Treatment of Major Depression in HIV-Seropositive Men

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Background: The purpose of this randomized double-blind, placebo-controlled study was to compare the efficacy and safety of fluoxetine plus group psychotherapy versus group psychotherapy alone in HIV-seropositive men (based on 1986 CDC classes II, III, and IV.C.2) who had been diagnosed with major depressive disorder (DSM-III-R).

Method: During a 7-week trial, patients were treated with fluoxetine 20–60 mg or placebo 1–3 capsules per day and were seen in weekly supportive group psychotherapy. In addition, subjects were rated on the 17-item Hamilton Rating Scale for Depression (HAM-D-17), Clinical Global Impressions scales for Improvement (CGI-I) and Severity of Illness (CGI-S), and the short version of the Beck Depression Inventory (BDI-13). Of the 47 patients enrolled in the study, 25 were administered fluoxetine and 22 were given placebo.

Results: Subjects who received fluoxetine began to show significantly more improvement than patients who received placebo on both self- and observer-rated scales by the end of the first week of treatment. By endpoint, patients treated with fluoxetine experienced greater mean changes from baseline compared with placebo-treated patients on the HAM-D-17 (12.1 vs. 6.6; $F = 6.53$, $df = 1,45$; $p < .05$) and BDI-13 (5.9 vs. 1.2; $F = 5.73$, $df = 1,45$; $p < .05$), and a greater percentage of fluoxetine-treated patients experienced a ≥ 50% in HAM-D-17 scores (64% vs. 23%; $\chi^2 = 8.60$, $df = 1$, $p < .01$). Differences were particularly apparent in subjects whose initial depressive episodes were rated as severe (i.e., HAM-D-17 score ≥ 24). Severely depressed patients treated with fluoxetine had an endpoint CGI-I of 1.4 compared with an endpoint CGI-I of 2.7 for patients treated with placebo ($F = 6.02$, $df = 1,11$; $p < .05$). Further, side effects were generally mild and transient. The most frequently noted effects reported by subjects treated with fluoxetine were nausea, dry mouth, headache, and diarrhea, in decreasing order of frequency.

Conclusion: This study supports the efficacy and safety of fluoxetine over and above group psychotherapy for the treatment of HIV-associated major depression.

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There is now little question that antidepressant medications are effective treatments for most individuals with moderate to moderately severe major depressions. However, the effectiveness of antidepressants is less well established for very mild[1,2] or extremely severe[3] episodes, or for major depressive episodes that occur in the context of comorbid medical illness.[4] Since all effective antidepressant agents have significant toxicities and the potential for drug interactions,[5] it is important to carefully assess their safety and efficacy in medically ill patients so that rational treatment decisions can be made regarding their use. Assessment is especially needed when alternative and potentially safer treatments may be available. A case in point is the treatment of major depression in patients who are seropositive for human immunodeficiency virus (HIV). These patients often suffer multiple medical complications and tend to receive a number of potentially toxic medications during the course of their illness. Thus, they can ill afford to receive yet more medications that can potentiate additional adverse effects unless the treatment is safe and clearly warranted by a favorable risk-benefit ratio. However, despite the prevalence of depressive symptoms and syndromes in individuals who are HIV-seropositive, there is as yet no consensus regarding the relative efficacy of various treatment modalities.

Current major depressive episodes have been estimated to be present in 7% to 20% of all HIV-seropositive patients.[6–15] Multiple factors may contribute to the onset of a major depressive episode in persons with HIV infection: the direct result of HIV on the brain, stigmatization, occupational disability, isolation from social supports, alterations in body image, bereavement, loss of friends, debilitation, and the knowledge of having a terminal illness.[16] In addition, there may be an elevated lifetime

prevalence of major depression and possible comorbid substance use in the homosexual/bisexual population, a group at high risk for HIV infection,[6,8,13,17] and secondary physiologic effects on mood may be produced by opportunistic infections, malignancies, and pharmacologic agents used to treat these diseases and infections. Therefore, major depressive episodes in HIV-seropositive individuals may be a final common pathway for a variety of etiologic agents or factors, and it is not clear that any one treatment modality is applicable to all.

