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Safety and Effectiveness of Continuation Antidepressant Versus Mood Stabilizer Monotherapy for Relapse-prevention of Bipolar II Depression: A Randomized, Double-blind, Parallel-group, Prospective Study

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Abstract

Objective—Compare the safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy for preventing depressive relapse in bipolar II disorder.

Methods—Subjects 18 years old with bipolar II depression (n=129) were randomized to double-blind venlafaxine or lithium monotherapy for 12 weeks. Responders with a 50% reduction in depression score were continued for an additional 6 months of relapse-prevention monotherapy. Primary outcome was depressive relapse during continuation monotherapy. Secondary outcomes included sustained response rate from initiation of treatment to study end-point, relapse hazard, time to relapse, change in mania ratings, and frequency of treatment-emergent sub-syndromal hypomania and/or depressive episodes.

Results—Venlafaxine produced greater sustained response rate versus lithium ($p<0.0001$); however, there was no difference in relapse rate for venlafaxine (7.5%) versus lithium (26.7%) ($p=0.079$); relapse hazard ($p=0.073$), or time to relapse ($p=0.090$) between treatment conditions during continuation monotherapy. There were no group differences in mania rating scores over time and no difference in frequency or duration of syndromal or sub-syndromal hypomanic episodes. There were more sub-syndromal depressive episodes during lithium monotherapy ($p=0.03$).

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Limitations—Sample size was limited by the lower sustained response rate for lithium versus venlafaxine; study was not specifically powered to detect differences in treatment-emergent hypomanic or depressive episodes between groups.

Conclusion—Results suggest that continuation venlafaxine monotherapy may provide similar prophylactic effectiveness relative to lithium, with no difference in treatment-emergent hypomanic episodes and without the need for frequent serum lithium level and metabolic monitoring. Larger, prospective trials are needed to confirm these observations.

Keywords

Bipolar II disorder; Bipolar II depression; venlafaxine; lithium; antidepressant; mood conversion; relapse-prevention; clinical trial

Introduction

The use of antidepressant medication to treat bipolar type II disorder remains a controversial practice (Bond et al., 2008; Gitlin and Frye, 2012; Pacchiarotti et al., 2013; Parker, 2015; Parker et al., 2006). Practice guidelines for long-term therapy of bipolar II disorder generally recommend mood stabilizer monotherapy and the discontinuation of antidepressant medication within 12-20 weeks after recovery (American Psychiatric Association, 2006; Fountoulakis et al., 2005; Sachs et al., 2000; Yatham et al., 1997). This time frame for discontinuing prophylactic antidepressant therapy is considerably shorter than that recommended for unipolar depression (Reimherr et al., 1998). However, this recommendation is not based upon evidence that bipolar patients require less prophylactic antidepressant therapy than unipolar patients. Instead, the reluctance to use prophylactic antidepressant therapy for bipolar depression is primarily due to concerns over antidepressant-induced mania (Ghaemi et al., 2000; Goldberg and Nassir Ghaemi, 2005; Goldberg and Truman, 2003; Truman and Goldberg, 2007).

Studies of mixed populations of bipolar I and II depressed patients have reported increases in manic symptoms and depressive relapse during antidepressant prophylaxis (Altshuler et al., 1995; Ghaemi et al., 2004; Leverich et al., 2006; Sachs et al., 2007). For example, one controlled trial reported adequate antidepressant effectiveness, but more treatment-emergent manic symptoms during venlafaxine versus sertraline or bupropion therapy (Leverich et al., 2006). Another study of continuation bupropion versus desipramine found only modest sustained antidepressant response with no difference between the two drugs, but a higher manic switch rate during desipramine treatment (Sachs et al., 1994). A retrospective study found that 44% of subjects with a history of prior mood conversion episodes had at least one manic switch episode during antidepressant therapy and that concurrent mood stabilizer therapy provided little or no protection against treatment-emergent manic switch episodes (Goldberg and Truman, 2003). A recent retrospective chart-review study of bipolar I and II patients found higher manic switch rates during antidepressant monotherapy versus combined antidepressant plus mood stabilizer therapy (Viktorin et al., 2014).

