIV/AIDS was initially identified among white men who have sex with men, but now heterosexual women are increasingly affected. The prevalence estimates of HIV/AIDS among women shifted from 14% of adults in 1992 [3] to 22% by the end of 2003 [2]. The largest increases have been among African American and Hispanic women, who together represented about 25% of all US women [4] but accounted for 83% of the AIDS diagnoses reported in 2003 [5,6]. HIV infection has become the leading cause of death in African American women 25 to 34 years old and is among the four leading causes of death for African American women 20 to 24 and 35 to 44 years old and Hispanic women 35 to 44 years old [7]. New infections are also increasing among young people (13–24 years old), who represented about 12% of individuals diagnosed with HIV/AIDS in 2003 [2].

Depressive Disorders

Depression is prevalent among individuals living with HIV, with evidence suggesting that up to one third of people with HIV/AIDS may have mood disorders or clinically significant depressive symptoms [7–9]. Prevalence estimates derived from epidemiologic studies of depression in HIV-positive individuals have shown wide variations, ranging from 4% to 22% for HIV-positive men [7] and from 2% to 18% for HIV-positive women [8,9]. A recent well-designed epidemiologic study screened a sample of 2864 HIV-positive patients. Almost one half were identified as having a psychiatric disorder. More than one third of the sample were positive for major depression, and more than one fourth of the sample were positive for dysthymia [7,8].

The growing number of new HIV infections among women has focused more investigation upon depression in this population. Furthermore, the higher reported prevalence rates of depression among women in the general population suggest that women may be more vulnerable than men [9,10] to the onset of depression during illness. Recent evidence provides support for this assumption [9].

In a recent well-designed study of 765 HIV-positive women, chronic depression symptoms were present in 42%, and intermittent depressive symptoms were present in 35% [10]. Morrison and colleagues [9] compared 93 HIV-positive women with 62 demographically matched controls and found a much higher prevalence of major depressive disorder in HIV-positive women (19.4%) compared with HIV-negative controls (4.8%).

Together with the increasing evidence that depression is prevalent among HIV-positive individuals, clinical experience and recent research describe the important connections among depression, physical and emotional health of individuals living with HIV, and medical outcomes. Depressive symptoms and psychological stress have been associated with poor outcomes for these patients, including more rapid progression of HIV/AIDS, higher mortality rates, poor compliance with treatment, and greater impairments in psychosocial function [11–18]. Also, studies examining neuroimmune relationships in HIV/AIDS suggest that depression causes biologic changes in endocrine and immune function that may contribute to disease progression and mortality [19,20].

Depression also may complicate the course of illness in HIV-positive individuals. Recent data suggest an association between a history of depression and significant delays in the initiation of treatment with protease inhibitors, one of the major components in many HAART regimens [21,22••].

Taken together, clinical experience and research findings suggest that recognizing and treating depression is essential to the prevention of morbidity and mortality in HIV-positive individuals. The evidence linking depression and mortality in HIV-positive individuals is strong, pointing to the need for early recognition and aggressive treatment.

Management of Depressive Disorders in HIV/AIDS: Somatic Therapies

Effective treatments are available for depressive disorders in people living with HIV/AIDS. Many well-controlled studies have demonstrated the efficacy of antidepressant treatments and psychotherapy for depression in HIV/AIDS [22••]. Unfortunately, these effective treatments do not reach many of the HIV-positive individuals who might benefit. One major barrier to effective treatment has been the challenge of diagnosing depression in the presence of HIV/AIDS [23,24].

Diagnosing depression in the presence of HIV/AIDS can be complicated. It can be difficult to distinguish the symptoms of depression from those of the physical symptoms of HIV/AIDS itself (eg, fatigue, pain, anorexia, insomnia, anhedonia, and dysphoria). Loss of interest or inability to experience pleasure may be the result of physical suffering or disability. Excessive somatic complaints and poor adherence to or refusal of medical treatments may be manifestations of depression as well [25]. The syndrome of demoralization, manifested by hopelessness, and a desire for hastened death related to advanced AIDS may be difficult to distinguish from depression [26]. Few screening tools available to the clinician have been validated in the medically ill and may aid the clinician in diagnosing depression. Some commonly used tools are the Center for Epidemiologic Studies Depression Scale, the Hospital Anxiety and Depression Scale, the Beck Depression Inventory II, and the Patient Health Questionnaire. Furthermore, evidence suggests that depression screening has resulted in greater recognition of depression among individuals with medical illnesses [27]. However, the evidence further suggests that this recognition has not translated into more effective management or better treatment outcomes. There is a tendency among family members and clinicians to discount depressive symptoms as a predictable response to the illness or to minimize the importance of these symptoms relative to the medical treatment.

Although it is true that depressive symptoms are common in HIV-positive individuals at the time of first diagnosis, the persistence of moderate to severe depression, depressed mood, and anhedonia should prompt the clinician to complete a comprehensive evaluation for depression and, if it is present, initiate treatment [28]. When present, these symptoms are most indicative of depression and not HIV disease [29]. Treatment of depressive symptoms in patients with HIV infection improves psychosocial functioning and quality of life [30].

