An Open Trial of Adjunctive Escitalopram in Bipolar Depression

Manoela Fonseca, M.D.; Jair C. Soares, M.D.; John P. Hatch, Ph.D.; Aida P. Santin, M.D.; and Flavio Kapczinski, M.D., Ph.D.

Objective: This study was designed to evaluate the efficacy and safety of a highly potent and selective serotonergic antidepressant, escitalopram, in the treatment of bipolar depression.

Method: Twenty outpatients with DSM-IV bipolar depression types I and II were enrolled in a 12-week open trial of escitalopram, 10 mg daily, adjunctive to their ongoing mood stabilizer. Assessments were carried out using the Hamilton Rating Scale for Depression (HAM-D), the Young Mania Rating Scale (YMRS), and the Clinical Global Impressions for Severity (CGI-S) and Improvement (CGI-I) scales. The study was conducted from August 2003 to February 2004.

Results: Escitalopram was associated with significant improvement as measured by the HAM-D total score, which showed a mean reduction from baseline (mean = 20.9, SD = 4.2) to endpoint (mean = 8.9, SD = 3.6; $p < .001$) of 12 points. The mean CGI-S score decreased by 3.3 points (baseline: mean = 4.8, SD = 0.7; week 12: mean = 1.5, SD = 0.6; $p < .001$). Adverse events emerged in 75% of the patients (N = 15), usually of mild-to-moderate severity. Four dropouts took place due to manic switch (N = 1), hypomanic symptoms (N = 2), and hospitalization due to the emergence of suicidal ideation and psychosis (N = 1).

Conclusion: These findings suggest that escitalopram in association with mood stabilizers may be an effective and reasonably well-tolerated treatment for patients with moderate-to-severe bipolar depression. The switch rate was similar to what is described in the literature for the selective serotonin reuptake inhibitors. Randomized controlled trials of escitalopram in bipolar depression are warranted.

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Received Feb. 1, 2005; accepted Dec. 1, 2005. *From the Psychiatry Research Unit, Federal University of Rio Grande do Sul, Porto Alegre, Brazil (Drs. Fonseca and Kapczinski); the MOOD-CNS Program, Division of Mood and Anxiety Disorders, the Department of Psychiatry, the University of Texas Health Science Center at San Antonio (Drs. Fonseca, Soares, and Hatch); the Psychiatry Service, South Texas Veterans Health Care System, Audie L. Murphy Division, San Antonio, Tex. (Drs. Fonseca and Soares); the Psychiatry Service, Clinical Hospital of Porto Alegre, Federal University of Rio Grande do Sul, School of Medicine, Porto Alegre, Brazil (Drs. Fonseca, Santin, and Kapczinski); and the Department of Orthodontics, The University of Texas Health Science Center at San Antonio (Dr. Hatch).*

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Corresponding author and reprints: Manoela Fonseca, M.D., Department of Psychiatry, Division of Mood and Anxiety Disorders, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr., San Antonio, TX 78229-3900 (e-mail: fonsecam2@uthscsa.edu).

Bipolar disorder is a chronic, usually episodic, and severe mental health problem associated with significant morbidity, disability, and an important economic burden. Despite its high prevalence and morbidity, the depressive phase of bipolar disorder remains understudied, especially when compared to the extensive literature about the manic phase of bipolar disorder and unipolar depression. Bipolar depression is usually difficult to treat; it is generally persistent and insidious, involves a long recovery time, and is associated with suicide risk.[1,2]

Bipolar and unipolar depression share clinical and phenomenological similarities but seem to have important biological differences.[3,4] Effective treatments for unipolar depression could also be effective for bipolar depression, but the literature on unipolar disorder cannot simply be extended to bipolar disorder. The treatment of bipolar depression with antidepressants remains controversial, and clinical guidelines usually recommend avoiding antidepressants. However, there are no firm data to support this recommendation.[5] Antidepressants have been related to mania or hypomania switch and cycle acceleration,[6–8] but the extent to which this is a specific effect of the antidepressant treatment or is related to the natural course of the disorder, as well as the comparative risk across various antidepressant agents, is still unknown. Some studies link noradrenergic drugs to a higher risk of mania induction and a worse clinical course.[9–12]

Escitalopram is a highly selective and potent serotonergic medication[13]; thus, it may hold potential as an effective treatment for bipolar depression. The aim of this study was to evaluate the efficacy and safety of escitalopram as an adjunctive therapy for bipolar depression types I and II in patients with poor response to ongoing treatment with mood stabilizers, despite stable doses and therapeutic serum levels for the last 4 weeks. A secondary objective was to assess the risk of induction of mania and hypomania with the adjunctive use of escitalopram.

