Antidepressant Treatment of Depression in HIV-Seropositive Women

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Background: This study aimed to assess the effectiveness of fluoxetine and sertraline in treating depressed women who are seropositive for the human immunodeficiency virus (HIV) and to document barriers to study participation.

Method: Ambulatory HIV-seropositive women with DSM-IV depressive disorders were enrolled in an 8-week, open trial of fluoxetine (N = 21) or sertraline (N = 9) initiated at standard dosages. Outcome measures included the Clinical Global Impressions-Improvement scale (CGI), Hamilton Rating Scale for Depression (HAM-D), Beck Depression Inventory (BDI), physical function ratings, and CD4 count.

Results: Thirty-six women were screened for the study and 30 were enrolled. Mean age was 35.5 years and HIV risk was primarily intravenous drug use (N = 16; 53%) or heterosexual contact (N = 12; 40%). Sixteen (53%) were Hispanic, 11 (37%) were African American, and 3 (10%) were white. Mean ± SD CD4 count was 463 ± 312 cells/μL, and 30% had acquired immunodeficiency syndrome (AIDS). Eighteen women (60%) completed the trial (14 fluoxetine: dose range, 10–40 mg/day; 4 sertraline: dose range, 25–100 mg/day). Of completers, 14 (78%) were clinical responders by CGI and reduction in HAM-D > 50%. Statistically significant reductions were seen in HAM-D and BDI scores, but not in measures of physical function or CD4 count. The most frequent adverse effects were anxiety, overstimulation, and insomnia. Reasons for nonparticipation or dropout included refusal to accept antidepressants on account of negative bias, preferring psychotherapy alone, adverse effects, and relapse to illicit drugs.

Conclusion: While HIV-seropositive women may benefit from antidepressant treatment, multiple barriers to successful treatment exist. Aggressive outreach, education, and attention to the complex psychosocial needs of HIV-seropositive women are essential components of depression treatment in this population.

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The prevalence and treatment of depressive disorders in women who are seropositive for the human immunodeficiency virus (HIV) has received little research attention, despite the fact that in the general population depression is more common in women than men.[1] The relatively few studies concerning rates of depressive disorders among HIV-seropositive women have documented rates of current major depression and/or dysthymia ranging from 0% among women in active military service,[2] to 5% among former substance-using women with > 6 months recovery,[3] to 19% among HIV-seropositive pregnant[4] and injection drug–using women,[5] to 47% of HIV-seropositive women seen in an infectious disease clinic.[6] While these prevalence rates are consistent with, if not higher than, those for HIV-seropositive men,[7] very few women participated in published studies of antidepressant treatment in HIV. In fact, of approximately 680 persons in the HIV depression treatment literature randomly assigned to receive either antidepressant or placebo, approximately 37 (5%) have been women.[8–14] These studies have suffered substantial attrition (15%–55%), and many of those who withdrew were women. Thus, it is unknown whether the generally favorable antidepressant response rates (usually between 70% and 90%) reported in the HIV literature reliably apply to women.

In the only prior study of antidepressant treatment of HIV-seropositive women,[14] a double-blind comparison of fluoxetine versus desipramine conducted in a public sector outpatient clinic by Schwartz and McDaniel,[14] only 14 (54%) of 26 women who were eligible for the study actually initiated treatment and 12 (86%) of 14 completed the 6-week trial. Nine (75%) of these 12 women were rated as much or very much improved, with no difference between treatments, but the authors noted persistence of signifi-

cant residual depressive symptoms. Reasons cited for nonparticipation in this study included active substance abuse, nonadherence with clinical visits due to psychosocial problems and child care responsibilities, and suspicion about participation in medication research studies. The latter findings regarding research participation of HIV-seropositive women are consistent with those from nonpsychiatric HIV clinical trials.[15]

Given the paucity of research information about antidepressant treatment of HIV-seropositive women, the current study was undertaken (1) to augment the small amount of available data regarding the effectiveness of antidepressants in treating HIV-seropositive women with depressive disorders and (2) to document barriers to study participation. The study was designed to enhance participation by not including a placebo arm, by offering sertraline as an alternative to fluoxetine (because the latter is regarded with particular suspicion by some), by providing remuneration for transportation, and by being located primarily in a multidisciplinary HIV clinic with psychosocial and supportive services including case management and child care.

