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Effectiveness of Adjunctive Antidepressant Treatment for Bipolar Depression

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ABSTRACT

BACKGROUND

Episodes of depression are the most frequent cause of disability among patients with bipolar disorder. The effectiveness and safety of standard antidepressant agents for depressive episodes associated with bipolar disorder (bipolar depression) have not been well studied. Our study was designed to determine whether adjunctive antidepressant therapy reduces symptoms of bipolar depression without increasing the risk of mania.

METHODS

In this double-blind, placebo-controlled study, we randomly assigned subjects with bipolar depression to receive up to 26 weeks of treatment with a mood stabilizer plus adjunctive antidepressant therapy or a mood stabilizer plus a matching placebo, under conditions generalizable to routine clinical care. A standardized clinical monitoring form adapted from the mood-disorder modules of the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, was used at all follow-up visits. The primary outcome was the percentage of subjects in each treatment group meeting the criterion for a durable recovery (8 consecutive weeks of euthymia). Secondary effectiveness outcomes and rates of treatment-emergent affective switch (a switch to mania or hypomania early in the course of treatment) were also examined.

RESULTS

Forty-two of the 179 subjects (23.5%) receiving a mood stabilizer plus adjunctive antidepressant therapy had a durable recovery, as did 51 of the 187 subjects (27.3%) receiving a mood stabilizer plus a matching placebo ($P=0.40$). Modest nonsignificant trends favoring the group receiving a mood stabilizer plus placebo were observed across the secondary outcomes. Rates of treatment-emergent affective switch were similar in the two groups.

CONCLUSIONS

The use of adjunctive, standard antidepressant medication, as compared with the use of mood stabilizers, was not associated with increased efficacy or with increased risk of treatment-emergent affective switch. Longer-term outcome studies are needed to fully assess the benefits and risks of antidepressant therapy for bipolar disorder. (ClinicalTrials.gov number, NCT00012558.)

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BIPOLEAR DISORDER, THE SIXTH-LEADING cause of disability worldwide,¹ is a chronic and recurrent psychiatric illness with a lifetime prevalence of just under 4%² and annual costs that exceed those of diabetes or recurrent (unipolar) major depressive disorder.³ Although abnormal mood elevation is the cardinal diagnostic feature that distinguishes bipolar disorder from recurrent major depressive disorder, depression that alternates with manic episodes (bipolar depression) is the leading cause of impairment and death among patients with bipolar disorders.⁴⁻⁶

Two main limitations related to standard antidepressant medications hamper their use in the treatment of bipolar depression. First, though these agents have proved to be efficacious in treating unipolar depression, the data providing support for their use in treating bipolar depression are minimal and are not considered to be sufficient to guide clinical practice. Second, the widely held belief that antidepressants can induce new episodes of abnormal mood elevation or accelerate the rate of cycling has been neither confirmed nor refuted by placebo-controlled studies.

Adequately powered, well-controlled studies are needed to show the effectiveness of treatments for bipolar depression under conditions of routine clinical practice. Pivotal studies sponsored by pharmaceutical companies are designed primarily to demonstrate efficacy for purposes of regulatory approval. These studies typically involve narrow eligibility requirements and short-term cross-sectional outcomes, which limit the generalizability of the results to routine clinical practice.

The Food and Drug Administration (FDA) has not approved any of the more than 25 standard antidepressants for the treatment of bipolar depression. However, standard antidepressants are commonly used as adjuncts to mood-stabilizing medication for the treatment of bipolar depression, despite limited evidence of the short-term and long-term efficacies and the putative risk of treatment-emergent mania or hypomania.⁷⁻¹⁰ Furthermore, in a placebo-controlled study in which subjects using therapeutic doses of the mood stabilizer lithium were randomly assigned to receive concurrent treatment with a standard antidepressant (paroxetine or imipramine) or placebo, those receiving lithium plus an antidepressant did not have a significant advantage over those receiving lithium plus placebo.¹¹ Indeed, the only large positive trial of standard antidepressant treatment for bipolar depression published to date involved com-

ination treatment with an atypical antipsychotic drug, rather than a traditional (non-dopamine blocking) mood stabilizer.¹² In that study, the combination of olanzapine and fluoxetine was superior to placebo as well as to olanzapine alone. However, the study did not address the effectiveness of standard antidepressants used in conjunction with lithium or valproate; thus, its results may not be generalizable to the treatment of patients with bipolar depression who typically seek treatment.

