A Randomized Trial Comparing Paroxetine and Venlafaxine in the Treatment of Bipolar Depressed Patients Taking Mood Stabilizers

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Background: The treatment of depressive episodes occurring in bipolar patients taking mood stabilizers is an understudied area of research with outstanding clinical consequences. This study was aimed to assess and compare the efficacy and safety of 2 different antidepressant drugs, paroxetine and venlafaxine, in this indication.

Method: Sixty DSM-IV bipolar patients, each presenting with a major depressive episode while receiving mood stabilizers, were randomly assigned to either paroxetine (N = 30) or venlafaxine (N = 30) for 6 weeks in a single-blind manner. They had to score higher than 17 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17) and have their mood stabilizer blood levels within the therapeutic range. Efficacy was measured by the HAM-D. Reports of side effects were collected at each visit; switch to mania or hypomania was specifically assessed by the Young Mania Rating Scale at 5 of 7 visits.

Results: Significant improvements in HAM-D scores were observed in both paroxetine- and venlafaxine-treated patients (Wilcoxon $p < .0001$). There were no significant differences in either efficacy or safety measures between the 2 drugs. By intention-to-treat analysis, 43% (N = 13) of patients taking paroxetine and 48% (N = 14) taking venlafaxine were considered to be responders. Only 3% (N = 1) of patients switched to hypomania or mania in the paroxetine group, whereas 13% (N = 4) switched in the venlafaxine group.

Conclusion: Paroxetine and venlafaxine are both effective and safe in the treatment of depressive breakthrough episodes in bipolar disorder. There was a suggestion of a slightly higher risk for switch to mania or hypomania with venlafaxine.

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The treatment of depression in bipolar disorder represents an understudied area in clinical psychiatry that needs further research owing to the frequency of depressive episodes in bipolar disorder, the high rates of associated suicidality and comorbid psychiatric and substance-use disorders, and the negative impact on psychosocial functioning and quality of life.[1] The potential for bipolar patients to experience a switch to hypomania, mania, or rapid cycling during the treatment of depression remains an important clinical question. To date, the use of mood stabilizers as first-line treatment for bipolar depression has been advocated by many authors,[2,3] but the concomitant use of antidepressant drugs is still both common practice and controversial. Third generation antidepressants, such as venlafaxine, have not yet been assessed in controlled studies, although Amsterdam[4] reported positive results and no mood swings in a sample of depressed bipolar II patients. Other reports have shown some efficacy of the addition of paroxetine to mood stabilizers and a very low risk of switching to mania.[5,6]

The potential interest in comparing paroxetine and venlafaxine in the treatment of bipolar depression derives from their different mechanisms of action. Paroxetine is a selective serotonin reuptake inhibitor (SSRI) with little action on noradrenergic and cholinergic receptors, and venlafaxine is a serotonin-norepinephrine reuptake inhibitor (SNRI) with almost no anticholinergic effects. Therefore, differences in efficacy and safety profile, particularly switch risk, may be hypothesized. For instance, a double-blind, randomized study showed a significantly

higher response rate for venlafaxine (52%) compared with paroxetine (33%) in treatment-resistant depressed patients, though it is not clear how many, if any, of those patients were bipolar.[7] On the other hand, some anecdotal reports suggest a higher risk for switch to mania or hypomania for drugs that have norepinephrine reuptake inhibiting properties[8,9] and even further evidence for drugs that combine noradrenergic and anticholinergic effects, like tricyclic antidepressants.[10]

The aim of the study was to assess and compare the efficacy and safety of paroxetine and venlafaxine in the treatment of bipolar depressed patients who were already taking mood stabilizers and to address carefully the risk of induction of mania or hypomania for each drug. Although trials assessing the efficacy of antidepressants have generally been performed in a monotherapy design, in bipolar disorder, monotherapy is more the exception than the rule, and most guidelines advocate the combination of mood stabilizers and antidepressants, particularly when treating "breakthrough" episodes occurring during mood-stabilizing therapy.[11]

METHOD

Patients

This study enrolled 60 DSM-IV bipolar depressed patients in a single(rater)-blind, randomized comparative design aimed to assess and compare the efficacy and safety of paroxetine and venlafaxine as adjuncts to prior mood-stabilizing treatment for breakthrough depressive episodes. The study was conducted according to the Declaration of Helsinki, and all patients provided informed written consent to participate. The Ethics Committee of the Hospital Clinic, University of Barcelona, Barcelona, Spain, approved the protocol.

