Antidepressant Efficacy in HIV-Seropositive Outpatients With Major Depressive Disorder: An Open Trial of Nefazodone

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Background: Treatment studies of major depression in patients who are seropositive for the human immunodeficiency virus (HIV) have shown comparable efficacy for both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Nefazodone appears to be more tolerable than TCAs and similar to SSRIs. This study examined the efficacy and tolerability of nefazodone in an open 12-week trial of HIV-seropositive outpatients with major depressive disorder.

Method: Fifteen HIV-seropositive patients with DSM-IV major depressive disorder and a 21-item Hamilton Rating Scale for Depression (HAM-D) score of ≥ 18 were treated with open-label nefazodone for 12 weeks. Hamilton Rating Scale for Anxiety, HAM-D, Clinical Global Impressions scale, and Systematic Assessment for Treatment Emergent Events general inquiry (for safety and tolerability) scores were obtained at weeks 2, 4, 6, 8, and 12.

Results: Of 15 patients receiving nefazodone, 4 discontinued treatment (1 for adverse effects). Of 11 patients who completed the trial, 8 (73%) were classified as full responders with a 50% reduction in HAM-D scores and final CGI score of 1 or 2, and 10 (91%) were classified as partial responders (only 50% reduction in HAM-D scores). Nefazodone-treated subjects experienced few total adverse effects (mean = 1.5), no sexual side effects, and low rates of adverse-effect–related dropout (1 subject, 7%).

Conclusion: Depressed HIV-seropositive outpatients respond to nefazodone comparably to other outpatient populations and have few adverse effects, suggesting that nefazodone may have a role in the treatment of depression in HIV-seropositive patients. Potential drug interactions with protease inhibitors indicate that it is essential to evaluate for appropriate dosing to avoid adverse effects and increase overall antidepressant efficacy.

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Literature establishing the prevalence of major depressive disorder in individuals who are seropositive for the human immunodeficiency virus (HIV) has documented that depression is greater (22%–61%)[1–3] in both HIV-seropositive and at-risk populations compared with lifetime and current estimates in community samples.[4,5] Recently, in HIV-seropositive outpatients, we found comparably greater efficacy for patients taking imipramine or paroxetine compared with placebo with increased side-effect–related dropout rates for imipramine (12/25; 48%) compared with paroxetine (5/25; 20%).[6]

Overall effectiveness of antidepressants in HIV-seropositive patients is related to their tolerability.[6] Despite their greater tolerability, selective serotonin reuptake inhibitors (SSRIs) may still exacerbate some of the most common somatic symptoms seen in HIV-seropositive patients, including sleep disturbance, weight loss, sexual dysfunction, decreased energy, and fatigue. Since adverse experiences appear to determine overall effectiveness of antidepressants, we decided to investigate nefazodone in HIV-seropositive outpatients with major depression. In the general population, nefazodone is equally effective but better tolerated than imipramine[7] and fluoxetine,[8] equally effective and without sexual dysfunction compared with sertraline,[9] and equally effective and tolerable compared with paroxetine.[10] From these studies, it appears that nefazodone is as effective and yet as well or better tolerated than SSRIs owing to a reduced incidence of sexual side effects.

This study sought to determine in a 12-week open trial whether nefazodone, a short half-life serotonin reuptake inhibitor and 5-HT_2 receptor antagonist, has efficacy and tolerability (i.e., few side effects and side-effect–related dropouts) in HIV-seropositive outpatients with major depressive disorder.

METHOD

Sample

The sample consisted of 15 HIV-seropositive subjects with HIV infection, ranging from the presymptomatic to full-blown acquired immunodeficiency syndrome (AIDS), from the King County Madison Clinic, an outpa-

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tient HIV clinic in Seattle, Washington. Screening criteria included a current diagnosis of major depressive disorder according to a Structured Clinical Interview for DSM-IV (SCID)[11] and a score of ≥ 18 on the 21-item Hamilton Rating Scale for Depression (HAM-D).[12] Exclusion criteria included alcohol or substance abuse within the last month, prior diagnosis of organic brain syndrome, dementia, severe concurrent HIV-related physical illness, current treatment with psychotherapy, high suicide risk, or a history of bipolar disorder, traumatic head injury, or psychosis. All subjects gave written informed consent.

