Adjunctive Armodafinil for Major Depressive Episodes Associated With Bipolar I Disorder: A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Proof-of-Concept Study

Joseph R. Calabrese, MD; Terence A. Ketter, MD; James M. Youakim, MD; Jane M. Tiller, MBChB, FRCPsych; Ronghua Yang, PhD; and Mark A. Frye, MD

Objective: To evaluate the efficacy and safety of armodafinil, the longer-lasting isomer of modafinil, when used adjunctively in patients with bipolar depression.

Method: In this 8-week, multicenter, randomized, double-blind, placebo-controlled study conducted between June 2007 and December 2008, patients who were experiencing a major depressive episode associated with bipolar I disorder (according to *DSM-IV-TR* criteria) despite treatment with lithium, olanzapine, or valproic acid were randomly assigned to adjunctive armodafinil 150 mg/d (n = 128) or placebo (n = 129) administered once daily in the morning. The primary outcome measure was change from baseline in the total 30-item Inventory of Depressive Symptomatology, Clinician-Rated (IDS-C_{30}) score. Secondary outcomes included changes from baseline in scores on the Montgomery-Åsberg Depression Rating Scale, among other psychological symptom scales. Statistical analyses were performed using analysis of covariance (ANCOVA), with study drug and concurrent mood stabilizer treatment for bipolar disorder as factors and the corresponding baseline value as a covariate. A prespecified sensitivity analysis was done using analysis of variance (ANOVA) if a statistically significant treatment-by-baseline interaction was found. Tolerability was also assessed.

Results: A significant baseline-by-treatment interaction in the total IDS-C_{30} score ($P = .08$) was found. Patients administered adjunctive armodafinil showed greater improvement in depressive symptoms as seen in the greater mean ± SD change on the total IDS-C_{30} score (−15.8 ± 11.57) compared with the placebo group (−12.8 ± 12.54) (ANOVA: $P = .044$; ANCOVA: $P = .074$). No differences between treatment groups were observed in secondary outcomes. Adverse events reported more frequently in patients receiving adjunctive armodafinil were headache, diarrhea, and insomnia. Armodafinil was not associated with an increased incidence and/or severity of suicidality, depression, or mania or with changes in metabolic profile measurements.

Conclusions: In this proof-of-concept study, adjunctive armodafinil 150 mg/d appeared to improve depressive symptoms according to some, but not all, measures and was generally well tolerated in patients with bipolar depression.

Trial Registration: clinicaltrials.gov Identifier: NCT00481195

J Clin Psychiatry 2010;71(10):1363–1370

Submitted: *December 9, 2009; accepted May 20, 2010.*
Online ahead of print: *July 27, 2010 (doi:10.4088/JCP.09m05900gry).*
Corresponding author: *Joseph R. Calabrese, MD, 10524 Euclid Ave, Room 12-135, Cleveland, OH 44106 (joseph.calabrese@UHhospitals.org).*

Bipolar disorder is a lifelong, episodic mood disorder in which illness-related deficits in mood and cognition result in substantial disability associated with work, family, and social life.[1] It is estimated across countries that 1% of the general adult population has bipolar I disorder[2] but that the full spectrum of bipolar disorders increases the lifetime prevalence to 4.5% (1.0% for bipolar I, 1.1% for bipolar II, and 2.4% for subthreshold bipolar disorder).[3] On the softer end of the spectrum, among those disorders characterized by hypomanic episodes, depressive symptoms are even more prominent than bipolar I disorder.[4] The majority of the symptom burden and disability associated with bipolar disorder occurs when patients are in the depressive phase of the illness.[5,6] Patients are most likely to commit suicide, which is believed to occur in 15% of patients, during the depressed phase.[7] Growing evidence suggests that there is an increased prevalence of comorbid medical illnesses (most often cardiovascular disease and diabetes) associated with bipolar disorder compared to the age-adjusted general population. These comorbid conditions are now believed to be the primary explanation for why patients with the disorder die approximately 25 years earlier than the general population.[8,9] Unfortunately, although there are numerous treatments for mania, there are only a limited number of effective treatments for the depressed phase of the disorder. For these reasons, there is a compelling need to develop more effective and better tolerated treatments for this disorder, particularly those targeting the depressed phase of the illness—the mood state that accounts for the greatest morbidity and mortality.[10,11]

The Stanley Foundation Bipolar Network recently conducted a study with modafinil,[12] a medication with a mechanism of action different from any agent previously studied—primarily medications in the antidepressant, antipsychotic, and anticonvulsant classes—for the treatment of bipolar depression. In the 6-week, randomized, double-blind, placebo-controlled study, adjunctive modafinil was shown to possess efficacy in the treatment of major depressive episodes associated with bipolar I or II disorder, independent of the compound's effect on sleepiness or fatigue.[12] Armodafinil, the longer-lasting isomer of modafinil, has been shown to be effective for, and approved in the United States for, once-daily treatment of excessive sleepiness associated with treated obstructive sleep apnea,[13,14] shift work disorder,[15] and narcolepsy.[16] However, armodafinil has never been studied as an adjunctive treatment for bipolar depression. This proof-of-concept study was designed to evaluate the antidepressant efficacy of armodafinil when used adjunctively in patients

with bipolar I disorder whose major depressive episode was inadequately responsive to treatment with lithium, valproic acid, and/or olanzapine.

METHOD

Study Design

This 8-week, randomized, double-blind, placebo-controlled, parallel-group, fixed-dosage, multicenter, proof-of-concept study evaluated armodafinil 150 mg/d, administered once daily in the morning, in patients with bipolar I disorder who were experiencing a major depressive episode despite adequate treatment with lithium, olanzapine, or valproic acid. Medical record documentation or a medical history provided by the patient and reliable informants was used to establish at least 1 previous manic or mixed episode. The study was conducted at 42 centers in the United States, Romania, Bulgaria, and Hungary from June 2007 to December 2008. It was conducted in accordance with the International Conference on Harmonisation's Guideline for Good Clinical Practice[17] and approved by the independent ethics committee or institutional review board at each participating center. Written informed consent was obtained from each patient prior to screening.