Two small studies[18,19] have supported the efficacy of group psychotherapy in HIV-seropositive patients with major depression. In a case report of 6 HIV-seropositive men and women who participated in a psychoeducational, supportive, and cognitively oriented psychotherapy group, Levine et al.[18] reported a reduction in symptoms of depression and anxiety. Targ et al.[19] reported favorable results in 18 HIV-seropositive homosexual men who had mild-to-moderate major depressive episodes and were enrolled in a 12-week structured group therapy that emphasized active skills and behavioral coping. Kelly et al.[20] found that HIV-seropositive patients treated with group psychotherapy, which was not geared to major depression, experienced reductions in depressive symptoms relative to a non–psychotherapy-treated comparison group. Furthermore, subjects treated in group therapy that emphasized social support generally showed more improvement than subjects who received cognitive-behavioral interventions.[20]

Treatment with antidepressant agents also has shown promise, although there are few controlled studies assessing their safety and efficacy in HIV-seropositive patients with major depression.[6,21] However, a growing number of reports suggest that antidepressant medications might positively affect the course and morbidity of such depressions.[22] Similarly, reports of uncontrolled trials with imipramine,[23] desipramine,[21] amitriptyline,[21] fluoxetine,[21,24–27] paroxetine,[28] bupropion,[21] sertraline,[29] fluvoxamine,[30] and ECT[31] have been promising. In a randomized, double-blind study comparing desipramine and methylphenidate, Fernandez et al.[32] found both medications equally effective, but not all subjects in the study were diagnosed with major depression. In a retrospective chart review of 45 HIV-seropositive men and 45 matched seronegative men treated with antidepressant medications in a psychiatric outpatient clinic, one study[17] reported that relatively asymptomatic HIV-seropositive men did better and experienced fewer side effects than men with more advanced HIV disease and that, of the antidepressant medications used, imipramine and fluoxetine appeared to have the most positive benefit-to-risk ratios. More recently, a placebo-controlled, double-blind, randomized trial[26] found imipramine safe and effective. On the other hand, a relatively small, controlled, double-blind study of HIV-seropositive homosexual men with mild-to-moderate major depressive episodes found no advantage for fluoxetine over and above structured group psychotherapy.[19]

Thus, both group therapy and antidepressant medication may be effective treatments for major depressive episodes associated with HIV infection. Is group therapy alone sufficient or is there enough of an advantage to adding an antidepressant medication—along with its attendant toxicities, potential for drug interactions, and cost—to warrant coadministration of these 2 treatment modalities? To help answer that question, this report summarizes the safety and efficacy results of a randomized, double-blind, placebo-controlled study comparing group therapy plus fluoxetine with group therapy plus placebo in men who were HIV-seropositive and diagnosed with major depressive episodes.

METHOD

Subjects

This study was conducted as part of a larger study by the University of California, San Diego (UCSD), HIV Neurobehavioral Research Center (HNRC), which has been performing longitudinal neuropsychiatric and behavioral evaluations with a cohort of approximately 400 HIV-seropositive persons at varying disease stages and approximately 100 HIV-"at risk" controls. The HNRC study is described in more detail elsewhere.[33] Inclusion criteria for the treatment study were the following: HIV-seropositive and meet Centers for Disease Control and Prevention class II, III, or IV.C.2 criteria (based on the 1986 classification system; this is equivalent in most respects to category A or B HIV disease, using the current 1993 classification)[34]; currently experiencing a major depressive episode of moderate to severe intensity; not acutely ill; not taking psychotropic medications; not currently abusing alcohol or other drugs[33]; not cognitively impaired as measured by a score of > 27 on the Mini-Mental State Examination[35]; not considered acutely or imminently suicidal as measured by a score of 0 or 1 on item 3 of the Hamilton Rating Scale for Depression (HAM-D)[36]; and without psychosis or bipolar mood disorder.

