

# Comparison of Short-Term Venlafaxine Versus Lithium Monotherapy for Bipolar II Major Depressive Episode

## *A Randomized Open-Label Study*

Jay D. Amsterdam, MD\* and Justine Shults, PhD\*†

**Objective:** Practice guidelines for the initial treatment of bipolar II (BP II) major depressive episode (MDE) recommend mood stabilizer (MS) monotherapy or combined MS plus antidepressant drug (AD) therapy. We hypothesized that initial AD monotherapy would be superior to MS monotherapy for BP II MDE with a low hypomanic switch rate.

**Methods:** Bipolar II MDE patients were randomized to a 12-week open-label treatment with either venlafaxine monotherapy (n = 43) or lithium carbonate monotherapy (n = 40). The primary outcome measure was the 28-item Hamilton Depression Rating Scale (HAM-D 28). The secondary outcome measures included the Young Mania Rating Scale (YMRS), clinical global impressions severity and change ratings, and the proportion of patients classified as responder (with  $\geq 50\%$  reduction in baseline HAM-D score) or as remitter (final HAM-D score,  $\leq 8$ ).

**Results:** Thirty-four venlafaxine-treated patients (79.1%) and 15 lithium-treated patients (37.5%) completed the trial ( $P < 0.0005$ ). Venlafaxine monotherapy produced a greater reduction in HAM-D 28 scores, with a difference in change of  $-6.57$  points (95% confidence interval,  $-11.97$  to  $-1.18$ ) ( $P = 0.017$ ) between treatment conditions. There was a greater proportion of venlafaxine-treated (vs lithium-treated) patients classified either as treatment responder (58.1% vs 20.0%;  $P < 0.0005$ ) or as treatment remitter (44.2% vs 7.5%;  $P < 0.0005$ ) for the HAM-D 28 scores. There was no significant increase in mean YMRS scores over time in the venlafaxine (vs lithium) treatment condition, and no significant increase in mean YMRS scores at any study visit compared with baseline for either treatment.

**Conclusions:** Results from this study suggest that AD monotherapy with venlafaxine may be an effective initial therapy for BP II MDE with a low hypomanic switch rate.

(*J Clin Psychopharmacol* 2008;28:171–181)

\*Department of Psychiatry, Depression Research Unit; and †Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Received June 18, 2007; accepted after revision November 19, 2007.

This work was supported by a research grant from the Stanley Medical Research Institute, Chevy Chase, Md, and the Jack Warsaw Fund for Research in Biological Psychiatry (Depression Research Unit, University of Pennsylvania School of Medicine, Philadelphia, Pa).

Address correspondence and reprint requests to Jay D. Amsterdam, MD, Depression Research Unit, University Science Center—3rd Floor, 3535 Market St, Philadelphia, PA 19104-3309. E-mail: jamsterd@mail.med.upenn.edu.

Copyright © 2008 by Lippincott Williams & Wilkins

ISSN: 0271-0749/08/2802-0171

DOI: 10.1097/JCP.0b013e318166c4e6

The most common phenotypic expression of bipolar illness is bipolar II (BP II) disorder.<sup>1–5</sup> Initially described in 1976,<sup>6</sup> it is characterized in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision [DSM-IV-TR])*, by a preponderance of depressive episodes with a lifetime prevalence of at least 1 hypomanic episode lasting a minimum of 4 days. Bipolar II disorder is difficult to diagnose, often presents as a mixed hypomanic and depressive state, and frequently goes unrecognized.<sup>2–4,7,8</sup> It is diagnostically stable over time<sup>9–11</sup> and rarely evolves into bipolar I (BP I) disorder.<sup>11–17</sup> There is also evidence that BP II disorder is a distinct entity from BP I disorder based on genetic and biologic factors.<sup>1,11,18–20</sup> It is highly recurrent, with most illness time spent in depressive episodes.<sup>1,21–24</sup> As a result, it is associated with substantial morbidity and mortality.<sup>22,25–32</sup>

Practice guidelines for the treatment of BP II major depressive episode (MDE) are largely empirical and based on the recommendations for treating BP I MDE.<sup>33–40</sup> None have been based on controlled clinical trials, and none have endorsed the use of antidepressant drug (AD) monotherapy because of concerns of AD-induced mania.<sup>41–45</sup> The American Psychiatric Association<sup>33,34</sup> recommends that initial treatment of BP II MDE begins with mood stabilizer (MS) monotherapy or with the combination of MS and AD therapy (with the AD therapy administered at the lowest effective dose for the shortest time necessary). Another expert panel of psychiatrists recommends initiating MS monotherapy and avoiding AD monotherapy altogether,<sup>37</sup> with any previously established AD therapy tapered and discontinued within 12 weeks after remission.<sup>37</sup> In contrast, the Expert Consensus Panel for Bipolar Disorder<sup>35</sup> suggests that AD monotherapy may be considered in BP II MDE patients with a history of minimal hypomania. Other practice guidelines recommend starting MS monotherapy for mild to moderate BP II depression, and combine MS and AD therapy for more severe depressive symptoms.<sup>38,39</sup> Finally, Dantzer and Osseir<sup>40</sup> recommend bupropion as an initial therapy for BP II MDE, although this recommendation is not based on controlled prospective trials.

Early studies of MS monotherapy did not show consistent antidepressant efficacy in mixed populations of BP I and II depressions.<sup>41–51</sup> However, a 12-week prospective study of fluoxetine monotherapy in 839 MDE patients found a similar response rate among 89 BP II MDE patients compared with 89 age- and sex-matched unipolar patients (selected from the remaining 750 unipolar patients).<sup>13</sup> Moreover,

in their study, symptoms suggestive of syndromal or subsyndromal hypomania occurred in only 3 (3.8%) of 80 BP II patients and in 2 (0.3%) of 661 unipolar patients.<sup>13</sup> A subsequent 6-week trial using venlafaxine monotherapy in 16 BP II and 26 unipolar MDE patients also found similar response rates among diagnostic groups with no reported hypomanic episodes.<sup>52</sup> More recently, we prospectively treated 37 BP II MDE patients with fluoxetine monotherapy for 8 weeks and found a remission rate of 48%.<sup>14,15</sup> Three patients (7.34%) had a mild hypomanic episode that did not require discontinuation of treatment. In that study, mean Young Mania Rating Scale (YMRS)<sup>53</sup> scores did not significantly increase during fluoxetine monotherapy.<sup>14,15</sup>

We now present results from a prospective, randomized, open-label comparison of venlafaxine versus lithium monotherapy for BP II MDE. We hypothesized that venlafaxine monotherapy would be superior to lithium monotherapy with a similar hypomanic switch rate.

## MATERIALS AND METHODS

### Study Setting

The trial was conducted at the Depression Research Unit of the University of Pennsylvania Medical Center. The investigative site, established in 1966, is an outpatient clinical and research facility that examines approximately 500 new mood disorders patients and treats approximately 150 patients per year in clinical research studies.

### Patient Selection

Outpatients 18 years and older, with a *DSM-IV* Axis I diagnosis of BP II disorder and current *DSM-IV* Axis I diagnosis of acute (<2 years) or chronic (≥2 years) MDE, were included. All patients had a baseline 17-item Hamilton Depression Rating Scale<sup>54</sup> (HAM-D 17) score of 18 or higher. Patients with a comorbid *DSM-IV* Axis I diagnosis other than MDE were not excluded from the study if the comorbid condition did not constitute the primary disorder. Patients were excluded if they had a history of mania or psychosis, substance abuse or dependence in the preceding 3 months, nonresponse to venlafaxine or lithium therapy within the current MDE, or had sensitivity to venlafaxine or lithium. Other exclusion criteria were the presence of an unstable medical condition, pregnancy or nursing, TSH level of 5 uIU/mL or higher, significant cardiac, hepatic, or renal disease, dementia, malignancy, or use of chemotherapy, concurrent AD, MS, neuroleptic, tranquilizer, or over-the-counter antidepressant preparation.

