An Open Trial of Reboxetine in HIV-Seropositive Outpatients With Major Depressive Disorder

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Background: The prevalence of major depressive disorder (MDD) in human immunodeficiency virus (HIV)-seropositive patients is higher than in the general population. The treatment of comorbidities of HIV infection, such as depression, is an important target in the clinical management of these patients. The use of antidepressants in HIV patients can be complicated by the pharmacokinetic interaction between antidepressants and antiretroviral agents. Several antidepressants and antiretrovirals are metabolized by cytochrome P450 (CYP450). Reboxetine is a noradrenergic antidepressant that is not metabolized by CYP450 and may offer a valuable option in the treatment of MDD in HIV-seropositive patients.

Method: Twenty HIV-infected outpatients with MDD according to DSM-IV criteria were treated with reboxetine, 8 mg/day, for 12 weeks within an open trial design. Outcome measures included the Montgomery-Asberg Depression Rating Scale (MADRS) and a side effect profile. Data were gathered from July 2000 to March 2001.

Results: Seventy-five percent of patients (N = 15) completed the trial. All patients who completed the trial had an improvement equal to or higher than a 50% reduction in their MADRS scores at endpoint. The most frequent adverse effects were insomnia, sweating, and shivering.

Conclusion: Within this open trial, reboxetine was found to be effective in reducing depressive symptoms in HIV illness. The rate of dropout (25%) suggests that reboxetine may be well tolerated in this population.

(J Clin Psychiatry 2003;64:421–424)

Received Jan. 19, 2002; accepted Aug. 8, 2002. From the Department of Psychiatry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

This study was supported by a grant from the Brazilian Foundation for the Development of Higher Education Personnel. Pharmacia Company provided the reboxetine for this study.

Presented at the New Research Poster Session of the 153rd annual meeting of the American Psychiatric Association, May 9–12, 2001, New Orleans, La.

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Major depressive disorder (MDD) is the most commonly observed Axis I disorder in community samples.[1] The prevalence of MDD is elevated compared with general population rates in several studies of both HIV-positive and HIV-negative patients.[2] Data emerging from randomized placebo-controlled trials suggest that MDD in patients with HIV illness can be successfully treated with imipramine,[3] fluoxetine,[4,5] and paroxetine.[6] Data obtained in open trials suggest that other antidepressants such as sertraline[7] and nefazodone[8] are effective in treating MDD in HIV-seropositive patients. Therefore, the key issue in the treatment of MDD in HIV illness seems to be tolerability and not efficacy,[8] as several agents have already qualified to treat this condition. In a randomized controlled trial comparing paroxetine, imipramine, and placebo,[6] 48% of the patients who were treated with imipramine discontinued treatment, as compared with 20% taking paroxetine and 24% taking placebo. A randomized controlled trial comparing fluoxetine and placebo showed a 30% dropout rate.[4] In an open trial using sertraline, 18% of the patients discontinued the medication due to side effects.[7] An open trial conducted with nefazodone showed that the rate of dropout was 7%.[8]

Reboxetine is a new antidepressant drug, acting as a selective norepinephrine reuptake inhibitor (NRI).[9] In vitro studies have shown that reboxetine does not interact significantly with cytochrome P450 (CYP450) isoenzymes.[10] Patients treated with reboxetine were more likely to experience efficacy in the absence of side effects when compared to patients treated with tricyclic antidepressants.[11] In comparator trials with fluoxetine, patients receiving reboxetine were less likely to experience agitation, nervousness, anxiety, or gastrointestinal events.[12] It is not clear whether side effects induced by antidepressant drugs are more frequent in HIV patients than in the general population. However, the use of selective serotonin reuptake inhibitors (SSRIs) in HIV-seropositive patients may exacerbate some of the most common somatic symptoms seen in these patients, such us sleep disturbance, weight loss, sexual dysfunction, decreased energy, and fatigue.[8] Since reboxetine presents a differential side effect profile and does not interact significantly with CYP450,

we decided to investigate the efficacy and tolerability of this drug in HIV-seropositive outpatients.

METHOD

Sample

The sample consisted of 20 HIV-seropositive outpatients with the diagnosis of MDD. Inclusion criteria were age of 18 to 50 years, a current DSM-IV[13] diagnosis of MDD according to a Structured Clinical Interview for DSM-IV criteria (SCID),[14] and HIV infection. Patients were excluded from the study if they met any of the following criteria: positive history of mental or behavioral disorders resulting from the use of psychoactive substances within the last year, dementia associated with HIV, history of opportunistic infection of the central nervous system, or bipolar disorder. The local Ethics Committee approved the protocol, and all patients gave written informed consent. Data were gathered from July 2000 to March 2001.

