Citalopram as Adjunctive Therapy in Bipolar Depression

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Background: The treatment of bipolar depression remains a major clinical challenge. The effectiveness and safety of adjunctive citalopram were evaluated in DSM-IV–diagnosed bipolar depressed patients in a 5-site study.

Method: The treatment strategy consisted of an open-label add-on design in which patients received 8 weeks of acute treatment with citalopram adjunctive to their ongoing treatment with mood stabilizers. Ongoing treatment with 1 antipsychotic, 1 anxiolytic, and 1 hypnotic agent was permitted. Responders to the 8-week trial then received 16 weeks of additional treatment with citalopram.

Results: Forty-five subjects entered the trial; 12 dropped out before the end of the acute treatment phase. Of the 33 patients who completed the acute treatment phase, 64% (N = 21) were responders and 36% (N = 12) were nonresponders. In the continuation phase of the study, 14 patients achieved sustained remission, 3 patients did not achieve remission before completing 16 weeks of continuation treatment, 2 patients experienced a relapse, and 2 patients dropped out of the study and did not have a chance to remit. In spite of the extensive concomitant medication usage allowed in this study, citalopram treatment was well tolerated and the level of reported adverse events (including headache, nausea, diarrhea, and sexual dysfunction) relatively low.

Conclusion: The high response rate, the high rate of sustained remission, and the low rate of adverse events strongly support the use of citalopram as a treatment for bipolar I or II depression. These findings should stimulate a controlled double-blind trial to demonstrate even more clearly the usefulness of this drug in the therapeutic regimen for bipolar disorder.

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Bipolar disorder is a chronic, complex, and episodic illness that affects approximately 1.0% to 1.5% of the U.S. population.[1] For patients with bipolar disorder, the goal of treatment is to induce and sustain remission from recurrent episodes of mania and depression. While pharmacotherapy with mood stabilizers is well established as the treatment of choice for acute mania and prophylaxis for future episodes of mania, the treatment of the acute bipolar depressive state as well as treatment to prevent future episodes of depression remains a considerable challenge.[2] Current guidelines for initiating antidepressant therapy in bipolar states are not very clear, nor is it resolved how long to treat with an antidepressant compound during the continuation and recovery phases of bipolar depression.[3] This is in contrast to the knowledge base and availability of specific guidelines for the duration of treatment with antidepressants in unipolar disorder. A paucity of controlled treatment trials has made recommendations for the management of bipolar depression more difficult. Another problem is the potential for antidepressants to trigger a switch into mania.[4–6] As the majority of bipolar patients are treated with multiple medications, the incremental side effect burden and potential for drug-drug interactions are also of concern when adding an antidepressant to the treatment regimen.

Citalopram hydrobromide is a highly selective serotonin reuptake inhibitor (SSRI) that has been shown to be safe, effective, and well tolerated in the treatment of

unipolar depression, with a low potential for causing drug-drug interactions. Like other SSRIs, citalopram is thought to be less likely than heterocyclic antidepressants to cause manic switch. This is based on a number of studies suggesting that heterocyclic antidepressants are more frequently associated with manic switches.[7,8] The purpose of this study was to assess the effectiveness and safety of citalopram as add-on therapy in the acute treatment of bipolar I and II patients with depression or depressive symptoms despite at least 4 weeks of treatment with a mood stabilizer. A second purpose of this study was to assess the likelihood that individuals who have responded acutely will go on to achieve sustained remission over a 16-week continuation phase.

METHOD

Patients

Subjects for the study were recruited at 5 academic medical centers in the United States and included male or female inpatients or outpatients between the ages of 18 and 70 years. Patients were required to meet DSM-IV diagnostic criteria for bipolar I or II depression (with a 17-item Hamilton Rating Scale for Depression [HAM-D][9] score ≥ 15) or DSM-IV criteria for bipolar I or II subsyndromal depression (with a 17-item HAM-D ≥ 10) despite at least 4 weeks of treatment with an adequate dose of a mood stabilizer. A score of ≤ 12 on the Young Mania Rating Scale (YMRS)[10] and ≤ 70 on the Global Assessment of Functioning scale (GAF)[11] also were required at baseline. Exclusion criteria included a DSM-IV diagnosis of mania, rapid-cycling, mixed, or currently psychotic forms of bipolar disorder, schizophrenia and other psychotic disorders, dissociative disorders or any other psychiatric diagnoses on Axis I that do not match the inclusion criteria diagnoses; a history of alcohol or substance abuse within the 3 months prior to the study; suicidal behavior or a history of suicide attempt within the previous 3 months; or an unstable or untreated medical disorder. Women who were pregnant, breastfeeding, or of childbearing potential (unless practicing a medically accepted form of birth control) also were excluded from the study. All patients provided written, informed consent to participate.