Patients

To be included in this study, outpatient men or women between 18 and 65 years of age underwent a 1- to 2-week screening period during which they had to be diagnosed as experiencing a major depressive episode associated with bipolar I disorder, using the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders.[18] The patient's major depressive episode had to have started at least 4 weeks and no more than 12 months before the screening visit. Symptom severity requirements included (1) a 16-item Quick Inventory of Depressive Symptomatology, Self-Report ($QIDS\text{-}SR_{16}$)[19] score ≥ 13; (2) a Clinical Global Impressions-Bipolar Version (CGI-BP)[20] rating for depression ≥ 4 (at least moderately ill); and (3) a Young Mania Rating Scale (YMRS)[21] total score ≤ 10, with a score of 0 or 1 on items 1 (elevated mood), 2 (increased motor activity-energy), and 3 (sexual interest). In addition, the major depressive episode was required to be inadequately responsive to treatment with 1 or 2 of the following—lithium, olanzapine, or valproic acid—for at least 8 weeks prior to screening. Patients had to be taking olanzapine at a dose of ≥ 5 mg/d, lithium with plasma levels of ≥ 0.6 mEq/L, or valproic acid with plasma levels of ≥ 50 μg/mL for ≥ 4 weeks prior to baseline.

Patients were excluded if they had (1) been receiving psychotherapy started within 2 months before screening, or any cognitive-behavioral therapy within 2 months before screening, or any psychotherapy targeting the symptoms of depression; (2) any clinically significant uncontrolled medical or surgical condition (treated or untreated); (3) another Axis I disorder that was the primary focus of treatment within 6 months before screening, or any Axis II disorder that would interfere with the conduct of the study; (4) active psychotic symptoms; (5) a history of alcohol or substance abuse or dependence (except nicotine) within 3 months of screening, or current substance abuse; (6) a history of stimulant-induced mania; (7) < 6 hours/night of sleep during the 4 weeks before screening; (8) previous treatment with modafinil or armodafinil; (9) a history of clinically significant cutaneous drug reaction or a history of clinically significant hypersensitivity reaction; (10) a score of ≥ 20 on the Hamilton Anxiety Rating Scale (HARS)[22]; (11) a decrease of ≥ 25% on the Montgomery-Åsberg Depression Rating Scale (MADRS)[23] or a decrease of ≥ 30% on the $QIDS\text{-}SR_{16}$ during screening; (12) a risk of imminent self-harm or a score of ≥ 4 on item 10 (suicidal thoughts) of the MADRS or a score of ≥ 2 on item 18 (suicidal ideation) of the 30-item Inventory of Depressive Symptomatology, Clinician-Rated ($IDS\text{-}C_{30}$)[24]; or (13) any history of homicidal ideation or significant aggression. Women of childbearing potential who were unwilling to use a medically accepted method of birth control, including a barrier method in conjunction with a steroidal contraceptive, were also excluded.

Screening assessments also included history of suicidality using the Columbia Suicide History Form,[25] medical and psychiatric history, vital signs measurements, clinical laboratory tests (including a pregnancy test for women of childbearing age), physical exam, electrocardiogram (ECG), urine drug screen, and review of prior and concomitant medications.

Treatments

Eligible patients were randomly assigned in a 1:1 ratio to armodafinil 150 mg/d or matching placebo. The study drug was administered once daily in the morning beginning with 50 mg/d (1 tablet) on day 1 and was titrated by 50-mg increments on days 2 and 4 to 150 mg/d (3 tablets). During the study, the investigator could decrease the dose to 100 mg/d in the interest of safety or tolerability. Once the dose was lowered, however, it could not be increased.

Outcome Measures

During the treatment period, visits to the clinic were scheduled for weeks 1, 2, 3, 4, 6, and 8. A safety follow-up evaluation was performed 1 week after the patient's last dose of study drug.

Efficacy. The primary outcome measure was the mean change from baseline to final visit in the total score on the $IDS\text{-}C_{30}$, a standardized, 30-item, clinician-rated scale used to assess the severity of a patient's depressive symptoms on the basis of *DSM-IV* criteria.[24]

Scales used to assess the secondary outcome measures included the $IDS\text{-}C_{30}$, MADRS, HARS, CGI-BP, $QIDS\text{-}SR_{16}$, and Quality of Life Enjoyment and Satisfaction Questionnaire, Short Form (Q-LES-Q-SF).[26] The secondary outcomes assessed using the $IDS\text{-}C_{30}$ were mean change from baseline in total score at each visit; mean change from baseline to weeks 4 and 8 and the final visit in the combined score for insomnia-related items 1 (sleep-onset insomnia), 2 (mid-nocturnal insomnia), and 3 (early morning insomnia); mean

© Copyright 2010 Physicians Postgraduate Press, Inc.

change in combined score for energy-related items 4 (hypersomnia), 20 (energy/fatigability), 23 (psychomotor slowing), and 30 (psychomotor agitation); and mean change in individual score for items 4 (hypersomnia) and 5 (sad mood). The response (> 50% reduction in total score) and remission (total score of ≤ 11) rates on the IDS-C_{30} at each visit and the sustained (over the final 4 weeks) response and remission rates on the IDS-C_{30} at final visit were also measured. Additional secondary outcome measures for severity of depressive symptoms included the change from baseline in the MADRS total score and on individual items 1 (apparent sadness) and 2 (reported sadness) at weeks 4 and 8 and the final visit and the change from baseline in the QIDS-SR_{16} total score at each visit. Anxiety and quality of life were measured by the change from baseline in the HARS and Q-LES-Q-SF scores, respectively, at weeks 4 and 8 and at final visit. The proportion of responders according to the CGI-BP ratings (much improved [a rating of 2] or very much improved [a rating of 1]) was assessed for depression, mania, and bipolar disorder at each visit.

Tolerability. Adverse events were recorded at all patient contacts. Vital signs measurements and concomitant medication usage were evaluated at all visits, while ECG and physical exams were performed at screening and final visit. The effects of armodafinil on sleep were assessed by asking questions at all visits, including time to fall asleep at night, number of times awake at night, time spent awake and time spent asleep at night, and time sleeping during the day. Clinical laboratory testing was performed at weeks 1, 4, and 8. If at any time during the study period an evaluation of suicidality was necessary, the investigator used the Columbia Suicide Severity Rating Scale[27] in addition to clinical evaluation.