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is a collaboration sponsored by the National Institute of Mental Health designed to evaluate the effectiveness of treatments for bipolar disorder and to provide results that are generalizable to routine clinical practice.¹³ STEP-BD recruited a representative group of patients with bipolar disorder who were seeking treatment and used clinically meaningful outcomes. We report results from a controlled trial within STEP-BD evaluating the effectiveness of standard antidepressants for the short-term treatment of major depressive episodes in patients with bipolar disorder.

METHODS

The STEP-BD collaborators conducted this multicenter, double-blind, randomized, placebo-controlled, parallel-group study of standard antidepressants (either bupropion or paroxetine) as adjuncts to treatment with mood stabilizers (lithium, valproate, carbamazepine, or other FDA-approved antimanic agents) at 22 centers in the United States between November 1999 and July 2005. Subjects with bipolar I or bipolar II disorder were treated for up to 26 weeks to evaluate the effectiveness, safety, and tolerability of the adjunctive use of antidepressant medication. The study was approved by the institutional review board at each site and was overseen by a data and safety monitoring board.

The rationale for the design and methods of the STEP-BD trials has been described previously.¹³ The STEP-BD protocol was critiqued by a committee of external experts and consumer advocates and was posted for public review.

SELECTION OF SUBJECTS

Study subjects were at least 18 years old and met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), for a ma-

major depressive episode associated with bipolar I or bipolar II disorder. The diagnosis of bipolar disorder was confirmed at entry into STEP-BD by using an affective disorder evaluation form adapted from the Structured Clinical Interview for DSM-IV¹⁴ and by the independent administration of the Mini-International Neuropsychiatric Interview.¹⁵ We excluded subjects with a history of intolerance or nonresponse to both bupropion and paroxetine, as well as those requiring current short-term treatment for a coexisting substance-abuse disorder or requiring the addition of antipsychotic medication or a change in the dose of a long-term antipsychotic medication. Subjects enrolled in STEP-BD provided additional written informed consent for our study. At the time of randomization, all subjects agreed to receive a concomitant mood stabilizer.

INTERVENTIONS

Subjects were assigned to double-blind treatment with a mood stabilizer plus an adjunctive antidepressant or a mood stabilizer plus a matching placebo with the use of an equipoise-stratified randomization method.¹⁶ This method enabled treating psychiatrists to choose from three randomization strata (placebo vs. bupropion, placebo vs. paroxetine, and placebo vs. either antidepressant) and thus allowed for the inclusion of subjects with a clear preference for a given antidepressant. STEP-BD clinicians, trained and certified in the use of a clinical monitoring form and other study scales, selected the mood stabilizers and managed all medications.¹²

Paroxetine and bupropion were selected to represent the standard antidepressants most commonly prescribed for bipolar depression, since these agents have different mechanisms of action and adverse-effect profiles.^{9,11,16,17} Use of these antidepressants is associated with low rates of switch to mania or hypomania early in the course of treatment (treatment-emergent affective switch). Mood stabilizers were initially limited to lithium, valproate, the combination of lithium and valproate, or carbamazepine. In 2004, the protocol was amended to define mood stabilizers operationally as any FDA-approved antimanic agent.

Mood-stabilizing medications were adjusted clinically to target the therapeutic range for each drug. Standard antidepressant medications in use at randomization were tapered by at least 50% during the first week after randomization and were not permitted after the second week. All other

clinically indicated medications were permitted. Subjects also had the option of remaining with their nonstudy psychotherapist, of having no psychosocial intervention, or of being enrolled into a STEP-BD trial comparing long-term (intensive) psychosocial interventions with a short-term (brief) psychoeducational intervention.¹⁸

Paroxetine or matching placebo was initiated at 10 mg daily and increased to a maximum of 40 mg daily. A sustained-release preparation of bupropion or matching placebo was initiated at 150 mg daily and increased to a maximum of 375 mg daily. Four follow-up assessments were scheduled over the first 6 weeks. Subjects who had severe adverse effects or met criteria for hypomania or mania discontinued the antidepressant or placebo and received open treatment while remaining in STEP-BD. After 6 weeks, subjects who had a response continued the double-blind treatment with monthly follow-up for up to 20 more weeks; those who did not were offered further increases in the dose of the antidepressant or placebo or open-label increase in the dose, with follow-up scheduled at 2-week intervals over the next 10 weeks.