Procedure and Instruments

A modified SCID was used to assess current diagnoses. Subjects with a DSM-IV diagnosis of major depressive disorder according to SCID interview and a score of ≥ 18 on the 21-item HAM-D entered the trial. The same ratings were obtained (HAM-D, Hamilton Rating Scale for Anxiety [HAM-A],[13] Clinical Global Impressions [CGI],[14] Mini-Mental State Examination [MMSE],[15] Systematic Assessment for Treatment Emergent Events [SAFTEE] general inquiry[16]) as in our previous double-blind trial[6] of paroxetine and imipramine. Following clinical assays (CD4 cell count, CD4 percentage, and HIV viral load), subjects were started on nefazodone therapy at 75 mg twice daily, increasing to 150 mg twice daily after 7 days. After reaching this level, the dose was increased as clinically indicated.

Assessments were made at baseline and weeks 2, 4, 6, 8, and 12 using the HAM-D, the HAM-A, and the CGI. The Brief Symptom Inventory (BSI)[17] was used at baseline to provide a more extensive clinical description of the groups. The SAFTEE general inquiry was used to retrieve unbiased medication-related side effects volunteered by patients at every visit using the general screening item, "Have you had any health related or physical problems since your last visit?" If patients described a new complaint, they were asked to describe it in more detail to determine if it was new or preexisting. Preexisting symptoms or complaints were not scored as side effects. A checklist based on the SAFETEE general inquiry was used at the termination of the study to classify reported side effects into categorical groups. All clinical ratings were made by the first author (A.J.E.).

HIV Illness Assessment

HIV viral markers (CD4 cell count, CD4 percentage, and HIV viral load) were measured within 2 weeks of the trial initiation. CD4 cell count and percentage were analyzed at the University of Washington Hematopathology Laboratory, where analysis is performed as a standard clinical assay. HIV-1 RNA, the amount of viral RNA in plasma (viral load), was also analyzed at initiation of the trial by the University of Washington Hematopathology Laboratory using the Hoffman-LaRoche (Basel, Switzerland) Amplicor Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) assay.[18] HIV-related and AIDS-defining symptoms were assessed at baseline and week 12 using a checklist based on 1993 Centers for Disease Control (CDC) AIDS-defining conditions.[19]

Data Analysis

Patients who completed the trial were compared with patients who dropped out by using t test and chi-square analysis for continuous and dichotomous variables, respectively. In order to examine changes in depression, anxiety, and improvement, paired t tests between baseline and week 12 were conducted. In addition, response rates were examined. Partial remission was defined as a 50% (or more) decrease in HAM-D from baseline and full remission as a 50% (or more) reduction in HAM-D with a final HAM-D score of 7 or less.[20] Using CGI, response was defined as a final CGI improvement rating of 1 (very much better) or 2 (much better). These analyses were performed on the patients who completed the entire trial and the intent-to-treat sample, with the last observation carried forward (LOCF) for those completing 4 weeks of the trial. Differences in CD4 cell count, CD4 percentage, RNA viral load, and number of HIV-related and AIDS-defining symptoms were examined for patients with and without a response to nefazodone by using t tests. Differences between the number of side effects experienced by patients on protease inhibitor therapy and the number experienced by those on triple-drug antiretroviral therapy were evaluated using t tests.

RESULTS

Demographics and Clinical Characteristics

Fifteen HIV-seropositive patients with DSM-IV major depressive disorder were treated with nefazodone. A summary of the HIV illness status and clinical characteristics of the nefazodone-treated patient group is presented in Table 1. None of the patients who entered the trial had preexisting HIV central nervous system disease or medical characteristics that might be associated with an atypical response to treatment (see exclusionary criteria in methods). Of those that entered the trial, 9 (60.0%) had previously received antidepressant treatment and 5 (33.3%) had received previous psychotherapy. With initial MMSE scores of 30 out of 30, no patients exhibited gross cognitive impairment; therefore, no posttreatment cognitive assessment was anticipated.

There were no significant differences between subjects who dropped out (N = 4) and those who completed (N = 11) the trial on demographic, medical illness (CD4 percentage, CD4 cell count, HIV viral RNA, HIV-related symptoms, or AIDS-defining conditions), or psychiatric characteristics (including prior depressive episodes, comorbid dysthymia, and previous antidepressant treatment).