When the study was designed, an exclusion criterion was the use of antiretroviral agents. However, it immediately became clear that recruitment would be an impossible task as almost all patients (80%) referred to the study were taking at least 1 antiretroviral agent, most commonly zidovudine (commonly referred to as ZDU or AZT), and almost 20% were taking more than 1 agent. The study was completed before the widespread use of protease inhibitors.

Subjects were directly referred either from the HNRC (N = 17) or from the UCSD Outpatient Psychiatric Services (N = 30). Regardless of referral source, all subjects completed identical screening and diagnostic procedures. After complete description of the study to the subjects, written informed consent was obtained.

Assessments

Diagnoses were made on the basis of the Structured Clinical Interview for DSM-III-R (SCID)[37] and DSM-III-R criteria,[38] except the duration of the present episode had to be 4 rather than 2 weeks to maximize the probability of excluding patients with a severe adjustment disorder rather than a major depressive episode. Patients also completed the short version of the Beck Depression Inventory (BDI-13) at baseline and at weekly follow-up visits.[39] The HAM-D was completed at intake and baseline and at each weekly follow-up visit.

In addition to the SCID and HAM-D, all subjects were rated by the clinician with 6-point Clinical Global Impressions Severity of Illness (CGI-S) and Improvement (CGI-I) scores at baseline and at weekly follow-up visits.[40]

Side effects were elicited with open-ended questions at each follow-up visit. Each side effect was rated according to its intensity, probable relationship to study drug, course, duration, and treatment, if any. Until a side effect was considered resolved, it was discussed and rated at all subsequent visits.

Study Design

To control for the confounding factor of clinician contact with the subjects, as well as to address the ethical issue of committing seriously depressed individuals to a placebo group, all subjects were assigned to a concomitant supportive and educative psychotherapy group. The group was co-led by a male licensed clinical social worker experienced in working with HIV-seropositive men and a female predoctoral level psychology graduate student who were blind to study drug assignment. Initially, group participation was intended to last only 8 weeks. However, because of the almost uniform request of subjects to be allowed to continue, and to ensure an adequate number of subjects to maintain the group during periods of lagging enrollment, the group soon became an ongoing group that accommodated new subjects as they entered the study. Subjects were required to remain in the group for at least 7 weeks, but had the option of continuing at the end of the study. Thus, new subjects received support from both the verbal and the nonverbal encouragement of others who were no longer acutely depressed and who often had found adaptive ways of living with their illness. The group emphasized education about HIV and depression, mutual support, sharing, coping strategies, and utilizing community resources. Although this group was not specifically a cognitive-behavioral or interpersonal psychotherapy group, correcting cognitive distortions and ameliorating interpersonal stressors often became part of the group's work.

At the intake interview, subjects were given the SCID and HAM-D. Subjects who met the study entry criteria and signed a consent form were asked to take 1 capsule (inert placebo) daily for the next 7 days (single-blind washout phase) and to return 1 week later. Subjects who continued to meet inclusion criteria and whose HAM-D scores had not decreased by 20% or more were randomly assigned to receive either fluoxetine 20 mg daily or identical-appearing placebo (double-blind phase).

Subjects then entered the 7-week acute treatment phase of the study. During this phase, subjects were seen weekly by the same evaluator who completed the intake and baseline ratings. At each weekly visit, the HAM-D, BDI-13, CGI-S, CGI-I, and side effect ratings were completed. Subjects were instructed to take 1 capsule each day (i.e., fluoxetine 20 mg or placebo) for the first 3 weeks of the study. Depending on response and side effects, the dose could be increased to 2 capsules daily (i.e., fluoxetine 40 mg or placebo) beginning the 4th week and to 3 capsules daily (i.e., fluoxetine 60 mg or placebo) by the 5th week. Similarly, at any time the dose could be decreased to as few as 1 capsule every other day if side effects dictated such a regimen. The same study physician (J.P.) prescribed medications to each patient at each visit. In those few instances when she was unavailable, the principal investigator (S.Z.) prescribed medications. At each visit, unused capsules were collected and counted to check for compliance.