To be enrolled, patients were required to fulfill DSM-IV criteria for bipolar disorder and for a major depressive episode with a score over 17 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17).[12] In addition, they had to be on treatment with at least 1 mood stabilizer for at least 6 months prior to the onset of the present episode and free of any antidepressant or antipsychotic medication for at least 3 months. Patients were excluded if they had taken paroxetine or venlafaxine before. Anxiolytics could be continued during the study period. Patients actively abusing alcohol or other psychotropics, having a history of serious organic disease, or considered at risk of attempting suicide were excluded. Pregnant or breastfeeding women were also excluded, and women of childbearing age were required to use a medically acceptable method of contraception during the study period. Patients rating 8 or more on the Young Mania Rating Scale (YMRS)[13] at baseline were also excluded. Additionally, patients were required to have had previously therapeutic blood levels of mood stabilizers (lithium, 0.7 mg/L; carbamazepine, 4 μg/mL; valproate, 50 μg/mL). Their dosages were held constant during the study period.

Assessments

All patients in our research program are assessed by means of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) in order to establish a definite diagnosis of bipolar disorder. For this trial, they were additionally checked for the presence of depression using a DSM-IV criteria checklist. Patients were randomly assigned to 1 of 2 antidepressants (paroxetine or venlafaxine) for an acute clinical trial of 6-week duration. At the baseline visit, a complete medical and psychiatric history was obtained; a physical examination was carried out; and the HAM-D, the YMRS, and the Clinical Global Impressions (CGI) for severity[14] were administered. Subsequently, HAM-D, YMRS, and CGI ratings were obtained at week 1, week 2, week 4, and week 6 (endpoint). Spontaneously reported adverse events were collected at each visit.

The primary outcome measure was defined as the last-observation-carried-forward (LOCF) HAM-D score. Response was defined as a decrease in the HAM-D score of more than 50% from baseline to endpoint. Remission was defined as a HAM-D score of less than 10 and a CGI score of 1.

Switch was defined as a YMRS score above 11 and DSM-IV criteria for mania or hypomania. HAM-D, YMRS, and CGI ratings were assessed by a rater (A.M.-A.) who was blind to the nature of the treatment.

Treatment Doses

Doses of the 2 drugs being tested were adjusted according to response and tolerability, starting from 37.5 mg twice daily of venlafaxine and 20 mg/day of paroxetine in the morning. The rate of titration for each antidepressant agent was calculated to ensure safety and minimize side effects, allowing for 75-mg/day increments for venlafaxine and 10-mg/day increments for paroxetine every week.

The patient and the treating physician were not blinded to the nature of the treatment, but the rater was. No information was given to the patient about any expectations related to the efficacy in bipolar depression of any of the drugs being tested, except that they both had proved to be safe and efficacious in the treatment of unipolar depression.

Statistical Analysis

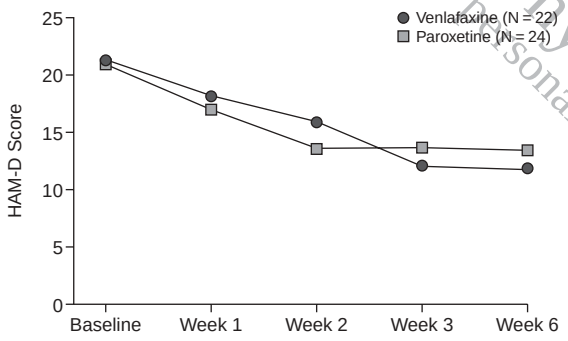
Data were analyzed on an intention-to-treat (ITT) basis; all patients who took at least 1 dose of a study drug and had at least 1 study assessment were included. An LOCF analysis was performed, although completers' analyses were also performed to give further information. Baseline variables, response rates, remission rates, and switch rates were compared using chi-square or Student t test. Significance was set at the $p < .05$ level (2-tailed).

Table 1. Baseline Characteristics of Bipolar Depressed Patients Treated With Paroxetine or Venlafaxine[a]

	Paroxetine (N = 30)		Venlafaxine (N = 30)	
Characteristic	N	%	N	%
Sex, female	19	63	21	70
Bipolar I	23	77	21	70
Bipolar II	7	23	9	30
Rapid cyclers	3	10	3	10
Mood stabilizers (MS)	28	93	29	97
Lithium	19	63	23	77
Valproate	9	30	6	20
Carbamazepine	7	23	9	30
Other	6	20	3	10
	Mean	SD	Mean	SD
Age, y	47.1	15.2	45.5	13.7
HAM-D score	20.7	3.0	21.2	3.2
CGI score	4.2	0.9	4.5	0.7
Duration of current MS treatment, mo	38.8	21.5	32.3	22.9

[a]No significant differences between groups.
Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression.