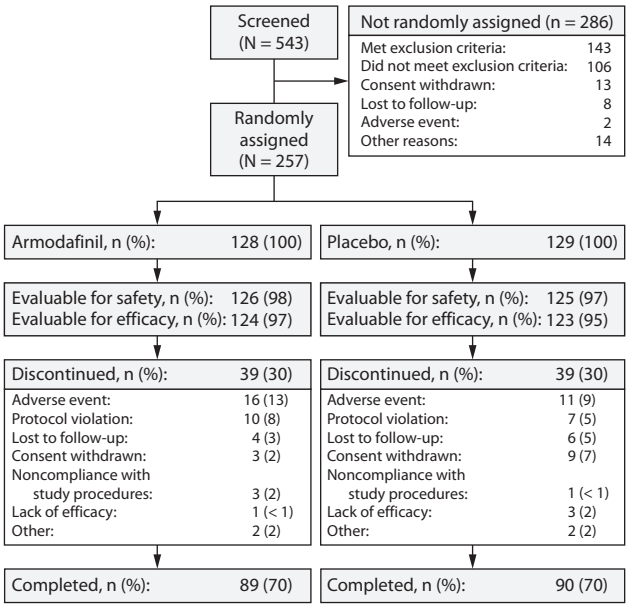
The YMRS was used at baseline and at each visit to assess the presence of hypomanic or manic symptoms. Any patient with a YMRS score ≥ 15, or who met the criteria for manic or mixed episode, was immediately withdrawn from the study.

Data obtained regarding metabolic changes included baseline body weight, baseline body mass index, changes in body weight (including the proportion of subjects experiencing a clinically significant change [ie, a change of ≥ 7%], absolute change in body weight, and the proportion of subjects reporting increased body weight as an adverse event), change from baseline in blood cholesterol, and change from baseline in blood glucose.

Statistical Analysis

The safety analysis set included all patients who received at least 1 dose of study drug. The efficacy analysis set included all patients who received at least 1 dose of study drug and completed at least 1 postbaseline IDS-C_{30} assessment. For the efficacy analysis, a last-observation-carried-forward approach was used for the final visit. Patient demographics, patient baseline characteristics, and continuous variables were summarized using descriptive statistics. Tolerability outcomes were summarized using descriptive statistics for continuous variables and patient counts and percentages for categorical variables.

Figure 1. Disposition of Patients With Bipolar Depression Receiving Adjunctive Armodafinil 150 mg/d or Placebo



The primary and secondary efficacy variables were analyzed using an analysis of covariance (ANCOVA), with study drug and concurrent mood stabilizer treatment for bipolar disorder as factors and the corresponding baseline value as a covariate. Analysis of covariance assumes there is no significant treatment-by-baseline interaction. If there was a significant treatment-by-baseline interaction ($P \leq .10$), the primary efficacy variable was to be analyzed using analysis of variance (ANOVA) as a sensitivity analysis. For each test, a 2-sided P value below .05 was considered to indicate statistical significance. All categorical variables were analyzed using a Cochran-Mantel-Haenszel test controlling for concurrent treatment for bipolar I disorder at each visit.

RESULTS

Patient Disposition

Of the 543 patients screened (Figure 1), 257 were randomly assigned to receive adjunctive armodafinil (n = 128) or placebo (n = 129). The safety group included the 251 patients (98%) who received at least 1 dose of study medication. Of these, 247 patients (96%) had at least 1 postbaseline assessment and were analyzed for efficacy in the intent-to-treat population. The percentage of patients in each arm who completed the study was identical (70%). The most common reason for withdrawal in both groups was related to adverse events; 16 patients (13%) in the armodafinil group and 11 patients (9%) in the placebo group discontinued for this reason.

There were no significant differences in demographic characteristics between the groups (Table 1). The mean ± SD age was 43.7 ± 11.47 years, and 54% were women. The baseline clinical characteristics were also similar for both groups, with mean baseline MADRS scores consistent with moderate to severe depression.[28]

Table 1. Patient Baseline Demographic and Clinical Characteristics by Treatment Group (N = 257)

Characteristic	Armodafinil (n = 128)	Placebo (n = 129)
Age, mean ± SD, y	42.6 ± 11.34	44.9 ± 11.53
Gender, male, n (%)	64 (50)	53 (41)
Race, n (%)		
White	87 (68)	91 (71)
Black	35 (27)	35 (27)
Other	6 (5)	3 (2)
Height, mean ± SD, cm	171.3 ± 9.61	170.3 ± 10.47
Weight, mean ± SD, kg	88.7 ± 21.29	86.3 ± 21.35
Body mass index (kg/m^2), mean ± SD	30.4 ± 7.77	29.8 ± 7.49
Columbia Suicide History Form, n (%)		
Actual attempts	17 (13)	37 (29)
Ever thought of committing suicide	40 (31)	60 (47)
Bipolar I medications, n (%)		
Olanzapine	43 (34)	34 (26)
Lithium	37 (29)	35 (27)
Valproic acid[a]	57 (45)	65 (50)
CGI-BP ratings for depression, n (%)		
Moderately ill	94 (73)	87 (67)
Markedly ill	32 (25)	38 (30)
Severely ill	2 (2)	4 (3)
IDS-C_{30}[b] total score, mean ± SD	37.4 ± 7.42	36.3 ± 6.74
MADRS[b] total score, mean ± SD	26.6 ± 6.11	27.3 ± 5.42
QIDS-SR_{16}[b] total score, mean ± SD	16.3 ± 2.85	15.9 ± 2.66
Q-LES-Q-SF[b] total score, mean ± SD	44.7 ± 9.19	43.3 ± 9.39
HARS[b] total score, mean ± SD	13.3 ± 3.65	13.5 ± 3.54
YMRS[c] total score, mean ± SD	4.5 ± 2.65	4.5 ± 2.58

[a]Includes valproic acid, valproate semisodium, and valproate sodium.
[b]Efficacy analysis group (armodafinil, n = 124; placebo, n = 123).
[c]Safety analysis group (armodafinil, n = 126; placebo, n = 125).
Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Version; HARS = Hamilton Anxiety Rating Scale; IDS-C_{30} = 30-item Inventory of Depressive Symptomatology, Clinician-Rated; MADRS = Montgomery-Åsberg Depression Rating Scale; QIDS-SR_{16} = 16-item Quick Inventory of Depressive Symptomatology, Self-Report; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; YMRS = Young Mania Rating Scale.