Treatment

Eligible patients were entered into an 8-week, open-label acute treatment trial of citalopram as add-on therapy to ongoing treatment with either lithium (plasma level of 0.6–1.5 mEq/L), divalproex sodium (50–120 μg/mL), carbamazepine (4–12 μg/mL), or the combination of lithium and divalproex sodium or lithium and carbamazepine. The use of any antidepressant was discontinued at least 1 week before beginning treatment with citalopram. Continued treatment with 1 antipsychotic, 1 anxiolytic, and 1 hypnotic was permitted throughout the trial at the same dose and schedule the patient had been receiving at baseline, unless side effects considered to be secondary to polypharmacy emerged, in which case dosages could be adjusted. Citalopram treatment was initiated at 20 mg taken once daily and, depending on response, could be increased in 20-mg increments every 2 weeks to a maximum of 60 mg/day. The citalopram dosage could be reduced at any time if adverse events emerged; however, patients unable to tolerate at least 10 mg/day were withdrawn from the study. Responders to citalopram during the 8-week acute treatment phase were eligible for 16 weeks of continuation treatment. During the continuation phase, citalopram doses could be adjusted within the range of 10 to 60 mg/day as clinically indicated.

Assessments

Assessments were performed at baseline and at weeks 1, 2, 3, 4, 6, and 8 of the acute treatment phase. Patients eligible for continuation treatment were assessed at 4-week intervals for 16 weeks. The primary measure of efficacy was the 17-item HAM-D.[9] Secondary measures included an expanded 25-item HAM-D that included the 8-item Pittsburgh Reversed Vegetative Symptom Scale[12] that measures features of anergic depression, the Clinical Global Impressions (CGI) Severity and Improvement scores,[13] the YMRS,[10] and the GAF.[11] Treatment response was defined prospectively as a ≥ 50% reduction in the 17-item HAM-D total score by week 8, in the absence of mania, hypomania, or mixed state. Remission from depression was defined as HAM-D total score ≤ 7 and CGI-Improvement score ≤ 2 after week 8, in the absence of mania, hypomania, or mixed state. Among patients meeting criteria for response or remission, relapse was defined using DSM-IV criteria for major depressive episode (17-item HAM-D ≥ 15 and CGI-Severity ≥ 4) or minor depressive episode (17-item HAM-D ≥ 10 and CGI-Severity ≥ 3). Raters across the 5 sites had to achieve a reliability kappa of at least .70 on the HAM-D and the YMRS.

Safety and tolerability were assessed by adverse event monitoring (using the Adverse Event Record), physical examination, vital signs, laboratory assessments, and electrocardiogram. Plasma levels for mood stabilizers were determined at screen and weeks 1, 8, and end of study. Concomitant medications were monitored at all visits.

Statistical Analyses

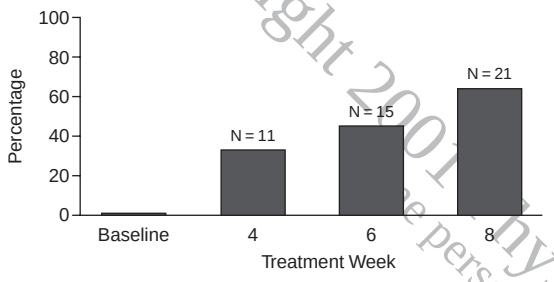
The primary analysis was to calculate the percentage of patients at 4 and 8 weeks of citalopram treatment who met response criteria. Of the subjects who responded, the proportions of patients who achieved a full remission and those who relapsed were also calculated. Secondary analyses were performed to identify factors that could influence response. Factors that were examined were demographics such as age and gender and illness descriptors such as age at onset, duration of episode, number of previ-

Table 1. Baseline Characteristics of 45 Patients With Bipolar Depression[a]

Characteristic	Value
Age, y, mean ± SD (median)	42.2 ± 11.5 (43)
Gender, % male	66.7
Bipolar I, %	66.7
Major depression, %	68.9
HAM-D, 17-item, mean ± SD (median)	16.8 ± 4.3 (16)
CGI-Severity, mean ± SD	3.9 ± 0.6
GAF, mean ± SD	56.7 ± 5.1
YMRS, mean ± SD	3.0 ± 3.2

[a]Abbreviations: CGI = Clinical Global Impressions scale, GAF = Global Assessment of Functioning scale, HAM-D = Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.