METHOD

Sample

The study was carried out at 2 sites between November 1995 and May 1998, when highly active antiretroviral therapy (HAART) with protease inhibitors came into widespread use. Most of the women were referred for evaluation and treatment of depression at a multidisciplinary metropolitan HIV/acquired immunodeficiency syndrome (AIDS) care center at Cornell (New York, N.Y.). The rest were recruited from community-based organizations and treated at an HIV depression research program at Columbia (also in New York, N.Y.). Women were invited to participate if they met criteria for a current depressive disorder (major depressive disorder, subthreshold major or minor depressive disorder, or dysthymic disorder). Potential subjects were excluded if they had a history of mania or psychosis, had abused substances in the past 3 months (with negative urine toxicology screen at entry), had positive pregnancy test, would not agree to utilize barrier contraception, had unstable medical illness, or had moderate-to-severe cognitive impairment as evidenced by a Mini-Mental State Examination (MMSE)[16] score < 20. Women who agreed to participate gave informed consent after the study procedures and possible side effects were explained.

Measures

Psychiatric diagnosis. The Structured Clinical Interview for DSM-IV (SCID) was used to diagnose past and current psychiatric disorders.[17]

Depressive symptoms and global improvement. At baseline and weeks 4 and 8, the structured interview version of the 17-item Hamilton Rating Scale for Depression (HAM-D)[18] was administered by a study clinician and the Beck Depression Inventory (BDI)[19] was filled out by each study participant. Subjects were also given a Clinical Global Impressions Severity and Improvement scale (CGI)[20] score at baseline and study completion. The CGI is a 7-point scale, with higher scores indicating greater improvement.

Physical function. At study baseline and completion, a self-report Physical Limitations Questionnaire (Phys-L) was given as a measure of physical function.[21] The Phys-L lists 10 physical activities in descending order of difficulty. Subjects respond, "Yes, I can do this" (score = 2), "Yes, but only slowly" (score = 1), or "No, I can't do this" (score = 0). Items are summed to obtain a total score (range, 0–24), with higher scores indicating more physical limitations. As a clinical rating of physical function, each subject was also given a Karnofsky Performance score at baseline.[22] Scores range in increments of 10 from 0 (deceased) to 100 (fully functional).

HIV illness markers. Baseline laboratory tests included CD4+ lymphocyte count, complete blood count and serum chemistries, serum pregnancy test, and urine toxicology screen. In a subset of 10 subjects, CD4 counts were taken at baseline and study completion to investigate the effect, if any, of antidepressant treatment on enumerative measures of immune function. HIV illness stage was determined according to 1993 Centers for Disease Control criteria.[23]

Adverse effects. Potential adverse effects and their severity (mild, moderate, severe) were assessed at baseline and at each study visit, so that treatment-emergent or exacerbated symptoms could be detected.

Procedure

If eligible for the study, women were invited to participate in an 8-week open trial of fluoxetine. If they refused fluoxetine, they were offered sertraline. Treatment was initiated at standard starting dosages (20 mg/day for fluoxetine, 50 mg/day for sertraline) because they were generally well-tolerated by HIV-seropositive subjects in prior research conducted by the authors.[8,9,13] Dosage could be adjusted upward or downward after 2 weeks on the basis of clinical response or adverse effects. Women were seen every 2 weeks and assessments were done at baseline and weeks 4 and 8 of the study. Study visits lasted approximately 45 minutes, were supportive in nature, and were oriented primarily toward depressive symptom assessment and medication management. When possible, the reason for study nonparticipation or dropout was recorded.

Treatment Outcome

For study completers, pretreatment and posttreatment scores on the HAM-D, BDI, and Phys-L, as well as CD4 count (in the subset of 10 women), were compared using

Table 1. Demographic Characteristics of Study Participants (N = 30)[a]