Statistical Analysis

Treatment differences for continuous measures (e.g., HAM-D-17 and BDI-13 total scores) were tested by an analysis of variance (ANOVA) model. Differences in proportions (e.g., percentage of responders) were determined by use of chi-square (χ^2) statistics. All statistical testing was 2-tailed. Differences resulting in a p value of $< .05$ were considered to be statistically significant; p values $> .05$ but $< .10$ were considered to be a trend. The intent-to-treat sample included all subjects who were given double-blind medications and who completed at least 1 follow-up assessment. The last-observation-carried-forward (LOCF) analysis included subjects who completed the study as well as those who dropped out of the trial before completing 7 weeks of double-blind treatment; the last score available for the dropouts was carried forward in the analysis for all subsequent trial time periods. For the HAM-D-17 and BDI-13 measures, analyses were performed on change from baseline scores rather than raw scores to correct for differences in baseline scores between groups. As recommended by Keppel,[41] each of the between-group analyses was treated as a separate ANOVA at each timepoint, rather than using an average error term in a repeated measures design.

The primary efficacy variables were changes from baseline at each visit in mean HAM-D-17 total scores and in mean BDI-13 scores. Moreover, 2 additional efficacy analyses divided subjects into "responders" and "nonresponders." In these analyses, responders were defined by

Table 1. General Characteristics of Men Entering Study

Characteristic	Fluoxetine (N=25)	Placebo (N=22)
Age, y (mean ± SD)	36.2 ± 5.9	34.9 ± 9.3
Education, y (mean ± SD)	13.4 ± 1.8	13.5 ± 3.1
Years since known seroconversion (mean ± SD)	2.7 ± 1.6	3.3 ± 2.1
Patients with duration of present major depressive episode ≥ 6 mo, N (%)	11 (44%)	10 (46%)
Patients with ≥ 1 previous major depressive episode, N (%)	16 (64%)	12 (55%)
Patients with prior antidepressant treatment, N (%)	9 (38%)	6 (28%)
17-item Hamilton Rating Scale for Depression total score (mean ± SD)	20.4 ± 4.1	20.2 ± 5.8
13-item Beck Depression Inventory (mean ± SD)	14.0 ± 7.2	13.7 ± 5.0

Table 2. Primary Efficacy Values at Endpoint*

Measure	Fluoxetine	Placebo	F or χ^2	df	p Value
HAM-D-17					
Change from baseline (mean ± SD)	12.1 ± 6.9	6.6 ± 7.8	6.53	1,45	< .05
Patients with ≥ 50% reduction, N (%)	16 (64%)	5 (23%)	8.60	1	< .01
BDI-13					
Change from baseline (mean ± SD)	5.9 ± 6.6	1.2 ± 6.8	5.73	1,45	< .05
CGI-I					
Mean score	2.1	2.6	1.91	1,45	NS
Patients with scores of 1 (very much improved) or 2 (much improved, N (%)	16 (64%)	11 (48%)	1.25	1	NS

*Abbreviations: BDI = Beck Depression Inventory, CGI-I = Clinical Global Impressions-Improvement scale, HAM-D = Hamilton Rating Scale for Depression.

(1) a drop of ≥ 50% in HAM-D total score between baseline and any visit and (2) a CGI-I of 1 (very much improved) or 2 (much improved) at the end of treatment. Finally, to test whether severity of depression was an important factor for outcome, the 2 treatment groups were divided on the basis of baseline HAM-D scores into severe (score ≥ 24) and mild-moderate (score < 24) depression, and endpoint analyses were repeated.

RESULTS

Baseline Subject Characteristics

Fifty subjects were seen at intake and given placebo medication for 1 week. However, 3 patients were not randomized at baseline because 1 was a placebo responder and 2 were protocol violators. Thus, 47 subjects with major depressive episodes were randomly assigned to the double-blind treatment phase of this parallel-group, placebo-controlled study. Twenty-five subjects were assigned to the fluoxetine group and 22 to the placebo group.