Table 1. Characteristics of 15 HIV+ Depressed Outpatients[a]

Variable	Value
Demographics	
Years of age, mean ± SD	36.5 ± 9.4
Male, N (%)	15 (100)
Years of education, mean ± SD	14.0 ± 2.3
White, N (%)	13 (86.7)
Single, N (%)	7 (46.7)
Unemployed, N (%)	9 (60.0)
HIV illness	
Asymptomatic, N (%)	4 (26.7)
Symptomatic, N (%)	2 (13.3)
AIDS, N (%)	9 (60.0)
Known duration HIV+ (mo), mean ± SD	70.6 ± 53.8
Viral data, mean ± SD	
CD4 cell count	266 ± 262
CD4 percentage	14.7 ± 12.7
Viral RNA	18.8 ± 46.1
Medications	
No medications, N (%)	3 (20.0)
Non–HIV-related medications, mean ± SD	1.4 ± 1.4
HIV-related medications,[b] mean ± SD	3.6 ± 2.8
Zidovudine, N (%)	9 (60.0)
Protease inhibitor therapy, N (%)	8 (53.3)
Ritonavir	1 (6.7)
Indinavir	5 (33.3)
Saquinavir	2 (13.3)
DSM-IV diagnosis	
Major depressive disorder, single episode, N (%)	2 (13.3)
Major depressive disorder, recurrent, N (%)	13 (86.7)
Dysthymia, N (%)	3 (20.0)
Major depressive disorder + dysthymia, N (%)	3 (20.0)
Length of depressive disorder (mo), mean ± SD	10.9 ± 10.6
Major depressive disorder < 1 y, N (%)	9 (60.0)
History of substance abuse, N (%)	10 (66.6)
Alcohol	7 (46.7)
Marijuana	5 (33.3)
Cocaine/amphetamine	4 (26.7)
Symptom checklist,[c] mean ± SD	
Depression	2.68 ± 0.75
Anxiety	2.02 ± 0.65

[a]Abbreviations: AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus, HIV+ = HIV-seropositive.
[b]HIV-related medications, e.g. fluconazole, dapsone, clarithromycin.
[c]Brief Symptom Inventory.[17]

Treatment

The mean ± SD scores for the HAM-D and HAM-A at baseline were 26.9 ± 5.3 (range, 18–34) and 27.9 ± 6.1 (range, 13–38), respectively. The baseline BSI scores were 2.68 ± 0.75 for depression and 2.02 ± 0.65 for anxiety. Active treatment was received for at least 6 weeks by 13 (86.7%) of 15 and by 11(73.3%) of 15 for 12 weeks. While all patients received at least 300 mg/day of nefazodone, those completing at least 6 weeks of treatment (N = 13) received a mean dose of 371.4 ± 61.1 mg/day. Reason for dropout of nefazodone-treated patients included adverse reactions/drug-drug interaction (N = 1), worsening HIV illness (N = 2), and lost to follow-up (N = 1). Among the 11 completers, there was no improvement or change in HIV disease status during the treatment trial.

Table 2. Nefazodone Responder Analysis[a]

	Intent-to-Treat (N = 14)		Completer (N = 11)	
Assessment	N	%	N	%
HAM-D Total				
Week 8				
Partial remission[b]	12	85.7	10	90.9
Full remission[c]	5	35.7	4	36.4
Week 12				
Partial remission[b]	13	92.8	10	90.9
Full remission[c]	9	64.3	8	72.7
Clinical Global Impressions (CGI)[d]				
Week 8	13	92.8	10	90.9
Week 12	8	57.1	7	63.6

[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
[b]Partial remission ≥ 50% reduction in HAM-D from baseline.
[c]Full remission ≥ 50% reduction in HAM-D from baseline and final HAM-D ≤ 7.
[d]Patients with a global rating of 1 or 2 (very much improved or much improved).

Results of completer and intent-to-treat analyses were similar (Table 2) with stable partial response of 80% at both 8 and 12 weeks, while full response increased from 35% at week 8 to 60% to 70% at week 12. Mean HAM-D scores in 12-week completers (N = 11) declined from 26.4 ± 5.6 at baseline to 8.2 ± 7.2 at week 12 ($t = 9.71$, $df = 10$, $p = .000$). Mean HAM-A scores declined from 28.3 ± 7.4 at baseline to 16.9 ± 7.7 at week 12 ($t = 4.54$, $df = 10$, $p = .001$). CGI ratings were also rated as improved with a mean ± SD of 1.6 ± 0.9 (range, 1–4) at week 12.

