



Preliminary communication

Venlafaxine versus lithium monotherapy of rapid and non-rapid cycling patients with bipolar II major depressive episode: A randomized, parallel group, open-label trial

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Abstract

Background: There is a paucity of controlled clinical data on the best initial therapy for treating patients with bipolar type II (BP II) major depressive episode (MDE). In this analysis, we examined the safety and antidepressant efficacy of short-term venlafaxine versus lithium monotherapy in rapid and non-rapid cycling patients with BP II MDE. We hypothesized that lithium would have superior efficacy to venlafaxine, with fewer syndromal and sub-syndromal hypomanic and mixed mood conversions in the rapid cycling BP II MDE patients.

Methods: Patients were randomized to monotherapy with either venlafaxine 37.5–375 mg daily or lithium 300–2100 mg daily for 12 weeks. The primary outcome measure was the 28-item Hamilton Depression Rating (HAM-D 28), with embedded ‘typical’ HAM-D 17 and ‘atypical’ HAM-D 17-R symptom scores. Secondary outcomes included the Young Mania Rating Scale (YMRS), clinical global impressions severity (CGI/S) and change (CGI/C) ratings, the proportion of responders (with $\geq 50\%$ reduction in baseline HAM-D score) and remitters (with a final HAM-D score ≤ 8), and the proportion of patients with syndromal and sub-syndromal mood conversions.

Results: Forty-three patients received venlafaxine (12 rapid cycling) and 40 patients received lithium (15 rapid cycling): 48 (57.8%) were women and 69 (82.1%) were Caucasian. Thirty-three patients (39.8%) prematurely discontinued therapy: 11 for lack of efficacy, 13 for adverse events, 2 for non-compliance, and 7 who were lost to follow up. Venlafaxine produced a greater reduction in HAM-D 28 ($p=0.001$) and HAM-D 17 ($p=0.002$) scores (versus lithium) that was independent of cycling status (0.358). Venlafaxine also resulted in a higher rate of responders ($p=0.021$) and remitters ($p=0.001$) in rapid cycling patients. There was no significant difference in baseline mean YMRS scores, or mean YMRS change scores over time, between rapid and non-rapid cycling patients. Venlafaxine did not result in a higher proportion of mood conversions (versus lithium) in either the rapid or non-rapid cycling patients.

Limitations: This was a secondary analysis of rapid versus non-rapid cycling BP II MDE patients. The study was originally powered to detect differences in efficacy between treatment conditions, and was not specifically powered to detect differences in efficacy or mood conversion episodes between rapid and non-rapid cycling groups. We used a conservative life-time definition of rapid cycling (i.e., an average ≥ 4 affective episodes per year). We did not employ a patient-recorded daily chrono-record to identify ultra-short mood conversions. The study used a randomized, parallel group, open-label design.

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Conclusion: These observations from this exploratory analysis suggest that venlafaxine monotherapy may be more effective than lithium monotherapy, with a similar mood conversion rate, in rapid and non-rapid cycling patients with BP II MDE. These data support prior observations that venlafaxine monotherapy may be effective initial treatment for BP II MDE.

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1. Introduction

The most common phenotypic expression of bipolar illness is Bipolar II (BP II) disorder. It is highly recurrent, with the majority of episodes being depressive (Dunner et al., 1976; Simpson et al., 1993; Akiskal, 2005; Akiskal and Benazzi, 2005; Berk and Dodd, 2005; Sato et al., 2005). While antidepressant use has been associated with cycle acceleration in BP I disorder (Wehr and Goodwin, 1987; Goodwin and Jamison, 1990), the presence of antidepressant-induced rapid cycling in BP II disorder has been more difficult to establish (Akiskal and Benazzi, 2005; Benazzi, 1997). To date, most reports of drug-induced cycling in BP II disorder derive from uncontrolled studies or retrospective chart reviews of mixed BP I and BP II populations (Leverich et al., 2006; Stoll et al., 1994; Altshuler et al., 1995; Goodwin and Ghaemi, 1998; Ghaemi et al., 2003; Goldberg and Truman, 2003; Ghaemi et al., 2004; Marangell et al., 2004; Truman et al., 2007; Goldberg and McElroy, 2007). For example, several naturalistic studies have found higher manic switch rates during antidepressant (20%–84%) versus combined antidepressant plus mood stabilizer (32%) therapy (Goodwin and Ghaemi, 1998; Ghaemi et al., 2003; Goldberg and Truman, 2003; Ghaemi et al., 2004). More recently, Leverich et al. (2006) reported a higher frequency of syndromal and sub-syndromal hypomanic and mixed mood conversion episodes during venlafaxine (versus sertraline or bupropion) therapy in a study of mixed BP I, BP II, BP NOS, and BP schizo-affective patients. A recent retrospective, self-report study of 332 BP patients who had previously received antidepressant therapy found that 44% reported at least 1 mood conversion episode, and patients with a history of multiple antidepressant trials have an increased likelihood of reporting mood conversions. Moreover, the risk of mood conversion was more likely in BP patients who had ever experienced a mood conversion during tricyclic antidepressant (TCA), serotonin reuptake inhibitors (SSRI), or bupropion therapy (Truman et al., 2007).

In contrast, several prospective controlled clinical trials of fluoxetine monotherapy (Amsterdam et al., 1998, 2004; Amsterdam and Shults, 2005; Parker et al., 2006)

and venlafaxine monotherapy (Amsterdam, 1998; Amsterdam and Garcia-Espana, 2000; Parker and Parker, 2003) of BP II major depressive episode (MDE) have found relatively low hypomanic switch rates. None of these studies, however, have specifically examined efficacy and mood conversion rates in BP II MDE patients with rapid versus non-rapid cycling disorder.