EFFECTIVENESS OUTCOMES

At study entry, subjects were assessed with the use of the Clinical Monitoring Form for mood disorders¹⁹ and formal mood-rating scales. The Clinical Monitoring Form is a composite assessment tool developed for use in clinical practice; it includes a version of the current mood modules of the Structured Clinical Interview for DSM-IV, modified to include continuous symptom subscales for depression (SUM-D) and mood elevation (SUM-ME), in addition to questions about categorical outcomes. SUM-D scores range from 0 to 22 and SUM-ME scores range from 0 to 16; higher scores indicate more severe symptoms. The SUM-D and SUM-ME subscales are well correlated with formal rating scales: the Montgomery-Asberg Depression Rating Scale and the Young Mania Rating Scale, respectively.¹⁹ The formal rating scales were administered by independent raters at study entry and also quarterly, for quality control. The Clinical Monitoring Form was administered at every follow-up visit.

The a priori primary outcome was durable recovery, defined as euthymia for at least 8 consecutive weeks. Subjects were also classified on the basis of secondary outcomes, defined in Table 1. Treatment-effectiveness response rates were based on subjects whose SUM-D scores improved by at

Table 1. Effectiveness Outcomes.

Outcome	Definition	Time Frame	Comment
Durable recovery (primary outcome)	At least 8 consecutive weeks of euthymia (no more than two depressive or two manic symptoms)	Onset by 16 wk	Consistent with the DSM-IV definition of recovery
Transient remission	1–7 Consecutive weeks of euthymia	Onset by 16 wk	DSM-IV criteria for hypomania and mania not met
Treatment-emergent affective switch	DSM-IV criteria for hypomania or mania met or intervention by treating clinician for clinically significant treatment-emergent mood elevation	By 16 wk or before reaching criteria for durable recovery (up to 26 wk)	—
No response	16 Wk reached without at least 1 wk of euthymia	16 wk	Receiving treatment without clinically significant improvement
Subject withdrawn owing to adverse effects without meeting criteria for first four outcomes	—	Any	—
Other reasons for early termination	Treatment discontinued owing to noncompliance, loss to follow-up, or administrative or other reasons	Any	—
Treatment-effectiveness response	50% Improvement from baseline SUM-D score* without meeting DSM-IV criteria for hypomania or mania	By 16 wk	Response rates modified as suggested in the effectiveness literature to more accurately capture beneficial response; used to facilitate comparison with data from Stanley Foundation Bipolar Network studies
Traditional efficacy equivalent	Durable recovery, transient remission, and treatment-emergent affective switch	Any	Used for comparison with data in the efficacy literature

* Scores range from 0 to 22; higher scores indicate more severe symptoms.

least 50% from their baseline scores and who did not meet the DSM-IV criteria for hypomania or mania.

STATISTICAL ANALYSIS

Summary statistics for continuous variables are presented as means with standard deviations or medians with interquartile ranges. Summary statistics for discrete variables are presented as percentages. Parametric and nonparametric analysis-of-variance methods and chi-square tests were used to compare the rates of baseline clinical and demographic characteristics, characteristics of the clinical course, side effects, and serious adverse events between the two groups.

Analyses included all subjects who were randomly assigned to a treatment group. Except where noted, analyses are based on the last observation carried forward. Logistic-regression models were used to determine whether there was an independent effect of treatment on outcome rates after

adjustment for site and antidepressant preference (none, for paroxetine, or for bupropion). Given the observed rate of recovery of 27.3% among subjects receiving a mood stabilizer plus a matching placebo, the study had a statistical power of 80% to detect an absolute difference of 15% between the two groups in rates of recovery. A P value of 0.05 was considered to indicate statistical significance.

RESULTS

CHARACTERISTICS AND DISPOSITION OF SUBJECTS

Figure 1 shows the disposition of study subjects. There were no significant differences in the demographic or clinical characteristics of the two treatment groups at baseline (Table 2). Data on the course of treatment are listed in Table 3. There was no significant difference between the two groups in the mean time in treatment.