### Procedures

Patients provided informed consent in accordance with the ethical standards of the institutional review board of the University of Pennsylvania. The study was conducted using the *Principles of Good Clinical Practice Guidelines*, with oversight monitoring by the local office of human research and by an independent data and safety

monitoring board. Figure 1 displays the Consolidated Standards of Reporting Trials' flow diagram of patient enrollment in the study.

A psychiatric and medical history was obtained using the Structured Diagnostic Interview for *DSM-IV* format.<sup>55</sup> Physical examination and laboratory tests were performed, including blood cell count, electrolytes, glucose, hepatic enzymes, urea nitrogen, creatinine, and thyroid panel analysis, pregnancy test (in women), urinalysis, urine drug screen, and electrocardiography. Estimates of the number of prior depressive and hypomanic episodes were obtained using the Structured Diagnostic Interview for *DSM-IV*<sup>55</sup> as defined by the *DSM-IV-TR* criteria. In addition, the number of prior subsyndromal hypomanic (ie, hyperthymic) episodes lasting less than 4 days was estimated.

Structured ratings of the 28-item Hamilton Depression Rating Scale (HAM-D 28) and YMRS were obtained by a study physician or nurse. Symptom ratings were obtained with attribution as to the origin of the symptom. For example, insomnia could be recorded either as a depressive symptom on the HAM-D or as a hypomanic symptom on the YMRS. It could also be simultaneously recorded on both rating instruments as a mixed depressive and hypomanic symptom if the evaluator attributed the insomnia to the presence of both depression and hypomania. This rating method sometimes resulted in baseline YMRS scores that were above zero.

### Treatment

Patients discontinued their previously established ineffective or partially effective psychotropic drug therapy before randomization to treatment in the study. Patients who had a baseline HAM-D 17 score of 18 or higher were randomized to open-label monotherapy with either venlafaxine or lithium. Efficacy and safety measures were obtained at baseline and at study weeks 1, 2, 4, 6, 8, 10, and 12. Uniformity of treatment procedures was achieved using a structured clinical management format.<sup>56</sup>

Venlafaxine monotherapy was initiated at 37.5 mg/d and increased to 75 mg/d during the first week of treatment. The dose was titrated upward in 37.5- or 75-mg increments every week, to a maximum dosage of 375 mg/d by week 4 of treatment. This dose was maintained for an additional 8 weeks. The venlafaxine dose could be reduced to a minimum of 37.5 mg/d, depending on tolerability. Patients unable to tolerate a dose of 37.5 mg/d discontinued participation in the trial. Venlafaxine was administered on a once- or twice-daily basis.<sup>52</sup>

Lithium dosing was initiated at 600 mg/d for 1 week, and a serum lithium level was obtained. Based on tolerability and a minimum lithium level of 0.5 mmol/L, the dose of lithium was increased to 900 mg/d during the second week of treatment. This process was then repeated until a steady-state lithium level of 0.5 to 1.5 mmol/L was achieved at week 4 of therapy, and then maintained for an additional 8 weeks. Lithium 300-mg capsules were administered on a once- or twice-daily basis up to 900 mg/d, and twice daily at doses exceeding 900 mg/d. Patients who were unable to maintain a minimum serum lithium level of 0.5 mmol/L were

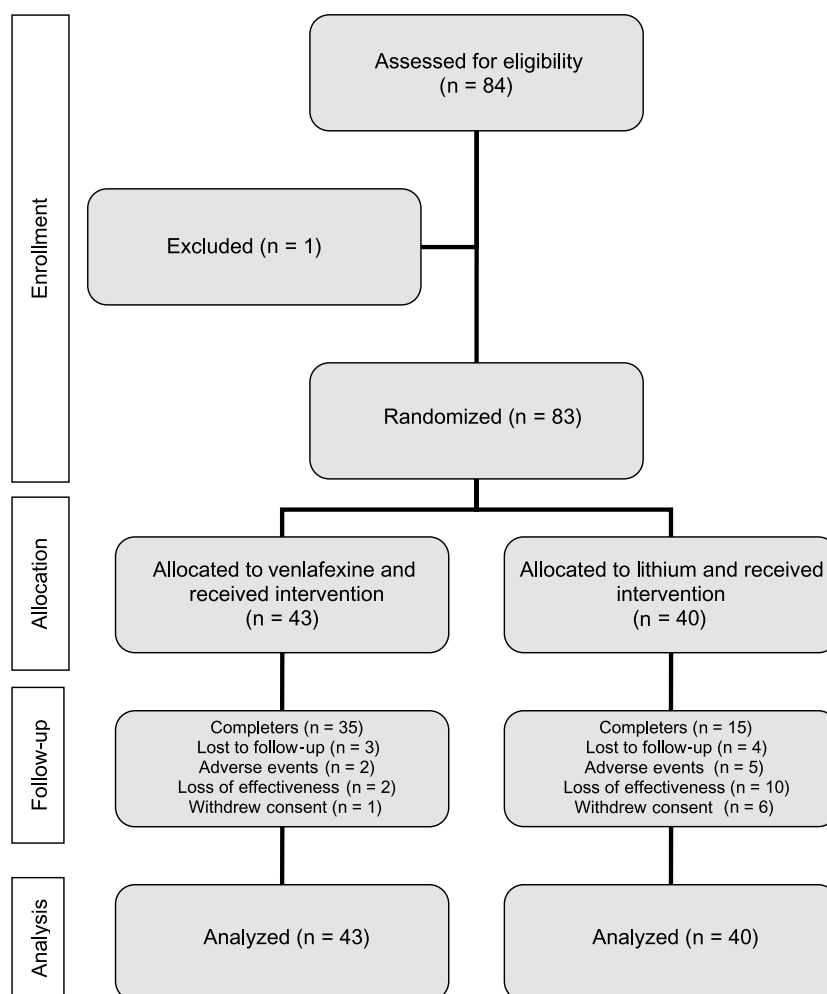


FIGURE 1. Consolidated Standards of Reporting Trials' flow diagram of patient enrollment.

discontinued from the trial. Serum lithium levels were obtained as close as possible to 12 hours after the preceding dose of lithium.

Concomitant therapy with zolpidem 5 to 10 mg, zaleplon 5 to 20 mg, or trazodone 25 to 75 mg was permitted for severe insomnia.

### Outcome Measures

The primary outcome measure is the HAM-D 28 (with embedded HAM-D 17 and HAM-D 17 atypical symptom [HAM-D 17-R]) rating.<sup>57</sup> Secondary outcome measures included change in YMRS, Clinical Global Impressions–Severity (CGI/S) and Change (CGI/C) scores,<sup>58</sup> and the proportion of responder (with  $\geq 50\%$  reduction in baseline HAM-D score) and remitter (final HAM-D score,  $\leq 8$ ) patients.

### Sample Size Justification

The study was powered to detect a difference in response rates of 60% (for venlafaxine) versus 30% (for lithium) based on a 2-group  $\chi^2$  test with a 2-sided significance level of 0.05. The number of subjects needed

to distinguish between these response rates with 80% power was 42 per group.

### Statistical Procedures

Initial analyses were descriptive and included means, medians, ranges, SD, and 95% confidence interval (CI). Sex-specific analyses were also conducted because females are thought to have a higher risk for AD-induced hypomania.<sup>59,60</sup> Box plots were constructed to compare change over time between treatment conditions and to verify that the change was linear. Overlaid individual-level plots of outcomes versus time were assessed using the *xtline* procedure in Stata 9.1.