Measures

Psychiatric diagnosis. The SCID[14] was used to diagnose past and current psychiatric disorders.

Depressive symptoms. Assessments were made at baseline and at weeks 2, 4, 6, 8, and 12 using the Montgomery-Asberg Depression Rating Scale (MADRS).[15,16]

HIV illness stage. The patients' HIV illness stage was determined according to the 1993 U.S. Centers for Disease Control and Prevention (CDC) criteria.[17]

Adverse effects. Adverse effects were directly assessed at baseline and at weeks 2, 4, 6, 8, and 12, using the question, "Have you had any health-related or physical problems since your last visit?"

Procedure

If eligible for the study, the patients were invited to participate in a 12-week open-label trial with reboxetine. Treatment was initiated and maintained throughout the study at a standard dose of 8 mg/day, divided into 2 doses per day. The assessments were at weeks 1–4, 6, 8, and 12. The MADRS assessment was carried out at baseline and at weeks 2, 4, 6, 8, and 12. Study visits took approximately 40 minutes, and patients received support and orientation for continuing the treatment. The adverse effects were assessed and detailed at each visit and treated by standard agents if of clinical relevance. Data were analyzed using EPI-INFO and SPSS software (SPSS for Windows 10.0, SPSS, Inc., Chicago, Ill.) All tests were 2-tailed, with an alpha level of .05.

RESULTS

Demographics and Clinical Characteristics

Twenty HIV-seropositive patients with DSM-IV MDD were included in the study, and 15 (75%) completed the 12-week treatment. Three patients were lost to follow-up, and 2 were excluded from the study. A summary of the demographic and HIV illness characteristics of the reboxetine-treated patients is presented in Table 1. The sample consisted of 9 men and 11 women, with a mean age of 39.7 years. Mean duration of HIV illness status was 51.3 months, and HIV infection was contracted primarily from heterosexual contact (65% of the cases [N = 15]). There were no significant differences between patients who dropped out (N = 5) and those who completed the trial (N = 15) on demographic characteristics.

Table 1. Characteristics of 20 HIV-Seropositive Depressed Outpatients

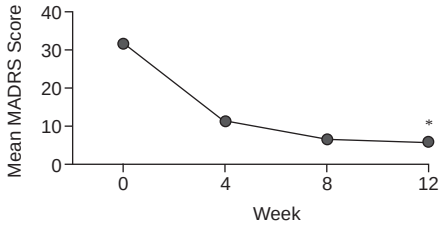
Variable	Value
Demographics	
Age, mean ± SD, y	40 ± 13
Gender, N (%)	
Women	11 (55)
Men	9 (45)
Marital status, N (%)	
Married	11 (55)
Single	5 (25)
Widowed/divorced	4 (20)
Ethnic background, N (%)	
White	14 (70)
African Brazilian	6 (30)
Education, mean ± SD, y	7 ± 4
Income source, N (%)	
Social Security	13 (65)
Employed	4 (20)
Unemployed, no Social Security	3 (15)
HIV illness	
Duration of HIV-illness status, mean ± SD, mo	51 ± 38
CDC criteria, N (%)	
Class A	8 (40)
Class B	4 (20)
Class C	8 (40)
Primary source of HIV infection, N (%)	
Heterosexual contact	13 (65)
Homosexual contact	3 (15)
Intravenous drug use	2 (10)
Blood transfusion	2 (10)
Current use of ARV medications, N (%)[a]	
No medication	3 (6.3)
NRTIs	30 (62.5)
NNRTIs	8 (16.7)
PIs	7 (14.6)
CD4 cell count, mean ± SD[b]	418 ± 264
DSM-IV diagnosis, N (%)	
Major depressive disorder, single episode	10 (50)
Major depressive disorder, recurrent	8 (40)
Dysthymia	2 (10)
History of substance use	3 (15)

[a]Some subjects were using more than 1 drug.
[b]Twelve subjects had data on CD4 cell count, and data were missing for 3 subjects.
Abbreviations: ARV = antiretroviral agent, CDC = Centers for Disease Control and Prevention, HIV = human immunodeficiency virus, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor.

Treatment Response

There was a statistically significant ($p < .001$) reduction in MADRS scores between baseline measures and

Figure 1. Treatment Response on the Montgomery-Asberg Rating Scale (MADRS) in Depressed HIV-Positive Outpatients Treated With Reboxetine (N = 15)



*p < .001.
Abbreviation: HIV = human immunodeficiency virus.