The administration of sedative-hypnotics up to 3 times a week was permitted during the study. Fewer patients in the armodafinil group (13%) received concomitant benzodiazepines or sleep aids compared with patients in the placebo group (24%). The most common sedative-hypnotics taken in the armodafinil and placebo groups, respectively, were as follows: lorazepam, 6% and 6%; zolpidem, 4% and 13%; and clonazepam, 2% and 2%.

Efficacy

Primary analyses. Mean ± SD baseline IDS-C_{30} scores were 37.4 ± 7.42 for patients in the armodafinil group and 36.3 ± 6.74 for patients in the placebo group. Patients who received adjunctive armodafinil at a dose of 150 mg/d, once daily in the morning, demonstrated significantly greater improvement in depressive symptoms compared with the placebo group (Figure 2). Analysis of the primary outcome measure showed that mean ± SD decreases from baseline to final visit on the IDS-C_{30} were −15.8 ± 11.57 compared with −12.8 ± 12.54 following armodafinil and placebo administration, respectively (ANCOVA with baseline as a covariate, $P = .0742$). However, a statistically significant treatment-by-baseline interaction ($P = .08$) was seen in the IDS-C_{30} total score, which violated the assumption of parallelism on which the ANCOVA was based. Therefore, as specified in the study protocol, the data were analyzed using ANOVA without baseline as a covariate, and a statistically significant ($P = .0439$) benefit of armodafinil over placebo was observed. The treatment-by-baseline interaction observed in the analysis of the total score from the IDS-C_{30} appeared to be related to improvement following placebo administration observed in some patients who had a baseline IDS-C_{30} total score above 40, as shown in the distribution of baseline scores and change in total IDS-C_{30} score by individuals (Figure 3).

Secondary analyses. Total scores from the IDS-C_{30} showed that administration of adjunctive armodafinil resulted in greater improvement in depressive symptomatology for patients in the armodafinil group when compared with those in the placebo group at each visit, although these differences did not always reach statistical significance (Table 2). No differences were seen in IDS-C_{30} response or remission rates or in rates of response or remission sustained over the last 4 weeks of study drug administration (Table 3). The mean ± SD change in MADRS score from baseline to final visit was −12.5 ± 10.21 within the armodafinil group compared with −11.0 ± 10.47 within the placebo group (ANCOVA, $P = .097$). No significant improvement was observed in any other secondary outcome measures of depression, anxiety, bipolar disorder, or quality of life as assessed by the MADRS, HARS, CGI-BP, QIDS-SR_{16}, or Q-LES-Q-SF.

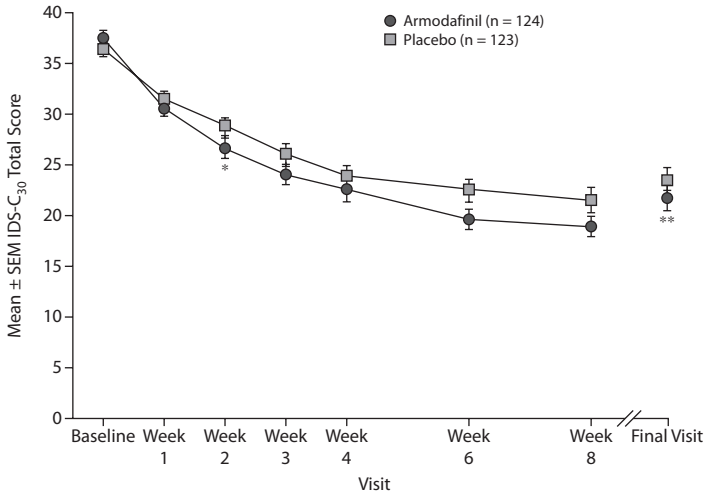
Safety and Tolerability

The most common adverse events in patients receiving adjunctive armodafinil were headache (11% vs 10% for patients receiving placebo), insomnia (10% vs 8%), and diarrhea (10% vs 6%) (Table 4). The adverse events were generally mild to moderate in intensity. Six patients experienced a serious adverse event during the study, including mania (2 in the placebo group), depression (1 in the armodafinil group; 1 in the placebo group), epididymal cyst (1 in the armodafinil group), and small intestinal obstruction (1 in the armodafinil group). Sixteen patients (13%) in the armodafinil group discontinued treatment due to an adverse event compared with 11 patients (9%) in the placebo group. The most common adverse events cited by patients in the armodafinil group as the reason for discontinuation included anxiety (n = 3), depression (n = 2), and restlessness (n = 2).

Patients receiving armodafinil experienced a similar incidence of psychiatric adverse events compared with patients in the placebo group. Of the psychiatric adverse events reported, only insomnia (10% vs 8% in the placebo group), restlessness (6% vs < 1%), anxiety (4% vs 2%), and hypomania (2% vs < 1%) were experienced more often in the armodafinil group compared with the placebo group. Three patients in the armodafinil group experienced an adverse event of mania, hypomania, or mixed episode (1 with mania and 2 with hypomania), but no patients discontinued due to these adverse events. Seven patients in the placebo group reported these adverse events (5 with mania, 1 with hypomania, and 1 with a mixed episode) and 5 discontinued the study. There was no overall difference between groups in symptoms of mania and hypomania, as shown

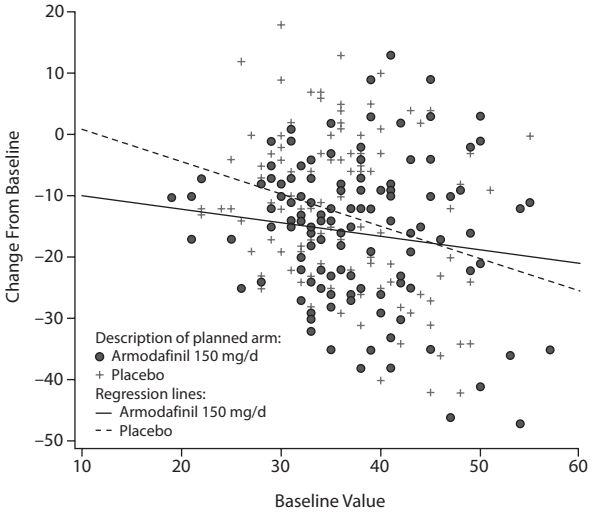
© Copyright 2010 Physicians Postgraduate Press, Inc.