Primary comparisons implemented quasi-least squares<sup>61</sup> with the *xtqls* procedure for Stata 9.1.<sup>62</sup> Quasi-least squares analysis is based on generalized estimating equations and, similarly, adjusts for the correlation between repeated measurements on the subjects by specifying a working correlation structure of the pattern of association for measurements on each subject. Quasi-least squares analysis was applied to allow for implementation of the Markov correlation structure that models the correlation between repeated measurements  $y_{ij}$  and  $y_{ik}$  from patient  $i$  at time  $t_{ij}$  and  $t_{ik}$  as

$Corr(y_{ij}, y_{ik}) = \alpha^{|t_{ij} - t_{ik}|}$ . This structure was biologically plausible because it forced the correlation between measurements to be smaller when they were measured further apart in time.<sup>62</sup> It also allowed for unequal spacing of measurements in time, which can occur in clinical trials.

A regression model for the expected outcome value for subject *i* at visit *j* was used to test the primary hypothesis that change in HAM-D 28 (and other outcome) scores differed significantly between treatment conditions:

$$E(y_{ij}) = \beta_0 + \beta_1 \text{baseline} + \beta_2 I(\text{Venlafaxine}) + \beta_3 \text{time} + \beta_4 I(\text{Venlafaxine}) \times \text{time}, \tag{1}$$

where *I*(Venlafaxine) takes a value of 1 for venlafaxine and a value of 0 for lithium; baseline = baseline HAM-D 28 score; time = days since baseline for *i* = 1, 2, ..., 84 and *j* = 1, 2, ..., *n<sub>i</sub>*. The model (1) adjusted for the baseline value by including baseline HAM-D 28 as a covariate. The actual date of each visit was used to calculate time in days from baseline.

The expected HAM-D 28 score for each treatment group was calculated using model (1). For example, for a baseline HAM-D 28 score of 24: substitution of *baseline* = 24, *I*(Venlafaxine) = 0 and *time* = 0 in equation 1 yields  $E(y_{ij}) = \beta_0 + 24\beta_1$ . The change over time is  $[\beta_0 + 24\beta_1 + \beta_2 + 77(\beta_3 + \beta_4)] - (\beta_0 + 24\beta_1 + \beta_2) = 77(\beta_3 + \beta_4)$  for venlafaxine, and is  $(\beta_0 + 24\beta_1 + 77\beta_3) - (\beta_0 + 24\beta_1) = 77\beta_3$  for lithium. Change over time differed significantly between conditions if  $\beta_4$  differed significantly from 0, with a greater reduction for venlafaxine if  $\beta_4 < 0$ . The primary hypothesis was therefore tested via the null hypothesis,  $H_0: \beta_4 = 0$  and by assessing whether  $\hat{\beta}_4 < 0$ . We also estimated the difference in change over time between conditions ( $77\hat{\beta}_4$ ) with 95% CI for  $77\hat{\beta}_4$ .

Regression model (1) was also used to examine the change for secondary outcome measures. Fisher exact test was used to compare the proportion of responder and remitter between treatment conditions. In addition, the proportions of patients (with 95% CI) with YMRS cutoff scores of 8 or higher and 12 or higher were computed in each treatment group and were compared using Fisher exact test. In addition, the *t* test and Wilcoxon rank sum test were used to compare the YMRS scores between treatment conditions at each measurement occasion. Quasi-least squares regression models were modified to include demographic and clinical variables to assess whether results were sensitive to the adjustment for these variables.

Finally, we conducted a sensitivity analysis because of the presence of significant differences between the treatment groups at baseline whereby the lithium-treated group had more prior hypomanic episodes, more prior MDEs, an earlier age of illness onset, and longer current MDE duration. We therefore modified the regression models described previously to include these additional factors.

## RESULTS

### Enrollment

Of 84 patients enrolled in the trial, 83 had a baseline study visit and at least 1 postbaseline outcome evaluation: 43 on venlafaxine and 40 on lithium. One patient (1.2%) was a screen failure and did not have a baseline visit. Thirty-three patients (39.8%) discontinued treatment before completing the trial: 11 for lack of efficacy, 13 for adverse events, 2 for noncompliance, and 7 who withdrew consent and were lost to follow-up.

Demographic data from 84 patients included: 48 (57%) women; 69 (82.1%) white, 7 (8.3%) African American, 2 (2.4%) Asian, 3 (3.6%) Hispanic, and 3 (3.6%) other. Mean

**TABLE 1.** Clinical Characteristics of BP II MDE Treatment Groups

	Venlafaxine (n = 43)	Lithium (n = 40)	P
Sex, F/M	23:20	24:16	0.51
White, %	86.1	77.5	0.57
Age, mean (SD)/range, yrs	37.8 (13.3)/19–73	36.3 (13.4)/18–74	0.59
Age at first MDE, mean (SD)/range, yrs	20.8 (10.5)/5–57	16.6 (5.7)/6–38	0.03
Age at first hypomanic episode, mean (SD)/range, yrs	22.0 (8.8)/13–57	20.7 (6.7)/8–38	0.14
No. prior MDEs, mean (SD)/range	6.7 (6.0)/0–30	8.5 (8.1)/0–35	0.25
No. prior hypomanic episodes, mean/range	14.6/1–200	24.9/1–110	0.12
No. prior subsyndromal hypomanic episodes, mean (SD)/range	42.7 (49.2)/0–200	45.9 (59.5)/0–200	0.68
No. prior antidepressants, mean (SD)/range	2.9 (2.37)/1–10	2.30 (0.71)/1–12	NS
No. prior MS, mean (SD)/range	0.58 (1.1)/0–6	0.45 (0.7)/0–3	NS
Illness duration, mean/range, yrs	17.3/1–46	19.8/2–55	0.66
Current MDE, mean/range, mos	14.1/1–90	16.5/0.75–84	0.73
Baseline HAM-D 28, mean (SD)	28.9 (7.5)	28.58 (7.5)	0.72
Baseline YMRS, mean (SD)	0.26 (0.85)	1.2 (2.58)	0.02
Daily dose, mean* (SD)/range, mg	185.6 (92.04)/0–450	966.24 (410.9)/0–2400	—
Serum lithium level, mean (SD)/range, mmol/L	—	0.64 (0.265)/0.29–1.5	—

\*Mean of maximum dose for all treatment visits.

NS indicates not significant.

(SD) age was 37.2 (13.4) years (range, 18–74 years); mean (SD) age at first MDE was 18.7 (8.7) years (range, 5–57 years); mean (SD) age at first hypomanic episode was 20.7 (8.2) years (range, 8–57 years). Mean (SD) illness duration was 18.5 (12.0) years (range, 1–55 years); mean (SD) duration of current MDE was 15.0 (19.3) months (range, 0.75–90 months). The mean (SD) number of prior MDEs was 7.7 (7.2; range, 0–35), the mean (SD) number of prior hypomanic episodes was 42.8 (54.1; range, 1–200), and the mean (SD) number of prior subsyndromal hypomanic episodes was 20.1 (32.0; range, 0–200). Seventy-two patients (85.7%) received prior psychotropic medication: 70 (92.2%) received 1 or more prior AD, 29 (40.3%) received 1 or more MS, and 25 (34.7%) received 1 or more atypical antipsychotic or tranquilizer drug. Only 2 patients (2.8%) received prior MS monotherapy, whereas 32 patients (44.4%) received prior AD monotherapy and 14 patients (19.4%) received combined AD plus MS therapy. Of the prior AD exposures, 57.5% were selective serotonin reuptake inhibitors, 11.7% were bupropion, and 8.5% were venlafaxine. Of the prior MS exposures, 32.6% were lithium, and 20.9% were divalproex.

**Efficacy**

Table 1 displays patient characteristics by treatment condition. Thirty-four venlafaxine-treated patients (79.1%) and 15 lithium-treated patients (37.5%) completed the entire trial ( $P < 0.0005$ , Fisher exact test).