Table 2. Specific Adverse Events Observed in 20 HIV-Positive Depressive Outpatients[a]

Adverse Event	N	%
Insomnia	6	30
Sweating	3	15
Shivering	3	15
Nausea	2	10
Vomiting	1	5
Dizziness	1	5
Urinary retention	1	5
Mania	1	5

[a]Including 2 patients who dropped out due to adverse events and mania. Seventeen of the 20 patients experienced an adverse event.
Abbreviation: HIV = human immunodeficiency virus.

endpoint. The mean ± SD MADRS score changed from 31.7 ± 7.5 at baseline to 5.3 ± 4.3 at week 12. All patients received at least 8 mg/day of reboxetine. Overall depressive symptoms displayed a 50% reduction at the fourth week of treatment (Figure 1). The comparison between baseline and endpoint scores was controlled for CD4 cell count and HIV illness stage according to CDC criteria.

Two patients were excluded from the study: 1 patient discontinued within the first week due to multiple side effects, and another patient was excluded after switching into mania (this patient did not have prior history of bipolar disorder). Three patients dropped out within the first week of treatment. These dropouts were due to the fact that these patients did not come to their appointments.

Adverse Effects

The most frequent adverse events are shown in Table 2. Only 1 (5%) of 20 patients dropped out because of multiple side effects (dizziness, nausea, vomiting, urinary retention, and shivering). This patient was initiated with 8 mg/day (divided into 2 doses) of reboxetine. Three days after, he showed dizziness, nausea, and shivering. On the seventh day, the dose was reduced to 4 mg/day (twice daily) and the patient showed vomiting and urinary retention. At this point, this patient was excluded from the study. This patient was not on antiretroviral drug treatment at that time. The most frequent side effects were insomnia (6/17, 30%), sweating (3/17, 15%), and shivering (3/17, 15%).

DISCUSSION

Reboxetine reduced symptoms of depression in HIV-seropositive patients. Seventy-five percent of the patients completed the 12 weeks of treatment. One patient dropped out due to severe side effects, and 1 patient was excluded after switching to mania. As far as we are aware, this is the first report on the use of reboxetine in this population.

Evidence from previous trials suggests that different classes of antidepressants are effective for treating MDD in HIV-seropositive patients.[3–8] The critical factor in choosing an antidepressant for the treatment of these patients seems to be tolerability. In a randomized clinical trial comparing imipramine, paroxetine, and placebo, the number of dropouts in HIV patients with MDD was 48% for those treated with imipramine and 20% for patients treated with paroxetine.[6] This suggests that the side effects associated with the use of tricyclics are not well tolerated in this population. The present study showed a dropout rate of 25%, which is comparable to the dropout rates in trials of SSRIs such as fluoxetine,[4] paroxetine,[6] and sertraline.[7]

There are studies suggesting that SSRIs are a good choice for the treatment of depression in HIV-seropositive patients.[4–6] However, SSRIs are known to induce side effects such as sleep disturbance, weight loss, sexual dysfunction, decreased energy, and fatigue. It is not clear whether bodily symptoms and side effects induced by antidepressants are more frequently reported in HIV patients than in the general population. As far as we are aware, no clinical trials have yet been conducted to assess this specific question.

Reboxetine is a selective NRI and presents a differential side effect profile as compared with SSRIs. Therefore, reboxetine may be a useful treatment in patients who do not tolerate SSRIs. Unlike paroxetine and fluoxetine, reboxetine does not inhibit CYP2D6, which is the main site of metabolism of protease inhibitors, which are frequently included in the pharmacologic treatment of HIV infection. Reboxetine may offer a valuable option for patients using protease inhibitors in their antiretroviral treatment.

Limitations of the present study reflect the open-label exploratory design used. Further studies on the use of reboxetine in HIV patients should be designed in a way that results can be compared with those of other drugs that are better studied in this sample of patients. The sample size of the present study (N = 20) is not different from the usual sample size of studies designed to explore issues not yet covered in the scientific literature. When studies on

HIV-infected patients are carried out, demographic variables are important information to be considered. The present study reflects demographic data of the Brazilian population such as education level and high rates of heterosexual transmission of HIV infection.[18] The education level of the patients in the present study is lower than that reported in previous studies. The way that this may affect the generalization of this data set is not clear. Another limitation of the present study is that the exclusion of patients using drugs of abuse was carried out using information provided by the patient and not urine toxicologic screen.

The present study suggests that reboxetine is an effective treatment for HIV-seropositive patients suffering from MDD. Reboxetine presents a differential mechanism of action, side effects profile, and path of metabolism compared with SSRIs. Reboxetine seems to offer a valuable choice in treating HIV patients with MDD.

Drug names: fluoxetine (Prozac and others), imipramine (Surmontil, Tofranil, and others), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft).

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