Figure 2. Mean ± SEM Change From Baseline in Total Score on the 30-Item Inventory of Depressive Symptomatology, Clinician-Rated (IDS-C_{30}) for Patients With Bipolar Depression Receiving Adjunctive Armodafinil 150 mg/d Versus Placebo



*P = .027 (ANCOVA) versus placebo.
**P = .044 (ANOVA) and P = .074 (ANCOVA) versus placebo.
Abbreviations: ANCOVA = analysis of covariance, ANOVA = analysis of variance.

Figure 3. Change From Baseline to Final Visit in Total Scores on the 30-Item Inventory of Depressive Symptomatology, Clinician-Rated (IDS-C_{30}) in Patients Receiving Adjunctive Armodafinil 150 mg/d or Placebo[a]



[a]Treatment-by-baseline interaction, P = .08.

by the mean ± SD change from baseline to final visit in the total score on the YMRS of −0.6 ± 3.45 for those patients receiving armodafinil compared with 0.6 ± 4.62 for those receiving placebo. Two patients in each group experienced an adverse event of worsening depression, and all 4 patients discontinued because of the depression. While no suicide attempts were reported during this study, 6 patients (3 in each group) reported emergent or worsening suicidal ideation. One patient in the armodafinil group discontinued because of suicidal ideation. Results from the sleep questionnaire showed no clinically relevant mean changes in nighttime sleep between groups.

There were no significant changes in mean clinical laboratory values, ECG parameters, and physical exam findings for patients receiving adjunctive armodafinil. No hypersensitivity reactions or serious skin-related adverse events were reported. One patient in the armodafinil group discontinued because of acute urticaria that resolved upon stopping the drug. Mean ± SD increases in heart rate of 2.6 ± 9.08 beats per minute within the armodafinil group and 1.9 ± 10.17 beats per minute within the placebo group were not considered clinically meaningful by study investigators. A mild elevation in gamma glutamyltransferase (GGT) and a mild decrease in uric acid in the armodafinil group compared with the placebo group were consistent with the known profile of armodafinil.

Baseline body weight and body mass index were comparable between groups (see Table 1). The mean absolute ± SD increase in body weight from baseline to final visit was 0.1 ± 3.23 kg for patients in the armodafinil group and 1.0 ± 2.64 kg for patients in the placebo group. Clinically significant increases (≥ 7%) in body weight were reported by 4 patients receiving armodafinil and 8 patients receiving placebo. The number of patients reporting weight gain as an adverse event was 1 (< 1%) in the armodafinil group and 6 (5%) in the placebo group. Clinically significant decreases (≥ 7%) in body weight were reported by 4 patients receiving armodafinil and no patient receiving placebo. The mean change from baseline to final visit in total cholesterol was 0.0 ± 0.65 mmol/L for patients in the armodafinil group vs −0.1 ± 0.69 mmol/L in the placebo group. The mean change from baseline in blood glucose was 0.1 ± 1.09 mmol/L for patients in the armodafinil group and 0.4 ± 1.68 mmol/L for patients in the placebo group.

DISCUSSION

This proof-of-concept study is the first randomized, parallel-group, placebo-controlled study to evaluate the efficacy of adjunctive armodafinil in the treatment of bipolar I depression over 8 weeks. According to the primary outcome analysis, the adjunctive use of armodafinil was found to significantly improve depressive symptoms compared with placebo, with a mean difference of 3.0 points between the groups in reduction from baseline in the total IDS-C_{30} score at final visit. Decreases from baseline in the IDS-C_{30} score at final visit for the armodafinil and placebo groups were −15.8 and −12.8 points, respectively, in the current study. In a prior study[12] with modafinil and placebo in patients with bipolar disease, the differences from baseline in IDS-C_{30} scores were −10.5 points for modafinil and −5.82 points for placebo. Again, the placebo response for modafinil looks considerably smaller than the armodafinil response. This finding suggests that a larger placebo effect (rather than

Table 2. Mean ± SD Change in IDS-C_{30} Total Score From Baseline to Individual Visits

Visit	Armodafinil (n = 124), Mean ± SD	Placebo (n = 123), Mean ± SD	*P* Value	95% CI
Week 1	−6.7 ± 8.47	−4.8 ± 6.74	.0795	−3.67 to 0.21
Week 2	−10.6 ± 10.09	−7.7 ± 8.81	.0272	−5.16 to −0.31
Week 3	−13.0 ± 10.15	−10.6 ± 9.62	.0802	−5.06 to 0.29
Week 4	−14.2 ± 10.88	−12.6 ± 8.78	.2407	−4.33 to 1.09
Week 6	−16.8 ± 11.10	−14.1 ± 10.55	.0502	−6.03 to 0.00
Week 8	−17.8 ± 10.60	−14.9 ± 11.98	.0612	−6.17 to 0.14
Final visit	−15.8 ± 11.57	−12.8 ± 12.54	.0439[a]	−5.67 to 0.27

[a]Due to the significant treatment-by-baseline interaction ($P \leq .10$), the primary efficacy variable was analyzed using analysis of variance as a sensitivity analysis.
Abbreviation: IDS-C_{30} = 30-item Inventory of Depressive Symptomatology, Clinician-Rated.