Figure 2 displays the box plots of HAM-D 28 scores over time for each treatment condition. The graph suggests the presence of a greater reduction in HAM-D scores over time for venlafaxine versus lithium monotherapy. Quasi-least squares analysis indicates that there was a significant reduction over time for the HAM-D 28, HAM-D 17, and HAM-D 17-R for both treatment conditions. The difference between treatment conditions was estimated with  $77\hat{\beta}_4$ , with 95% CI for  $77\beta_4$ , where  $\beta_4$  is the regression coefficient for the time  $\times$  treatment interaction term. Change over time be-

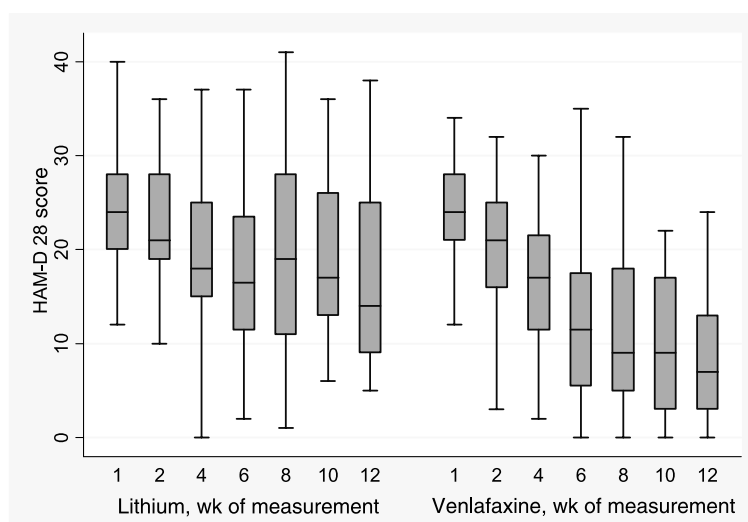
**TABLE 2.** Estimated Difference in Overall Change Between Treatment Groups (Venlafaxine – Lithium) Using Regression Model (1)

Outcome	Estimated Difference in Overall Change Between Treatment Groups ( $77\hat{\beta}_4$ )	95% CI for Difference in Overall Change Between Treatment Groups
HAM-D 28	-6.57	-11.97 to -1.18
HAM-D 17	-4.51	-8.36 to -0.66
HAM-D 17-R	-4.81	-8.69 to -0.93
YMRS	0.02	-0.71 to 0.76

tween treatments (ie,  $H_0: \beta_4 = 0$ ) was also compared. There was a greater reduction during venlafaxine monotherapy for HAM-D 28 ( $77\hat{\beta}_4 = -6.57$ ; 95% CI, -11.97 to -1.18) ( $P = 0.017$ ), HAM-D 17 ( $77\hat{\beta}_4 = -4.51$ ; 95% CI, -8.36 to -0.66) ( $P = 0.022$ ), and HAM-D 17-R ( $77\hat{\beta}_4 = -4.81$ ; 95% CI, -8.69 to -0.93) ( $P = 0.015$ ) ratings. The reduction over time in HAM-D 28 score was therefore 6.57 (95% CI, 1.18 to 11.97) greater for venlafaxine versus lithium. There was also a greater improvement over time in the CGI/S score ( $77\hat{\beta}_4 = -1.15$ ; 95% CI, -1.83 to -0.47) ( $P = 0.009$ ) during venlafaxine monotherapy, although a similar improvement in CGI/C scores was not seen ( $77\hat{\beta}_4 = -0.45$ ; 95% CI, -1.27 to 0.31) ( $P = 0.247$ ).

Table 2 displays the estimated difference in change over time between conditions ( $77\hat{\beta}_4$ ) with 95% CI for  $77\beta_4$ . For example, for HAM-D 28  $77\hat{\beta}_4 = -6.57$  with 95% CI, -11.97 to -1.18. This indicates that the estimated reduction in HAM-D 28 scores was 6.57 greater for venlafaxine versus lithium. The negative value (-1.18) for the upper limit of 95% CI indicates that the reduction in HAM-D 28 scores was significantly greater for venlafaxine versus lithium.

There was a greater proportion of venlafaxine-treated (vs lithium-treated) patients classified as responder: HAM-D



**FIGURE 2.** Box plots of HAM-D 28 scores versus week of measurement during venlafaxine or lithium monotherapy.

**TABLE 3.** Mean (SD) YMRS Scores for Venlafaxine Versus Lithium Treatment Conditions

	Baseline	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
Venlafaxine	0.26 (0.85)	0.14 (0.68)	0.41 (1.20)	0.40 (2.37)	0.45 (1.72)	0.85 (3.18)	0.43 (1.27)	0.44 (1.19)
Lithium	1.2 (2.58)	0.46 (1.27)	0.46 (1.22)	0.67 (1.71)	0.29 (0.90)	0.72 (1.81)	1.14 (2.78)	0.87 (1.68)
<i>P</i> *	0.02	0.16	0.88	0.59	0.59	0.86	0.19	0.31

\*Analyzed using *t* test and Wilcoxon rank sum test.

28 [60.4%] of 43 vs 8 [20.0%] of 40;  $P < 0.0005$ ), HAM-D 17 (25 [58.1%] of 43 vs 8 [20.0%] of 40) ( $P = 0.001$ ), and HAM-D 17-R (26 [60.5%] of 43 vs 8 [20.0%] of 40;  $P < 0.0005$ ), respectively. Similarly, there was a greater proportion of venlafaxine-treated (vs lithium-treated) patients classified as remitter: HAM-D 28 (19 [44.2%] of 43 vs 3 [7.5%] of 40;  $P < 0.0005$ ), HAM-D 17 (25 [58.1%] of 43 vs 6 [15.0%] of 40;  $P < 0.0005$ ), and HAM-D 17-R (25 [58.1%] of 43 vs 7 [17.5%] of 40;  $P < 0.0005$ ), respectively.

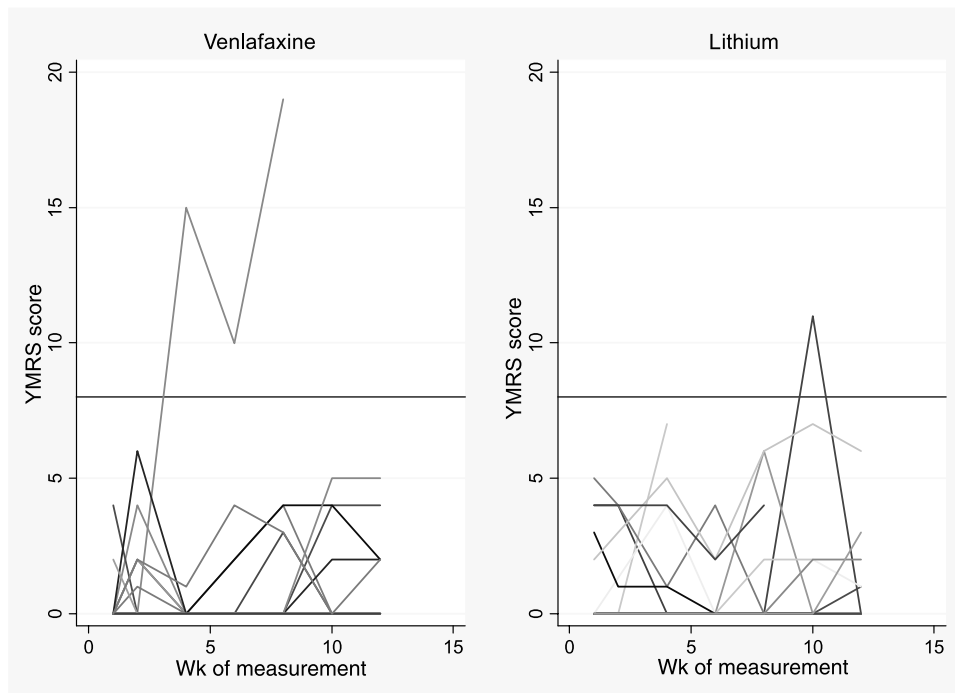
In addition to the intent-to-treat analysis, we repeated the calculations using completer data in the denominator. We again found a greater proportion of venlafaxine-treated (26 [76.5%] of 34) versus lithium-treated (8 [53.3%] of 15) patients classified as responder on the final HAM-D 28 ( $P = 0.18$ ), HAM-D 17 (25 [73.5%] of 34 vs 8 [53.3%] of 15) ( $P = 0.20$ ), and HAM-D 17-R (26 [76.5%] of 34 vs 8 [53.3%] of 15;  $P = 0.18$ ), respectively. Similarly, there was a greater proportion of venlafaxine-treated (19 [55.9%] of 34) versus lithium-treated (3 [20.0%] of 15) patients classified as remitter on the final HAM-D 28 ( $P = 0.03$ ), HAM-D 17 (25 [73.5%] of 34

vs 6 [40.0%] of 15;  $P = 0.051$ ), and HAM-D 17-R (25 [73.5%] of 34 vs 7 [46.7%] of 15;  $P = 0.10$ ), respectively.