Variable	Value
Age, mean (SD), y	36 (8.4)
Ethnicity, N (%)	
Hispanic	16 (53)
African American	11 (37)
White	3 (10)
Primary HIV risk, N (%)	
Intravenous drug use	16 (53)
Heterosexual sex	12 (40)
Blood transfusion	1 (3.5)
Unknown	1 (3.5)
Relationship status, N (%)	
Partner	13 (43)
Widowed	5 (17)
Single/separated/divorced	8 (27)
Married	4 (13)
No. of children, mean (SD)	2 (2.5)
Education in years, mean (SD)	11 (1.7)
Yearly income in dollars, mean (SD)	6217 (4820)
Income source, N (%)	
Public assistance	15 (50)
Social security	13 (43)
Private disability	1 (3.5)
Employed	1 (3.5)
CD4 count, mean (SD), cells/μL	463 (312)
Range, cells/μL	16–1266
AIDS diagnosis, N (%)	9 (30)
Karnofsky score, mean (SD)	92 (9)
Phys-L score, mean (SD)	17 (3)
HIV medications, mean (SD)	4 (3)
Antiretroviral therapy, N (%)	12 (40)

[a]Abbreviations: AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus, Phys-L = Physical Limitations Questionnaire.

Table 2. Current and Lifetime DSM-IV (SCID) Psychiatric Diagnoses of Study Participants (N = 30)[a]

Psychiatric Diagnosis	N	%[b]
Current		
Major depressive disorder	23	77
Major depressive disorder plus dysthymia	4	13
Minor depressive disorder	1	3
Dysthymic disorder	2	7
Panic disorder	4	13
Obsessive-compulsive disorder	2	7
Lifetime		
Major depressive disorder	16	53
Opioid dependence	15	50
Cocaine dependence	14	47
Alcohol dependence	8	27
Cannabis dependence	6	20

[a]Abbreviation: SCID = Structured Clinical Interview for DSM-IV.
[b]Percentages exceed 100% owing to multiple diagnoses for individual subjects.

paired-samples t tests. Subjects were considered clinical responders if their mood was rated as much or very much improved on the CGI (a score of 1 or 2) and if they had a > 50% reduction in their HAM-D score. In addition, study completers and dropouts were compared on baseline depression and HIV illness measures to determine if there were distinguishing characteristics that may have affected study participation.

All data were analyzed using SPSS software. All tests were 2-tailed, with an alpha level of .05.

RESULTS

Sample

Thirty-six women were screened and met inclusion criteria for the study, 30 participated, and 18 completed the 8-week trial. There were no significant differences in baseline demographic, psychiatric, cognitive, medical, or HIV treatment characteristics between women who completed the study and those who declined study participation (N = 6) or dropped out (N = 12) (data not shown).

Table 1 outlines demographic and HIV illness characteristics for the 30 study participants. Fifty-three percent were Hispanic (primarily of Puerto Rican and Dominican descent), 37% were African American, and 10% were white. Approximately half reported either intravenous drug use or heterosexual intercourse as their HIV risk factor. Women with heterosexual transmission reported unprotected intercourse during periods of active drug use (N = 6) or with a substance-using primary partner (N = 6). There were no significant ethnic differences in reported HIV risk. Nearly two thirds were married or in a significant relationship; however, 8 lived alone caring for children under 10 years old. In terms of education, 14 women did not finish high school, 4 had passed a high school equivalency examination, 7 graduated high school, 4 had some college, and 1 had a master's degree. Mean MMSE score was 25 (range, 20–30), with 11 subjects in the mildly impaired range (score = 20–25) due to deficits in attention and concentration. Only 1 subject was working, with the rest primarily supported by public assistance and social security. Mean personal income was below poverty level; however, many subjects received rent supplements and none of them was homeless.

Regarding DSM-IV psychiatric diagnosis (Table 2), lifetime psychiatric and substance use disorders were common, with approximately half of the patients having a history of major depressive disorder, heroin dependence, and/or cocaine dependence. In terms of current disorders, 90% had a diagnosis of major depressive disorder and 20% had comorbid anxiety disorders (panic and/or obsessive-compulsive disorder). Six (20%) were receiving methadone maintenance treatment, and another 3 (10%) were in other drug treatment programs (2 residential, 1 outpatient).