Table 3. Change From Baseline to Final Visit in Secondary Efficacy Measurements

Measure	Armodafinil (n = 124)	Placebo (n = 123)	*P* Value
IDS-C_{30}, n (%)			
Response	46 (37)	47 (38)	.8960
Remission	30 (24)	22 (18)	.1980
IDS-C_{30} sustained at final visit, n (%)			
Response	23 (19)	17 (14)	.3129
Remission	13 (10)	8 (7)	.2575
MADRS, mean ± SD	−12.5 ± 10.21	−11.0 ± 10.47	.0965
QIDS-SR_{16}, mean ± SD	−7.4 ± 4.85	−6.7 ± 5.52	.3814
CGI-BP responder,[a] n (%)			
Depression	64 (52)	60 (49)	.6631
Mania	8 (6)	4 (3)	.2263
Bipolar disorder	60 (48)	58 (44)	.4774
IDS-C_{30} items, mean ± SD			
Insomnia-related (items 1, 2, and 3)	−1.6 ± 2.43	−1.2 ± 2.72	.1565
Hypersomnia (item 4)	−0.4 ± 0.85	−0.2 ± 0.80	.0862
Fatigue and energy-related (items 4, 20, 23, and 30)	−2.5 ± 2.41	−2.1 ± 2.53	.1927
Sad mood (item 5)	−1.1 ± 0.96	−1.0 ± 0.98	.5663
MADRS items, mean ± SD			
Apparent sadness (item 1)	−1.7 ± 1.56	−1.5 ± 1.62	.1556
Reported sadness (item 2)	−2.0 ± 1.63	−1.7 ± 1.62	.1661
HARS, mean ± SD	−3.8 ± 5.64	−3.8 ± 5.00	.7791
Q-LES-Q-SF, mean ± SD	8.3 ± 10.26	8.2 ± 11.16	.5427

[a]Proportion of patients "much improved" or "very much improved."
Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Version; HARS = Hamilton Anxiety Rating Scale; IDS-C_{30} = 30-item Inventory of Depressive Symptomatology, Clinician-Rated; MADRS = Montgomery-Åsberg Depression Rating Scale; QIDS-SR_{16} = 16-item Quick Inventory of Depressive Symptomatology, Self-Report; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form.

a smaller drug effect, or some combination thereof) may have contributed to a less robust efficacy finding with the current study. Compared to baseline, there was also a numerically but not significantly greater decrease in severity of symptoms according to the IDS-C_{30} at each visit.

Results for the mean MADRS total score at final visit in the armodafinil compared with placebo group did not confirm the results observed for the IDS-C_{30}. No significant differences between treatment groups were observed in the secondary outcome analyses.

Of the patients randomly assigned, 70% in each group completed the entire study. This completion rate is higher

Table 4. Adverse Events Reported in ≥ 5% of Patients Treated With Armodafinil

Adverse Event	Armodafinil (n = 126), n (%)	Placebo (n = 125), n (%)
Headache	14 (11)	12 (10)
Insomnia	13 (10)	10 (8)
Diarrhea	12 (10)	8 (6)
Nausea	9 (7)	6 (5)
Dry mouth	8 (6)	5 (4)
Restlessness	7 (6)	1 (< 1)
Somnolence	6 (5)	2 (2)
Upper respiratory tract infection	6 (5)	9 (7)

than rates seen previously (46%–60%) in studies of adjunctive treatments for bipolar depression.[29–31] The high completion rate and the lack of difference in discontinuations due to adverse events between groups (armodafinil 13% vs placebo 9%) indicate that armodafinil 150 mg/d is generally well tolerated for use in patients with bipolar I disorder currently being administered lithium, valproic acid, and/or olanzapine. The most frequently reported adverse events among patients who received armodafinil were headache, diarrhea, and insomnia. Among psychiatric adverse events, insomnia, restlessness, anxiety, and hypomania were reported more in the armodafinil group compared with the placebo group, although the reported incidences were ≤ 10% for all of these events, and the differences from the incidences in the placebo group were small. No differences were observed between the groups on the basis of responses on the sleep questionnaire or the mean change in YMRS score from baseline to final visit. The lack of observed differences in blood sugar, total cholesterol, rates of clinically significant increases in body weight (≥ 7%), and absolute differences in body weight between groups suggests that armodafinil has a benign metabolic profile.

At present, quetiapine is the only medication approved by regulatory agencies for use as a monotherapy in the treatment of major depressive episodes associated with bipolar I or II disorder.[30,31] In clinical practice, the short-term use of the conventional antidepressants and the atypical antipsychotic agents is quite common. However, only 1 combination formulation, the olanzapine-fluoxetine combination,[29] has been approved for use.[32] The guidelines for bipolar disorder from the British Association for Psychopharmacology[33] report that there is an evidence base supporting the adjunctive use of antidepressants in bipolar depression but caution against first-line use of antidepressants.[33] In addition, clinical studies have reported conflicting results regarding the efficacy of antidepressants in patients experiencing a major depressive episode associated with bipolar disorder, including one large, double-blind, randomized study[34] of patients with bipolar I or II depression in which the adjunctive use of antidepressants failed to confer additional benefit over mood stabilizers alone.[34]

There is one large-scale, double-blind, placebo-controlled study that has been successfully conducted for the adjunctive treatment of bipolar depression.[35] The use of adjunctive designs noticeably improves the generalizability of findings

© Copyright 2010 Physicians Postgraduate Press, Inc.

from clinical studies because most patients with bipolar disorder will require combination therapy. This study is unique in that it represents an initial large-scale attempt to develop an adjunctive medication other than a psychotropic drug (antipsychotic, anticonvulsant, or antidepressant) for the treatment of depressive symptoms associated with bipolar disorder. There exists a need to develop other classes of medications for use in the treatment of mood disorders, especially medications with potentially novel mechanisms of action and benign adverse event profiles. However, this study had several limitations—most notable among them is the lack of confirmation of the primary outcome analysis by the various secondary outcome measures, which challenges the reliability and validity of the primary finding. We believe this discrepancy may possibly be explained by the significant correlation between the distribution of baseline total scores and the change from baseline by individuals on the primary outcome measure, which is graphically displayed in Figure 3 and shows improvement observed following placebo administration in some patients who had baseline IDS-C_{30} total scores of 40 and above.

We conclude that adjunctive armodafinil 150 mg/d improved depressive symptoms by some but not all measures and that armodafinil appears to be generally well tolerated for the treatment of nonpsychotic major depressive episodes associated with bipolar I disorder in patients who are currently not responding to treatment with lithium, valproic acid, and/or olanzapine. Further research of adjunctive armodafinil is warranted for the treatment of acute bipolar depression.