In a primary analysis examining the safety and efficacy of initial venlafaxine versus lithium monotherapy of BP II MDE, we reported that venlafaxine monotherapy produced a greater reduction in depressive symptoms versus lithium (95% CI=(−11.97,−1.18)) ($p=0.017$) and a greater proportion of treatment responders (58.1% versus 12.5%) ($p<0.0005$) and treatment remitters (44.2% versus 7.5%) ($p<0.0005$). Moreover, we found no difference over time in the rate of treatment-emergent hypomanic symptoms during venlafaxine versus lithium monotherapy (Amsterdam and Shults, 2008).

In the current analysis, we present additional comparative safety and efficacy results of venlafaxine versus lithium monotherapy in rapid and non-rapid cycling patients with BP II MDE. We hypothesize that lithium may have superior efficacy to venlafaxine monotherapy with a lower mood conversion rate in the rapid cycling patients relative to the non-rapid cycling patients.

2. Methods

2.1. Subjects

Outpatients ≥ 18 years old with a DSM IV Axis I diagnosis of BP II disorder and a current diagnosis of MDE were enrolled. All had a baseline 17-item Hamilton Depression Rating (HAM-D 17) (Williams, 1988) score ≥ 18 . Patients with a co-morbid DSM IV Axis I diagnosis were not specifically excluded from the trial if the co-morbid 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, were unresponsive to venlafaxine or lithium therapy within the current MDE, or were sensitive to venlafaxine or lithium carbonate. Other exclusion criteria were the presence of an unstable medical condition, pregnancy or nursing, thyrotropin level ≥ 5 $\mu\text{IU/mL}$,

significant hepatic or renal disease, dementia, or malignancy. Concurrent antidepressant, mood stabilizer, atypical neuroleptic, tranquilizer, or over-the-counter antidepressant preparations were not permitted.

2.2. Procedures

Eighty-four patients provided informed consent in accordance with the ethical standards of the Institutional Review Board of the University. The study was conducted using the Principles of Good Clinical Practice Guidelines, with oversight by the local Office of Human Research and by an independent Data and Safety Monitoring Board.

A psychiatric and medical history was obtained using the Structured Diagnostic Interview for DSM IV format (First et al., 2001). A physical examination and laboratory tests were performed that included blood count, electrolytes, hepatic and renal panel, thyroid panel, pregnancy test (in women), urinalysis, urine drug screen, and electrocardiogram.

The number of prior MDEs, hypomanic episodes (≥ 4 days duration), and sub-syndromal hypomanic episodes (< 4 days duration) was estimated over the total illness duration using the SCID format (First et al., 2001) as defined by DSM IV-TR criteria. Patients were conservatively classified as rapid cycling if they endorsed a life-time average of ≥ 4 affective episodes (i.e., MDE, hypomania, mixed affective episodes) per year using the equation: (Total MDE+hypomania+mixed episode)/total illness duration, where the total of all affective episodes represents the number of prior episodes, and the illness duration is measured in years.

Structured symptom ratings were obtained using the 28-item HAM-D and Young Mania Rating Scale (YMRS) (Young et al., 1978) with attribution as to the origin of the symptom. For example, insomnia could be recorded on the HAM-D as a depressive symptom, or recorded on the YMRS as a hypomanic symptom. It could be simultaneously recorded on both instruments as a mixed depressive and hypomanic symptom. This rating method sometimes resulted in baseline YMRS scores that were above zero.

2.3. Treatment

Patients who were not drug free at the time of study enrollment had their prior ineffective or partially effective medication tapered and discontinued before randomization. Patients who had a baseline HAM-D 17 score ≥ 18 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 conducted using a structured management format (Fawcett et al., 1987).

Venlafaxine monotherapy was initiated at 37.5 mg daily and increased to 75 mg daily during the first week of treatment. The dose was titrated upward in 37.5 mg or 75 mg increments every week to a maximum dose of 375 mg daily by week 4 of treatment. This dose was maintained for an additional 8 weeks. The dose could be reduced to a minimum of 37.5 mg daily, depending upon tolerability. Patients who were unable to tolerate 37.5 mg daily were discontinued from the trial. Venlafaxine was administered on a once or twice daily basis (Amsterdam, 1998; Amsterdam and Garcia-Espana, 2000).

Lithium monotherapy was initiated at 600 mg daily for 1 week and a serum lithium level was obtained. Based upon tolerability and a minimum lithium level of 0.5 mmol/L, the dose of lithium was increased to 900 mg daily during the second week of treatment. This process was then repeated until a steady state serum lithium level of 0.5–1.5 mmol/L was achieved at week 4 of treatment. This dose was then maintained for 8 additional weeks. Lithium was administered on a once or twice daily basis up to 900 mg daily, and twice daily at doses exceeding 900 mg daily. Patients who were unable to achieve a minimum serum lithium level of 0.5 mmol/L were discontinued from the trial. Lithium levels were obtained as close to 12 h as possible after the last dose of lithium.

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

2.4. Outcome measures

The primary outcome measure was the HAM-D 28 rating (with embedded 'typical' HAM-D 17 and 'atypical' HAM-D 17-R symptom cores) (Williams, 1988; Reimherr et al., 1998). Secondary outcomes included change in YMRS over time, clinical global impressions severity (CGI/S) and change (CGI/C) ratings (Guy, 1976), and the proportion of responders with a $\geq 50\%$ reduction in baseline HAM-D score, and the proportion of remitters with a final HAM-D score ≤ 8 .