Finally, we conducted a sensitivity analysis because of the presence of significant differences between the treatment groups at baseline whereby the lithium-treated group had more prior hypomanic episodes, more prior MDEs, had an earlier age of illness onset, and had longer current MDE duration. We modified the regression models to include these additional factors. The results were unchanged.

### Hypomanic Symptoms

The median and mean (SD) YMRS scores at baseline (before randomization) for all patients were 0 and 0.71 (1.93), respectively. The median YMRS scores at each week after randomization for venlafaxine versus lithium were 0 versus 0, whereas the mean (SD) YMRS scores for venlafaxine versus lithium are displayed in Table 3. A *t* test and Wilcoxon rank sum test were used to compare the YMRS scores between treatment conditions at each measurement occasion. Mean YMRS scores were slightly higher at all weeks for the lithium-treated versus the venlafaxine-treated



**FIGURE 3.** Individual-level (overlaid) profile plots of YMRS scores versus week of measurement during lithium or venlafaxine monotherapy, by treatment group. A horizontal line is displayed at YMRS = 8.

group, except for week 6 when the mean YMRS score was slightly higher in the venlafaxine-treated group. There was no significant difference in mean YMRS scores at any week, except for baseline when the YMRS scores were significantly higher for the lithium-treated group ( $P = 0.02$ ).

Figure 3 displays overlaid individual-level plots of YMRS scores over time for each treatment condition. This figure also displays the horizontal line of the conservative YMRS cutoff value of 8 or higher for subsyndromal hypomanic and hypomanic symptoms. Only 2 patients (2.5%; 95% CI, 0.3 to 8.6) had a YMRS score of 8 or higher on at least 1 study visit: 1 patient on venlafaxine (2.4%; 95% CI, 0.06 to 12.6), and 1 patient on lithium (2.6%; 95% CI, 0.06 to 13.5) ( $P = 0.99$ ).

Using a slightly less conservative YMRS cutoff score of 12 or higher, only 1 venlafaxine-treated patient (2.4%) and no lithium-treated patient had this score ( $P = 0.99$ ) (note that the venlafaxine-treated patient with a YMRS score  $\geq 8$  was the same subject with the YMRS score  $\geq 12$ ). Quasi-least squares analysis indicated that there was no significant increase in YMRS scores over time with venlafaxine (vs lithium), and no significant increase in YMRS scores at any study visit (vs baseline) for either treatment condition. The estimated difference in the overall change in YMRS score between treatment conditions was  $77\beta_4 = 0.02$  (95% CI,  $-0.71$  to  $0.76$ ) greater for venlafaxine versus lithium. This represents a difference between treatments in YMRS change scores from baseline to week 12 of 0.02, which is clinically and statistically insignificant. Finally, bivariate and quasi-least squares analyses failed to identify any demographic or clinical variable associated with change in YMRS ratings.

### Missing Data

There were 83 subjects at baseline, 81 at week 1, 76 at week 2, 73 at week 4, 68 at week 6, 64 at week 8, 56 at week 10, and 49 at week 12. The mean number of measurements per subject was 5.5 (median, 7). We used intent-to-treat with a regression model that allowed for a variable number of observations, so that no subject was dropped from the data analysis. Secondary analyses were used to assess the sensitivity of our findings to missing data by replacing the missing value(s) on each subject with baseline value(s) in the regression analyses. There was no difference between the 2 approaches (with the exception that venlafaxine efficacy was more pronounced for the imputed data).

### Safety

Thirteen patients (15.7%) withdrew from treatment due to an adverse event. There was 1 serious adverse event in the lithium-treated group, which was judged to be unrelated to drug therapy. Table 4 displays the frequency of reported and elicited adverse events from 83 patients who completed the baseline evaluation. Most adverse events were rated as mild or moderate in intensity. There were no clinically meaningful changes in vital signs, physical findings, or laboratory values. There were no cases of lithium toxicity. Finally, there were 2 occurrences of hypomania during venlafaxine and 1 occurrence with lithium. Two venlafaxine-treated patients and 1

**TABLE 4.** Number (%) of Adverse Event Occurrences

Body System	Adverse Event	Venlafaxine (n = 43)	Lithium (n = 40)
Body as a whole	Cardiovascular	7 (16.4)	4 (10.0)
	Dizziness	3 (7.0)	5 (12.5)
	Flulike symptoms	11 (25.6)	4 (10.0)
	Headaches	15 (34.9)	13 (32.5)
	Increased appetite	2 (4.7)	0 (0.0)
	Jitteriness	1 (2.3)	2 (5.0)
	Nose bleeds	2 (4.7)	0 (0.0)
	Polydipsia	4 (9.3)	25 (62.5)
	Polyuria	2 (4.7)	27 (67.5)
	Rash/Itchiness	7 (16.3)	3 (7.5)
	Restless leg	0 (0.0)	2 (5.0)
	Sweating	6 (14.0)	2 (5.0)
	Tremor	6 (14.0)	22 (55.0)
	Weight gain	4 (9.3)	8 (20.0)
	Yawning	2 (4.7)	0 (0.0)
	Other	11 (25.6)	16 (40.0)
	Gastrointestinal system	Constipation	10 (23.3)
Diarrhea		4 (9.3)	8 (20.0)
Dry mouth		14 (32.6)	4 (10.0)
Dyspepsia		1 (2.3)	2 (5.0)
Gastrointestinal upset		5 (11.6)	9 (22.5)
Metallic taste		0 (0.0)	2 (5.0)
Nausea/vomiting		11 (25.6)	19 (47.5)
Psychiatric	Abnormal dreams	6 (14.0)	1 (2.5)
	Agitation/anxiety	5 (11.6)	1 (2.5)
	Thinking difficulty	7 (16.3)	13 (32.5)
	Hypomania	2 (4.7)	0 (0.0)
	Sleep disturbance	11 (25.6)	3 (7.5)
	Irritability	2 (4.7)	1 (2.5)
	Lethargy	1 (2.3)	3 (7.5)
	Somnolence	13 (30.2)	9 (22.5)
	Suicidal ideation	0 (0.0)	1 (2.5)
	Sexual	Delayed orgasm	10 (23.3)
Sexual dysfunction		4 (9.3)	0 (0.0)

One patient discontinued treatment of hypomanic induction (venlafaxine), and 1 patient discontinued treatment of increasing suicidal ideation (lithium).

lithium-treated patient received concurrent treatment of insomnia with zolpidem or zaleplon, and 1 venlafaxine-treated and 3 lithium-treated patients received trazadone for insomnia. Finally, 1 venlafaxine-treated patient discontinued treatment of hypomania, and 1 patient discontinued lithium treatment of increased suicidal ideation.