The demographic and clinical characteristics of subjects in each group were similar (Table 1), with no significant differences between groups with respect to demographic, diagnostic, or psychiatric history variables. In general, the sample consisted of young men who had recurrent major depressive disorders and whose present episode had been continuing for at least several months. On average, the men in this study had been seropositive for about 3 years prior to entry into the study. There were no statistically significant differences between groups in terms of referral source, number of other medications received, or CDC classification.

Patient Discontinuations

Of the 47 subjects who entered the double-blind treatment phase, 37 (79%) completed the full 7 weeks of treatment. The completion rate in the fluoxetine group (N = 21, 84%) was similar to that in the placebo group (N = 16, 73%). In the fluoxetine group, the causes of premature discontinuation were as follows: resuming substance use, N = 1 (4%); lack of efficacy, N = 1 (4%); non–treatment-related illness, N = 1 (4%); and lost to follow-up, N = 1 (4%). For the placebo group, the reasons for premature termination were as follows: resuming substance use, N = 1 (5%); lack of efficacy, N = 1 (5%); non–treatment-related illness, N = 1 (5%); lost to follow-up, N = 1 (5%); side effects, N = 1 (5%); and caretaking responsibilities, N = 1 (5%).

Drug Administration

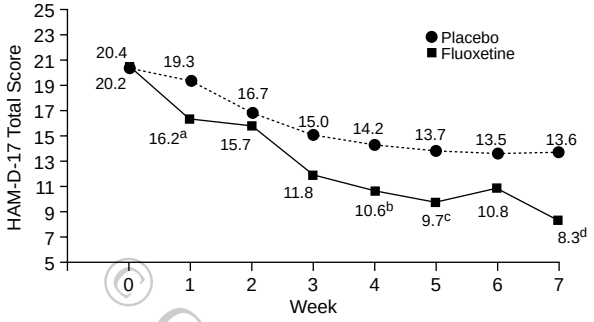
The mean duration of double-blind therapy in the fluoxetine and placebo group was, respectively, 6.4 weeks and 5.8 weeks. The mean final daily dosages for the fluoxetine group was 1.7 capsules (36 mg) and 1.8 capsules for the placebo group.

Efficacy

Primary efficacy results at the last visit are presented in Table 2. By the end of treatment, statistically significant differences favoring group psychotherapy plus fluoxetine over group psychotherapy plus placebo were seen in mean change from baseline scores for both the HAM-D-17 and BDI-13 scales ($p < .05$), as well as in the overall responder rate defined as a reduction of at least 50% on HAM-D-17 total scores ($p < .01$).

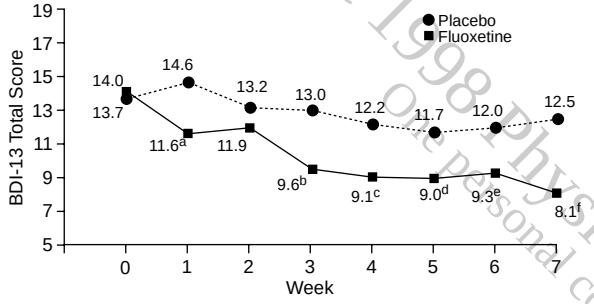
Both treatment groups showed equivalent scores on the 17-item HAM-D scale at baseline (Figure 1). The fluoxetine cohort showed a significant advantage over the placebo cohort beginning at week 1 and continuing throughout the remainder of the 7-week trial, although not always at statistically significant levels. By the end of week 1, the fluoxetine group showed a mean ± SD decrease from baseline of 4.2 ± 5.0 on the HAM-D-17 total score, whereas the placebo group showed a mean de-

Figure 1. Mean Weekly HAM-D-17 Scores



[a]F = 6.34, df = 1,45; p = .015.
[b]F = 3.70, df = 1,44; p = .06.
[c]F = 4.36, df = 1,45; p = .04.
[d]F = 6.53, df = 1,45; p = .014.