2.5. Sample size justification

The study was powered to detect a difference in response rates of 60% for all venlafaxine-treated patients and 30% for all lithium-treated patients, based on a two-group chi-square test with a 2-sided 0.05 significance level. The number of subjects needed to

distinguish between these response rates with 80% power was 42 per group. We note, however, that the study was *not* powered to detect differences in treatment response or mood conversion rates between rapid and non-rapid cycling groups. The analyses presented in this report are secondary, or exploratory, in nature and should not be considered confirmatory.

2.6. Statistical procedures

Analyses were performed using the intent-to-treat principle whereby no subject was dropped from the analysis. Stata 9.0 was used to conduct the analyses, with two-sided tests of hypotheses and a p -value < 0.05 as the criterion for statistical significance.

Initial analyses were descriptive and included means, medians, ranges, standard deviation (SD), and 95% confidence interval (CI). Box plots were constructed to compare change over time between treatment conditions in rapid and non-rapid cycling patients to verify that 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 (QLS) (Chaganty and Shults, 1999) with the *xtqls* procedure for Stata 9.1 (Shults et al., 2007). QLS is a method in the framework of generalized estimating equation (GEE) that allows for easier 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 $\text{Corr}(y_{ij}, y_{ik}) = \alpha^{|\frac{t_{ij}-t_{ik}}{\Delta}|}$. QLS with the Markov correlation structure was applied in our primary comparison of venlafaxine versus lithium (Amsterdam and Shults, 2008). For the current analysis, the models applied previously were generalized to take rapid cycling status into account. The following regression model for the expected value of HAM-D scores for subject i at visit j was used to test the primary hypothesis that the treatment effects differ between rapid and non-rapid cycling groups over time:

$$E(y_{ij}) = \beta_0 + \beta_1 \text{time} + \beta_2 \text{baseline} + \beta_3 I(\text{venlafaxine}) + \beta_4 I(\text{rc}) + \beta_5 I(\text{venlafaxine}) \times \text{time} + \beta_6 I(\text{rc}) \times \text{time} + \beta_7 I(\text{rc}) \times I(\text{venlafaxine}) + \beta_8 I(\text{rc}) \times I(\text{venlafaxine}) \times \text{time} \quad (1)$$

where $I(\text{venlafaxine})=1$ for venlafaxine patients and 0 otherwise; $I(\text{rc})=1$ for rapid cycling and 0 for non-rapid cycling patients; baseline indicates the patients' baseline HAM-D scores; time represents the time in days since the first visit, for $i=1,2,\dots,84$ and $j=1,2,\dots,n_i$. We included the

baseline HAM-D score as a covariate to adjust for baseline values of the outcome. We used the time in days from the first visit to account for unequal spacing of study visits. We tested for a significant time \times treatment \times rapid cycling 3-way interaction, by testing the hypothesis $H_0: \beta_8=0$ versus $H_1: \beta_8 \neq 0$. A significant 3-way interaction $I(\text{rc}) \times I(\text{venlafaxine}) \times \text{time}$ would indicate that the effect of treatment differed by cycling status, and that the effect changed over time.

Based on the coefficient estimates and p -values of covariates for each of the HAM-D outcomes, the final models for each of the HAM-D scores were:

$$E(\text{HAM17}) = \beta_0 + \beta_1 \text{time} + \beta_2 \text{baseline} + \beta_3 I(\text{venlafaxine}) + \beta_4 I(\text{rc}) + \beta_5 I(\text{venlafaxine}) \times \text{time} + \beta_6 I(\text{rc}) \times \text{time} \quad (2)$$

$$E(\text{HAM17R}) = \beta_0 + \beta_1 \text{time} + \beta_2 \text{baseline} + \beta_3 I(\text{venlafaxine}) + \beta_4 I(\text{rc}) + \beta_5 I(\text{venlafaxine}) \times \text{time} \quad (3)$$

$$E(\text{HAM28}) = \beta_0 + \beta_1 \text{time} + \beta_2 \text{baseline} + \beta_3 I(\text{venlafaxine}) + \beta_4 I(\text{rc}) + \beta_5 I(\text{venlafaxine}) \times \text{time} + \beta_6 I(\text{rc}) \times \text{time}. \quad (4)$$

In order to test whether the proportions of responders and remitters differ between treatments by cycling status, chi-square and Fisher exact tests were used to analyze categorical outcomes. Using the responder (1=responder and 0=non-responder) as a binary outcome, we fit the following logistic regression model:

$$\text{logit}(\text{response rate}) = \beta_0 + \beta_1 I(\text{rc}) + \beta_2 I(\text{venlafaxine}) + \beta_3 I(\text{rc}) \times I(\text{venlafaxine}).$$

We tested the hypothesis $\beta_3=0$ to examine whether cycling status significantly impacted treatment response. To determine the final regression model, we used the 'saturated model' with the backward selection method. We removed the variable with the highest p -value at each successive step until all the remaining variables in the model were statistically significant. We used the Hosmer–Lemeshow test for goodness-of-fit for the logistic regression model. To assess the quality of the prediction rule based on this model, we calculated the area under the curve (AUC). The AUC is based upon the sensitivity and specificity of tests for rapid cycling constructed at all possible cutoff values of the estimated probability of being a rapid cyclist. The AUC takes value