METHOD

Subjects

This study was conducted in an academic psychiatric outpatient clinic in Porto Alegre, Brazil, from August 2003 to February 2004. Eligibility criteria required patients to be at least 18 years of age; meet DSM-IV[14] criteria for bipolar I or II disorder, current major depressive episode; and have a minimum score of 16 on the 17-item Hamilton Rating Scale for Depression (HAM-D).[15] The diagnosis was confirmed by the Structural Clinical Interview for DSM-IV (SCID-I).[16] In addition, patients had to be on treatment with at least 1 mood stabilizer that had been given at stable doses for the last 4 weeks and present therapeutic serum levels at baseline (lithium 0.6–1.5 mEq/L, valproic acid 50–100 μg/mL, and carbamazepine 4–12 μg/mL). A baseline score of 12 or less on the Young Mania Rating Scale (YMRS)[17] was also required.

Patients who had a mixed or manic episode, psychotic features, acute suicidal ideation, any current Axis I diagnoses other than bipolar disorder, history of alcohol or substance abuse or dependence within the last 6 months, abnormal thyroid function tests, any unstable or untreated medical condition, or current psychiatric hospitalization were excluded. Pregnant and lactating women also were excluded. All women of childbearing age were required to use a medically accepted form of contraception during the study.

Study Design and Procedures

Eligible subjects were enrolled in a 12-week open trial of 10 mg daily of escitalopram as adjunctive therapy to their ongoing treatment with mood stabilizers. Patients on antidepressant therapy were required to complete a washout period of at least 1 week before joining the study. Fluoxetine, because of its long half-life, was discontinued at least 6 weeks prior to starting the treatment with escitalopram. Patients were permitted concurrent use of a benzodiazepine or an antipsychotic as needed for the control of agitation or insomnia if they were on such medication prior to the beginning of the trial. The dose of the mood stabilizers, benzodiazepines, or antipsychotics could not be augmented during the study.

Clinical assessments were conducted at baseline and at weeks 1, 2, 4, 6, 8, 10, and 12. At the baseline visit, complete medical and psychiatric histories were obtained by a trained psychiatrist. Clinical status was assessed using the HAM-D, the YMRS, and the Clinical Global Impressions for Severity (CGI-S) scale.[18] A physical examination, laboratory tests, and an electrocardiogram were also performed at baseline. At every subsequent visit, the HAM-D, the YMRS, the CGI for Improvement (CGI-I),[18] vital signs, and adverse events were assessed. At each visit, adverse events were initially elicited spontaneously and later assessed using an extensive list of possible adverse events.[19] Severity of adverse events was rated based on the patients' subjective report and the assessor's clinical experience. The laboratory tests, including the serum levels of mood stabilizers, were repeated at week 12.

Outcome

The primary outcome measure was the HAM-D total score at the 12-week follow-up visit. A positive treatment response was defined as a reduction in the HAM-D total score of at least 50% from baseline and a CGI-S ≤ 2 in the absence of a manic, hypomanic, or mixed episode at the end of week 12. Remission was defined by a HAM-D total score ≤ 7 and a CGI-S score of 1 at the endpoint. Relapse was defined by DSM-IV criteria for major depression, a HAM-D total score ≥ 16, and a CGI-S ≥ 4. Switch to mania was defined by a YMRS total score > 12 and DSM-IV criteria for a manic episode. Switch to hypomania was defined by DSM-IV criteria for a hypomanic episode.