There was no relationship between depression response and HIV illness status, baseline symptom severity, lifetime psychiatric history, or history of or treatment for depression or chronicity of depression.

Adverse Events

A summary of the reported treatment-emergent adverse events are reported in Table 3. Only 1 (7%) of 15 subjects dropped out due to adverse events in the open trial. This patient dropped out because a drug interaction with ritonavir caused headache, confusion, dizziness, and anxiety.

This patient was initiated on 75 mg of nefazodone twice daily for 7 days, then was increased to 150 mg twice daily. Two days after increasing the nefazodone dose to 150 mg twice daily, he began to reexperience the initial side effects of headache and dizziness and, in addition, reported disorientation and confusion, derealization, intense anxiety, and agitation. At this point, he called his physician to report that he was nauseated, and although he felt the medication had reduced his depressive symptoms, he was discontinuing the nefazodone because he could not tolerate these adverse side effects. The patient was evaluated by both his internist and neurologist, both of whom specialize in HIV disease management, for medical or neurologic signs and symptoms of HIV-related infection

Table 3. Nefazodone Adverse Events[a]

Side Effect[b]	N	%
Anxiety	2	13.3
Confusion	1	6.7
Constipation	1	6.7
Blurry vision	0	0
Diarrhea	0	0
Dizziness/light-headedness	7	46.7
Dry mouth	1	6.7
Fatigue/weakness	0	0
Headache	3	20.0
Heart palpitations	0	0
Poor memory/concentration	0	0
Nausea	2	13.3
Sedation	2	13.3
Sexual dysfunction		
Ejaculation	0	0
Orgasm	0	0
Erection	0	0
Skin rash	0	0

[a]This table includes the individual who dropped out owing to adverse events.
[b]Number (mean ± SD) of adverse effects = 1.5 ± 1.2.

or complications. After a thorough medical workup that revealed no active medical or neurologic symptoms or abnormal laboratory findings, the nefazodone was discontinued and these symptoms resolved over 3 days. The patient had no prior history of the adverse side effects that emerged during treatment and relapsed into another depressive episode within 2 weeks after discontinuation of nefazodone. This case demonstrates the importance of potential drug-drug interactions and the necessity for proper monitoring and safety evaluation of patients who are initiated on antidepressants while receiving antiretroviral therapies.

Overall, nefazodone-treated patients appeared to tolerate treatment, with low dropout rates due to adverse effects (1/15, 7%). The incidence of dizziness/light-headedness was 47% while that of headache was 20%. The prevalence of sexual dysfunction (problems with ejaculation, orgasm, or erection) in patients was assessed through patient interviews (through both SCID and HAM-D) at baseline, and there was no additional sexual dysfunction reported during treatment (see Table 3).

Because of the adverse effects experienced by the patient who dropped out, we wanted to evaluate whether the patients who were taking protease inhibitors or receiving triple-drug therapy (2 nucleoside reverse transcriptase inhibitors [RTI] plus a protease inhibitor or 2 nucleoside RTIs plus a non-nucleoside RTI) experienced a greater number or different type of side effects. We found no significant relationship for increased side effects associated with protease inhibitor or triple-drug therapy.

DISCUSSION

In this 12-week open trial of nefazodone treatment for major depressive disorder in HIV-seropositive outpatients, a high rate of efficacy was demonstrated regardless of HIV-related immunosuppression or stage of illness. Although a small open trial, this sample is very similar to both previously reported open and controlled trials of antidepressants in HIV-seropositive patients. In addition, since there have been few controlled trials reporting SSRI[6] and tricyclic antidepressant (TCA)[6,21] effects on HIV-related depression, it is important to describe the effects of newer antidepressants since they may have different tolerability profiles that affect overall effectiveness. Similarly, with the difficulty in recruitment and retention of HIV-seropositive patients for controlled trials, the reporting of open trials becomes even more significant. Clinically meaningful comparisons between drugs require a direct head-to-head comparison in a controlled trial while at the same time evaluating their overall effectiveness. The overall effectiveness (ultimate rate of response in those initially given the drug) adjusts the response rate to account for patients who drop out and will be greater for drugs that have fewer adverse effects and are easier to tolerate.

