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Rapid versus Non-rapid Cycling Bipolar II Depression: Response to Venlafaxine and Lithium and Hypomanic Risk

Lorenzo Lorenzo-Luaces, MA^{a,b}, Jay D. Amsterdam, MD^a, Irene Soeller, MSN^{a,c}, and Robert J. DeRubeis, PhD^{a,b}

^aDepression Research Unit, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania School of Medicine, Philadelphia, PA

^bDepartment of Psychology, University of Pennsylvania, Philadelphia, PA

^cDepartment of Family Medicine and Community Health, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Abstract

Objective—To examine the safety and effectiveness of antidepressant versus mood stabilizer monotherapy in rapid versus non-rapid cycling bipolar II disorder.

Method—Subjects 18 years old with bipolar II depression (n=129) were randomized to double-blind venlafaxine or lithium carbonate monotherapy for 12 weeks. Responders (n=59) received continuation monotherapy for 6 additional months.

Results—Rapid cycling did not affect frequency of response or change over time in depressive symptoms. Rapid cycling status did not affect frequency of depressive relapse or sustained treatment response. Rapid cyclers were more likely to experience hypomanic symptoms ($p=0.005$) during continuation monotherapy; however, rates were similar in venlafaxine (17.6%) and lithium (42.9%) ($p=0.31$).

Conclusion—Rapid cycling status may not be associated with an increased risk of diminished response or greater depressive relapse during venlafaxine, relative to lithium monotherapy, in bipolar II subjects. Additional randomized studies are needed to confirm these findings.

Keywords

Bipolar disorder; Depression; rapid cycling; lithium; venlafaxine; antidepressant; manic switch episodes

Address correspondence regarding this article to: Jay D. Amsterdam, M.D., Depression Research Unit, University of Pennsylvania, 3535 Market Street, Philadelphia, PA. 19104, Telephone: (215) 662-3462; Telefax: (215) 662-6443, ; Email: jamsterd@mail.med.upenn.edu

Declaration of interest

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INTRODUCTION

In no area of psychiatry is the use of antidepressant therapy more challenging or controversial than in the treatment of patients with rapid cycling bipolar disorder (1–3). For example, Ghaemi (4) and others (5) assert that antidepressants are mood *de*-stabilizers for patients with rapid-cycling bipolar I and II disorder. These authors associate rapid cycling status with an increased risk of manic switch episodes, mixed episodes, cycle acceleration, depressive relapse and lack of antidepressant effectiveness. By contrast, Parker et al. (6), relying on data from a sample of patients with rapid-cycling bipolar II disorder, have suggested that antidepressants may have mood-stabilizing properties. Others have argued that there may be a role for antidepressants in specific subgroups of patients with rapid-cycling bipolar disorder (7, 8). Most practice guidelines, however, recommend that patients with rapid cycling bipolar depression avoid antidepressant monotherapy and that mood stabilizer monotherapy, or the combination of a mood stabilizer and an antidepressant, should be used to treat depressive episodes (9–11). Despite these recommendations, antidepressant monotherapy continues to be widely prescribed for patients with both rapid and non-rapid cycling bipolar depression (12), perhaps because other medications seem less efficacious (13). Thus, controversy continues regarding the safety and effectiveness of antidepressant use in rapid cycling bipolar patients (12, 14, 15).

Rapid cycling syndrome may be more common in individuals with bipolar type II disorder (16), and may also be associated with poor response to treatments (1). Some investigators have reported rapid cycling to be associated with antidepressant use *per se* (14, 17); although this association has not been universally observed (18, 19). For example, in one naturalistic study of 109 bipolar patients followed up to 36 years, rapid cycling occurred during antidepressant use in 77% of patients, with only one-third recovering from rapid cycling syndrome (2). Similarly, Wehr et al. (20) reported rapid cycling in 51% of bipolar I depressed patients taking an antidepressant. In that sample, however, 37% of patients spontaneously recovered from rapid cycling *during* continued antidepressant use. Caution must be taken when interpreting these findings because rapid cycling patients are more likely to spend more time depressed than hypomanic. As a result, they spend more time on antidepressants. This raises the possibility of a spurious correlation between antidepressant use and rapid cycling status that is observed in naturalistic treatment studies (19) and highlights the need for prospective and randomized studies on this topic.