In terms of HIV illness status, mean baseline CD4 count was 463 cells/μL and one third of the women had an AIDS diagnosis. While the majority reported medical symptoms possibly attributable to HIV, physical function was mildly to moderately impaired, as indicated by the mean physical limitations scale and Karnofsky Performance Scale scores. In terms of HIV treatment, 14 were taking no antiretrovirals, 2 subjects seen early in the study

Table 3. Paired Comparisons of Pretreatment and Posttreatment Depression Measures, Physical Limitations, and CD4 Count for Study Completers (N = 18)[a]

	Baseline		Week 8			
Variable	Mean	SD	Mean	SD	t	p
HAM-D total	24	7	9	8	8.7	< .0001
HAM-D affective	10	3	3	3	9.8	< .0001
HAM-D vegetative	10	4	5	4	4.9	< .0001
BDI total	28	11	13	11	5.6	< .0001
BDI cognitive	19	8	9	8	5.0	< .0001
BDI somatic	9	4	4	3	4.8	< .0001
Phys-L	17	4	17	4	0.08	NS
CD4, cells/μL[b]	506	195	477	230	1.2	NS

[a]Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression.
[b]N = 10.

were taking nucleoside reverse transcriptase inhibitor (NRTI) monotherapy, 6 were on dual NRTI therapy, and 8 were on HAART. Several women had other chronic medical conditions such as chronic renal failure requiring dialysis (N = 1), rheumatoid arthritis (N = 1), asthma (N = 1), pulmonary hypertension (N = 1), and treated hypothyroidism (N = 1).

Attrition

The 6 women who declined to participate in the study were unwilling to accept antidepressant medication, preferring to try psychotherapy first. Several mentioned the negative reputation of psychotropics in their community and in substance abuse treatment programs. Of the 12 women who agreed to participate and who dropped out of the study, 7 were prescribed fluoxetine and 5 were prescribed sertraline. Five dropped out of the study owing to adverse effects (see below); 4 were lost to follow-up (2 who were not in drug treatment were suspected of drug relapse); 2 had an attitude change about antidepressant medication after bringing study medication home and discussing it with family and friends; and 1, who was not in drug treatment, was dropped owing to a known drug relapse.

Treatment Response

Of the 18 women who completed the study, 14 received fluoxetine (mean = 21 mg/day; range, 10–40 mg/day), and 4 received sertraline (mean = 56 mg/day; range, 25–100 mg/day). Fourteen (78%) of study completers were clinical responders according to combined CGI and HAM-D criteria. Broken down by ethnicity, 7 (88%) of 8 Hispanic women, 6 (86%) of 7 African American women, and 1 (33%) of 3 white women responded, but the lower response among the latter group did not reach statistical significance ($\chi^2 = 4.1$, p = .13). Otherwise, treatment responders did not differ from nonresponders in terms of baseline demographic, psychiatric, cognitive, medical, or HIV treatment characteristics (data not shown). Notably, all 6 women with AIDS responded to treatment, compared with 8 (67%) of 12 of women without AIDS ($\chi^2 = 2.6$, p = .1).

Table 3 contains pretreatment and posttreatment means and t test results for depression and HIV illness measures among study completers. BDI and HAM-D total and cognitive/affective and somatic/vegetative subscale scores all decreased significantly, on the order of 50%. When considered separately, Hispanic and African American women, but not white women, experienced similar reductions in depressive symptoms. Subjects with and without AIDS also experienced similar improvement. Overall, mean scores at study completion on the HAM-D and BDI were indicative of mild residual depressive symptoms. While there was reduction in somatic/vegetative symptoms of depression, the mean physical limitations score was not significantly different between baseline and completion. In addition, there was no change in mean CD4 count between baseline and completion for the 10 women with these measures.

Adverse Effects

Five study participants (17%) dropped out of the study due to adverse effects: all of them reported increased anxiety or overstimulation and 4 (13%) of them reported insomnia. In addition, 3 subjects (10%) had nausea, 2 (7%) each reported headaches and feeling "high," and 1 (3%) reported anorgasmia. Women who dropped out owing to adverse effects did not differ from completers in terms of demographic, psychiatric, medical, or HIV treatment characteristics.

DISCUSSION

This study addressed the effectiveness of and barriers related to antidepressant treatment of depressed HIV-seropositive women. The women studied were typical of those seen in an urban HIV clinic, with a high percentage being either Hispanic or African American, living below poverty level, and having a prior history of depression and substance dependence. Despite the supportive clinical and research settings, open-label design, and aggressive outreach and follow-up, depressed HIV-seropositive women were difficult to recruit and maintain in this treatment study. Half of the women referred and who could have benefitted from antidepressants completed this treatment study.