Figure 1. Cumulative Response to Citalopram Among 33 Patients Completing 8 Weeks of Treatment



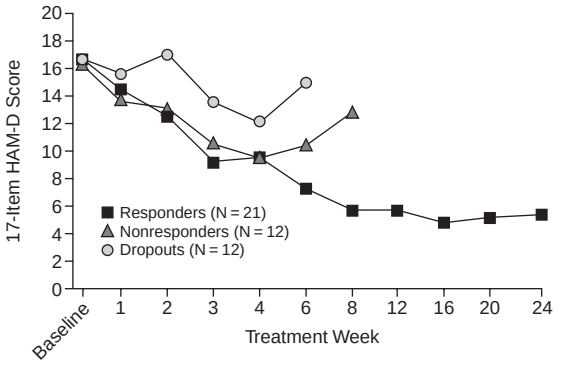
ous episodes, and baseline severity as measured by the 17-item HAM-D. Group t tests between responders and nonresponders or chi-square tests for contingency tables were used to perform the secondary analyses.

RESULTS

Patient Characteristics

Forty-five patients with a median age of 43 years (mean ± SD = 42.2 ± 11.5 years) (Table 1) entered the protocol. Thirty of the patients were male. Two thirds of the group had a diagnosis of bipolar I and the other third was bipolar II. Sixty-nine percent were experiencing a major depressive episode, and the rest were suffering from a minor depressive episode. The group was relatively ill at baseline, with a mean ± SD HAM-D score of 16.8 ± 4.3 (median = 16.0), CGI-Severity score of 3.9 ± 0.6, GAF score of 56.7 ± 5.1, and YMRS score of 3.0 ± 3.2 (Table 1). Baseline HAM-D scores were 18.7 ± 3.8 (median = 18.0) for the 31 patients with a major depressive episode and 12.6 ± 1.9 (median = 12.0) for those with subsyndromal depression. Of the 45 patients who enrolled in the study, 23 were taking lithium, 18 were receiving valproate, 4 were taking carbamazepine, and the remaining 3 were being treated with both lithium and valproate. Additionally, 11 of the 45 patients were taking an antipsychotic compound and 20 of the patients were taking either an anxiolytic or hypnotic compound.

Figure 2. Mean 17-Item Hamilton Rating Scale for Depression (HAM-D) Scores Among 45 Bipolar Patients During Acute and Continuation Treatment With Add-On Citalopram



Efficacy

The starting dose of citalopram for all patients was 20 mg once daily; the mean dose for all subjects was 34.7 ± 16.5 mg with a range of 20 to 80 mg and a median dose of 30 mg. A total of 33 patients (73%) completed the 8-week acute treatment phase. Twelve patients did not complete the acute treatment phase: 5 patients were dropped for noncompliance, 2 patients were dropped because they required treatment for mania or hypomania, 2 patients were hospitalized for severe depressive symptomatology, and 3 patients were dropped after a Coordinating Center review determined that they did not meet entry criteria. The Cohen d effect size for the completers (N = 33) was large at 1.73 for the 17-item HAM-D and 1.69 for the 25-item HAM-D. Of those patients completing 8 weeks of citalopram treatment, 21 (64%) were considered responders and were eligible for 16 weeks of continuation treatment. Among eventual responders, 11 of 21 had responded by week 4 and 15 of 21 had responded by week 6 (Figure 1). Responders during the 8-week acute treatment phase showed sustained response or continued improvement over time on the 17-item HAM-D (Figure 2), the 25-item HAM-D (Figure 3), the CGI-Severity of Illness (Figure 4), and the GAF (Figure 5). There was no difference in outcome between bipolar I and bipolar II ($\chi^2 = 3.00$, df = 2, p = .22) or between patients divided into full major depressive episode and subsyndromal depression ($\chi^2 = 1.84$, df = 2, p = .40); this was true of the treatment completers as well ($\chi^2 = 0.89$, df = 1, p = .35 and $\chi^2 = 1.07$, df = 1, p = .30). With respect to dividing patients into either the bipolar I versus II subgroups or the full MDD versus subsyndromal depression subgroups, neither division showed any different intent-to-treat or completer response rate.