Table 1
Clinical and demographic characteristics by cycling status

	Rapid cycling (<i>n</i> =27)	Non-rapid cycling (<i>n</i> =57)	<i>p</i> -value**
Female	70.37%	50.88%	0.092
Caucasian	77.78%	84.21%	0.47
Age (yrs)*	30.5 (9.6)/19–50	40.4 (13.9)/18–74	0.001
Age 1st MDE*	16.2 (4.5)/6–30	19.8 (10.0)/5–57	0.079
Age 1st hypomania*	16.5 (3.3)/8–22	23.1 (8.6)/12–57	0.0003
Number prior MDEs*	9.7 (9.7)/0–35	6.7 (5.4)/1–24	0.074
Number prior hypomania*	43.2 (46.7)/2–200	8.6 (9.8)/0–40	<0.001
Number prior sub-syndromal hypomania*	86.6 (61.6)/13–200	14.1 (19.4)/0–100	<0.001
Illness duration (yrs)*	14.0 (10.6)/2–36	20.6 (12.2)/1–55	0.019
Current MDE length (mos)*	14.2 (20.1)/0.75–90	16.4 (19.2)/1–84	0.640
Number prior treatments*	4.1 (2.8)/1–13	4.8 (3.6)/1–20	0.422
Baseline HAM-D 28*	30.4 (5.1)/19–40	28.6 (7.8)/5–46	0.259
Baseline HAM-D 17*	22.6 (4.6)/14–31	20.3 (5.1)/13–35	0.056
Baseline HAM-D 17-R*	21.7 (3.9)/14–30	20.6 (5.4)/7–32	0.344
Baseline YMRS*	0.56 (2.2)/0–11	0.79 (1.8)/0–10	0.607

*Mean (SD)/range.

***p*-value from chi-square test (for comparison of % female and % Caucasian); or, *t*-test (for comparison of means between groups).

of 0.50–1.0, with the value closer to 1.0 indicating a better prediction rule.

The proportion of patients (with 95% CI) with a YMRS cutoff score ≥ 8 and a YMRS cutoff score ≥ 12 was computed for rapid and non-rapid cycling patients in each treatment group, and were compared using Fisher's exact test.

Finally, QLS regression models were modified to include demographic and clinical variables to assess whether results were sensitive to adjustment for these variables.

3. Results

3.1. Enrollment

Eighty-four patients were enrolled in the trial: 48 (57%) were women and 69 (82.1%) were Caucasian. Mean (SD) age was 37.2 (13.4) years (range 18–74 years); mean age at 1st MDE was 18.7 (8.7) years (range 5–57 years); mean age at 1st hypomanic episode was 20.7 (8.2) years (range 8–57 years). Mean illness duration was 18.5 (12.0) years (range 1–55 years); mean duration of

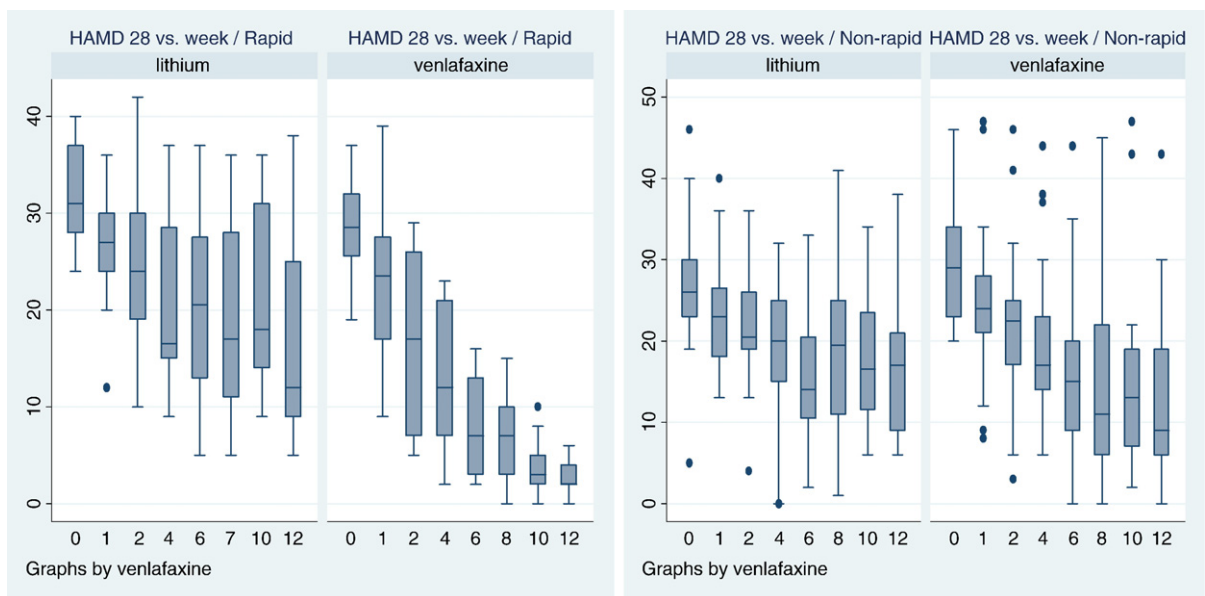


Fig. 1. Comparisons of treatment effects on HAM-D 28 over time by cycling status.

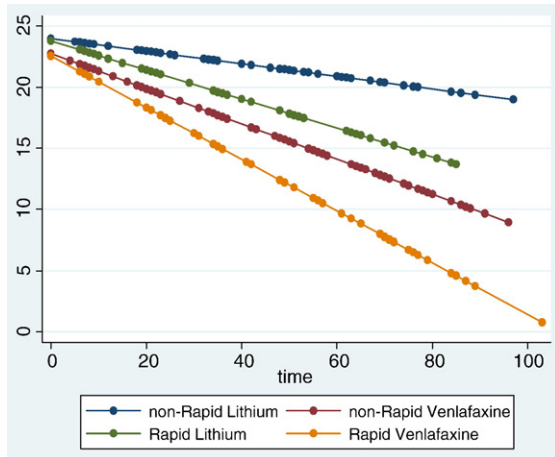


Fig. 2. Predicted HAM-D 28 over time.

current MDE was 15.0 (19.3) months (range 0.75–90 months). The mean number of prior MDEs was 7.7 (7.2) (range 0–35); mean number of prior hypomanic

episodes was 42.8 (54.1) (range 0–200); and, the mean number of prior sub-syndromal hypomanic or mixed episodes was 20.1 (32.0) (range 0–200). Thirty-two patients (38.0%) received prior antidepressant monotherapy and only 2 patients (2.4%) received prior MS monotherapy.