Drug names: armodafinil (Nuvigil), clonazepam (Klonopin and others), lithium (Lithobid and others), lorazepam (Ativan and others), modafinil (Provigil), olanzapine (Zyprexa), olanzapine-fluoxetine (Symbyax), valproate sodium (Depacon and others), valproic acid (Stavzor, Depakene, and others), zolpidem (Ambien, Edluar, and others).

Author affiliations: Department of Psychiatry, Case Western Reserve University, Cleveland, Ohio (Dr Calabrese); Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California (Dr Ketter); Cephalon, Inc, Frazer, Pennsylvania (Drs Youakim, Tiller, and Yang); and Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota (Dr Frye).

Study investigators: Valentin Akabaliev, MD, MHAT—Sveti Georgi, Plovdiv, Bulgaria; Csaba Almási, MD, Nyíro Gyula Hospital, Psychiatry II, Budapest, Hungary; Valerie Arnold, MD, Clinical Neuroscience Solutions Inc, Memphis, Tennessee; Mohammed Bari, MD, Synergy Clinical Research Center, National City, California; Benny Barnhart, MD, Grayline Clinical Drug Trials, Wichita Falls, Texas; Christopher Benbow, MD, California Neuropsychopharmacology Clinical Research Institute, San Diego, California; Prakash Bhatia, MD, Synergy Clinical Research Center, Escondido, California; Joel Breving, MD, Behavioral Medical Research of Brooklyn, Brooklyn, New York; Joseph R. Calabrese, MD, University Hospitals Case Medical Center, Cleveland, Ohio; John Carman, MD, Carman Research, Smyrna, Georgia; Bernadette D'Souza, MD, Midwest Clinical Research Center, Dayton, Ohio; David Flaherty, DO, Fidelity Clinical Research, Lauderhill, Florida; Lorentina Florescu, MD, Cabinetul Medical Lorentina 2102 S.R.L, Targoviste, Romania; Susanna Goldstein, MD, Medical and Behavioral Health Research, New York, New York; Daniel Gruener, MD, CRI Worldwide, Philadelphia, Pennsylvania; Svetlozar Haralanov, MD, SHATNPsy—Sveti Naum, Sofia, Bulgaria; Alexander Horwitz, MD, Oregon Center for Clinical Investigations Inc, Salem, Oregon; Luchezar Hranov, MD, SHATNPsy—Sveti Naum, Sofia, Bulgaria; John Joyce, MD, Clinical Neuroscience Solutions Inc, Jacksonville, Florida; Terence A. Ketter, MD, Stanford University Medical Center, Stanford, California; Arifulla Khan, MD, Northwest Clinical Research Center, Bellevue, Washington; Mary Ann Knesevich, MD, University Hills Clinical Research, Irving, Texas; James Knutson, MD, Kirkland, Washington; David Krefetz, DO, CRI Worldwide LLC, Willingboro, New Jersey; Jelena Kunovac, MD, Excell Research, Oceanside, California; Maria Ladea, MD, Spitalul Clinic de Psihiatrie, Bucuresti, Romania; Michael Lesem, MD, Claghorn-Lesem Research Clinic, Bellaire, Texas; Michael Levy, MD, Behavioral Medical Research of Staten Island, Staten Island, New York; Mirela Manea, MD, Spitalul Clinic de Psihiatrie, Bucuresti, Romania; Raymond Manning, MD, CNRI Los Angeles LLC, Pico Rivera, California; Gabriel Marinescu, MD, Spitalul Judetean Arges Sectia Psihiatrie, Pitesti, Romania; Janice Miller, MD, Janus Center for Psychiatric Research, West Palm Beach, Florida; Paul Miller, MD, Pacific Clinical Research Medical Group, Orange, California; William Patterson, MD, Birmingham Research Group, Birmingham, Alabama; Joachim Raese, MD, Pacific Clinical Research Medical Group, Orange, California; Robert Riesenberg, MD, Atlanta Center for Clinical Research, Atlanta, Georgia; Mihaela Rosca, MD, SC Corpores Sana Medical SRL, Bucuresti, Romania; Norman Rosenthal, MD, Capital Clinical Research Associates, Rockville, Maryland; Maria Sandulescu, MD, Spitalul de Psihiatrie Titan, Bucuresti, Romania; Loris Sayyan, MD, DistrDispPsyDIU, Burgas, Bulgaria; Veronique Sebastian, MD, Sooner Clinical Research, Oklahoma City, Oklahoma; Mary Stedman, MD, Stedman Clinical Trials LLC, Tampa, Florida; Dana Stiles, MD, Piedmont Clinical Trials Inc, Winston-Salem, North Carolina; Kathleen Toups, MD, Bay Area Research Institute, Lafayette, California; Rayna Tzvetkova Dimitrova, MD, DistrDispPsyDIU Plovdiv, Plovdiv, Bulgaria; Csilla Varga, MD, Szabolcs-Szatmár-Bereg Megyei Önk. Psychiatric Hospital, Nagykálló, Hungary; Nicholas Vatakis, MD, Social Psychiatry Research Institute, Bronx, New York; Cherian Verghese, MD, MRCPsych, Keystone Clinical Studies LLC, Norristown, Pennsylvania; Richard Weisler, MD, Raleigh, North Carolina; Inna Yuryev-Golger, MD, Social Psychiatry Research Institute, Brooklyn, New York.