We also examined whether baseline mood-stabilizing medication contributed to treatment outcome. With respect to the administration of either lithium carbonate or valpro-

Figure 3. Mean 25-Item Hamilton Rating Scale for Depression (HAM-D) Scores Among 45 Bipolar Patients During Acute and Continuation Treatment With Add-On Citalopram

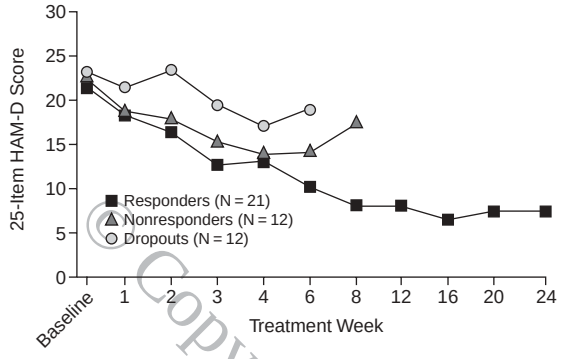


Figure 4. Mean Clinical Global Impressions (CGI) Severity Scores Among 45 Bipolar Patients During Acute and Continuation Treatment With Add-On Citalopram

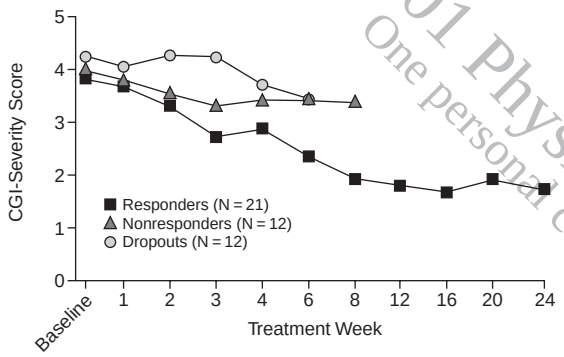


Figure 5. Mean Global Assessment of Functioning (GAF) Scores Among 45 Bipolar Patients During Acute and Continuation Treatment With Add-On Citalopram

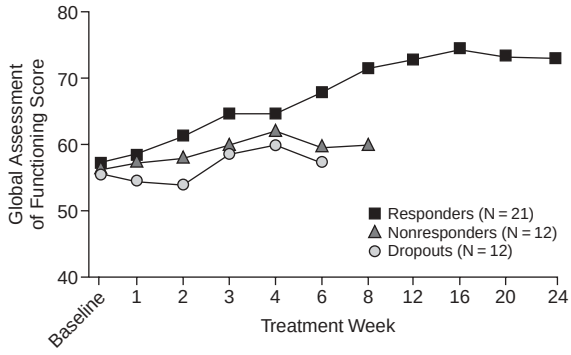


Table 2. Common Adverse Events[a] Among 45 Bipolar Patients Treated With Add-On Citalopram

Adverse Event	Mild	Moderate	Severe
Central nervous system			
Headache	11	5	…
Somnolence	3	3	1
Tremor	6	…	
Weakness/fatigue	2	2	…
Dizziness	4	…	…
Gastrointestinal			
Nausea	9	11	…
Diarrhea	6	4	…
Sexual dysfunction[b]	1	3	1

[a]Includes adverse events reported by at least 4 patients.
[b]Includes decreased libido, impotence, and ejaculatory dysfunction.

ate, there was no significant impact on immediate treatment outcome or continuation phase outcome. Other variables such as gender (47% of both men and women responded), illness severity, age at onset ($\chi^2 = .1.48$, df = 2, p = .48), duration of current episode ($\chi^2 = .1.71$, df = 2, p = .42), and number of previous episodes ($\chi^2 = .2.37$, df = 2, p = .31) were examined and found not to relate significantly to treatment outcome. When the 8-item HAM-D supplement on anergia was examined with regard to treatment outcome, responders had a significantly lower score than the nonresponders and dropouts combined ($t = 2.0$, df = 43, $p < .05$). During the continuation phase, 14 (67%) of 21 patients achieved sustained remission, while 2 patients relapsed, 3 failed to remit, and 2 discontinued treatment before remission was achieved.