In contrast, controlled trials of long-term antidepressant monotherapy in recovered bipolar II depressed patients suggest good sustained efficacy during antidepressant therapy with a low

manic switch rate (Altshuler et al., 2009; Amsterdam et al., 1998; Amsterdam et al., 2013; Amsterdam and Shults, 2010b; Kupfer et al., 2001; Parker et al., 2006). For example, a 26-week continuation trial of fluoxetine monotherapy found a similar relapse rate in recovered bipolar II depressed (22%) versus recovered unipolar depressed (33%) subjects with similar hypomanic switch rates (Amsterdam et al., 1998). A subsequent randomized, double-blind, placebo-controlled, 50-week continuation study of fluoxetine versus lithium monotherapy found no difference in the proportion of subjects who relapsed on fluoxetine (32.1%), lithium (57.7%), or placebo (51.9%) ($p=0.14$) (Amsterdam and Shults, 2010b). A subsequent post hoc analysis of recovered rapid cycling versus non-rapid cycling bipolar II subjects also found no difference in relapse rate based on cycling status during continuation antidepressant or mood stabilizer monotherapy with similar rates of treatment-emergent hypomanic symptoms (Amsterdam et al., 2013).

Data on the relative long-term efficacy of antidepressant versus mood stabilizer monotherapy in bipolar II are limited. We present data from the first randomized, double-blind, parallel-group, 6-month relapse-prevention study of the safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy in bipolar II subjects recovered from acute depression (Trial Registration number NCT00602537). Based upon preliminary open-label observations (Amsterdam et al., 1998; Amsterdam and Shults, 2008; Amsterdam et al., 2010), we hypothesized that venlafaxine monotherapy would be superior to lithium monotherapy in preventing depressive relapse and the two treatments would be associated with similar levels of treatment-emergent manic and/or depressive symptoms.

Methods

Subjects

This study contained a new cohort of subjects distinct from that of all prior bipolar II depression studies conducted by our group ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT00602537). Outpatients 18 years old with a DSM-IV-TR Axis I diagnosis of bipolar II disorder and current major depressive episode with a 17-item Hamilton Rating Scale for Depression (HRSD) (Williams, 1988) score ≥ 16 were recruited. Exclusion criteria were: prior mania or psychosis, substance abuse or dependence within the preceding 3 months, non-response to venlafaxine or lithium within the current episode, sensitivity to venlafaxine or lithium, presence of unstable medical condition, pregnancy or nursing, renal or hepatic insufficiency, dementia, malignancy, or concurrent use of antidepressant or mood stabilizer medication.

Procedures

Informed consent was obtained in accordance with the ethical standards of the Institutional Review Board. The study was conducted using Good Clinical Practice guidelines (International Conference on Harmonisation Working Group, 1996) with oversight by the local Office of Human Research and an independent Data and Safety Monitoring Board. Psychiatric history was verified using the Structured Clinical Interview for DSM-IV (SCID) Axis I disorders (First et al., 2002). Medical history, physical examination, and laboratory tests (including renal and thyroid panels, pregnancy test in women, drug screen, and electrocardiogram) were performed. Best estimates of the number of prior major depressive

and hypomanic episodes (as defined by DSM IV criteria) that occurred since the onset of the disorder were obtained from subjects at their initial interview using SCID interview format.

Structured 17-item HRSD and Young Mania Rating Scale (YMRS) (Young et al., 1978) measures were obtained by a study clinician blind to treatment condition. Symptom ratings were obtained with attribution as to the origin of the symptom. For example, insomnia could be recorded on the HRSD scale as a depressive symptom, or recorded on the YMRS as a hypomanic symptom, or simultaneously recorded on both rating scales as a mixed hypomanic and depressive symptom. This rating method sometimes resulted in baseline YMRS scores above zero. The procedure has been employed as a 'real world' means of distinguishing mood conversion episodes from depressive symptom (Amsterdam and Shults, 2008, 2010a, b; Amsterdam et al., 2010).

Randomization

Blocked randomization was performed with randomly selected block sizes containing group numbers randomly permuted within each block using the random number generator in Stata statistical software. All study subjects, treating clinicians, research coordinators, and data managers were blinded to the treatment condition. Treatment allocation codes for emergency un-blinding were maintained on the Investigational Drug Service at the medical center.