Figure 2. Mean Weekly BDI-13 Scores



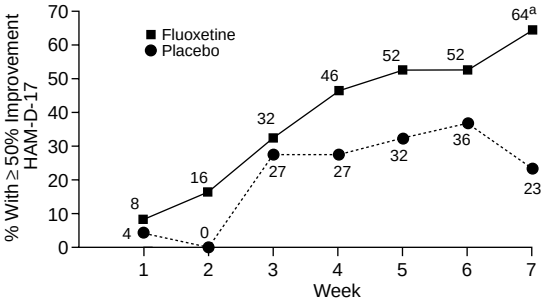
[a]F = 5.43, df = 1,45; p = .025.
[b]F = 5.00, df = 1,45; p = .03.
[c]F = 3.25, df = 1,45; p = .08.
[d]F = 2.91, df = 1,45; p = .09.
[e]F = 3.05, df = 1,45; p = .09.
[f]F = 5.73, df = 1,45; p = .02.

crease of only 0.9 ± 4.6 points (F = 6.34, df = 1,45; p = .015). Differences favoring fluoxetine over placebo reached statistical significance at weeks 5 and 7, while a statistical trend favoring fluoxetine was noted at week 4.

Similarly, early differences favoring fluoxetine over placebo were seen on the BDI-13 (Figure 2). At the end of week 1, the fluoxetine group showed a mean decrease from baseline of 2.4 ± 4.6, while the placebo group showed a mean increase of 0.9 ± 5.0 (F = 5.43, df = 1,45; p = .025). Statistical trends favoring fluoxetine over placebo were noted at weeks 4, 5, and 6, while differences reached statistical significance at weeks 3 and 7.

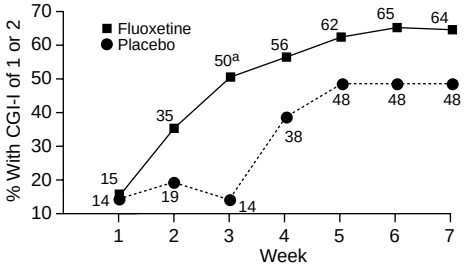
Figures 3 and 4 show differences in responder rates between patients treated with group psychotherapy plus fluoxetine versus those treated with group psychotherapy plus placebo. As can be seen from Figure 3, the result appears to favor fluoxetine over placebo in terms of the percentage of subjects with ≥ 50% improvement on HAM-D-17 scores, but the difference reached statistical significance only at week 7. Similarly, the percentage of

Figure 3. Weekly Percentage of Subjects With ≥ 50% Improvement in Total HAM-D-17 Scores



[a]χ^2 = 8.60, df = 1, p = .005.

Figure 4. Weekly Percentage of Subjects With CGI-I 1 (Very Much Improved) or 2 (Much Improved) Scores



[a]χ^2 = 6.60, df = 1, p = .01.

subjects who were rated as either “very much improved” or “much improved” on the CGI-I appeared to favor fluoxetine, but the difference reached statistically significant levels only at week 3.

To test whether severity of depression related to improvement, subjects were divided into those with mild-to-moderate depression on the basis of a total baseline HAM-D-17 score of less than 24 and those with relatively severe depressions by virtue of a total baseline HAM-D-17 score of 24 or greater. Of the 35 subjects with mild-to-moderate depression, 19 were treated with fluoxetine and 16 with placebo. Of the remaining 12 subjects with severe depression, 6 received fluoxetine and 6 placebo. Improvement in each cohort was measured by endpoint mean CGI-I scores. As can be seen in Figure 5, the mild-to-moderate severity cohort improved equally well whether treated by group psychotherapy plus fluoxetine or group psychotherapy plus placebo; however, in the severely depressed group, subjects treated with group psychotherapy plus fluoxetine did significantly better than subjects treated with group psychotherapy plus placebo (endpoint mean CGI-I score 1.4 vs. 2.7; F = 6.02, df = 1,11; p = .03). While severely depressed subjects treated with fluoxetine appeared to do even better than mildly depressed patients, the opposite was true for placebo patients. Similar trends were seen on all outcome measures.