Data Analysis

Statistical analyses were performed using SPSS software version 12.0.2 (SPSS, Inc., Chicago, Ill.). The association between sociodemographic and clinical variables and the dichotomous measures of outcome was assessed using Fisher exact test and an exact Kruskal Wallis test. Outcomes that were measured on a continuous scale were analyzed with a 1-way repeated measures analysis of variance using the SPSS Mixed Models procedure with an unstructured covariance matrix. Four subjects were lost to follow-up near the end of the trial. Both available case and intention-to-treat analyses were performed on the primary outcome measure. Available case analysis included all subjects up to the point when they left the study. Intention-to-treat analyses employed last-observation-carried-forward as well as estimation of 6.9% missing values using an expectation-maximization algorithm. Available case and intention-to-treat methods of analysis yielded the same results, so we report only the intention-to-treat analysis. Pairwise post hoc comparisons of each post baseline mean versus the baseline mean were tested for statistical significance using the Sidak adjustment. Statistical significance was defined as $p < .05$.

Table 1. Baseline Characteristics of Bipolar Patients Treated With Adjunctive Escitalopram (N = 20)

Characteristic	N	%
Gender		
Male	3	15
Female	17	85
Race		
White	17	85
Nonwhite	3	15
Marital status		
Married/cohabiting	13	65
Not married	7	35
Occupation		
Full-time job/student	6	30
No occupation/housewife	14	70
Family history of mood disorders	19	95
Bipolar disorder		
Type I	16	80
Type II	4	20
Rapid cyclers	3	15
Intensity of current episode		
Moderate	16	80
Severe	4	20
Prior hospitalization for a mood episode	13	65
	Mean	SD
Age, y (range, 22–51 y)	39.4	8.7
Years of schooling	10.1	4.9
Age at first hospitalization, y	31.3	9.5
Previous hospitalizations for a mood episode (range, 1–25)	3.7	6.8
Duration of illness, y	16.1	8.9
CGI-S total score	4.8	0.7
HAM-D total score	20.9	4.2
YMRS total score	0.1	0.4

Abbreviations: CGI-S = Clinical Global Impressions for Severity scale, HAM-D = Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.

Table 2. Mood Stabilizer Therapy of Bipolar Patients Treated With Adjunctive Escitalopram (N = 20)

	N	%
Monotherapy		
Lithium	4	20
Valproic acid	4	20
Carbamazepine	3	15
Subtotal	11	55
Combination therapy		
Lithium + valproic acid	7	35
Lithium + carbamazepine	1	5
Lithium + oxcarbazepine	1	5
Subtotal	9	45

Dose ranges: lithium, 600–1500 mg/day; valproic acid, 1000–1500 mg/day; carbamazepine, 600–1000 mg/day; oxcarbazepine, 300 mg/day.

Table 3. Lifetime Prevalence of Axis I Comorbidities in Bipolar Patients Treated With Adjunctive Escitalopram (N = 20)[a]

Comorbidity	N	%
Anxiety disorders		
Panic disorder with agoraphobia	4	20
Agoraphobia	4	20
Specific phobia	5	25
Social phobia	1	5
Obsessive-compulsive disorder	1	5
Total	15	75
Substance use disorders[b]		
Alcohol abuse	5	25
Cocaine dependence	2	10
Amphetamine abuse	2	10
Total	9	45
None	4	20

[a]Categories are not mutually exclusive. Percentage based on total number of lifetime diagnoses.
[b]In remission for over 6 months.

Informed Consent/Ethics Review

The Ethics Committee of the Clinical Hospital of Porto Alegre, Brazil, approved this study protocol. All patients provided written informed consent prior to participation.

RESULTS

Baseline Demographics and Clinical Characteristics

A total of 20 patients were enrolled in the study; 16 (80%) of them had a diagnosis of bipolar disorder type I. Of 13 patients who had a prior hospitalization for a mood episode, a depressive episode was responsible for the first hospitalization in 69.2% (N = 9). Nine (56.3%) of the bipolar I disorder patients (N = 16) had 5 or more manic episodes during their lives. Eighty-five percent of patients (N = 17) had numerous depressive episodes, which could not be properly recorded. Seventy-five percent (N = 3) of bipolar II disorder patients (N = 4) had numerous previous hypomanic episodes. More detailed clinical and demographic information is provided in Table 1.