Treatment

Venlafaxine was initiated at 37.5mg daily and increased to 75mg daily during week 1 of treatment. The dose was then titrated upward in 37.5mg or 75mg increments every week to a maximum of 375mg daily by week 4 of treatment. This dose was then maintained for an additional 8 weeks of therapy. Venlafaxine could be reduced to a minimum of 75mg daily based upon tolerability and response. Subjects unable to tolerate a minimum venlafaxine dose of 75mg daily were discontinued from the trial without un-blinding the study clinician (and treated as clinically warranted).

Lithium was initiated at 300mg daily and increased to 600mg daily during week 1 of treatment; and a serum lithium level was obtained. Based upon clinical response, tolerability and a serum lithium level of 0.8-1.5mEq/L, the dose of lithium could be increased to 900mg daily during week 2 of therapy. Another lithium level was obtained, and the dose increased to 1200mg daily during week three of therapy based upon clinical response and serum lithium level. We anticipated that the majority of patients would attain a therapeutic lithium dose and plasma level by week 4 of therapy. Lithium was then maintained at the maximum tolerated dose for an additional 8 weeks. Subjects unable to tolerate a minimum lithium dose of 300mg daily or a therapeutic lithium level were discontinued from the trial without un-blinding the study clinician (and treated as clinically warranted).

Steady state lithium levels were obtained 12 hours after the last lithium dose. To maintain blinded conditions, blood samples for 'true' or 'sham' lithium levels were obtained from all subjects. An un-blinded study doctor provided the blinded study clinician with a written report of either a 'true' lithium level, for subjects on lithium, or a 'sham' lithium level, for subjects on venlafaxine. For the latter group, 'sham' lithium levels were provided to the

study clinician in a fashion that mimicked ‘true’ lithium levels. This allowed the blinded clinician to maximize medication dosing of both treatments in a safe and clinically appropriate fashion. Short-term zolpidem (10mg) or trazodone (75mg) were permitted for severe insomnia up to study week 4, but they were prescribed infrequently.

Initial monotherapy was administered for 12 weeks. Response was defined as a 50% reduction in baseline 17-item HRSD score plus a final Clinical Global Impression / Severity (CGI/S) (Guy, 1976) score 3. Responders were enrolled into continuation therapy on their established dose of double-blind medication for 6 additional months. Outcome measures were obtained at continuation weeks 16, 20, 24, 30 and 36. Assurance of blinding ratings were obtained from study subjects and clinician at the completion of treatment.

Protocol-designated primary outcome was the proportion of subjects in each treatment condition with depressive relapse during continuation monotherapy. Depressive relapse was defined as an HSRD score 14 plus a CGI/S score of 4 for at least 14 days. Secondary outcomes were the estimated rate of sustained response from start of treatment to study endpoint (Hollon et al., 2005), relapse hazard, time to relapse (in days), change over time in YMRS score, proportion of subjects with YMRS scores 8 at any time during continuation monotherapy, and the frequency and duration of treatment-emergent syndromal or sub-syndromal hypomanic and/or depressive symptoms (Amsterdam et al., 1998; Amsterdam et al., 2013; Amsterdam and Shults, 2010a).

Frequency of treatment-emergent syndromal and sub-syndromal hypomanic and/or depressive symptoms were assessed via subject telephone reports and clinician-elicited information of mood conversion symptoms during the preceding treatment period performed at each study visit using the YMRS and HRSD scale. Given the broad consensus that bipolar II disorder may be characterized by frequent sub-syndromal hypomanic and/or depressive symptom lasting for brief durations (Altshuler et al., 2009), treatment-emergent hypomanic and/or depressive episodes during continuation monotherapy were defined in the following ways: Hypomanic symptoms - (i) syndromal hypomania meeting DSM IV criteria; (ii) type I sub-syndromal hypomania with 4 symptoms lasting 3 days; (iii) type II sub-syndromal hypomania with <3 symptoms lasting >4 days; and, (iv) type III sub-syndromal hypomania with <3 symptoms lasting <3 days. Depressive symptoms - (i) reoccurrence of DSM-IV major depressive episode; (ii) type I minor depressive episode with >5 symptoms lasting <14 days, or 4 symptoms lasting 14 days; (iii) type II minor depressive episode with 4 symptoms lasting 7 days; and, (iv) type III minor depressive episode with 4 symptoms lasting <7 days. Subjects experiencing treatment-emergent hypomanic and/or depressive symptoms underwent double-blind rescue therapy via upward or downward adjustment of medication dose within the allowable dosage (and lithium level) parameters.