### DISCUSSION

Despite a paucity of controlled clinical data supporting the initial use of MS monotherapy for BP II MDE, it remains the most frequently recommended therapy.<sup>33-39</sup> To date, however, there are few controlled clinical trials supporting this strategy. Early studies found tricyclic antidepressant (TCA) monotherapy (or combined lithium plus TCA therapy)

to be superior to lithium monotherapy.<sup>46,63</sup> These studies generally included mixed BP I and BP II MDE populations. As a result, conclusions about the relative efficacy of MS versus AD monotherapy for BP II MDE remain limited. A recent 12-month efficacy trial comparing 2 MS monotherapies, lithium versus carbamazepine, in BP I and BP II MDE patients found a modest (33%) response rate for both therapies, with neither treatment reducing the time spent in depression.<sup>51</sup> Although newer MS agents may have improved antidepressant efficacy, most studies have focused exclusively on BP I disorder.<sup>64–71</sup>

The recommendation for using initial MS monotherapy for BP II MDE derives principally from results of BP I MDE studies of TCA-induced manic switch episodes.<sup>41–44,46</sup> Estimates of AD-induced manic and hypomanic switch rates in BP disorder have ranged either from 2% to 70% and are largely based on observations with TCAs in BP I MDE patients<sup>42,46,72–79</sup> or from naturalistic or chart review studies of mixed BP I and BP II populations.<sup>42,66,75</sup> In contrast, patients with BP II disorder may be less likely to have AD-induced hypomania.<sup>13–17,76–82</sup> In 1 prospective study, Kupfer et al<sup>78</sup> found that BP II patients were no more likely than unipolar patients to develop hypomania during AD monotherapy.

More recently, we examined the efficacy and hypomanic switch rate of fluoxetine monotherapy for 8 weeks in 37 BP II MDE patients.<sup>14,16</sup> Fourteen patients (38%) responded to treatment with a final HAM-D score of 9 or lower. We found no change in mean YMRS scores at any study visit compared with baseline ( $P = 0.93$ ). Only 3 patients (8.1%) had a YMRS score of 8 or higher at 2 study visits, and only 3 patients (8.1%) met *DSM-IV* criteria for a brief hypomanic episode. In a separate 6-week dose-escalation study of venlafaxine monotherapy up to 225 mg/d in 17 BP II and 31 unipolar MDE patients, venlafaxine resulted in a significant reduction in HAM-D 17 scores in both patient groups ( $P < 0.001$ ), with no difference in efficacy between groups. We observed no hypomanic episodes.

Results from the present study extend these earlier observations and suggest that initial AD monotherapy with venlafaxine may be an effective treatment of BP II MDE with a low hypomanic switch rate. We observed a greater reduction in HAM-D 28, HAM-D 17, HAM-D 17-R, and CGI/S ratings during venlafaxine (vs lithium) monotherapy. We also found a greater proportion of treatment responder and remitter patients with venlafaxine monotherapy. In contrast to the expected high frequency of hypomanic and subsyndromal hypomanic symptoms during venlafaxine monotherapy, we observed no significant increase in YMRS scores over time with either venlafaxine or lithium monotherapy ( $P = 0.85$ ).

Other investigators have reported a higher frequency of hypomanic symptoms during venlafaxine therapy. For example, Vieta et al<sup>83</sup> reported a higher manic switch rate with venlafaxine compared with paroxetine, whereas Leverich et al<sup>84</sup> observed a greater frequency of hypomanic symptoms during venlafaxine treatment compared with sertraline and bupropion. However, these studies were either limited to patients with BP I disorder<sup>83</sup> or included a mixed population of BP I, BP II, BP not otherwise specified, and schizoaffective

patients.<sup>84</sup> In addition, the studies of Altshuler et al<sup>82</sup> and Leverich et al<sup>84</sup> had several methodological shortcomings, including unbalanced dispensing of bupropion that may have led to outcome bias against venlafaxine. Moreover, these studies did not specifically compare AD with MS monotherapy, and all patients were taking concurrent MS and/or atypical antipsychotic therapy.

Several caveats should be considered in the interpretation of the present findings. For example, our study did not use a patient-recorded daily chronorecord for identifying ultrashort affective episodes. It is possible that we missed the presence of subsyndromal hypomanic or episodes that occurred between study visits. However, the estimated difference in change in YMRS scores across all study visits was only 0.02 (95% CI,  $-0.98$  to  $1.03$ ) for venlafaxine (vs lithium) monotherapy. Nevertheless, the failure to find a difference in YMRS scores over time between treatment conditions is not proof that a difference did not exist. In addition, we would note that although this study was powered to detect differences in response rates between treatment conditions, it was not powered to detect differences in hypomanic switch rates between treatments. In this regard, larger sample sizes would have been required to detect a significant difference in hypomanic switch rates, if these were assumed to be small and similar between the 2 treatment conditions. Nevertheless, the observed treatment group difference in change in YMRS scores of 0.02 for 12 weeks during venlafaxine monotherapy is clinically and statistically insignificant.

It is possible that the frequency of venlafaxine-induced hypomanic symptoms may have been higher had a longer treatment duration been used. However, observations from our prior fluoxetine and venlafaxine monotherapy studies indicated that most treatment-emergent hypomanic symptoms occurred before week 6 of treatment, if at all.<sup>13–17,52</sup>

The lack of a placebo control group placed constraints on our ability to assess the true comparative efficacy of venlafaxine versus lithium monotherapy, as well as our ability to determine the true comparative hypomania switch rate during venlafaxine and lithium treatments. It is possible that the low frequency of hypomanic symptoms during venlafaxine monotherapy represents the background frequency in patients with BP II MDE, rather than true drug-induced hypomanic symptoms. Whereas Vieta et al<sup>83</sup> and Leverich et al<sup>84</sup> found higher manic symptom rates with venlafaxine in BP I MDE patients, other investigators have reported a low incidence of drug-induced hypomanic symptoms during venlafaxine monotherapy in patients with BP II disorder<sup>82,85</sup> and have suggested that venlafaxine may act as an MS in some BP II patients.<sup>85,86</sup>

It is possible that a slower dose titration of lithium (vs venlafaxine), because of the need to achieve therapeutic lithium levels, may have disadvantaged lithium, and that this difference resulted in a superiority of venlafaxine treatment. However, patients in both treatment conditions had a gradual dose increase based on symptom change and tolerability. Although the mean (SD) maximum dose of venlafaxine was 186 (92) mg/d, the maximum lithium dose of 966.24 (410.9) mg/d was limited by a maximum serum lithium level of 1.5 mmol/L. Thus, it is possible that the modest

efficacy of lithium was an artifact that may have disappeared with higher lithium doses. However, we would also note that a mean (SD) daily lithium dose of 966.2 (410.9) mg and a mean (SD) serum lithium level of 0.64 (0.265) mmol/L may also have been responsible for the higher treatment discontinuation rate in the lithium (vs venlafaxine) treatment condition. Maximized lithium dosing was generally limited by adverse events. We would also note that standard dosing of venlafaxine or lithium for the initial treatment of BP II MDE has not yet been established, and the benefit of long-term AD or MS monotherapy for BP II disorder remains uncertain.

It is possible that the modest efficacy of lithium monotherapy was an artifact of the limited sample size and 12-week treatment duration, and that this finding may have disappeared with a larger sample size treated for a longer period. We would note, however, that this study was powered to detect differences in response rates of the HAM-D 28 during short-term monotherapy. The relative benefit of this treatment strategy during long-term, relapse-prevention therapy remains to be established.

Finally, we acknowledge the shortcoming of a randomized open-label study design, and note that this limitation may have introduced a study bias. We submit, however, that this methodological limitation does not invalidate the present results that support observations reported from earlier double-blind studies of BP II MDE therapy.<sup>14–17,77,82,84,86</sup> Moreover, we are unaware of any other adequately powered, prospective randomized studies to date comparing AD to MS monotherapy for BP II MDE. We would certainly recommend that future clinical trials of AD versus MS monotherapy for BP II MDE use a double-blind placebo-controlled design.