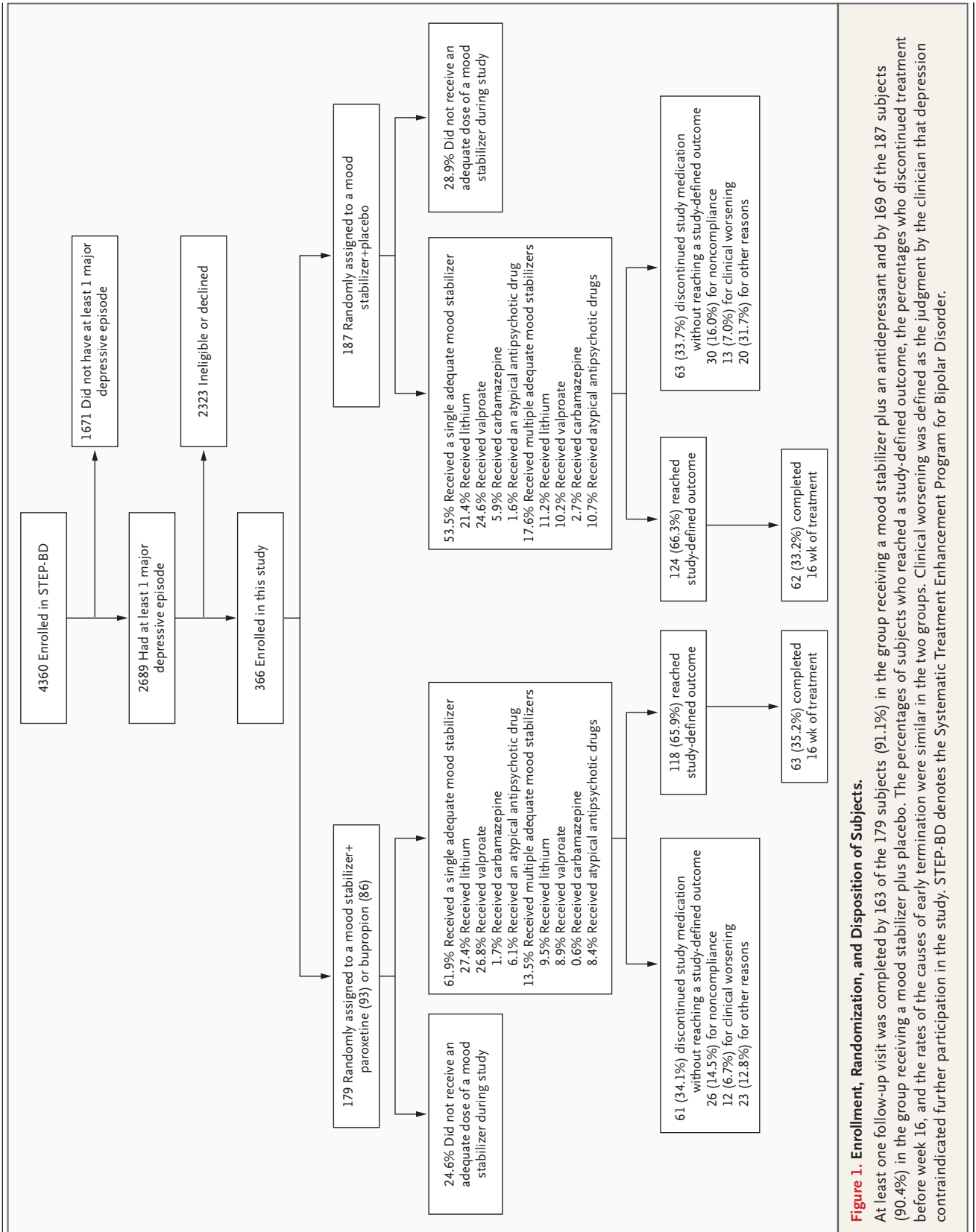


Figure 1. Enrollment, Randomization, and Disposition of Subjects.

At least one follow-up visit was completed by 163 of the 179 subjects (91.1%) in the group receiving a mood stabilizer plus an antidepressant and by 169 of the 187 subjects (90.4%) in the group receiving a mood stabilizer plus placebo. The percentages of subjects who reached a study-defined outcome, the percentages who discontinued treatment before week 16, and the rates of early termination were similar in the two groups. Clinical worsening was defined as the judgment by the clinician that depression contraindicated further participation in the study. STEP-BD denotes the Systematic Treatment Enhancement Program for Bipolar Disorder.