Although some reviews of the literature suggest a role of antidepressants in inducing treatment-emergent manic symptoms, other reviews do not support these conclusions (6, 7, 13, 19, 21). It is difficult to integrate these reviews because the available data on the use of antidepressants in rapid cycling bipolar patients comprises mixed populations of bipolar I and II patients, in non-randomized, open-label designs, employing a variety of antidepressants in conjunction with various mood stabilizers or atypical antipsychotics. In the context of concerns over rapid cycling and treatment-induced hypomania, a large placebo-controlled study exploring the efficacy of adjunctive treatments to mood stabilizer monotherapy called into question the efficacy of antidepressants for bipolar I and II depression altogether (22). By contrast, several randomized, controlled studies examining rapid cycling status in bipolar II depression have suggested that short-term and continuation

antidepressant monotherapy may be more effective than mood stabilizer therapy (6, 23–25). Moreover, these studies suggest a similar effectiveness in rapid and non-rapid cycling patients, and that antidepressant use does not precipitate a higher rate of treatment-emergent mood conversion episodes or rapid cycling syndrome (6, 23–25). While encouraging, the results of these studies run counter to treatment guidelines for rapid-cycling bipolar disorder. Thus, more studies focusing on individuals with rapid cycling bipolar II disorder are needed.

Aim of the study

This report is an exploratory analysis of the effectiveness and mood conversion rate of short-term and continuation antidepressant (venlafaxine) versus mood stabilizer (lithium carbonate) monotherapy for subjects with rapid versus non-rapid cycling bipolar II major depressive episode.

Material and methods

Subjects

The report is a secondary analysis of data from a randomized controlled comparison of venlafaxine monotherapy versus lithium carbonate monotherapy for bipolar II depression (ClinicalTrials.gov identifier: NCT00602537). The primary study outcomes and design features have been described elsewhere (26, 27). Briefly, outpatient subjects (≥ 18 years old) were enrolled in the study if they: 1) met the criteria for DSM IV-TR diagnosis of bipolar II disorder according to the *Structured Clinical Interview for DSM-IV Axis I disorders* (SCID-I) (28); 2) were currently experiencing a major depressive episode; and, 3) had a 17-item Hamilton Rating Scale for Depression (HRSD) (29) score ≥ 16. Exclusion criteria were: a history of prior mania or psychosis, substance use disorder within the preceding 3 months, sensitivity or non-response to venlafaxine or lithium within the current episode, the presence of an unstable medical condition, or concurrent use of antidepressant or mood stabilizer medication.

Procedures

Written informed consent was obtained in accordance with the ethical standards of the Institutional Review Board of the Hospital of the University of Pennsylvania. The study was conducted using Good Clinical Practice guidelines (30) with oversight by the local Office of Human Research and an independent Data and Safety Monitoring Board.

The number of prior major depressive episodes, hypomanic episodes, and sub-syndromal hypomanic episodes occurring since illness onset were estimated via detailed interview of subjects at the screen visit using the SCID-I format. Medical history, physical examination, and laboratory tests were also performed. Subjects were classified as rapid cycling if they had an average of ≥ 4 major depressive, hypomanic, and/or sub-syndromal hypomanic episodes per year using the following equation:

$$[\text{Total Number Major Depressive Episode} + \text{Syndromal Hypomanic Episodes} + \text{Sub-syndromal Hypomanic Episodes}] \div \text{Total Illness Duration (in years)}$$

Structured 28-item HRSD (29) and Young Mania Rating Scale (YMRS) (31) measures were obtained by a study clinician blind to treatment condition. Symptom ratings were obtained with attribution as to the origin of the symptom. This procedure has been employed in prior trials as a means of distinguishing hypomanic from depressive symptoms (23, 32).

Treatment

Acute monotherapy was administered for 12 weeks with outcomes measured at baseline, and weeks 1, 2, 4, 6, 8, 10, and 12. Response to treatment, the primary outcome measure, was defined as a 50% reduction in baseline 17-item HRSD score plus a final Clinical Global Impression / Severity (CGI/S) (33) score 3. Responders at week 12 were enrolled into continuation monotherapy on their established dose of double-blind medication for an additional 6 months. Outcome measures were obtained at continuation weeks 16, 20, 24, 30 and 36. Relapse was defined as a rise in the 17-item HRSD score 14 plus CGI/S score of 4 for 14 days.