Hesitancy to accept antidepressant medication per se, rather than resistance to research study participation, was the most often cited reason for refusal to enter this study, and in some instances, was the reason for withdrawing. Many women described "word on the street" against antidepressants and concerns about maintaining themselves "drug-free," without dependency on psychotropics. Related to this was a desire only to talk about problems through counseling, rather than to medicate symptoms. Further, family and support system opinion about antidepressant medication was very important in continuation in treatment. One study participant took fluoxetine for approximately 1 week; however, her mother flushed the medica-

tion down the toilet after she discovered the patient was taking it. The patient subsequently withdrew from the study, still having significant depressive symptoms.

Study attrition was significant: 40% of study participants dropped out of the trial. The adverse effects leading to dropout generally involved overstimulation and insomnia in the early stages of treatment with a selective serotonin reuptake inhibitor (SSRI), which has been reported in some[8,9,13,14] but not all[10,11] studies of SSRI treatment of depression in HIV. These adverse effects could not be predicted by baseline characteristics, but might have been mitigated by lower starting dosages (e.g., 10 mg/day of fluoxetine, 25 mg/day of sertraline) in some patients. Other known reasons for dropout included attitude change toward antidepressant treatment and illicit drug relapse. While adverse effects could not be excluded among women who were lost to follow-up, other possible reasons for dropout included domestic issues such as child care and violence, in addition to illicit drug relapse. Women who did or who were suspected of drug relapse were not in substance abuse treatment, underscoring the importance of such treatment in maintaining sobriety and treating depression in this population.

Among the women who did complete the study, 78% were clinical responders, similar to the percentage who responded in studies that included almost exclusively HIV-seropositive men[8–13] and in the only other study of HIV-seropositive women.[14] Both cognitive/affective and somatic/vegetative symptoms improved significantly. While somatic/vegetative symptoms of depression improved, actual physical function remained unchanged, suggesting that somatic symptoms but not actual physical limitations were secondary to depression. As in previous studies, antidepressant response did not appear to be mitigated by greater HIV illness severity (degree of immunosuppression or AIDS diagnosis) or influenced positively or negatively by antiretroviral treatment. Antidepressant treatment did not affect CD4 count. It is an encouraging preliminary finding that all study completers who had AIDS responded to treatment. This finding cannot be explained by other baseline characteristics such as depression severity or antiretroviral treatment, since these were similar for women with and without AIDS. Further, Hispanic and African American women were just as likely to respond to antidepressant treatment (88% and 86%, respectively). While only 1 of 3 white women responded, this group was too small to make meaningful comparisons.

Despite the high response rate, as a group, study completers had significant residual depressive symptoms, with the mean HAM-D and BDI scores in the "mildly depressed" range. This finding was also reported by Schwartz and McDaniel[14] in a sample of HIV-seropositive women who were more immunosuppressed. In the present study, residual symptoms may be partially attributable to suboptimal antidepressant dosing, with the mean fluoxetine and sertraline doses at 21 and 56 mg/day, respectively. However, ongoing distress related to psychosocial problems and coping with HIV illness may have contributed to residual symptoms.

The principal limitations of this study include small sample size and the lack of placebo and/or psychotherapy comparison groups. These limited the ability to elucidate differences in antidepressant response among subgroups of women (i.e., differing by ethnicity, HIV risk, and/or illness stage) and among different treatments. However, most prior studies that might have addressed these issues were unable to recruit and retain HIV-seropositive women despite considerable outreach,[8–13] and the only other study of HIV-seropositive women had similar recruitment and retention problems.[14] Thus, the limitations of the current study reflect the general difficulties in studying and treating this population, and the open design was specifically chosen as the best possible strategy to augment the limited available data.

In sum, HIV-seropositive women with depressive disorders who receive an adequate trial of selective serotonin reuptake inhibitors respond at rates similar to those for HIV-seropositive men, with relatively few adverse effects. However, the nonparticipation and attrition seen in this study reflect significant barriers to effective treatment of depression in this population. They underscore the need for a multimodal approach addressing concrete social challenges such as low income, child care, and domestic violence; stressing the need for substance abuse treatment; and addressing contrary attitudes and beliefs by providing individual, family, and community education about the benefits of antidepressant and psychotherapeutic treatment.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac), sertraline (Zoloft).

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