## CONCLUSIONS

This study compared venlafaxine monotherapy with lithium monotherapy for the initial treatment of BP II MDE. We hypothesized that venlafaxine monotherapy would be superior to lithium monotherapy with a similar hypomanic switch rate. We observed a significantly greater reduction of depressive symptoms during venlafaxine versus lithium monotherapy. There was also a significantly greater proportion of patients classified as treatment responder or remitter during venlafaxine monotherapy in an analysis that treated subjects who dropped out before the end of the study as nonresponders. These observations suggest that venlafaxine monotherapy may be a safe and effective initial treatment of BP II MDE with a low frequency of hypomanic symptoms.

## ACKNOWLEDGMENT

The authors thank Michelle Shwarz, MSED, for her assistance in data management and in the preparation of the manuscript.

## AUTHOR DISCLOSURE INFORMATION

Dr Amsterdam currently receives research grant support from the National Institute of Mental Health, Bethesda,

Md; the National Institutes of Health's National Center for Complementary and Alternative Medicine, Bethesda, Md; Lilly Research Laboratories, Indianapolis, Ind; and Sanofi Aventis, Bridgewater, NJ. He is on the speaker's bureau of Wyeth, Madison, NJ, and Bristol-Myer Squibb, New York, NY.

Dr Shults was supported by grant R01CA096885 from the National Institutes of Health.

## REFERENCES

1. Simpson SG, Folstein SE, Meyers DA, et al. Bipolar II: the most common bipolar phenotype? *Am J Psychiatry*. 1993;150:901–903.
2. Akiskal HS. The dark side of bipolarity: detecting bipolar depression in its pleomorphic expressions. *J Affect Disord*. 2005;84:107–115.
3. Akiskal HS, Benazzi F. Atypical depression: a variant of bipolar II or a bridge between unipolar and bipolar II? *J Affect Disord*. 2005;84:209–217.
4. Berk M, Dodd S. Bipolar II disorder: a review. *Bipolar Disord*. 2005;7:11–23.
5. Mendlowicz MV, Akiskal HS, Kelsoe JR, et al. Temperament in the clinical differentiation of depressed bipolar and unipolar major depressive patients. *J Affect Disord*. 2005;84:219–223.
6. Dunner DL, Fleiss JL, Fieve RR. The course of development of mania in patients with recurrent depression. *Am J Psychiatry*. 1976;133:905–908.
7. Benazzi F. Prevalence of bipolar II disorder in outpatient depression. A 203-case study in private practice. *J Affect Disord*. 1997;43:163–166.
8. Ghaemi SN, Sachs GS, Chiou AM, et al. Is bipolar disorder still under diagnosed? Are antidepressants over utilized? *J Affect Disord*. 1999;52:135–144.
9. Ayuso-Gutierrez JL, Ramos-Brieva JA. The course of manic-depressive illness: a comparative study of bipolar I and bipolar II patients. *J Affect Disord*. 1982;4:9–14.
10. Winokur G, Coryell W, Keller M, et al. A prospective follow-up of patients with bipolar and primary unipolar affective disorder. *Arch Gen Psychiatry*. 1993;50:457–465.
11. Coryell W, Endicott J, Maser JD, et al. Long-term stability of polarity distinctions in the affective disorders. *Am J Psychiatry*. 1995;152:385–390.
12. Peet M. Induction of mania with serotonin re-uptake inhibitors and tricyclic antidepressants. *Br J Psychiatry*. 1994;164:549–550.
13. Amsterdam JD, Garcia-Espana F, Fawcett J, et al. Efficacy and safety of fluoxetine in bipolar II major depressive episode. *J Clin Psychopharmacol*. 1998;18:435–440.
14. Amsterdam JD, Shults J, Brunswick DJ, et al. Short-term fluoxetine monotherapy for bipolar type II or bipolar NOS major depression—low manic switch rate. *Bipolar Disord*. 2004;6:75–81.
15. Amsterdam JD, Brunswick DJ. Antidepressant monotherapy for bipolar type II major depression. *Bipolar Disord*. 2003;5:388–395.
16. Amsterdam JD, Shults J. Fluoxetine monotherapy for bipolar type II and bipolar NOS major depression—a double-blind, placebo-substitution, continuation study. *Int Clin Psychopharmacol*. 2005;20:357–364.
17. Amsterdam JD, Shults J. Comparison of fluoxetine, olanzapine, and fluoxetine plus olanzapine in bipolar type I and bipolar type II major depression—lack of manic induction. *J Affect Disord*. 2005;87:121–130.
18. Coryell W. Bipolar II disorder: a progress report. *J Affect Disord*. 1996;41:159–162.
19. Vieta E, Gasto C, Otero A, et al. Differential features between bipolar I and bipolar II disorder. *Compr Psychiatry*. 1997;38:98–101.
20. Serretti A, Olgiati P. Profiles of “manic” symptoms in bipolar I, bipolar II and major depressive disorders. *J Affect Disord*. 2005;84:159–166.
21. Akiskal H. The spectrum of bipolar disorder beyond DSM. *J Clin Psychopharmacol*. 1996;16(suppl 1):S4–S14.
22. Kupfer DJ, Carpenter LL, Frank E. Is bipolar II a unique disorder? *Compr Psychiatry*. 1988;29:228–236.
23. Sharma V, Khan M, Smith A. A closer look at treatment resistant depression: is it due to a bipolar diathesis? *J Affect Disord*. 2005;84:251–257.
24. Bowden CL. A different depression: clinical distinctions between bipolar and unipolar depression. *J Affect Disord*. 2005;84:117–125.
25. O'Connell RA, Mayo JA, Flatow L, et al. Outcome of bipolar disorder on long-term treatment with lithium. *Br J Psychiatry*. 1991;159:123–129.