Selective Serotonin Reuptake Inhibitors

Several randomized studies have demonstrated the effectiveness of antidepressant agents for the treatment of depression in HIV-positive individuals. Most controlled studies have included tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) [22••]. Head-to-head efficacy studies comparing TCAs with SSRIs have found them to be equally effective, but the SSRIs have demonstrated more favorable side effect profiles and greater tolerability.

Of the SSRI agents, fluoxetine has been the most studied in well-controlled trials. In placebo-controlled trials, fluoxetine has demonstrated superior efficacy to placebo. In a placebo-controlled study of depressed HIV-positive individuals, 81 patients treated with fluoxetine were compared with 39 treated with placebo for 8 weeks. At study entry, 95% of the patients met criteria for major depression, and 51% had an AIDS-defining condition. Primary outcome measures were improvements on Clinical Global Impression (CGI) scale ratings and change in Hamilton Depression Scale (HAMD) scores. At 8 weeks, fluoxetine was more efficacious than placebo. Dropout rates were not significantly different between the two groups; however, the authors noted that those who dropped out were more likely to have greater severity of depression [31].

Several open-label studies have shown support for the efficacy of paroxetine [32,33] and sertraline [34]. In one of the few studies comparing the efficacies of SSRIs in HIV-positive individuals, Ferrando and colleagues [33] compared paroxetine, sertraline, and fluoxetine in 33 symptomatic HIV-positive patients. In this 6-week open trial, 83% of the participants reported improvements in depression and somatic symptoms related to HIV disease. Twenty-seven percent dropped out due to agitation, insomnia, or anxiety at weeks 1 and 3. However, this study was not powered to detect differences in efficacies of these agents, but it does support the other studies, suggesting that SSRIs reduce the symptoms of depression in HIV-positive individuals and that their side effects are better tolerated in this population.

Another small, open-label study examined citalopram in 20 men [35]. Fifty-five percent of this sample had a diagnosis of AIDS, and 70% of the sample was Hispanic. The primary outcome measures were reduction in HAMD scores and improvements in CGI scores. Fifty percent of those completing the study showed at least a 50% reduction in HAMD scores and improvements in CGI scores. Although these open studies must be interpreted with caution, the preponderance of the evidence supports the efficacy, safety, and tolerability of SSRIs. SSRIs are generally accepted as first-line treatment for depression in HIV-positive individuals due to their relative safety, tolerability, and favorable side effect profiles.

Only a few studies have specifically addressed antidepressant treatment in HIV-positive women. Schwartz and McDaniel [36] compared fluoxetine with desipramine in women with AIDS. Response rates were 53% for the fluoxetine group and 75% for the desipramine group. Ferrando et al. [34] compared fluoxetine with sertraline in a group of HIV-positive women, with response rates of 78% for fluoxetine and 75% for sertraline. These studies suggest that SSRIs are effective in reducing depressive symptoms in HIV-seropositive women.

Tricyclic Antidepressants

TCAs have proven efficacy for treating depression in HIV-seropositive patients [37,38•]. The efficacy of imipramine for depression in HIV-positive individuals was demonstrated by Rabkin et al. [39] in a double-blind, randomized, placebo-controlled trial of 97 HIV-seropositive patients. The investigators examined changes in depressive symptoms and immune parameters with treatment. In this study, 74% of the imipramine group and 26% of the placebo group showed improvement of depressive symptoms with no changes in $CD3^+/CD4^+$ cell counts at week 6 of the study. A significant number of patients—more than one third of those in the study—discontinued treatment because of anticholinergic side effects. Another study using a similar design [40] compared imipramine, paroxetine, and placebo in 75 HIV-positive individuals. The two antidepressants were found to be equally efficacious at 6, 8, and 12 weeks and were significantly more efficacious than placebo. Similar to the Rabkin et al. [39] study, many patients discontinued treatment due to side effects: 48% with imipramine, 20% with paroxetine, and 24% with placebo. In a study comparing psychotherapies and combination psychotherapy and imipramine, Markowitz et al. [41] enrolled 65 HIV-positive men and 4 women with major depression (53% with major depression, 32% with AIDS). In a 16-week trial comparing interpersonal psychotherapy, cognitive-behavioral therapy, supportive therapy with imipramine, and supportive therapy alone, interpersonal psychotherapy and supportive therapy with imipramine were superior to supportive therapy alone and cognitive-behavioral therapy in ameliorating depressive symptoms and improving physical functioning, suggesting that the combination of psychotherapy with medication is superior to either treatment alone in HIV-positive individuals.