Sample Size Justification

Sample size was initially based upon a minimum acute phase enrollment of 56 subjects per treatment condition. Detectable differences during continuation monotherapy were based upon 80% power via Fisher's exact test with 0.05 two-sided significance level. For example, if the group sizes during continuation therapy were venlafaxine =36 and lithium

=20, we would have 80% power to detect a difference in relapse rates of 10% versus 47%, 15% versus 55%, and 20% versus 61%.

Statistical Procedures

Analyses were conducted according to the intent-to-treat (ITT) principle on the sample of study responders who completed the acute treatment phase (n=59) with two-sided tests of hypotheses. Initial analyses summarized demographic and clinical variables for all subjects, and for treatment subgroups at the start of acute and continuation monotherapy. Group differences were explored using Fisher's exact test for categorical variables, t-tests for comparisons of means of continuous variables, and independent samples median tests for comparison of continuous variables with outliers. Kappa coefficients estimated the degree to which patients and clinicians guessed blinded treatment correctly, beyond what would be expected by chance. Differential acute and sustained response rates were examined using Fisher's exact test, as were differential relapse rates between treatments. Log rank tests were used to compare the survival distributions in regard to relapse for each treatment condition. Hazard ratios were estimated using the Cox regression test. Mean time to relapse was estimated using Kaplan-Meier test. Change over time in YMRS scores were assessed using generalized estimating equations (GEE). GEE models used a log-link function, chosen because the distributions of YMRS scores tended to conform to a Poisson, and an autoregressive correlation matrix (AR(1)) regressing on time, treatment condition, and their interaction. The proportions of subjects in each treatment condition with any increase in YMRS score over baseline at any study visit or whose total YMRS score was ≥ 8 at any study visit were compared using Fisher's exact test, as were the proportions of subjects in each treatment condition with treatment-emergent syndromal or subsyndromal hypomania or worsening of depressive symptoms.

Results

Enrollment

There were no significant group differences in baseline clinical or demographic characteristics among venlafaxine (n=65) and lithium (n=64) subjects. During acute monotherapy, 44 (67.7%) venlafaxine versus 22 (34.4%) lithium subjects responded (p=0.0002, Fisher's exact test). Of these, 7 exited the study prior to the acute phase endpoint, leaving a total of 59 subjects eligible for continuation monotherapy: venlafaxine (n=42) and lithium (n=17). There were no significant differences in clinical or demographic characteristics between these subject groups (Table 1). Prior to continuation therapy, however, 4 additional subjects (2 venlafaxine, 2 lithium) withdrew consent to participate, resulting in a final continuation sample of 55 subjects: venlafaxine (n=40) and lithium (n=15) (Figure 1).

Premature Treatment Discontinuation

Ten subjects (18.2%) stopped continuation treatment prematurely: venlafaxine (n=9; 22.5%) and lithium (n=1; 6.7%) (p=0.255, Fisher's exact test) (Figure 1). There were no reported serious adverse events in either treatment condition.

Assurance of Blinded Condition

Correct identification of study drug was made by subjects and clinicians 47.1% ($k=0.25$) and 37.7% ($k=0.18$) of the time, respectively; while 47% of subjects' guesses coincided with that of clinician 1 ($k=0.12$) and 41.5% coincided with that of clinician 2 ($k=-0.01$) in identifying treatment assignment. Thus, subjects and clinicians were adequately blinded.

Blinded Study Drug Dosage

Mean (SD) maximum daily venlafaxine dose was 253.9 (86.9) (range: 112.5–375)mg/day. Mean maximum daily lithium dose was 1,090 (401) (range: 300–1740)mg/day. Mean lithium level was 0.72 (0.24) (range: 0.30–1.08) mEq/L. Mean maximum 'sham' venlafaxine dose (i.e., for subjects taking lithium) was 239 (96) (range: 75–375)mg/day. Mean maximum 'sham' lithium dose (for subjects taking venlafaxine) was 1,158 (228) (range: 600–1500)mg/day with an average maximum 'sham' lithium level of 1.04 (0.17) (range: 0.70–1.40)mEq/L. Thus, blinded study drug dosing was similar among treatment conditions.