Table 2. Baseline Characteristics of Subjects, According to Treatment Group.*

Characteristic	Mood Stabilizer + Antidepressant (N=179)	Mood Stabilizer + Placebo (N=187)	P Value
Site — no. (%)			0.97
Massachusetts General Hospital	40 (22.3)	40 (21.4)	
Baylor College	18 (10.1)	19 (10.2)	
Case Western Reserve University	31 (17.3)	32 (17.1)	
University of Oklahoma	13 (7.3)	16 (8.6)	
University of Pittsburgh	17 (9.5)	20 (10.7)	
University of Pennsylvania	14 (7.8)	10 (5.3)	
Other	46 (25.7)	50 (26.7)	
Male sex — no./total no. (%)	75/177 (42.4)	82/187 (43.9)	0.78
Age at study entry			0.87
No. with data	177	185	
Yr	40.0±11.4	40.0±11.9	
Age at onset of bipolar symptoms			0.91
No. with data	172	179	
Yr	15.7±7.4	16.0±7.8	
White race — no./total no. (%)†	163/179 (91.1)	168/187 (89.8)	0.69
Education level — no./total no. (%)			0.52
Some high school or high-school graduate	38/172 (22.1)	34/176 (19.3)	
Some education after high school	55/172 (32.0)	58/176 (33.0)	
Associate, technical, college, or postgraduate degree	79/172 (45.9)	84/176 (47.7)	
Annual income — no./total no. (%)			0.51
<\$30,000	67/159 (42.1)	79/163 (48.5)	
\$30,000–\$74,999	59/159 (37.1)	55/163 (33.7)	
≥\$75,000	33/159 (20.8)	29/163 (17.8)	
Marital status — no./total no. (%)			
Married	61/174 (35.1)	54/176 (30.7)	
Never married	61/174 (35.1)	68/176 (38.6)	
Divorced, widowed, or separated	52/174 (29.9)	54/176 (30.7)	
Bipolar-disorder subtype — no./total no. (%)			0.92
I	118/172 (68.6)	122/182 (67.0)	
II	54/172 (31.4)	60/182 (33.0)	
Anxiety disorder — no./total no. (%)			
Current	58/133 (43.6)	66/136 (48.5)	0.42
Lifetime	86/133 (64.7)	86/136 (63.2)	0.81

TREATMENT OUTCOMES

Treatment outcomes are defined in Table 1 and summarized in Table 4. There were no significant differences between the two groups in the percentage of subjects meeting the criteria for any effectiveness outcome. However, modest nonsignificant trends consistently favored treatment with a mood stabilizer plus a matching placebo over treatment

with a mood stabilizer plus an adjunctive antidepressant. Similar percentages of subjects in each group did not have even a single week of euthymia over the first 16 weeks and were classified as having no response to an adequate course of treatment.

The rates of durable recovery were similar in the two groups among subjects with bipolar I dis-

Table 2. (Continued.)

Characteristic	Mood Stabilizer + Antidepressant (N=179)	Mood Stabilizer + Placebo (N=187)	P Value
Substance abuse — no./total no. (%)			
Current	22/132 (16.7)	21/134 (15.7)	0.83
Lifetime	77/132 (58.3)	82/134 (61.2)	0.63
≥10 Previous manic episodes	108/177 (61.0)	124/185 (67.0)	0.23
≥10 Previous depressive episodes	120/174 (69.0)	125/185 (67.6)	0.95
History of rapid cycling — no./total no. (%)	44/162 (27.2)	53/168 (31.5)	0.38
History of treatment-emergent affective switch — no./total no. (%)	59/153 (38.6)	67/157 (42.7)	0.46
Participant in STEP-BD randomized psychosocial treatment study — no./total no. (%)	112/165 (67.9)	124/178 (69.7)	0.72
Clinical rating scores‡			
SUM-D	6.2±2.9	6.2±3.1	0.79
SUM-ME			0.96
No. with data	158	163	
Score	1.1±1.1	1.1±1.1	
MADRS			0.77
No. with data	145	151	
Score	24.5±10.0	24.0±9.4	
YMRS			0.46
No. with data	146	150	
Score	5.8±4.9	5.8±5.7	
GAF			0.70
No. with data	157	163	
Score	55.95±8.2	55.4±7.8	
CGI severity-of-illness subscale			0.38
No. with data	157	162	
Score	3.9±0.9	3.8±0.8	
Days in STEP-BD study before randomization	197.5±301.6	166.7±263.2	0.28

* Plus–minus values are means ±SD. STEP-BD denotes the Systematic Treatment Enhancement Program for Bipolar Disorder.

† Race was self-reported.

‡ The SUM-D and SUM-ME are the continuous symptom subscales for depression and mood elevation (mania), respectively, from the Clinical Monitoring Form; scores range from 0 to 22 and 0 to 16, respectively, with higher scores indicating more severe symptoms. Scores on the Montgomery–Asberg Depression Rating Scale (MADRS) and the Young Mania Rating Scale (YMRS) range from 0 to 60, with higher scores indicating greater severity of symptoms of depression and of mania, respectively. Scores on the Global Assessment of Functioning (GAF) scale range from 1 to 100, with higher scores indicating better functioning. Scores on the Clinical Global Impression Scale of Illness Severity (CGI) range from 1 to 7, with higher scores indicating greater severity of illness.

order. Among subjects with bipolar II disorder, there was a nonsignificant trend toward a better response in the patients receiving a mood stabilizer plus placebo than in those receiving a mood stabilizer plus an antidepressant. In the group receiving a mood stabilizer and an antidepressant, response rates did not differ significantly between subjects with bipolar I disorder (25.4%) and those with bipolar II disorder (20.4%).