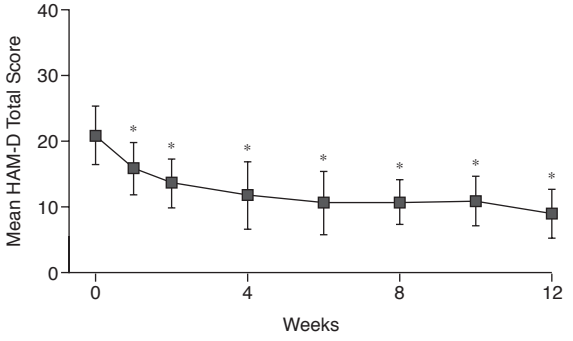
Lithium, monotherapy or in combination, was the most frequently prescribed mood stabilizer (65% of the patients, N = 13). Table 2 shows a detailed description of the mood stabilizer therapy. Thirteen patients (65%) were being treated with a benzodiazepine or antipsychotic. Clonazepam was the most frequently prescribed medication (84.6%, N = 11), with doses ranging from 0.25 to 4 mg/day. Other prescribed medications were levomepromazine (25–100 mg/day), chlorpromazine (50 mg/day), ziprasidone (40 mg/day), and olanzapine (2.5 mg/day). Six patients (30%) underwent antidepressant washout before starting the trial.

Eighty percent of the patients (N = 16), at some point in their lives, had an Axis I diagnosis comorbid with bipolar disorder. Anxiety disorders were the most prevalent comorbid diagnosis. Table 3 describes the lifetime prevalence of Axis I comorbidities.

Efficacy and Safety

Sixteen (80%) of the 20 patients completed the 12-week trial. The mean reduction in the HAM-D total score from baseline (mean = 20.9, SD = 4.2, range = 16–31) to endpoint (mean = 8.9, SD = 3.6, range = 3–17; $p < .001$) was 12 points (Figure 1), while the CGI-S mean reduction

Figure 1. Mean HAM-D Total Score as a Function of Time on Adjunctive Escitalopram Treatment (N = 20)[a]



[a]The 12-week assessment was the primary study endpoint. Mean HAM-D total score decreased significantly from baseline after 1 week of therapy and remained significantly improved for the duration of the trial.
*Indicates $p < .001$; Sidak adjusted compared to baseline.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Table 4. Incidence of Adverse Events Among Bipolar Patients Treated With Adjunctive Escitalopram (N = 20)[a]

Adverse Event	N	%
Central nervous system		
Headache	6	30
Somnolence	5	25
Insomnia	2	10
Cloudy vision	1	5
Dizziness	1	5
Anxiety	1	5
Gastrointestinal		
Nausea	5	25
Dry mouth	3	15
Iron taste	1	5
Vomiting	1	5
Sexual dysfunction[b]	2	10
Joint pain	1	5
Dry eyes	1	5
Tachycardia	1	5

[a]Includes all adverse events reported during the study.
[b]Anorgasmia and retarded ejaculation.

from baseline (mean = 4.8, SD = 0.7, range = 4–6) to the end of the trial (mean = 1.5, SD = 0.6, range = 1–3; $p < .001$) was 3.3 points.

Twelve patients (60%) met criteria for a positive treatment response at week 12; 6 of these (30%) obtained a full remission of the depressive episode. Four patients (20%) showed a poor response (a reduction less than 50% from the baseline HAM-D total score) at the end of the trial. Four patients (20%) were taken off the protocol prior to the study endpoint: 1 patient (bipolar I disorder) switched to a manic episode (YMRS score = 19) and was dropped from the study at week 4; 1 patient (bipolar I disorder) was dropped at week 6 because of the emergence of psychotic symptoms and suicidal ideation that required his immediate hospitalization; 2 patients (bipolar I disorder) developed mild hypomanic symptoms (YMRS score < 12) and were dropped at week 8. In these cases, all necessary measures were taken, and the antidepressant was discontinued. Fifteen patients (75%) experienced at least 1 adverse event. The most common adverse event was headache (N = 6; 30%), but two thirds of these patients had a history of headaches prior to starting treatment with escitalopram. Five patients described mild somnolence during the first and second weeks of treatment. Nausea was the most persistent adverse event; some patients experienced nausea until the end of the study. Adverse events were generally transitory and well-tolerated, with most of them described as mild to moderate. The incidence of adverse events during the study is listed in Table 4.