Depressive relapse

Primary Outcome - Seven subjects (12.7%) relapsed during continuation monotherapy: 3 (7.5%) on venlafaxine versus 4 (26.7%) on lithium ($p=0.079$, Fisher's Exact Test) (Table 2). Secondary Outcomes – There was a greater sustained response during continuation monotherapy for venlafaxine (43.1%) versus lithium (15.6%) ($p<0.0001$, Fisher's exact test). However, there was no significant difference in relapse hazard for venlafaxine versus lithium during continuation monotherapy (odds ratio=0.22, $x^2=3.21$, $p=0.07$). The estimated mean time to relapse was similar for venlafaxine 215.9 (SE=8.39, 95%CI=199.4–232.3)) days versus lithium 156.4 (SE=14.1, 95%CI=128.7–184.0)) days ($x^2(1)=2.88$, $p=0.09$) treatment conditions.

Treatment-emergent mood symptoms

Treatment-emergent sub-syndromal depressive episodes were significantly more likely during continuation lithium (73.3%) versus venlafaxine (37.5%) ($p=0.03$) (Table 2). The overall frequency of sub-syndromal hypomania was 10.9% with no differences among treatment conditions (Table 3). No subject met DSM IV criteria for hypomania. There were no group differences in estimated change over time for YMRS scores during continuation monotherapy ($\beta=-1.51$, SE=1.15, $x^2(1)=1.71$; $p=0.19$). Overall, 15.0% of venlafaxine versus 28.6% of lithium subjects experience any increase in YMRS score during continuation monotherapy ($p=0.42$, Fisher's exact test); while no venlafaxine subject (0%) and one lithium subject (7.7%) had a YMRS score ≥ 8 during continuation monotherapy ($p=0.27$, Fisher's exact test).

Discussion

Long-term antidepressant therapy for relapse-prevention of bipolar depression has received relatively little attention (Altshuler et al., 2003; Altshuler et al., 1995; Bond et al., 2008; Ghaemi et al., 2001; Ghaemi et al., 2004). Whereas some studies have reported benefit from continuation antidepressant therapy in patients who have recovered from bipolar depression

(Altshuler et al., 2009; Amsterdam et al., 1998; Amsterdam and Shults, 2010a, b; Kupfer et al., 2001), other studies have not confirmed this finding or have reported increased mood conversion rates during continuation antidepressant use (Altshuler et al., 1995; Ghaemi et al., 2004; Leverich et al., 2006; Sachs et al., 2007; Vieta, 2008; Viktorin et al., 2014). A retrospective chart review study by Altshuler et al. (2001) examined the risk of depressive relapse over one year in recovered bipolar depressed subjects who either continued or discontinued antidepressant therapy. Cessation of antidepressant therapy significantly increased the risk of depressive relapse without increasing the risk of mania. In a subsequent, prospective study, Altshuler et al. (2009) followed recovered bipolar subjects treated with antidepressant (plus mood stabilizer) therapy for one year. Forty-two subjects (69%) showed sustained response during continuation antidepressant therapy with 32 (53%) achieving remission. Only 8 subjects (13%) had mood conversion symptoms. These investigators concluded that continuation adjunctive antidepressant treatment would probably maintain response with a modest risk of manic symptoms. By contrast, Leverich et al. (2006) found that only 23% of bipolar subjects receiving maintenance antidepressant (plus mood stabilizer) therapy had sustained antidepressant response without mood conversion episodes. Similarly, Schneck et al. (2008) followed 1,191 bipolar patients (75% bipolar type I) for one year and found a 34% recovery rate, with a 61% mood conversion rate during antidepressant therapy. The findings from these studies are difficult to integrate because they contain mixed populations of bipolar I and bipolar II patients.

A conservative interpretation of findings from the present study suggest that venlafaxine monotherapy and lithium monotherapy appear to be similarly effective in preventing depressive relapse with no difference in the rate of treatment-emergent hypomanic symptoms. However, lithium-treated subjects appeared to experience significantly more treatment-emergent sub-syndromal depressive episodes during continuation monotherapy relative to venlafaxine.

Several caveats should be considered when interpreting the present results. We note the limited lithium sample size during continuation therapy, a result of the fact that a significantly greater proportion of subjects responded to venlafaxine, relative to lithium, during acute monotherapy (Figure 1). Thus, the study may not have been powered sufficiently to detect a between-condition difference in relapse rates.

Given the acute superiority of venlafaxine in the current study, a design better suited to explore the prophylactic effects of lithium versus venlafaxine might have been one in which all subjects received acute treatment with venlafaxine and responders were then randomized to continuation monotherapy with either venlafaxine or lithium.