Newer Antidepressant Agents

A growing number of studies have examined the newer antidepressant agents for the treatment of depression in HIV-positive individuals. Most of these studies have been open studies, but they suggest that several of the newer antidepressant agents may be useful for treating depression in HIV-seropositive individuals. Mirtazapine, nefazodone, venlafaxine, and sustained-release bupropion have been the best-studied novel agents with preliminary reports of efficacy. In an open trial of nefazodone in 15 outpatients, the response rate was 73%, with few adverse effects [42]. However, reports of nefazodone-induced liver toxicity limit its usefulness in HIV-positive individuals due to the high prevalence of hepatitis B and C infection among these individuals. Mirtazapine also has shown some benefit for cachectic patients with AIDS beyond its antidepressant effects, as it promotes weight gain and decreases nausea [43]. Preliminary data on bupropion show promise of efficacy in HIV-positive individuals. In a recent 6-week, open-label, flexible-dose trial of sustained-release bupropion in 20 HIV-seropositive depressed men and women, 12 patients attained remission at a mean dose of 265 mg/d. Fourteen patients reported some adverse events, and five patients discontinued the study because of side effects (panic attacks, agitation, and irritability) [44].

Psychostimulants

The stimulant medications methylphenidate and dextroamphetamine have been used to treat depression in HIV infection, specifically targeting depressed mood, fatigue, and cognitive impairment in advanced illness, usually when a rapid onset of action is desirable. Both agents have been studied in open and placebo-controlled trials with HIV-positive individuals. Dextroamphetamine treatment was studied in an open trial of 24 patients with AIDS and depression who

exhibited debilitatingly low energy levels. Improvements in mood and energy coincided with significant reductions in HAMD scores noted as early as week 2. Although systematic follow-up evaluations were not available, the treatment effects were maintained over 2 years [45]. This same group, later using dextroamphetamine in a placebo-controlled trial, showed significant improvements in initiative and mood in 73% of depressed patients assigned to active drug and 25% of those receiving placebo [46]. A double-blind trial examining fatigue in HIV-positive individuals compared methylphenidate, pemoline, and placebo in 144 HIV-positive patients. Improvements in fatigue were associated with improvement in subclinical depressive symptoms. Methylphenidate and pemoline were superior to placebo. Overstimulation was more common with the stimulants than with placebo [47]. These studies suggest that stimulants are effective for treating depression in HIV-positive individuals; however, much more research is needed.

Reductions in testosterone levels are common in individuals with HIV/AIDS and have been associated with changes in mood, appetite, and sexual function. Recent evidence suggests that testosterone supplementation for depression [48] and the adrenal steroid dehydroepiandrosterone [49] may improve mood.

Despite the efficacy of antidepressant agents for the treatment of depression in HIV-positive individuals, their side effect profiles may be difficult to tolerate. Many individuals living with HIV turn to herbal agents for depression treatment, with one of the most popular agents being St. John's wort. Use of these agents must be asked about among HIV-positive patients with depression. Studies examining St. John's wort show that the serum concentration of the protease inhibitor indinavir, metabolized by the 3A4 isoenzyme system, was markedly reduced by the use of this 3A4 inducer [50]. This reduction in indinavir levels was significant enough to potentially cause drug resistance and lead to treatment failure. These agents are best avoided with antiretroviral use.

Recommendations

Depression must be considered in individuals who are infected with HIV or who have progressed to AIDS. Screening for depression should occur. When it is identified, a comprehensive assessment should be completed, and treatment should be initiated.

The evidence suggests that treatment for psychiatric conditions affecting individuals living with HIV/AIDS should be the same as empirically validated treatments used for the general population. There are no absolute contraindications specific to HIV-infected individuals, but a strong knowledge of the metabolic pathways of psychotropic agents and the major metabolic pathways for antiretrovirals is essential to guide our decisions about psychotropic choices, given the potential adverse drug-drug interaction and increased sensitivity to side effects that have been reported in this population. The choice of antidepressant agents should be guided by the potential for drug interactions and the potential benefits and risks of the profiles of the prescribed medications. For example, sedating antidepressants such as mirtazapine may not be helpful for patients with fatigue as a symptom; however, its potential for weight gain may be of benefit in an anorexic, cachectic patient.

Conclusions

Despite 25 years of progress, the HIV epidemic is far from over, with new cases occurring daily. Effective treatments for HIV/AIDS have transformed this once-fatal illness into a chronic condition. HAART has created opportunities for better-quality lives for individuals living with HIV. However, the high prevalence of depression in this vulnerable population could prevent HIV-positive individuals from fully benefiting from these effective medical treatments. Depression contributes to morbidity and mortality that exceed those predicted by the illness itself. Depression interferes with adherence to treatments, worsens medical prognosis, impairs quality of life, and may hasten progression to AIDS. It must be aggressively identified and treated in this vulnerable population.

The preponderance of the evidence supports the effectiveness of antidepressant medications for the treatment of depression symptoms in HIV-positive individuals. Treating depression can improve the quality of life of individuals struggling with the demands of living with HIV/AIDS. The evidence suggests that SSRIs are effective, well tolerated, and safe, making them the agent of choice for this population.

People living with HIV/AIDS face many challenges and may benefit from well-validated psychosocial interventions. Comprehensive programs that integrate medical care, psychosocial interventions, and psychiatric treatment have been most effective in relieving psychosocial distress, improving adherence and coping, and ultimately improving quality of life. Current research focused on effective behavioral and somatic treatments for depression in people living with HIV/AIDS will continue to inform us of new and better treatments that will allow us as clinicians to offer more and better treatment options to our patients.

Disclosure

No potential conflict of interest relevant to this article was reported.

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