Eighty-three patients had a baseline study visit: 43 on venlafaxine and 40 on lithium. One patient (1.2%) was a screen failure and did not have a baseline evaluation. Thirty-three patients (39.8%) discontinued treatment before completing the trial: 11 for lack of efficacy, 13 for adverse events, 2 for non-compliance, and 7 who were lost to follow up. The mean number of measurements per subject was 5.5 and the median was 7. The number of subjects with a HAM-D measurement were 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.

Table 2

Estimated regression parameters for all HAM-D scores

	Coefficient estimate	Standard error	p-value	95% CI
<i>HAM-D 28</i>				
Time	-0.052	0.025	0.036	(-0.099,-0.003)
Baseline	0.416	0.156	0.008	(0.110,0.722)
<i>HAM-D 17</i>				
Venlafaxine	-1.228	1.348	0.362	(-3.869,1.413)
Rapid cycling	-0.207	1.542	0.893	(-3.229,2.816)
Venlafaxine×time	-0.092	0.029	0.001	(-0.149,-0.036)
Rapid cycling×time	-0.067	0.027	0.014	(-0.121,-0.014)
Intercept	11.856	4.513	0.009	(3.011,20.702)
<i>HAM-D 17-R</i>				
Time	-0.045	0.017	0.01	(-0.079,-0.011)
Baseline	0.58	0.136	<0.0005	(0.315,0.849)
<i>HAM-D 17-R</i>				
Venlafaxine	-0.501	0.951	0.598	(-2.364,1.362)
Rapid cycling	-0.634	1.089	0.561	(-2.769,1.501)
Venlafaxine×time	-0.063	0.02	0.002	(-0.103,-0.024)
Rapid cycling×time	-0.052	0.019	0.006	(-0.089,-0.015)
Intercept	4.834	2.876	0.093	(-0.804,10.471)
<i>HAM-D 17-R</i>				
Time	-0.052	0.016	0.001	(-0.084,-0.021)
Baseline	0.268	0.148	0.069	(-0.021,0.558)
<i>HAM-D 17-R</i>				
Venlafaxine	-0.903	1.009	0.371	(-2.882,1.076)
Rapid cycling	-1.988	1.165	0.088	(-4.272,0.296)
Venlafaxine×time	-0.063	0.021	0.003	(-0.104,-0.021)
Intercept	12.016	2.919	<0.0005	(6.296,17.737)

3.2. Cycling status

Clinical and demographic characteristics of rapid ($n=27$) and non-rapid ($n=57$) cycling patients are displayed in Table 1. Rapid cycling status was significantly associated with younger age at the time of the study and younger age at 1st hypomanic episode. Other potential risk factors for rapid cycling status included female gender, younger age at 1st MDE, and higher baseline HAM-D 17 score.

Logistic regression was performed using gender ($p=0.051$) and age at 1st hypomania ($p=0.001$) as covariates with cycling status. The Hosmer–Lemeshow goodness-of-fit test ($p=0.6984$) showed that the

Table 3

Expected values at baseline and week 12 for HAM-D measure

	Change	p-value	95% CI
<i>HAM-D 28</i>			
Venlafaxine rapid cycling	-16.269	<0.0005	(-19.814,-12.723)
Lithium rapid cycling	-9.149	<0.0005	(-13.585,-4.714)
Venlafaxine non-rapid cycling	-11.095	<0.0005	(-14.246,-7.943)
Lithium non-rapid cycling	-3.975	0.036	(-7.692,-0.258)
<i>HAM-D 17</i>			
Venlafaxine rapid cycling	-12.373	<0.0005	(-14.753,-9.994)
Lithium rapid cycling	-7.486	<0.0005	(-10.660,-4.312)
Venlafaxine non-rapid cycling	-8.356	<0.0005	(-10.586,-6.125)
Lithium non-rapid cycling	-3.468	0.010	(-6.108,-0.829)
<i>HAM-D 17-R</i>			
Venlafaxine rapid cycling	-8.850	<0.0005	(-10.875,-6.826)
Lithium rapid cycling	-4.035	<0.0005	(-6.479,-1.591)
Venlafaxine non-rapid cycling	-8.850	<0.0005	(-10.875,-6.826)
Lithium non-rapid cycling	-4.035	<0.001	(-6.479,-1.591)

Table 4
Response and remission rates by treatment condition and cycling status

	Rapid cycling			Non-rapid cycling		
	Venlafaxine (n=12)	Lithium (n=15)	p-value*	Venlafaxine (n=31)	Lithium (n=25)	p-value*
<i>Response</i>						
HAM-D 28	75.00	26.67	0.021	54.84	16.00	0.005
HAM-D 17	75.00	26.67	0.021	51.61	16.00	0.011
HAM-D 17-R	75.00	26.67	0.021	54.84	16.00	0.005
<i>Remission</i>						
HAM-D 28	75.00	6.67	0.001	32.26	8.00	0.047
HAM-D 17	75.00	20.00	0.007	51.61	12.00	0.002
HAM-D 17-R	75.00	20.00	0.007	51.61	16.00	0.011

*Fisher's Exact Test.

hypothesis of a reasonable fit was not rejected. The area under the curve (AUC) value was 0.803, indicating that the prediction rule based on this logistic model has good accuracy.