Analysis of results that were adjusted for acceptance or rejection of enrollment into the STEP-BD randomized psychosocial treatment study showed no significant differences between the two groups (adjusted $P=0.25$ for the primary outcome). The augmentation of drug therapy with brief or intensive psychotherapy carried no significant benefit. For the subgroup of 130 subjects who rejected random assignment to a protocol-specified

Table 3. Clinical Course of Study Subjects.*

Characteristic	Mood Stabilizer+ Antidepressant (N=179)	Mood Stabilizer+ Placebo (N=187)	P Value
No. of study visits	7.0±4.4	7.2±4.8	0.84
Maximum dose — mg			
Paroxetine — median (IQR)	30 (20–40)	30 (20–40)	
Bupropion — median (IQR)	300 (150–300)	300 (150–375)	
Dose at exit — mg			
Paroxetine — median (IQR)	30 (20–40)	30 (20–40)	
Bupropion — median (IQR)	300 (150–300)	300 (150–338)	
Days receiving treatment	88.0±63.65	84.4±63.11	0.77
Any mood stabilizer at randomization — no. (%)	156 (87.2)	160 (85.6)	0.73
Adequate mood stabilizer at randomization — no./total no. (%)	135/177 (76.3)	133/184 (72.3)	0.39
Adequate mood stabilizer after randomization — no./total no. (%)	154/177 (87.0)	154/184 (83.7)	0.37
Marked or grossly disabling adverse event — no. of subjects (%)†	17 (9.5)	13 (7.0)	0.37
Tremor	1	2	
Clinically significant elevation of serum aspartate aminotransferase‡	4	5	
Diarrhea	0	1	
Headache	0	1	
Sexual dysfunction	4	2	
Abdominal pain	1	0	
A feeling of being “out of it”	0	1	
Agitation	1	0	
Rash	2	1	
Swelling	1	0	
Abnormal vision	0	1	
Light-headedness	1	0	
Nausea	2	0	
Irritability	0	1	
Insomnia	1	0	
Prone to being argumentative	1	0	
Anxiety	0	1	
Serious adverse events — no. of subjects (%)§	8 (4.5)	10 (5.3)	0.70
Medical hospitalization	8	1	
Medical illness	0	2	
Psychiatric hospitalization			
For depression	0	3	
For suicidal ideation	4	5	
Psychiatric hospitalization not related to depression, mania, mixed symptoms, or suicidal ideation	2	1	
Increased frequency of suicidal ideation without hospitalization	0	1	

* Plus–minus values are means ±SD. Adequate mood stabilizers were as follows, defined according to the dose (or serum level) of the drug: aripiprazole, ≥15 mg per day; carbamazepine, ≥600 mg per day (or ≥4 µg per milliliter); divalproex, ≥750 mg per day (or ≥45 µg per milliliter); lithium, ≥900 mg per day (or ≥0.4 mmol per liter); olanzapine, ≥10 mg per day; quetiapine, ≥300 mg per day; risperidone, ≥1 mg per day; ziprasidone, ≥80 mg per day. IQR denotes interquartile range.

† Adverse events were defined as unwanted effects, rated as mild, moderate (affecting function to some degree but not requiring reduction or discontinuation of dose), marked (substantially impairing the ability to function in social or occupational role or requiring reduction or discontinuation of dose), or grossly disabling (substantially impairing simple activities of daily living). The sum of the adverse events exceeds the number of subjects because some subjects had more than one adverse event. Headache was reported twice by one patient.

‡ Clinically significant elevation of serum aspartate aminotransferase was defined as an elevation to more than twice the upper limit of the normal range or an elevation deemed by the clinician to warrant dose adjustment or discontinuation of medication.

§ Serious adverse events were defined as those that resulted in hospitalization, permanent disability, or death or required an intervention to prevent these outcomes. One patient was admitted to the hospital twice for medical reasons.