Potential conflicts of interest: **Dr Calabrese** has received federal funding from the Department of Defense, the Health Resources Services Administration, and the National Institute of Mental Health (NIMH); has received grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, The Cleveland Foundation, Eli Lilly, GlaxoSmithKline, Janssen, National Alliance for Schizophrenia and Depression (NARSAD), Repligen, The Stanley Medical Research Institute, Takeda, and Wyeth; has been an advisory board member for Abbott, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo, EPI-Q, Forest, France Foundation, GlaxoSmithKline, Janssen, Johnson & Johnson, Lundbeck, NeuroSearch, Ortho-McNeil, Otsuka, Pfizer, Repligen, Schering-Plough, Servier, Solvay, Supernus, Synosia, and Wyeth; and has been involved in continuing medical education (CME) activities supported by AstraZeneca, Bristol-Myers Squibb, France Foundation, GlaxoSmithKline, Janssen, Johnson & Johnson, sanofi-aventis, Schering-Plough, Pfizer, Solvay, and Wyeth. **Dr Ketter** has received grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Pfizer, Repligen, and Wyeth; has been a consultant for Abbott, AstraZeneca, Astellas, Bristol-Myers Squibb, Cephalon, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Jazz, Novartis, Organon (a part of Schering-Plough), Solvay, Valeant, Vanda, Wyeth, and XenoPort; and has received lecture honoraria from Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Noven, Otsuka, and Pfizer. Dr Ketter's spouse/partner is an employee and stock shareholder of Johnson & Johnson. **Dr Youakim** is an employee of Cephalon. **Dr Tiller** is an employee and stock shareholder of Cephalon. Dr Tiller's spouse/partner is an employee and stock shareholder of GlaxoSmithKline. **Dr Yang** is an employee and stock shareholder of Cephalon. **Dr Frye** has received grant/research support from Pfizer, NARSAD, NIMH, the National Institute of Alcohol Abuse and Alcoholism (NIAAA), and Mayo Foundation; has been a consultant for Bristol-Myers Squibb, Cephalon, Dainippon Sumitomo, Medtronic, Ortho-McNeil-Janssen, Johnson & Johnson, Schering-Plough, Sepracor, and Pfizer; and has been involved in CME activities supported by AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Otsuka, Pfizer, and Schering-Plough.

Funding/support: This study was sponsored by Cephalon, Inc, Frazer, Pennsylvania. Funding for graphical and administrative support was provided by Cephalon, Inc, to the Curry Rockefeller Group, LLC, Tarrytown, New York.

Previous presentation: Presented at the 8th International Conference on Bipolar Disorder; June 25–27, 2009; Pittsburgh, Pennsylvania.

Acknowledgment: The authors acknowledge Virginia R. Schobel, MSc, an employee of Cephalon, Inc, for editorial assistance.

REFERENCES

1. Judd LL, Schettler PJ, Solomon DA, et al. Psychosocial disability and work role function compared across the long-term course of bipolar I, bipolar II and unipolar major depressive disorders. *J Affect Disord*. 2008;108(1–2):49–58.
2. Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. *JAMA*. 1996;276(4):293–299.
3. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2007;64(5):543–552.
4. Akiskal HS, Akiskal KK, Lancrenon S, et al. Validating the bipolar spectrum in the French National EPIDEP Study: overview of the phenomenology and relative prevalence of its clinical prototypes. *J Affect Disord*. 2006;96(3):197–205.
5. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002;59(6):530–537.
6. Kupka RW, Altshuler LL, Nolen WA, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. *Bipolar Disord*. 2007;9(5):531–535.
7. Goodwin FK, Jamison KR. Suicide. In: *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression*. 2nd ed. New York, NY: Oxford University Press; 2007:247–272.
8. Allison DB, Newcomer JW, Dunn AL, et al. Obesity among those with mental disorders: a National Institute of Mental Health meeting report. *Am J Prev Med*. 2009;36(4):341–350.
9. Miller BJ, Paschall CB 3rd, Svendsen DP. Mortality and medical comorbidity among patients with serious mental illness. *Psychiatr Serv*. 2006;57(10):1482–1487.
10. Post RM, Denicoff KD, Leverich GS, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH Life Chart Method. *J Clin Psychiatry*. 2003;64(6):680–690, quiz 738–739.
11. Tondo L, Isacsson G, Baldessarini R. Suicidal behaviour in bipolar disorder: risk and prevention. *CNS Drugs*. 2003;17(7):491–511.
12. Frye MA, Grunze H, Suppes T, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry*. 2007;164(8):1242–1249.
13. Hirshkowitz M, Black JE, Wesnes K, et al. Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. *Respir Med*. 2007;101(3):616–627.
14. Roth T, White D, Schmidt-Nowara W, et al. Effects of armodafinil in the treatment of residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome: a 12-week, multicenter, double-blind, randomized, placebo-controlled study in nCPAP-adherent adults. *Clin Ther*. 2006;28(5):689–706.
15. Czeisler CA, Walsh JK, Wesnes KA, et al. Armodafinil for treatment of excessive sleepiness associated with shift work disorder: a randomized controlled study. *Mayo Clin Proc*. 2009;84(11):958–972.
16. Harsh JR, Hayduk R, Rosenberg R, et al. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. *Curr Med Res Opin*. 2006;22(4):761–774.
17. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice, E6(R1). Current Step 4 version. 10 June 1996. http://www.ich.org/LOB/media/MEDIA482.pdf. Accessed November 20, 2009.
18. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002.
19. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), Clinician Rating (QIDS-C), and Self-Report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573–583.
20. Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res*. 1997;73(3):159–171.
21. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
22. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55.
23. Åsberg M, Montgomery SA, Perris C, et al. A comprehensive psychopathological rating scale. *Acta Psychiatr Scand suppl*. 1978;57(271):5–27.
24. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996;26(3):477–486.
25. Oquendo MA, Halberstam B, Mann JJ. Risk factors for suicidal behavior: the utility and limitations of research instruments. In: First MB, ed. *Standardized Assessment for the Clinician*. Washington, DC: American Psychiatric Publishing; 2003:103–130.
26. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull*. 1993;29(2):321–326.
27. Posner K, Melvin GA, Stanley B, et al. Factors in the assessment of suicidality in youth. *CNS Spectr*. 2007;12(2):156–162.
28. Müller MJ, Himmerich H, Kienzle B, et al. Differentiating moderate and severe depression using the Montgomery-Åsberg Depression Rating Scale (MADRS). *J Affect Disord*. 2003;77(3):255–260.
29. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;60(11):1079–1088.
30. Calabrese JR, Keck PE Jr, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*. 2005;162(7):1351–1360.
31. Thase ME, Macfadden W, Weisler RH, et al; BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II Study). *J Clin Psychopharmacol*. 2006;26(6):600–609.
32. Perlis RH. Treatment of bipolar disorder: the evolving role of atypical antipsychotics. *Am J Manag Care*. 2007;13(suppl):S178–S188.
33. Goodwin GM; Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2009;23(4):346–388.
34. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*. 2007;356(17):1711–1722.
35. van der Loos ML, Mulder PG, Hartong EG, et al, for the LamLit Study Group. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009;70(2):223–231.