The study was not powered to detect a difference in YMRS scores between treatment groups; although failure to identify a difference between groups does not prove that a difference does not exist. Moreover, the lack of a placebo comparison group constrained our ability to determine the true relative mood conversion rate of venlafaxine and lithium monotherapy. It is possible that the low mood conversion rates seen in both treatment conditions during continuation monotherapy represent the frequency of naturally occurring manic and depressive symptoms and not drug-induced phenomena.

Although we found no difference in the frequency and duration of treatment-emergent hypomanic symptoms during continuation monotherapy, it is possible that employing different threshold criteria for sub-syndromal hypomanic episodes may have revealed such differences. Additionally, the frequency and duration of treatment-emergent mood conversion symptoms may have been greater in venlafaxine-treated subjects had depressive and hypomanic symptom been rated without attribution as to cause. For example, rating insomnia on both the HRSD and YMRS could have inflated YMRS scores. While this inflation is possible, a similar effect would be expected for both treatment conditions. We found no significant differences in YMRS scores among groups. It is also possible that the frequency and severity of mood conversion episodes during venlafaxine may have been greater if a longer treatment duration were employed. However, we found no clinically meaningful increase in YMRS scores throughout continuation monotherapy; an observation supported by prior studies of antidepressant monotherapy in bipolar II subjects (Altshuler et al., 2009; Amsterdam et al., 1998; Amsterdam et al., 2013; Amsterdam and Shults, 2010b; Kupfer et al., 2001; Parker et al., 2006).

In conclusion, this study found no significant difference in depressive relapse rates between venlafaxine and lithium continuation monotherapy. There were also no significant group differences in the frequency and duration of treatment-emergent syndromal or sub-syndromal hypomanic symptoms during continuation monotherapy. These findings, although not definitive, support prior observations by our group showing good prophylactic effectiveness and low hypomanic switch rates during continuation antidepressant monotherapy of bipolar II disorder. These observations deserve additional study and replication by independent research groups.

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HIGHLIGHTS

- Examined venlafaxine monotherapy versus lithium in recovered bipolar II depression
- Continuation venlafaxine resulted in a higher sustained response rate
- Similar relapse prevention rates were found between the two treatments
- Similar mood conversion rates were reported in venlafaxine relative to lithium
- Continuation venlafaxine may be a safe and effective alternative to lithium

Figure 1.
CONSORT diagram of subjects assigned to continuation venlafaxine or lithium

Table 1

Demographic and clinical characteristics of study subjects receiving continuation therapy.

	All subjects (n=59)		Venlafaxine (n=42)		Lithium (n=17)		p value
	N	%	n	%	n	%	
Female ^a	32	54.2	24	57.1	8	47.1	0.57
Non-Caucasian ^a	10	83.1	5	11.9	5	29.4	0.13
Inter-episode Recovery ^a	16	27.1	14	33.3	2	11.8	0.12

	Mean	SD	Mean	SD	Mean	SD	
Age at Entry into Study ^b	42.2	12.5	41.8	11.4	43.1	15.2	0.73
Age 1 st Major Depressive Episode ^a	18.5	7.1	19.0	7.7	17.4	5.4	0.37
Age 1 st hypomanic episode ^b	19.4	8.5	20.7	7.6	16.2	10.0	0.11
Number of lifetime major depressive episodes ^b	29.9	11.0	28.4	50.4	33.3	49.7	0.74
Number of lifetime hypomanic episodes ^b	41.9	61.4	45.8	66.4	32.2	47.3	0.45
Baseline HRSD Score ^b	19.2	3.5	19.4	3.6	18.8	3.3	0.59
Baseline YMRS Score ^b	0.8	1.6	0.8	1.7	0.6	1.4	0.64
Median Duration Major Depressive Episode (months) ^c	4	--	4.5	--	4.0	--	0.46
End of treatment HRSD Score	4.3	2.9	4.3	2.8	4.4	3.4	0.89

^c. HRSD = Hamilton Rating Scale for Depression. YMRS = Young Mania Rating Scale. mo.= months.^a p value from Fisher's exact test^b p value for comparison of means from independent samples t-test^c p value for comparison of medians from independent samples

Table 2
Treatment emergent depressive symptoms during venlafaxine (n=40) or lithium (n=15) continuation monotherapy.