Table 4. Outcomes According to Treatment Group.*

Outcome	Mood Stabilizer + Antidepressant (N=179)	Mood Stabilizer + Placebo (N=187)	P Value
	<i>number (percent)</i>		
Transient remission	32 (17.9)	40 (21.4)	0.40
Durable recovery (primary outcome)	42 (23.5)	51 (27.3)	0.40†
Transient remission or durable recovery	74 (41.3)	91 (48.7)	0.23
Treatment-effectiveness response	58 (32.4)	71 (38.0)	0.27
Treatment-emergent affective switch	18 (10.1)	20 (10.7)	0.84
Discontinuation of study medication because of adverse event	22 (12.3)	17 (9.1)	0.32

* The study used an equipoise-stratified design, which allowed for the analysis of data stratified by the acceptance or rejection of enrollment into randomized psychosocial treatment study of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Outcomes are defined in Table 1.

† The P value for the main effect of treatment on the primary outcome of durable recovery, adjusted for acceptance or rejection of enrollment into randomized psychosocial treatment study of the STEP-BD, was 0.25.

psychotherapy, rates of recovery were 17.9% (12 of 67 subjects) in the group receiving a mood stabilizer plus an antidepressant and 30.2% (19 of 63 subjects) in the group receiving a mood stabilizer plus placebo ($P=0.15$); for the subgroup of 106 subjects who underwent brief psychoeducation, 20.0% (11 of 55 subjects) and 19.6% (10 of 51 subjects), respectively ($P=0.99$); and for the subgroup of 130 subjects who underwent intensive psychotherapy, 33.3% (19 of 57 subjects) and 30.1% (22 of 73 subjects), respectively ($P=0.71$). Furthermore, there was no significant interaction between the augmentation of drug therapy with psychotherapy and the type of psychosocial intervention used ($P=0.28$).

ADVERSE EVENTS

The numbers of subjects with adverse events of more than moderate severity and with serious adverse events are reported in Table 3. The rate of any individual adverse event did not differ significantly between the two groups, and similar percentages of subjects in each group discontinued treatment owing to adverse events. The rate of hospitalization for suicidal ideation was low and was not significantly different between the two groups. Less than 1% of subjects in either group attempted suicide. No patients died.

There was no significant difference in the rates of prospectively observed treatment-emergent mania, hypomania, or mixed episodes between the patients receiving a mood stabilizer plus an antidepressant (10.1%) and those receiving a mood stabilizer plus placebo (10.7%). Among subjects

reporting treatment-emergent affective switch associated with one or more previous courses of treatment with antidepressants, response rates did not differ significantly between the group receiving a mood stabilizer plus an antidepressant and the group receiving a mood stabilizer plus placebo (13.6% and 25.4%, respectively; $P=0.10$), nor did the prospectively observed rates of treatment-emergent affective switch (10.2% and 17.9%, respectively; $P=0.22$). Among the subjects receiving a mood stabilizer plus an antidepressant, there were no significant differences in the rate of any primary or secondary outcome between subjects receiving bupropion and those receiving paroxetine.

DISCUSSION

This large, randomized, placebo-controlled effectiveness study found no evidence that treatment with a mood stabilizer and an antidepressant confers a benefit over treatment with a mood stabilizer alone. Rates of treatment-emergent mania or hypomania observed prospectively were similar among subjects receiving adjunctive antidepressants and those receiving placebo. Our data suggest that the short-term addition of bupropion or paroxetine to mood-stabilizer therapy does not increase the risk of cycling from depression to mania or hypomania. However, we did not study a "pure" placebo group (one in which no active psychotropic medication was administered) and hence cannot establish the effectiveness of treatment with a mood stabilizer alone.

There were several differences in the design of our study and that of previous studies. We primarily enrolled subjects who were already receiving clinical treatment at participating sites and who continued care with their usual provider. Our eligibility criteria permitted the entry of subjects with bipolar I or bipolar II disorder, including those with coexisting anxiety disorders, substance-abuse disorders, or psychotic symptoms, since epidemiologic evidence shows that most patients with bipolar disorder have such features.²⁰ We also allowed subjects to receive additional pharmacotherapy or psychotherapy. These differences may explain the disparity between our findings and those from the meta-analysis of efficacy studies by Gijsman et al.,²¹ which found standard antidepressants to be efficacious in the treatment of bipolar depression.

Our study design also differed from that of most efficacy studies in that it featured equipoise-randomization strata. This design allowed the entry of subjects who preferred to avoid one of the standard antidepressants, by eliminating the possibility that the subjects would be randomly assigned to a treatment they did not want to receive. Finally, our a priori, clinically meaningful, primary outcome of durable recovery was met if subjects had euthymia for 8 consecutive weeks. In contrast, most short-term efficacy studies designate as the primary outcome change from the baseline score on symptom-severity scales at a single visit. Our results are therefore likely to be more in accord with the expectations of clinicians and patients in the general population for treatment effectiveness than are the results of previous efficacy studies.