3.3. Treatment outcome

Box plots of HAM-D scores over time were constructed for rapid and non-rapid cycling patients on venlafaxine and lithium (Fig. 1).

Venlafaxine produced a greater reduction over time in HAM-D 28 ($p=0.001$) and HAM-D 17 ($p=0.002$) scores versus lithium. This difference did not depend upon cycling status for HAM-D 28 ($p=0.384$) or for HAM-D 17 ($p=0.358$) scores. Rapid cycling patients had a greater reduction in HAM-D 28 ($p=0.014$) and HAM-D 17 ($p=0.006$) scores versus non-rapid cycling patients. In contrast to initial expectations, however, this difference did not appear to depend upon treatment condition. Although the change in HAM-D 17-R scores was greater during venlafaxine versus lithium ($p=0.003$), the change did not differ significantly between rapid and non-rapid cycling patients ($p=0.314$) (Fig. 2). The interaction terms in regression model (1) were not significant for any HAM-D score (Table 2).

The magnitudes of expected change of HAM-D scores with the 95% CI are displayed in Table 3. The reductions in HAM-D 28, HAM-D 17, and HAM-D 17-R scores were significant for all patient groups. In particular, the reduction in HAM-D scores over time for the rapid cycling patients taking venlafaxine was large, with an expected reduction of 16.269 (95% CI=(12.723,19.814)) for HAM-D 28 and 12.373 (95% CI=(9.994,14.753)) for HAM-D 17. The expected reductions of HAM-D 17-R scores did not depend on cycling status and were 8.85 (95% CI=(6.826,10.875)) for venlafaxine and 4.035 (95% CI=(1.591,6.479)) for lithium ($p<0.001$).

The likelihood of response or remission did not depend on cycling status (Table 4). There was a significantly greater response rate with venlafaxine versus lithium for all HAM-D outcomes, with no significant interaction effect between treatment condition and cycling status. Similarly, there was a greater remission rate with venlafaxine versus lithium for all HAM-D outcomes, with no significant interaction effect between treatment condition and cycling status.

3.4. Hypomanic symptoms and cycling status

The mean and median YMRS scores by treatment condition and cycling status are displayed in Table 5. There was no significant difference in mean baseline YMRS scores ($p=0.6069$) or mean YMRS change scores over time ($p=0.8188$) between rapid and non-rapid cycling groups. There were 4 patients with a YMRS score ≥ 8 on at least one study visit (including baseline): 1 rapid cycling and 3 non-rapid cycling ($p=0.99$, Fisher exact). There was only 1 (non-rapid cyclist) patient with a YMRS score ≥ 12 at any study visit ($p=0.999$, Fisher exact).

Table 5
Median (mean) YMRS scores for treatment condition by cycling status

Study week	Rapid cycling		Non-rapid cycling	
	Venlafaxine (n=12)	Lithium (n=15)	Venlafaxine (n=31)	Lithium (n=25)
1	0.00 (0.00)	0.00 (0.60)	0.00 (0.20)	0.00 (0.38)
2	0.00 (0.27)	0.00 (0.53)	0.00 (0.47)	0.00 (0.40)
4	0.00 (0.00)	0.00 (0.83)	0.00 (0.59)	0.00 (0.57)
6	0.00 (0.18)	0.00 (0.33)	0.00 (0.55)	0.00 (0.25)
8	0.00 (0.40)	0.00 (1.64)	0.00 (1.00)	0.00 (0.00)
10	0.00 (0.00)	0.00 (1.22)	0.00 (0.58)	0.00 (1.08)
12	0.00 (0.00)	0.00 (1.33)	0.00 (0.60)	0.00 (0.56)

There were 7 patients with an increase in YMRS score (versus baseline) at two or more study visits: 1 rapid cycling patient on lithium and 1 on venlafaxine, 1 non-rapid cycling patient on lithium and 4 on venlafaxine ($p=0.6941$, 1-way ANOVA). Similarly, there was no

Table 6
Number of adverse event occurrences

Body system	Venlafaxine rapid cycling (n=33)	Venlafaxine non-rapid cycling (n=10)	Lithium rapid cycling (n=15)	Lithium non-rapid cycling (n=25)
<i>Body as a whole</i>				
Cardiovascular	0	8	3	5
Dizziness	1	2	1	4
Flu-like symptoms	4	7	3	1
Headaches	7	11	5	9
Increased appetite	0	0	1	1
Jitteriness	0	1	1	1
Nose bleeds	1	1	0	0
Polydipsia	1	4	11	14
Polyuria	0	5	18	19
Rash/itchiness	0	4	4	4
Restless leg	0	0	1	1
Sweating	1	6	1	2
Tremor	0	7	12	14
Weight gain	2	2	6	4
Yawning	0	2	0	0
Other	2	16	11	15
<i>Gastrointestinal</i>				
Constipation	3	9	2	0
Diarrhea	1	3	3	9
Dry mouth	3	12	1	3
Dyspepsia	1	0	1	1
GI upset	0	5	6	3
Metallic taste	0	0	0	3
Nausea/vomiting	4	7	7	20
<i>Psychiatric</i>				
Abnormal dreams	0	6	1	0
Agitation/anxiety	3	3	0	1
Thinking difficulty	2	5	8	7
Hypomania	0	1	0	1
Sub-syndromal hypomania	1	2	4	2
Mixed episode	1	2	0	1
Minor depression	0	1	0	0
Sleep disturbance	8	7	2	1
Irritability	1	1	0	1
Lethargy	0	1	1	3
Somnolence	4	12	5	5
Suicidal ideation	0	0	0	1
<i>Sexual</i>				
Delayed orgasm	2	0	1	1
Sexual dysfunction	1	4	0	0

Note: One patient discontinued treatment for hypomanic induction (venlafaxine) and 1 patient discontinued treatment for increasing suicidal ideation (lithium).

significant difference in the proportion of patients with any increase in YMRS score (versus baseline) by cycling status, i.e., rapid vs. non-rapid cycling patients ($p=0.8843$), rapid vs. non-rapid cycling patients on venlafaxine ($p=0.3181$), and rapid vs. non-rapid cycling patients on lithium ($p=0.2971$).