Figure 1. HAM-D Scores During the 6-Week Single-Blind Trial of Paroxetine and Venlafaxine in Bipolar Depression[a]



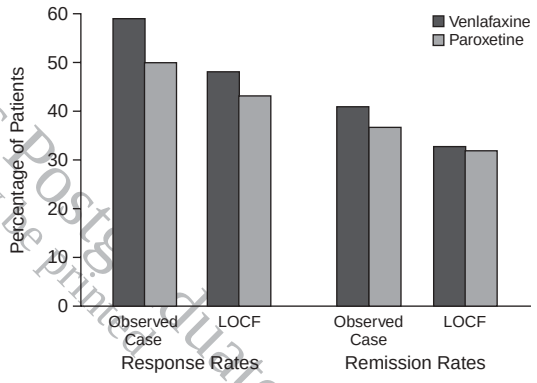
[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Table 2. Endpoint Results Comparing Paroxetine and Venlafaxine in the Treatment of Bipolar Depressed Patients Taking Mood Stabilizers[a]

	Paroxetine (N = 30)		Venlafaxine (N = 30)	
Endpoint Variable	N	%	N	%
Completers	24	80	22	73
Early discontinuation	6	20	8	27
Lack of efficacy	2	7	0	0
Switch to mania	1	3	4	13
Lost to follow-up	1	3	1	3
Side effects	1	3	1	3
Noncompliance	1	3	0	0
Responders/completers	12/24	50	13/22	59
Responders/LOCF	12/28	43	13/27	48
Remissions/completers	9/24	37	9/22	41
Remissions/LOCF	9/28	32	9/27	33
Any side effect	13	43	15	50
	Mean	SD	Mean	SD
Dosage, mg/day	32.3	11.2	179.2	91.0
HAM-D score	13.8	6.7	12.2	6.1
CGI score	2.7	1.9	2.7	1.6

[a]Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

Figure 2. Response and Remission Rates for Paroxetine- and Venlafaxine-Treated Patients With Bipolar Depression[a]



[a]Completer analyses; intention to treat. Response defined as a decrease in HAM-D scores of more than 50% from baseline to the endpoint. Remission defined as a HAM-D score of less than 10 and a CGI score of 1. Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

RESULTS

A total of 60 patients were enrolled in the study (30 on paroxetine and 30 on venlafaxine treatment), and 55 were included in the ITT and LOCF analysis (28 on paroxetine and 27 on venlafaxine treatment). The observed-case analysis included 24 patients on paroxetine and 22 on venlafaxine treatment. No baseline demographic or clinical characteristics were significantly different between both groups of patients (Table 1). There was a total of 14 dropouts. Reasons for discontinuation are shown in Table 2.

Efficacy

As shown in Figure 1 and Table 2, significant improvements in HAM-D rating scores between baseline and endpoint were observed in both paroxetine- and venlafaxine-treated patients (Wilcoxon $p < .0001$). The mean HAM-D change for paroxetine was –6.9 and for venlafaxine –9.0. CGI mean scores also significantly improved for both groups (Wilcoxon $p = .0002$). There was no significant difference between the 2 drugs on the endpoint HAM-D and CGI rating scores, response rates, and remission rates, according to observed-case analysis and LOCF (Figure 2). In all measures, venlafaxine was numerically but non-significantly superior to paroxetine. There was no difference in response and remission rates between bipolar I and bipolar II patients, nor between patients taking lithium and patients taking anticonvulsants.

Table 3. Incidence of Adverse Events During the 6-Week Trial[a]

	Paroxetine (N = 30)		Venlafaxine (N = 30)	
Adverse Event	N	%	N	%
Nausea	7	23	5	17
Dry mouth	1	3	4	13
Switch to (hypo)mania	1	3	4	13
Dizziness	2	7	3	10
Headache	3	10	1	3
Insomnia	0	0	3	10
Constipation	2	7	1	3
Anorgasmia	2	7	1	3
Rash	0	0	2	7
Anxiety	0	0	1	3
Ataxia	0	0	1	3
Somnolence	1	3	0	0

[a]No significant differences between groups.

Safety

The incidence of any adverse event was 43% (N = 13) for paroxetine and 50% (N = 15) for venlafaxine. No significant differences were noted between the 2 drugs concerning the incidence of adverse events (Table 3). The most common adverse event was nausea. Four patients taking venlafaxine and 1 taking paroxetine had a switch to hypomania or full mania. Specifically, the patient who switched during paroxetine treatment had a hypomanic episode (YMRS score = 17); 2 patients on venlafaxine therapy switched to full mania (YMRS score = 23 and 31), and 2 others switched to hypomania (YMRS score = 12 and 14). These episodes lasted for more than 1 week, even though they were promptly treated and the antidepressant was withdrawn. One patient had to be hospitalized due to mania. There was no significant difference between those patients who did and did not switch concerning baseline characteristics and treatment, including concomitant medications and doses of the drugs being tested. There was no suicide attempt during the trial.