Our study had several limitations. First, since antidepressants are not a homogeneous class, we cannot rule out the possibility that other antidepressant medications may be more efficacious or have a greater propensity to induce manic symptoms than our study medications. Nevertheless, bupropion and paroxetine are two of the most frequently recommended antidepressants for patients with bipolar disorder.²² Some studies suggest that antidepressants vary in their tendency to cause a switch to mania or hypomania, even when used as adjuncts to mood-stabilizing treatments.^{17,23,24} Notably, the largest of these studies — the double-blind comparison of bupropion, sertraline, and venlafaxine by the Stanley Foundation Bipolar Network — found no difference

in efficacy among the treatments but did find a significantly higher rate of switch from depression to mania or hypomania among subjects receiving venlafaxine than among those receiving bupropion or sertraline.^{9,24} Therefore, although neither paroxetine nor bupropion was associated with an increased rate of treatment-emergent affective switch in our study, other antidepressants may be. Our results are, however, largely in agreement with those from studies that associate selective serotonin-reuptake inhibitors and bupropion with lower rates of treatment-emergent affective switch than venlafaxine or desipramine.^{17,23}

Second, our efficacy and safety findings are based on a relatively brief period of observation. The primary outcome of 8 consecutive weeks of euthymia, however, reflects a considerably longer period than do the cross-sectional outcomes (response or remission) used in typical efficacy studies. Although an 8-week period of recovery may be too brief to be clinically meaningful for patients, an 8-week interval of wellness may be a better predictor of long-term outcome than are scores on cross-sectional rating scales. Effectiveness outcomes such as those used in our study may be more applicable to clinical practice than are short-term cross-sectional outcomes, since the apparent benefit based on cross-sectional outcomes may not be persistent and since nearly all traditional efficacy trials define outcomes on the basis of improvement in depression-rating scores without correction for rates of treatment-emergent affective switch. Results from traditional efficacy studies can thereby misclassify patients with emergent hypomania or mania as having had a response. The Stanley Foundation Bipolar Network, using outcome criteria corrected for rates of treatment-emergent affective switch, reported that 33.3% of patients with bipolar depression had a response to treatment with bupropion, 41.4% had a response to sertraline, and 35.6% had a response to venlafaxine²⁴; these response rates are similar to the treatment-effectiveness response rates reported here.

Third, many of our study subjects received some form of psychosocial intervention. Although the efficacy of psychosocial therapies has not been established for patients with acute bipolar depression,^{25,26} it is possible that the adjunctive use of psychosocial interventions limits the generalizability of our results or reduced our ability to detect the effects of antidepressant therapy. Psy-

chosocial intervention did not appear to affect the two study groups differently. The two groups had similar percentages of subjects who received psychosocial interventions, and similar response rates were found in the subgroups receiving any form of psychosocial intervention and in the subgroup that declined psychosocial treatment. Results of a longer-term STEP-BD study do provide support for use of the psychosocial interventions used in our study.¹⁸

Fourth, some of our findings rely on last-observation-carried-forward analyses. Such analyses generally involve the imputation of data, which raises concern about the degree to which incomplete follow-up influenced the results. However, data imputation was not required for analysis of the primary outcome (durable recovery) or of the majority of secondary outcomes reported in our study. These categorical outcomes represent subjects who actually reached a study-defined outcome. Some data for the change in SUM-D and SUM-ME scores were imputed, but this is unlikely to have influenced our outcomes, as it was required for only about one third of the subjects in each group.

Fifth, patients who had recently had a manic episode were likely to be underrepresented in our study. Clinicians caring for these potential subjects might have judged them to be at high risk for a switch from depression to mania or hypomania and therefore might have avoided enrolling them into our double-blind study that exposed subjects to a standard antidepressant. Thus, our results are likely to be applicable only to those patients with bipolar depression who are considered appropriate candidates for treatment with standard antidepressants.

In summary, for the treatment of bipolar depression, we found that mood-stabilizing monotherapy provides as much benefit as treatment with mood stabilizers combined with a standard antidepressant. There was no significant difference in the adverse effects, including switch to mania, between patients who received adjunctive antidepressants and those that did not. Further research examining the efficacy of different mood stabilizers for bipolar depression may be useful.

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