Active treatment was received by 14 (93%) of 15 of nefazodone-treated subjects for at least 4 weeks, and 11 (73%) of 15 subjects completed the entire trial. There was a 73% response rate for those completing 12 weeks of nefazodone. Nefazodone-treated patients had a low number of total adverse effects (mean = 1.5) and a low rate of dropout due to adverse effects (1/15, 7%) resulting in high overall effectiveness (> 90%). The most prevalent side effects were dizziness/light-headedness (47%) and headache (20%). Nefazodone-treated patients had no increase in sexual or erectile dysfunction. This is not surprising since nefazodone does not decrease libido like SSRIs or cause impotence like TCAs.[9,10,22,23]

Although the prevalence of dizziness and headache are elevated in the entire sample, it is unlikely that these side effects are due to interactions between nefazodone and ritonavir. The prevalence of ritonavir-reported dizziness is very low (2.2%),[24] and central nervous system penetration of ritonavir is known to be low.[25] There may be subclinical neurotoxicity from drug-drug interactions based on cytochrome P450 effects between the antiretrovirals and nefazodone. While we demonstrated no significant difference between those individuals that were on protease inhibitors (or triple-drug therapy) and those on other antiretroviral therapy or taking no medications, our comparisons were small and further study is needed.

Additionally, it is notable that there was a prevalence of headache of up to 20%. While this increase may appear to be related to nefazodone treatment, it is important to recognize that headache is common with patients taking zidovudine (commonly known as AZT). In this study, 9 (60%) of 15 patients were taking zidovudine. However, there was no significant relationship between headache and zidovudine treatment.

In studies that evaluated the prevalence of side effects, up to 31% of nefazodone-treated patients experienced headaches and up to 12% experienced dizziness.[21,26] In clinical trials where nefazodone was compared with placebo, the rates of headache and dizziness were 3% and 12%, respectively.[27] It is important to note that dizziness was dose-related, with a higher prevalence associated with increased doses (18% at > 300 mg/day versus 7% at < 300 mg/day).[27] These numbers are slightly different than those of our trial, suggesting there may have been some effect of drug interaction, yet statistically, we determined no differences related to protease inhibitors or zidovudine. These discrepancies may suggest that further evaluation via a controlled trial is needed. The rate of discontinuation of nefazodone in our trial (7%) was similar to a recent meta-analysis of 6 randomized placebo-controlled trials where 5% of nefazodone patients prematurely discontinued treatment.[7]

The overall effectiveness of nefazodone is greater than 90%, as compared with our previous controlled trial study[6] where effectiveness was 80% for paroxetine and 48% for imipramine. This finding is consistent with placebo-controlled trials in the general population comparing nefazodone and imipramine, where nefazodone was better tolerated with fewer dropouts and lower incidence of adverse effects during treatment.[22,28,29]

Although side-effect–related dropout is lower with nefazodone, the 1 patient who did drop out had a significant and potentially serious drug-drug interaction that led to discontinuation of therapy. We believe that this drug-drug interaction was related to nefazodone toxicity resulting from inhibition of its elimination by the potent cytochrome P450 inhibitor ritonavir. Ritonavir is a potent cytochrome P450 (CYP450) 3A4, 2D6, and 1A2 inhibitor.[30] Nefazodone is both metabolized by and inhibits CYP450 3A4 while its *m*-chlorophenylpiperazine (*m*-CPP) metabolite is subsequently metabolized by CYP450 2D6. When ritonavir is present, it potently inhibits CYP450 3A4 and therefore metabolism of nefazodone does not occur, thus increasing nefazodone levels in the body. While we were not able to measure blood levels of nefazodone pharmacologically, the patient reported a collection of symptoms that are consistent with nefazodone toxicity. In addition, this patient experienced dizziness, headache, anxiety, and confusion.

Nefazodone is contraindicated with ritonavir, and our report suggests that ritonavir and nefazodone should not be coprescribed, but toxicity appears to be dose related. Subsequent to this reported adverse event, the author (A.J.E.) has used nefazodone at significantly lower doses (50–100 mg/day) with ritonavir and demonstrated treatment effect through reduction of HAM-D scores (A.J.E., unpublished data, June 1997). In addition, although nefazodone is metabolized through the CYP450 3A4 system, its metabolite (*m*-CPP) is subsequently metabolized via the CYP450 2D6 system. As with ritonavir, the other protease inhibitors (indinavir, nelfinavir, saquinavir) are known to have inhibitory effects on the CYP450 2D6 system (indinavir > nelfinavir and saquinavir). Since the CYP450 2D6 system is known to be genetically polymorphic, and individuals may have different levels of this enzyme complex, a deficit or inhibition of this isozyme by protease inhibitors may lead to toxic effects. Although nefazodone and other protease inhibitors may lead to toxicity, our data do not support this possibility. In fact, for those patients taking protease inhibitors (8/15), 7 of 8 individuals were taking indinavir or saquinavir and had no reported adverse events at doses ranging from 300 to 500 mg daily of nefazodone. We have used nefazodone with all protease inhibitors successfully and without adverse events.