Figure 5. Percentage of Subjects With a CGI of 1 (Very Much Improved) or 2 (Much Improved) Score at Endpoint as a Function of Depression Severity at Baseline

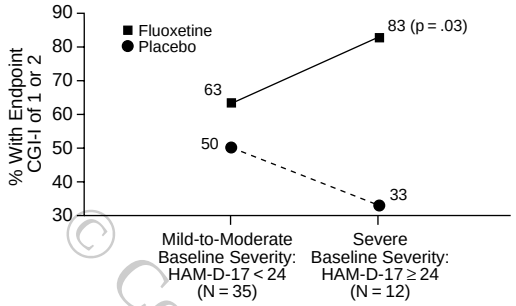


Table 3. Adverse Events Occurring in 3 or More Subjects

		Fluoxetine (N = 25)		Placebo (N = 22)	
Adverse Event	Total N	N	%	N	%
Nausea	17	12	48	5	23
Headaches	16	8	32	8	36
Diarrhea	9	6	24	3	14
Dry mouth	9	8	32	1	5
Loss of appetite	6	2	8	4	18
Agitation	6	2	8	4	18
Fatigue	4	3	12	1	5
Flu-like symptoms	4	2	8	2	9
Insomnia	4	0	0	4	18
Somnolence	3	3	12	0	0
Decreased libido	3	3	12	0	0
None	12	4	16	8	36

Adverse Events

A comparison of the number and percentage of subjects who experienced adverse events at 1 or more of the treatment evaluation periods is shown in Table 3. Of note, only 1 subject dropped out of the study because of an adverse event, and that person was an individual treated with placebo who dropped out after 4 weeks of treatment because of agitation. Four subjects treated with fluoxetine (16%) reported no side effects, while 8 of those treated with placebo (36%) were free of drug-related adverse events. The most frequently encountered adverse events in subjects treated with fluoxetine were gastrointestinal (nausea and/or diarrhea), but these also were common in placebo-treated subjects. Similarly, headaches were frequent in subjects treated with either fluoxetine or placebo, while dry mouth appeared more frequently in the fluoxetine-treated subjects. Sexual side effects were spontaneously mentioned by only 3 subjects (all on fluoxetine treatment), and no subjects in either group reported an increase in suicidal feelings.

DISCUSSION

The major findings of this study are, first, patients who are HIV-seropositive and experience a major depressive episode can and do respond to treatment for their depression; second, group psychotherapy may be sufficient for the treatment of major depressive episodes of mild severity in this population, but medications are an important component of treatment for more severe depressive episodes; and third, fluoxetine is an effective and well-tolerated antidepressant medication in this population.

As the HIV epidemic continues to spread worldwide, more HIV-seropositive men and women with major depressive episodes can be expected to require treatment. Yet, treatment guidelines for this population are scarce, and more studies assessing the safety, efficacy, and tolerability of antidepressant medications are needed. In general, this group of patients would be expected to have difficulties with many of the anticholinergic and antihistaminic side effects so common with the traditional tricyclic antidepressants[13,26]; consequently, the newer medications, which tend to be less anticholinergic and less sedating, might have some advantages. That is why fluoxetine was chosen as the active agent for the study. The results support previous observations that serotonin selective reuptake inhibitors (SSRIs) are, indeed, well tolerated and effective in HIV-seropositive individuals with major depression.[26,29]

It must be remembered that this was not a true placebo study—all subjects received supportive group therapy. Therefore, the question this study answered was whether fluoxetine, over and above supportive group psychotherapy, treats major depressive episodes more effectively and as safely as placebo medication. One previously published study[19] was unable to find an advantage of fluoxetine over placebo in HIV-seropositive persons who also were treated with structured group psychotherapy. However, only 18 subjects were studied, not all of whom met criteria for a major depressive episode.[19] Thus, the inability of the previous study to find drug-placebo differences may have been a function of the small sample size and the heterogeneous population.