Safety

Most patients (82%, N = 37) reported at least 1 adverse event during treatment; however, the vast majority of these events were described as mild to moderate in nature. The most frequently occurring adverse events included headache, gastrointestinal disturbances, drowsiness, and sexual dysfunction (Table 2). None of the patients who discontinued treatment prematurely did so because of adverse events, although 1 patient was in a manic episode at the time of discontinuation.

DISCUSSION

Even though the acute treatment of mania and the prevention of recurrences of mania have received considerable attention in recent years, this is not the case with respect to the acute treatment of bipolar depression.[14] A number of studies,[15,16] including a recent extensive bipolar registry report,[17] show that bipolar patients spend a great deal of their time with either mild or moderate depression. Indeed, bipolar depression is a major public health issue for researchers and clinicians to solve together. Unfortunately, despite consensus that response is a major objective in the clinical management of this complex disorder, several recent reviews indicate that the efficacy data on all drug classes used to treat bipolar depression demonstrate low rates of response.[2] There is some controversy as to

whether antidepressants work equally as well in unipolar depression as in bipolar depression (reference 18 and E. Frank, Ph.D., oral communication, June 2000). Part of this controversy is sparked by the debate as to whether unipolar depression and bipolar depression are significantly different from each other. However, features of bipolar depression, such as longer episode duration, increased likelihood of psychotic symptoms, and limited efficacy of antidepressant agents, point to a qualitative set of differences.[4–6]

There appear to be 3 major questions concerning the use of antidepressants in the treatment of bipolar depression. First and foremost is whether any class of drugs is better than any of the others and, within those classes, whether any drugs have a high degree of efficacy. Most reviews point to the current avoidance of tricyclics in the treatment of bipolar depression, which is based more on lack of efficacy than ease of use or side effect profile.[19] The recommendation for monoamine oxidase inhibitors (MAOIs) in the treatment of bipolar disorder remains a consistent one. The only disagreement is whether an MAOI is a first-line treatment or to be used only if previous treatment approaches have failed. The results of studies using SSRIs are more varied, with some studies showing a high degree of efficacy as compared to placebo.[2] Studies with mood stabilizers and some of the new anticonvulsants provide suggestive evidence but are not convincing to help us with definitive treatment approaches at this point in time.

The second question is whether a lack of efficacy coupled with a failure to achieve complete recovery underlies a risk for an immediate cycle switch and an inability to achieve sustained remission. Explanations could lie with our lack of understanding of the duration of treatment in the acute phase, with dosage issues, with the presence of a mood stabilizer, or differences in the underlying pathophysiology of bipolar depression versus unipolar depression. The implication is that treatment trials need to be longer in bipolar depression and that the methodology traditionally utilized for unipolar depression, such as 4- to 6-week treatment trials, may be inappropriate. Furthermore, since there is currently no true comparator drug available with proven efficacy for bipolar depression, it is difficult not to justify placebo-controlled trials.

A third question is when to discontinue an antidepressant if the patient has responded successfully and is currently in a euthymic state. The traditional strategy in bipolar disorder has been to discontinue the antidepressant as soon as possible and not even provide 4 months of continuation treatment so that manic switches can be avoided. However, this "common wisdom" has never been tested empirically. We do not have good evidence to point specifically to a time period for antidepressant treatment with mood stabilizers. The fact that most bipolar patients are experiencing continuous mild-to-moderate depression points to the need to conduct clinical trials with antidepressants for at least 6 to 12 months' duration after remission.

In reviewing the data in this study, we have concluded that citalopram, as add-on therapy to mood-stabilizing medication, was effective in a substantial proportion of patients with bipolar I or II depression. Patients who responded to citalopram during 8 weeks of acute treatment were likely to achieve sustained remission over 16 weeks of continuation treatment. Citalopram was generally well tolerated, with a relatively low incidence of adverse events, despite the extensive use of concomitant medications in this study. Results from this open-label study support the usefulness of citalopram as add-on therapy for the treatment of bipolar I or II depression. On the basis of these results, investigators can plan larger scale, controlled, double-blind studies, which now appear warranted.

Drug names: carbamazepine (Tegretol and others), citalopram (Celexa).

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