Episode	All Subjects			Venlafaxine			Lithium			^a p
	n	%	(95% CI)	n	%	(95% CI)	n	%	(95% CI)	
Major depressive episode	7	12.7%	(5.3 – 24.4%)	3	7.5%	(1.6 – 20.4%)	4	26.7%	(7.8 – 55.1%)	0.08
Type I minor depression	16	29.1%	(17.6 – 42.9%)	9	22.5%	(10.8 – 38.5%)	7	46.7%	(21.2 – 73.4%)	0.10
Type II minor depression	3	5.4%	(1.1 – 15.1%)	2	5.0%	(0.6 – 16.9%)	1	6.7%	(0.2 – 31.95%)	0.99
Type III minor depression	4	7.3%	(2.0 – 17.6%)	3	7.5%	(1.6 – 20.4%)	1	6.7%	(0.2 – 31.95%)	0.99
Any depression	26	47.3%	(33.7 – 61.2%)	15	37.5%	(22.7 – 54.2%)	11	73.3%	(44.9 – 92.2%)	0.03
Duration	M	SD	(95% CI)	M	SD	(95% CI)	M	SD	(95% CI)	^b p
Major depressive episode	51.3	56.0	(–0.6 – 103.1)	58.7	73.9	(–125.0 – 242.3)	45.8	50.4	(–34.5 – 126.0)	0.79
Type I minor depression	18.4	14.3	(10.8 – 26.0)	17.1	15.1	(5.5 – 28.8)	20.1	14.1	(7.1 – 33.2)	0.69
Type II minor depression	9.7	2.5	(3.4 – 15.9)	11.0	1.4	(–1.7 – 23.7)	7.0	--	--	0.26
Type III minor depression	4.0	1.8	(3.4 – 15.9)	4.7	1.5	(0.9 – 8.5)	2.0	--	--	0.27
Any depression	27.7	34.4	(13.8 – 44.6)	25.9	35.7	(6.1 – 45.6)	30.3	34.2	(7.3 – 53.27)	0.75

Some patients had more than one episode, total duration of episodes was used in these cases.

^a p value for comparison of proportion using Fisher's exact test

^b comparison of means using student's t test.

Table 3

Treatment emergent hypomanic symptoms during venlafaxine (n=40) or lithium (n=15) continuation monotherapy.

Episode	Full sample			Venlafaxine			Lithium			p^a
	N	%	(95% CI)	n	%	(95% CI)	n	%	(95% CI)	
Hypomania	0	0.0%	(0.0 – 6.5%)	0	0.0%	(0.0 – 8.8%)	0	0.0%	(0 – 21.8%)	--
Subsyndromal Type I	1	1.8%	(0.0 – 9.7%)	1	2.5%	(0.1 – 13.2%)	0	0.0%	(0 – 21.8%)	0.99
Subsyndromal Type II	3	5.4%	(1.1 – 15.1%)	1	2.5%	(0.1 – 13.2%)	2	13.3%	(1.7 – 40.5%)	0.18
Subsyndromal Type III	2	3.6%	(0.4 – 12.5%)	1	2.5%	(0.1 – 13.2%)	1	6.7%	(0.2 – 31.95%)	0.48
Any subsyndromal hypomania	6	10.9%	(4.1 – 19.2%)	3	7.5%	(1.6 – 20.4%)	3	20.0%	(4.3 – 48.1%)	0.33

Duration in days	M			SD			M			SD			p^b
	M	SD	(95% CI)	M	SD	(95% CI)	M	SD	(95% CI)	M	SD	(95% CI)	
Subsyndromal Type I	1	--	--	1	--	--	--	--	--	--	--	--	--
Subsyndromal Type II	9	5.0	(–3.4 – 21.4)	14	--	--	6.5	3.5	(–25.3 – 38.3)	0.33	--	--	0.33
Subsyndromal Type III	3	1.4	(–9.7 – 15.7)	2	--	--	4	--	--	--	--	--	--
Any subsyndromal hypomania	5.7	4.9	(0.5 – 10.8)	5.7	7.2	(–12.3 – 23.6)	5.7	2.9	(–1.5 – 12.8)	0.99	--	--	0.99

Some patients had more than one episode, total duration of episodes was used in these cases.

^a p value for comparison of proportion using Fisher's exact test

^b comparison of means using student's t test.