26. Dunner DL. Sub-types of bipolar affective disorder with particular regard to bipolar II. *Psychiatr Dev*. 1983;1:75–85.
27. Endicott J, Nee J, Andreasen N, et al. Bipolar II: combine or keep separate? *J Affect Disord*. 1985;8:17–28.
28. Akiskal HS, Cassano GB, Muzetti L, et al. Psychopathology, temperament, and past course in primary major depressions: 1. Review of evidence for a bipolar spectrum. *Psychopathology*. 1989;22:268–277.
29. Calabrese JR, Hirschfeld RM, Reed M, et al. Impact of bipolar disorder on a U.S. community sample. *J Clin Psychiatry*. 2003;64:425–432.
30. Perlis RH, Miyahara S, Marangell LB, et al, and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry*. 2004;1:875–881.
31. Simon NM, Otto MW, Weiss RD, et al, and the STEP-BD Investigators. Pharmacotherapy for bipolar disorder and comorbid conditions: baseline data from STEP-BD. *J Clin Psychopharmacol*. 2004;24:512–520.
32. Dunner DL. Bipolar disorders in DSM-IV: impact of inclusion of rapid cycling as a course modifier. *Neuropsychopharmacology*. 1998;19:189–193.
33. American Psychiatric Association. Practice guidelines for the treatment of patients with bipolar disorder. *Am J Psychiatry*. 1994;151:1–36.
34. American Psychiatric Association. Practice guidelines for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry*. 2002;159:1–50.
35. Expert Consensus Panel for Bipolar Disorder. Treatment of bipolar disorder. *J Clin Psychiatry*. 1996;57(suppl 12A):1–88.
36. Fountoulakis KN, Vieta E, Sanchez-Moreno J, et al. Treatment guidelines for bipolar disorder: a critical review. *J Affect Disord*. 2005;86:1–10.
37. Yatham LN, Kusumakar V, Parikh SV, et al. Bipolar depression: treatment options. *Can J Psychiatry*. 1997;42(suppl 2):87S–91S.
38. Sachs GS, Printz DJ, Kahn DA, et al. The Expert Consensus Guidelines™: Medication Treatment of Bipolar Disorder 2000. A Postgraduate Medicine Special Report. New York, NY: McGraw-Hill Book Co; 2000.
39. Thase ME, Sachs GS. Bipolar depression: pharmacotherapy and related therapeutic strategies. *Biol Psychiatry*. 2000;48:558–572.
40. Dantzer A, Osser DN. Algorithms for the pharmacotherapy of acute depression in patients with bipolar disorder. *Psychiatr Ann*. 1999;29:270–284.
41. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. *J Clin Psychiatry*. 2000;61:804–808.
42. Ghaemi SN, Klara JR, Ko JY, et al. Antidepressant treatment in bipolar versus unipolar depression. *Am J Psychiatry*. 2004;161:163–165.
43. Wehr TA, Goodwin FK. Can antidepressants cause mania and worsen the course of affective illness? *Am J Psychiatry*. 1987;144:1403–1411.
44. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. *Am J Psychiatry*. 1995;152:1130–1138.
45. Goldberg J, Ghaemi SN. Benefits and limitations of antidepressants and traditional mood stabilizers for treatment of bipolar depression. *Bipolar Disord*. 2005;7:3–12.
46. Goodwin FK, Jamison KR. *Manic Depressive Illness*. New York: Oxford University Press; 1990.
47. Bauer MS, Altshuler L, Evans DE, et al. Prevalence and distinct correlates of anxiety, substance, and combined morbidity in a multi-site public sector sample with bipolar disorder and the VA Cooperative Study #430 Team. *J Affect Disord*. 2005;85:301–315.
48. Rihmer Z, Pestalpy P. Bipolar II disorder and suicidal behavior. *Psychiatr Clin North Am*. 1999;22:667.
49. Geddes J, Goodwin G. Bipolar disorder: clinical uncertainty, evidence-based medicine and large-scale randomized trials. *Br J Psychiatry*. 2001;178(suppl 41):S191–S194.
50. Tondo L, Baldessarini RJ, Floris G. Long-term clinical effectiveness of lithium maintenance treatment in types I and II bipolar disorders. *Br J Psychiatry*. 2001;178(suppl 41):S184–S190.
51. Denicoff KD, Smith-Jackson EE, Disney ER, et al. Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J Clin Psychiatry*. 1997;58:470–478.
52. Amsterdam JD. Efficacy and safety of venlafaxine in bipolar type-II major depressive episode. *J Clin Psychopharmacol*. 1998;18:414–417.
53. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity, and sensitivity. *Br J Psychiatry*. 1978;133:429–435.
54. Williams JBW. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry*. 1988;45:742–747.
55. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/ PSY SCREEN)*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2001.
56. Fawcett J, Epstein P, Fiester SJ, et al. Clinical management—imipramine/placebo administration manual: NIMH Treatment of Depression Collaborative Research Program. *Psychopharmacol Bull*. 1987;23:309–324.
57. Reimherr FW, Amsterdam JD, Fawcett J, et al. Optimal length of continuation therapy: a prospective assessment during fluoxetine long-term treatment. *Am J Psychiatry*. 1998;55:1247–1253.
58. Guy W, ed. *ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338*. Washington, DC: US Department of Health, Education, and Welfare; 1976:218–222.
59. Leibenluft E. Women with bipolar illness: clinical and research issues. *Am J Psychiatry*. 1998;153:163–173.
60. Leibenluft E. Issues in the treatment of women with bipolar illness. *J Clin Psychiatry*. 1997;58(suppl 15):5–11.
61. Chaganty NR, Shults J. On eliminating the asymptotic bias in the quasi-least squares estimate of the correlation parameter. *J Stat Plan Inference*. 1999;76:127–144.
62. Shults J, Ratcliffe S, Leonard M. Improved generalized estimating equation analysis via xtqls for implementation of quasi-least squares in Stata. *Stata Journal*. 2007;7:147–166.
63. Prien RF, Klett CJ, Caffey EM Jr. Lithium carbonate and imipramine in prevention of affective episodes: a comparison in recurrent affective illness. *Arch Gen Psychiatry*. 1973;29:420–425.
64. Katzow JJ, Desai SP, Goodwin FK. Gabapentin treatment of mood disorders: a preliminary study. *J Clin Psychiatry*. 1998;59:426–429.
65. Ghaemi SN, Berv DA, Klugman J, et al. Oxcarbazepine treatment of bipolar disorder. *J Clin Psychiatry*. 2003;64:943–945.
66. Goldberg JF. When do antidepressants worsen the course of bipolar disorder? *J Psychiatr Pract*. 2003;9:181–194.
67. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. *J Clin Psychiatry*. 1999;60:79–88.
68. Marangell LB, Martinez JM, Ketter TA, et al, and the STEP-BD Investigators. Lamotrigine treatment of bipolar disorder: data from the first 500 patients in STEP-BD. *Bipolar Disord*. 2004;6:139–143.
69. 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;60:1079–1088.
70. Shelton RC. The use of antidepressants in novel combination therapies. *J Clin Psychiatry*. 2003;64(suppl 2):14–18.
71. Davis LL, Bartolucci A, Petty F. Divalproex in the treatment of bipolar depression: a placebo-controlled study. *J Affect Disord*. 2005;85:259–266.
72. Goodwin FK, Ghaemi SN. Understanding manic-depressive illness. *Arch Gen Psychiatry*. 1998;55:23–25.
73. Ghaemi SN, Hsu DJ, Soldami F, et al. Antidepressants in bipolar disorder: the case for caution. *Bipolar Disord*. 2003;5:421–433.
74. Bowden C. New concepts in mood stabilization: Evidence for the effectiveness of valproate and lamotrigine. *Eur Neuropsychopharmacol*. 1996;6(suppl 3):S98.
75. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. *Bipolar Disord*. 2003;5:407–420.
76. Cohn JB, Collins G, Ashbrook E, et al. A comparison of fluoxetine, imipramine and placebo in patients with bipolar depressive disorder. *Int Clin Psychopharmacol*. 1989;4:313–322.
77. Kupfer DJ, Chengappa KNR, Gelenberg AJ, et al. Citalopram as adjunctive therapy in bipolar depression. *J Clin Psychiatry*. 2001;62:985–990.
78. Kupfer DJ, Carpenter LL, Frank E. Possible role of antidepressants in precipitating mania and hypomania in recurrent depression. *Am J Psychiatry*. 1988;145:804–808.

79. Stoll AL, Mayer PV, Kolbrener M, et al. Antidepressant-associated mania—a controlled comparison with spontaneous mania. *Am J Psychiatry*. 1994;151:1642–1645.
80. Howland RH. Induction of mania with serotonin reuptake inhibitors. *J Clin Psychopharmacol*. 1996;16:425–427.
81. Amsterdam JD, Garcia-Espana F. Venlafaxine monotherapy in women with bipolar II depression. *J Affect Disord*. 2000;59:225–229.
82. Altshuler LL, Suppes T, Black DO, et al. Lower switch rate in depressed patients with bipolar II than bipolar I disorder treated adjunctively with second-generation antidepressants. *Am J Psychiatry*. 2006;163:313–315.
83. Vieta E, Martinez-Aran A, Goikolea JM, et al. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. *J Clin Psychiatry*. 2002;63:508–512.
84. Leverich GS, Altshuler LL, Frye MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. *Am J Psychiatry*. 2006;163:232–239.
85. Parker G, Parker K. Which antidepressants flick the switch? *Am J Psychiatry*. 2003;37:464.
86. Parker G, Tully L, Olley A, et al. SSRIs as mood stabilizers for bipolar II disorder: a proof of concept study. *J Affect Disord*. 2006;92:205–214.