The mean time to first rise in YMRS (versus baseline) was 3 and 8 days for rapid and non-rapid cycling patients on venlafaxine, respectively, and 12 and 11 days for rapid and non-rapid cycling patients on lithium, respectively ($p=0.6952$, 1-way ANOVA). Finally, QLS analysis indicated that there was no significant increase in YMRS scores over time in the rapid versus non-rapid cycling venlafaxine or lithium groups.

3.5. Safety

Thirteen patients (15.7%) withdrew from treatment as a result of an adverse event. There was one serious adverse event (i.e., increase in suicidal ideation) during lithium therapy that was judged to be unrelated to drug therapy. Table 5 displays the frequency of reported and elicited adverse events by treatment condition and cycling status from 83 patients who completed the baseline evaluation. The majority of 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. There were 2 occurrences of hypomania meeting DSM IV criteria in non-rapid cycling patients: 1 on venlafaxine and 1 on lithium. There were 9 occurrences of sub-syndromal hypomania: 3 during venlafaxine (1 in a rapid cycling patient) and 6 during lithium (4 in rapid cycling patients). There were 4 mixed mood episodes: 3 during venlafaxine (1 in a rapid cycling patient) and 1 during lithium in a non-rapid cycling patient. One venlafaxine patient discontinued treatment for hypomania and 1 lithium patient discontinued treatment for increased suicidal ideation (Table 6).

4. Discussion

To date, there have been few studies specifically examining the relative safety and efficacy of antidepressant versus mood stabilizer monotherapy of rapid and non-rapid cycling BP II patients. Several studies have suggested that antidepressant use may cause cycle acceleration in BP II patients (Wehr and Goodwin, 1987; Goodwin and Jamison, 1990; Altshuler et al., 1995; Goodwin and Ghaemi, 1998; Montgomery et al., 2000; Ghaemi et al., 2003; Goldberg and Truman, 2003; Ghaemi et al., 2004; Papadimitriou et al., 2005;

Goldberg and Ghaemi, 2005; Leverich et al., 2006; Truman et al., 2007). However, this has not been a universal finding (Amsterdam, 1998; Amsterdam et al., 1998; Amsterdam and Garcia-Espana, 2000; Amsterdam et al., 2004; Amsterdam and Shults, 2005; Parker et al., 2006; Amsterdam and Shults, 2008). Despite practice guidelines that recommend avoiding antidepressants in BP II MDE (American Psychiatric Association, 1994, 2002; Expert Consensus Panel for Bipolar Disorder, 1996; Yatham et al., 1997; Sachs et al., 2000; Thase and Sachs, 2000), antidepressants continue to be widely prescribed (Ghaemi et al., 2000). One survey found that 46% of all drugs prescribed to BP patients were antidepressants (Blanco et al., 2002), while another patient respondent survey found that 57% of BP patients were prescribed an antidepressant and only 13% were prescribed a mood stabilizer (Levine et al., 2000).

Prospective data on the risk of antidepressant-induced mood conversions in rapid and non-rapid cycling BP II patients are limited. Early studies have reported antidepressant-induced manic symptoms or cycle acceleration in mixed populations of BP I and II patients (Cohn et al., 1989; Stoll et al., 1994; Altshuler et al., 1995; Goodwin and Ghaemi, 1998; Levine et al., 2000; Kupfer et al., 2001; Ghaemi et al., 2003; Goldberg and Truman, 2003; Ghaemi et al., 2004; Marangell et al., 2004; Bowden, 2005; Goldberg and Ghaemi, 2005; Papadimitriou et al., 2005). More recently, Leverich et al. (2006) reported a higher ratio of syndromal to sub-syndromal mood conversion ratio during venlafaxine (versus sertraline or bupropion) therapy in a mixed population of BP I, BP II, BP NOS, and BP schizo-affective patients taking various mood stabilizers and/or atypical antipsychotic drugs. These investigators, and others (Montgomery et al., 2000; Goldberg and Ghaemi, 2005), cautioned that antidepressant use should be limited in BP II MDE patients.

Recent reports from the naturalistic *Systematic Treatment Enhancement Program for BP Disorder* (STEP-BD) study have been contradictory and often difficult to interpret. For example, a recent analysis by Truman et al. (2007) suggested that prior antidepressant treatment (including exposure to a TCA, SSRI, or bupropion) was associated with a greater likelihood of having mood conversion episodes. In addition, these investigators found that patients who had a shorter illness duration and multiple antidepressant exposures in the past were more likely to have mood conversions (Truman et al., 2007). Another analysis from the same study found no specific benefit from antidepressant therapy (in combination with mood stabilizers) in BP depression and an increase in the frequency of mood conversion episodes versus mood stabilizer monotherapy (Sachs et al., 2007).