DISCUSSION

This is one of very few controlled trials on the acute treatment of bipolar depression, and specifically the first to compare 2 different modern antidepressants, namely paroxetine and venlafaxine, in the treatment of acute breakthrough depressive episodes in bipolar patients receiving mood stabilizers. Both drugs proved to significantly improve mood in depressed bipolar patients. Even though nearly half of the patients experienced side effects, these did not lead to withdrawal from the study in most cases, and the drugs were generally well tolerated. Venlafaxine was numerically but not significantly superior to paroxetine in both efficacy and switch rates.

Although by ITT analyses only 43% responded to paroxetine and 48% to venlafaxine, these patients could be considered partially resistant because all of them suffered their index depressive episode while on treatment with mood stabilizers, which are considered first-line choices for bipolar depression.[11,14,15] On the other hand, most of the patients were enrolled at a quite early stage of their depressive episode, as they were required to be free of antidepressants for at least 3 months, so patients with chronic depression were less likely to be included.

It is generally assumed that all antidepressant medications that have been shown to be effective for patients with unipolar major depression are also probably effective for patients in the depressed phase of bipolar disorder. However, most medications being widely used in unipolar disorder have not been tested in bipolar populations. Besides, some evidence supports the hypothesis that antidepressants increase the bipolar patient's baseline risk of developing a manic or hypomanic episode,[3] and it is likely that there are outstanding differences among antidepressant drugs in this concern. Thus, only a few antidepressants, such as imipramine,[6,16,17] tranylcypromine,[16] fluoxetine,[17] desipramine,[18] bupropion,[18] moclobemide,[19] and paroxetine,[6] have been studied in randomized, controlled trials. Moreover, many of these trials had several methodological concerns such as small sample size, short follow-up, differences in concomitant use of mood stabilizers, and inconsistent definition of switching.

In this trial, the safety of paroxetine and venlafaxine was comparable and similar to that found in trials with depressed unipolar patients,[7] except for switch rates. Switch to hypomania has been reported to be very uncommon in unipolar depression but is not rare in bipolar samples.[10] Tricyclic antidepressants could be associated with the highest risk of switching, whereas SSRIs and lamotrigine could have the lowest.[10,20] The reasons for that are still unclear, but drugs with combined noradrenergic-serotonergic activity such as tricyclics and venlafaxine at doses up to 150 mg/day may be more prone to induce mania or hypomania. In this trial, 13% of venlafaxine-treated patients switched to mania or hypomania, in contrast with only 3% for paroxetine. Besides, the only switch related to paroxetine was just hypomanic, in contrast with 2 full-blown manic episodes in venlafaxine-treated patients, 1 of which led to hospitalization. The risk of venlafaxine-induced mania has already been reported.[21]

The mean doses of venlafaxine and paroxetine were 179 mg/day and 32 mg/day, respectively, which are within the usual range for both drugs. Since the doses were adjusted by the physicians according to response and tolerability, this study provides some clues about the average target dose for treating bipolar depression with paroxetine or venlafaxine in patients taking mood stabilizers.

The main limitations of this study are (1) the absence of a placebo arm, which would have provided useful information concerning efficacy and baseline switch-risk; (2) the single-blind design instead of double-blind, which

may have introduced some bias by means of the patient's expectations for each drug; (3) the concomitant use of several different mood-stabilizing drugs, which may account for some of the efficacy and side effects of the drugs being tested; (4) the relatively small sample size; and (5) the lack of a longer follow-up to ensure maintenance of efficacy and longer-term switch risk. Actually, this study focuses only on acute treatment. More data are needed about continuation antidepressant treatment in bipolar depression. Additionally, some measure of compliance, such as blood levels of paroxetine and venlafaxine, would have been useful. However, the fact that the patients were already receiving potentially effective drugs (mood stabilizers) without a positive response before entering the trial may have reduced the impact of a putative placebo response, and we think that this trial was closer to clinical practice than placebo-controlled monotherapy trials, which usually enroll extremely selected populations. Throughout the study, the blind of the trial was preserved for the rater, and given that an exclusion criterion was prior usage of either of the 2 drugs before the trial, there is no reason to suspect that the patient's expectations and response would have been different in a double-blind trial.

Despite the limitations described above, we believe that this trial also has some strengths that make it worth reporting: (1) the scarcity of controlled trials in bipolar depression; (2) the fact that the patients enrolled were taking mood stabilizers long before their depressive symptoms started, ensuring that we were dealing with true breakthrough episodes; and (3) the use of validated measures of efficacy and a clear definition of switch.

In conclusion, this study provides some evidence of the efficacy and safety of both paroxetine and venlafaxine in the treatment of bipolar depression in patients previously taking mood stabilizers. The rate of (hypo)manic switches in the venlafaxine group (13%) raises some concern about the use of this drug in mildly severe patients, although a larger survey should be conducted in order to replicate these preliminary findings.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), lamotrigine (Lamictal), paroxetine (Paxil), tranylcypromine (Parnate), venlafaxine (Effexor).

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