Our study was not designed to test the efficacy of group psychotherapy. A more structured, systematized form of group therapy might have further improved the efficacy of the group therapy plus placebo cohort. But even with the present design, group therapy appeared to be a potent intervention, perhaps accounting for some of the symptomatic improvement noted in both treatment cohorts and probably contributing to the relatively good compliance and low dropout rates. Indeed, it is possible that group therapy alone (i.e., without placebo) might have performed better than group therapy plus placebo, a condition unrealistic in general clinical practice.[42] Further studies testing the efficacy of group therapy and the degree to which it augments pharmacotherapy are warranted.

The results of this study suggest, first of all, that patients infected with HIV respond to treatment for their depression. It is important to remember that patients in this study were not merely suffering from transient demoralization or adjustment disorders. Rather, patients were carefully diagnosed and found to have major depressive episodes of long duration. They also had moderate-to-high HAM-D scores and often preexisting histories of recurrent major depression. Thus, it was not obvious that many patients would improve. Yet, patients treated with placebo capsules often showed substantial amelioration of their depressive symptoms.

The improvement noted in patients receiving group therapy plus placebo medications tends to confirm other reports concerning the importance of social supports and psychoeducation with respect to depressive symptoms in HIV-seropositive individuals[20,43–47] and is consistent with the results of the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program, which demonstrated the efficacy of a form of supportive psychotherapy, case management, in treating relatively mild depressions.[1] As in the NIMH Program, patients in this study with more severe depressions seemed to require antidepressant medication for optimal response. The diagnosis of major depression does not guarantee a homogeneous patient sample. Likely, the initial severity of illness is an important dimension to help clinicians select from among therapeutic options.

In this study, treatment with fluoxetine was well tolerated. Although most patients experienced some side effects, they tended to be mild and did not require specific intervention. The only dropout due to side effects was a placebo-treated patient who complained of treatment-emergent agitation. Interestingly, more fluoxetine-treated patients complained of sedation-type side effects (e.g., fatigue or somnolence) than of activation (e.g., anxiety, agitation, or insomnia); the only sexual side effect was decreased libido, which occurred in 3 patients treated with fluoxetine.

Because most patients were taking 1 or more antiviral agents, potential drug-drug interactions were an important concern. The most frequently utilized anti-HIV medication at the time of the study, zidovudine, would not be expected to have serious drug interactions with fluoxetine.[48] However, given the high rates of depression in seropositive patients and the increasing use of combinations of medications that work through different mechanisms of action for the treatment of HIV infection, there is reason to be concerned about potential drug interactions.[49] The newer antiviral agents, the protease inhibitors, are extensively metabolized by CYP3A4,[50] and also inhibit 3A4 to a significant extent.[51] Since fluoxetine may be a mild inhibitor of 3A4,[52] the potential for drug interactions exists, although, to date, no serious drug interactions involving the combination of protease inhibitors and SSRIs have been reported. Nevertheless, if SSRIs are administered concomitantly with a protease inhibitor, patients should be cautioned and appropriate monitoring employed until specific interaction studies are completed.

In summary, despite the improvement seen in some subjects treated with group therapy plus placebo, active treatment with fluoxetine appeared more efficacious than placebo treatment and was almost as well tolerated. It is certainly possible that other medications or types of psychotherapy might have been even more effective. Fluoxetine is not the only pharmacologic choice for HIV-seropositive patients with major depression.[21–23,29,32] Similarly, other forms of psychotherapy, such as interpersonal psychotherapy, may be more effective than supportive therapy.[47] Thus, further studies assessing the relative efficacy of different antidepressant medications, different psychotherapeutic approaches, single treatments, and combined approaches are in order. Meanwhile, the results of this acute treatment study indicate that fluoxetine is effective and well tolerated by most seropositive persons with major depression.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), methylphenidate (Ritalin), paroxetine (Paxil), sertraline (Zoloft), zidovudine (Retrovir).

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