In contrast, another report from the STEP-BD trial indicated that there may be a therapeutic advantage from antidepressant therapy, with a lower risk of manic and hypomanic conversions in BP II NDE versus BP I MDE patients (Baldassano et al., 2003). Findings from another recent study support these latter observations and found no association between antidepressant use and rapid cycling status in BP patients (Vo and Dunner, 2003). Moreover, several prospective clinical trials of fluoxetine and venlafaxine monotherapy have failed to find any clinically meaningful increase in mood conversion episodes or cycle acceleration in BP II MDE patients (Cohn et al., 1989; Amsterdam, 1998; Amsterdam and Garcia-Espana, 2000; Calabrese et al., 2001; Kupfer et al., 2001; Amsterdam et al., 2004; Amsterdam and Shults, 2005; Parker et al., 2006). In a recent 9-month double-blind, placebo-controlled, cross-over study of SSRI versus mood stabilizer monotherapy of BP II MDE patients, Parker et al. (2006) found fewer days in depression or hypomania during SSRI versus placebo therapy ($p=0.02$), with no rise in mean YMRS scores ($p=0.46$) and no SSRI-induced cycle acceleration.

Although mood stabilizers (e.g., lithium) have generally been considered as the ‘gold standard’ for treating BP depression, early studies suggested that patients with BP II disorder may respond less well to lithium therapy (Goodwin and Jamison, 1990; Calabrese et al., 2001). Similar findings have also emerged from the STEP-BD trial (Baldassano et al., 2003; Sachs et al., 2007; Truman et al., 2007). In a study examining factors that may influence response to lithium therapy, Dunner and Fieve (1974) found that rapid cycling status was a negative predictor of response to lithium therapy with 18% of rapid cycling, versus 59% of non-rapid cycling, BP patients responding to lithium ($p<0.05$). A longitudinal study of 360 BP I and BP II patients treated with lithium for an average of 13.3 years found no relationship between rapid cycling status and the number of prior MDEs or manic episodes per year (Baldessarini et al., 2000). In contrast to our initial expectations, we found that venlafaxine produced a greater reduction in HAM-D 28 ($p<0.001$) and HAM-D 17 ($p<0.001$) scores, and a greater response ($p=0.021$) and remission ($p=0.007$) rate versus lithium in rapid cycling BP II MDE patients.

A number of caveats should be considered in the interpretation of the present findings. The current analysis was exploratory in nature. The original study was powered to detect differences in efficacy between treatment conditions. The study was not, however, powered to detect differences in outcome between rapid versus non-rapid cycling patients. In addition, the study was not powered to detect differences in mood conversion rates between treatment conditions or between rapid

versus non-rapid cycling groups. Larger sample sizes would have been needed to detect differences in mood conversion rates, if the differences were small between groups. Moreover, the small difference in YMRS elevations over time in the treatment groups was not of clinical significance.

We employed a conservative definition of rapid cycling that was based upon a life-time average of ≥ 4 affective episodes per year occurring over the course of the illness (rather than ≥ 4 affective episodes in the previous 12 months). This conservative definition may have resulted in a rapid cycling BP II patient cohort with more chronic depression and fewer mood conversion episodes. In this regard, a recent analysis of 338 subjects from the STEP-BD trial found that BP patients with a short (versus chronic) illness duration were more likely to report a history of more mood conversions (odds ratio = 1.02, 95% CI = 1.01 to 1.04) (Truman et al., 2007). Moreover, the majority of the rapid cycling BP patients in the present study generally reported a history of hypomanic or mixed episodes occurring within, or temporally associated with, a subsequent BP MDE.

We did not employ a patient-recorded daily chronology to identify ultra-short affective episodes. Thus, it is possible that we missed the presence of ultra-short sub-syndromal hypomanic or mixed affective episodes that occurred between study visits (Leverich et al., 2006). It is also possible that the frequency of venlafaxine-induced mood conversions in the rapid cycling group may have been higher if a longer treatment duration had been employed. However, observations from prior fluoxetine and venlafaxine studies of BP II MDE patients found no increase in treatment-emergent mood conversions after week 6 of treatment (Amsterdam, 1998; Amsterdam et al., 1998; Amsterdam and Garcia-Espana, 2000; Parker and Parker, 2003; Amsterdam et al., 2004; Amsterdam and Shults, 2005; Parker et al., 2006).

It is possible that the modest dose titration of lithium advantaged venlafaxine therapy. While the venlafaxine dose was increased to a mean maximum of 186 (92) mg daily, the maximum lithium dose was limited by a serum lithium level of 1.5 mmol/L. Thus, it is possible that the modest efficacy of lithium was an artifact which may have disappeared with a higher dose.

Finally, it is possible that the randomized, open-label study design and lack of a placebo condition placed constraints upon our ability to detect the 'true' efficacy and mood conversion rates in the rapid and non-rapid cycling groups. It is also possible that the low frequency of mood conversions in all groups during venlafaxine and lithium therapy represents background symptoms, rather than true 'drug-induced' mood conversion symptoms. While some

BP studies have found a higher ratio of syndromal to sub-syndromal mood conversions during venlafaxine therapy (Leverich et al., 2006; Vieta et al., 2002), this has not been a universal finding (Amsterdam, 1998; Amsterdam and Garcia-Espana, 2000; Parker and Parker, 2003).

5. Conclusion

There has been a paucity of controlled studies examining the comparative safety and efficacy of antidepressant versus mood stabilizer therapy in rapid and non-rapid cycling BP disorder. The present analysis compared venlafaxine and lithium monotherapy in rapid and non-rapid cycling patients with BP II MDE. In contrast to initial expectations of lithium superiority in rapid cycling BP II patients, venlafaxine demonstrated significantly greater efficacy versus lithium, and a similar mood conversion rate. Although these data support prior observations that venlafaxine monotherapy may be an effective initial treatment for BP II MDE, the finding of this study should be considered as exploratory in nature and used to inform future hypotheses.

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Conflict of interest

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