Table 4. Recommendations for the Use of Nefazodone With Protease Inhibitors[a]

Drug	CYP450 System Inhibited	Nefazodone Dose Recommendation
Saquinavir	3A4	300–600 mg/d[b]
Nelfinavir	3A4	300–600 mg/d[b]
Indinavir	3A4, 2D6	≤ 300 mg qd
Ritonavir[c]	3A4, 2D6, 1A2	≤ 50–100 mg qd
Amprenavir	3A4, 2D6, 2C19	No clinical experience

[a]Physicians should use caution when prescribing nefazodone with all FDA-approved protease inhibitors. Start with *low doses* of nefazodone and *increase slowly*, observing for signs of nefazodone toxicity or nefazodone-related adverse effects (especially with ritonavir).
[b]Effective FDA-approved dose range in clinical trials.[28]
[c]If other protease inhibitors are combined with ritonavir (e.g., saquinavir), nefazodone dose recommendations should be those of ritonavir (or the most potent cytochrome inhibitor).

Our recommendations for individuals on indinavir would be that physicians start nefazodone at low doses and increase dosages slowly, watching for signs of toxicity or nefazodone-related side effects. Nelfinavir and saquinavir do not appear to require a dose reduction. It is important to remember that when highly active antiretroviral therapy is used in HIV-seropositive patients and at least 1 of the medications is ritonavir, the physician must reduce the dose of nefazodone or nefazodone toxicity may occur. Although amprenavir is not in routine clinical use, it is reported to primarily inhibit CYP450 3A4 and 2D6,[31] and, based on our knowledge of nefazodone and the other protease inhibitors' effects, when it becomes available, prescribing physicians should use caution when prescribing it with drugs metabolized through this system. We report a summary of our recommendations in Table 4 based on our data and clinical experience with nefazodone and protease inhibitors. Thus, when prescribing nefazodone with protease inhibitors, physicians should use caution, start with low doses, and increase the doses slowly, especially with ritonavir.

The present study had a number of limitations: (1) the nefazodone sample was male and prevents extrapolation to female patients, (2) a majority of subjects enrolled had

an AIDS diagnosis and therefore results may not be comparable to all HIV-seropositive patients, (3) the use of a nonblinded trial without a placebo component means that our data should be regarded as preliminary, and (4) there are limitations inherent in the use of a small sample size.

Although these data were collected in an open fashion, there are several important outcomes. Nefazodone can effectively treat major depressive disorder in HIV-seropositive outpatients. In addition, with low side-effect–related dropout, nefazodone may be as useful as other antidepressant medications that have been evaluated for the treatment of depression in HIV-seropositive populations. It is very difficult to recruit and retain HIV-seropositive patients into controlled antidepressant trials and often even more difficult to include patients from underrepresented groups (including women and minorities). Because of these difficulties, it may be that analyses (both open and controlled), like those recently reported comparing SSRI and TCA efficacy,[32] may be the most effective way to evaluate antidepressant efficacy in HIV-seropositive patients. Furthermore, it is essential that prescribing physicians understand the effects of antidepressant and antiretroviral drug-drug interactions (especially protease inhibitors or triple-drug therapy) since the resulting interactions and outcome affect adherence and, ultimately, overall effectiveness.

Drug names: clarithromycin (Biaxin), dapsone (Dapsone), fluconazole (Diflucan), fluoxetine (Prozac), imipramine (Tofranil and others), indinavir (Crixivan), nefazodone (Serzone), nelfinavir (Viracept), paroxetine (Paxil), ritonavir (Norvir), saquinavir (Invirase), sertraline (Zoloft), zidovudine (Retrovir).