DISCUSSION

To our knowledge, this is the first study to assess the efficacy and tolerability of escitalopram in bipolar depression. Our patients showed significant improvement soon after beginning escitalopram therapy, and improvement continued throughout the 12-week treatment period. Significant improvement occurred in the HAM-D total scores after just 1 week of treatment, and improvement progressed with further exposure to escitalopram. Furthermore, the degree of improvement was clinically meaningful, with half of the responders also meeting criteria for full remission of their depressive episode. Previous studies of escitalopram for depression were conducted in patients with major depressive disorder (MDD). In patients with MDD, escitalopram has been shown to be effective as compared to placebo and other antidepressants.[20–22]

Our study demonstrated that escitalopram was reasonably well tolerated; 75% of the patients described adverse events of mild-to-moderate severity. In a previous study[19] of escitalopram with 715 patients with MDD, 72.7% experienced adverse events. Headache and nausea were the most commonly described events, which is similar to our findings. In our study, somnolence, described in the first weeks of treatment, contributed to the reduction of insomnia and reduced the need for additional medication for insomnia. Sexual dysfunction was mild and did not lead to discontinuation of escitalopram therapy. Nausea, although persistent, also did not lead to interruption of the treatment. The persistence of nausea contrasts with a report by Wade et al.,[20] who described reduced frequency and intensity of nausea after the second week of treatment.

Some bipolar patients show considerable improvement with antidepressants, and some of them benefit from long-term antidepressant therapy. A 1-year follow-up study[23] demonstrated that the risk of relapse is highly associated with the discontinuation of antidepressants soon after remission, suggesting that long-term combination

therapy with antidepressants and mood stabilizers might be necessary in some patients with bipolar disorder. However, this was a preliminary study with possible recruitment bias, as the patients enrolled were only those who benefited or tolerated the antidepressant and did not switch to mania during the acute treatment phase.

We observed possible mania induction in only 1 patient (5%) and possible hypomania induction in 2 others (10%). The true incidence of switching from a depressive to a manic mood state with the addition of antidepressant therapy is not known. Neither do we know what factors predispose a given patient to switch mood states. Patients who easily develop manic symptoms probably should never, or hardly ever, be treated with antidepressants, even in association with mood stabilizers. Nemeroff et al.[24] suggested that antidepressants should only be prescribed in combination with mood stabilizers for patients that cannot tolerate high serum lithium levels. Young et al.[25] showed that paroxetine is as effective as a dual mood stabilizer combination, with the advantage of provoking fewer side effects. Another study, comparing antidepressant treatment in unipolar and bipolar depression, demonstrated that nonresponse rate, mania switching, and cycle acceleration were more frequent in bipolar patients, independent of the antidepressant type or addition of a mood stabilizer.[26] In the face of such contrasting findings, long-term controlled studies are needed to address the real risk of mania induction in different clinical categories of bipolar patients.

In bipolar depression trials, switch rates with fluoxetine range from 0% to 19%[27–29]; with paroxetine, from 0% to 5%[24,25,30,31]; with bupropion, from 0% to 54%[32–34]; with olanzapine and olanzapine-fluoxetine combination, from 0% to 6%[35,36]; with lamotrigine, 5.4%[37]; and with quetiapine, 3.2%.[38] The response and remission rates observed in our trial of escitalopram were similar to those described in the above studies of antidepressants, lamotrigine, olanzapine, or quetiapine.

The limitations of this study are those associated with any small nonrandomized and uncontrolled trial. It is impossible to conclusively ascribe the improvement observed to the escitalopram therapy as opposed to placebo effect, the cyclical nature of the disorder, or other nonspecific factors that cannot be controlled in such a study. Therefore, no treatment recommendations can be made based on the present results. However, if future randomized controlled trials confirm the efficacy and safety of adjunctive escitalopram therapy tentatively reported here, then it may hold the potential to materially improve the treatment of bipolar depression.

In conclusion, the high response and remission rates, as well as the good tolerability and safety demonstrated in this open trial, suggest that the use of escitalopram as adjunctive therapy to mood stabilizers in patients with moderate-to-severe bipolar depression types I and II may be a useful strategy. Double-blind randomized controlled trials of escitalopram in bipolar depression are warranted.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Equetro, and others), chlorpromazine (Thorazine, Sonazine, and others), clonazepam (Klonopin), escitalopram (Lexapro), fluoxetine (Prozac and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine/fluoxetine (Symbyax), oxcarbazepine (Trileptal), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), valproic acid (Depakene and others), ziprasidone (Geodon).

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