REFERENCES

1. Brown GR, Rundell JR, McManis SE, et al. Prevalence of psychiatric disorders in early stages of HIV infection. Psychosom Med 1992;54: 588–601
2. Perkins DO, Stern RA, Golden RN, et al. Mood disorders in HIV infections: prevalence and risk factors in a nonepicenter of the AIDS epidemic. Am J Psychiatry 1994;151:233–236
3. Rosenberger PH, Bornstein RA, Nasrallah RH, et al. Psychopathology in human immunodeficiency virus infection: lifetime and current assessment. Compr Psychiatry 1993;34:150–158
4. Robins LN, Helzer JD, Weissman MM, et al. Lifetime prevalence of specific psychiatric disorders in three sites. Arch Gen Psychiatry 1984;41: 949–958
5. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51: 8–19
6. Elliott AJ, Uldall KK, Bergam K, et al. A randomized, placebo-controlled trial of paroxetine versus imipramine in depressed HIV-positive outpatients. Am J Psychiatry 1998;155:367–372
7. Fawcett J, Marcus RN, Anton SF, et al. Response of anxiety and agitation symptoms during nefazodone treatment of major depression. J Clin Psychiatry 1995;56(suppl 6):37–42
8. Taylor DP, Carter RB, Eison AS, et al. Pharmacology and neurochemistry of nefazodone, a novel antidepressant drug. J Clin Psychiatry 1995;56 (suppl 6):3–11
9. Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry 1996;57 (suppl 2):53–62
10. Baldwin DS, Hawley CJ, Abed RT, et al. A multicenter double-blind comparison of nefazodone and paroxetine in the treatment of outpatients with moderate-to-severe depression. J Clin Psychiatry 1996;57(suppl 2): 46–52
11. Spitzer RL, Williams JBW, Gibbon M, et al. Structured Clinical Interview for DSM-IV. New York, NY: Biometric Research, New York State Psychiatric Institute; 1994
12. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296
13. Hamilton M. The assessment of anxiety. In: Trimble MR, ed. Benzodiazepines Divided. New York, NY: John Wiley & Sons; 1983:33–43
14. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976
15. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198
16. Rabkin JG, Markowitz JS, Ocepek-Welikson K, et al. General versus systematic inquiry about emergent clinical events with SAFTEE: implications for clinical research. J Clin Psychopharmacol 1992;12:3–10
17. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. Psychol Med 1983;13:595–605
18. Mulder J, McKinney N, Christopherson C, et al. Rapid and simple PCR assay for quantitation of human immunodeficiency virus type 1 RNA in plasma: application to acute retroviral infection. J Clin Microbiol 1994;32:292–300
19. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Morb Mortal Wkly Rep 1992;41(RR-17):1–18
20. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991;48:851–855
21. Rabkin JG, Rabkin R, Harrison W, et al. Effect of imipramine on mood and enumerative measures of immune status in depressed patients with HIV illness. Am J Psychiatry 1994;151:516–523
22. Rickels K, Schweizer E, Clary C, et al. Nefazodone and imipramine in major depression: a placebo-controlled trial. Br J Psychiatry 1994;164: 802–805
23. Segraves RT. Overview of sexual dysfunction complicating the treatment of depression. J Clin Psychiatry Monograph 1992;10(2):4–10
24. Norvir [package insert]. North Chicago, Ill: Abbott Laboratories; 1997
25. Denissen JF, Grabowski BA, Johnson MR, et al. Metabolism and disposition of the HIV-1 protease inhibitor ritonavir (ACT-538) in rats, dogs, and humans. Drug Metab Dispos Biol Fate Chem 1997;25:489–501
26. Davis R, Whittington R, Bryson HM. Nefazodone: a review of its pharmacology and clinical efficacy in the management of major depression. Drugs 1997;53:608–636
27. Serzone [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 1997
28. Feighner JP, Pambakian R, Fowler RC, et al. A comparison of nefazodone, imipramine, and placebo in patients with moderate to severe depression. Psychopharmacol Bull 1989;25:219–221
29. Cohn CK, Robinson DS, Roberts DL, et al. Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression. J Clin Psychiatry 1996;57(suppl 2): 15–18
30. Shader RI, Greenblatt DJ. Protease inhibitors and drug interactions: an alert. J Clin Psychopharmacol 1996;16:343–344
31. AIDS Clinical Trials Group (ACTG). 388 Drug Information Sheet. Research Triangle Park, NC: Glaxo-Wellcome; 1997
32. Wagner GJ, Rabkin JG, Rabkin R. A comparative analysis of standard and alternative antidepressants in the treatment of human immunodeficiency virus patients. Compr Psychiatry 1996;37:402–408