Venlafaxine was initiated at 37.5mg daily and increased to 75mg daily during week 1 of treatment. The dose was titrated upward in 37.5mg or 75mg increments every week (as tolerated) 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 venlafaxine dose of 75mg daily were discontinued from the trial.

Lithium carbonate was initiated at 300mg daily and increased to 600mg daily during week 1 of treatment. 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 then obtained, and the dose increased to 1200mg daily during week three of therapy based upon clinical response and serum lithium level. This procedure was repeated until a serum lithium level between 0.8–1.5mEq/L was achieved. Lithium was maintained at the maximum tolerated dose following week 4 of the trial. Subjects unable to tolerate a dose of 300mg daily or maintain a sustained minimum lithium level of 0.5mEq/L were discontinued from the trial. To maintain blinded treatment conditions for venlafaxine versus lithium, blood samples for ‘true’ lithium 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 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 (see 26, 27, for more details about the blinding procedures). Short-term zolpidem (10mg) or trazodone (75mg) were permitted, but rarely employed, for severe insomnia up to study week 4.

Treatment-emergent hypomanic symptoms

Frequency of treatment-emergent syndromal and sub-syndromal hypomanic symptoms were assessed via telephone reports and clinician-elicited information of mood conversion symptoms at each study visit using the YMRS. Given the broad consensus that bipolar II

disorder is characterized by frequent sub-syndromal hypomanic symptoms that last for a brief period of time (34), we employed three definitions of treatment-emergent hypomanic symptoms that differ in the number of symptoms and duration required, in addition to the DSM-IV TR definition of hypomania. Sub-syndromal episodes were defined as (i) type I sub-syndromal hypomania with 4 symptoms lasting 3 days; (ii) type II sub-syndromal hypomania with 3 symptoms lasting 4 days; and, (iii) type III sub-syndromal hypomania with 3 symptoms lasting 3 days.

Subjects experiencing treatment-emergent hypomanic symptoms underwent double-blind rescue therapy via upward or downward adjustment of medication dose within the allowable dosage (and lithium level) range.

Statistical Plan

All analyses were conducted using IBM SPSS v. 21 (IBM Corporation, NY). Data were analyzed according to the intent-to-treat principle based on a sample size of 129 subjects for the acute phase of treatment, and 55 for the sample of responders who completed acute treatment and went on to continuation treatment. Initial analyses summarized demographic and clinical variables at baseline and after response at week 12 for the entire subject sample as well as for rapid cyclers and non-rapid cyclers separately. Differences in variables between rapid and non-rapid cycling groups were explored using Fisher's exact test for categorical variables. T-tests for comparisons of means of continuous variables were used, unless the existence of outliers indicated that an independent samples median test was more appropriate.

Effectiveness and treatment-emergent hypomanic symptoms were the dependent variables in this report. In terms of effectiveness, the primary outcome for the acute study phase was response to venlafaxine or lithium monotherapy. The secondary outcome was change over time in HRSD scores. For the continuation phase of the study, depressive relapse was the primary outcome. We also report on an index, sustained response, which takes into account both the proportion who respond and the proportion of those patients who survive the continuation period (35). In terms of treatment-emergent-hypomanic symptoms, for the acute phase of treatment, we report change over time on the YMRS. For both the acute and continuation phase, we examined the proportion of patients who, at any point in the study, met criteria for treatment-emergent syndromal or sub-syndromal hypomania.

Effectiveness outcomes and treatment-emergent hypomanic symptoms were explored by 1) treatment condition, 2) rapid cycling status, and 3) the interaction of treatment condition and rapid cycling status. In these analyses, the term in the models for rapid cycling addressed whether there are differences between rapid cyclers and non-rapid cyclers in the dependent variables (e.g., change over time in the HRSD, depressive relapse, etc.), irrespective of treatments condition. The interaction between rapid cycling status and treatment condition examines whether the risk that rapid cycling status confers on diminished effectiveness or hypomanic induction is specific to one of the medications. If rapid cycling status is uniquely associated with treatment-emergent-hypomanic episodes – or loss of efficacy – in venlafaxine but not in lithium, there should be a statistical interaction between treatment

condition and rapid cycling status in the prediction of depression outcomes or treatment-emergent hypomania.

Differential response between rapid versus non-rapid cycling groups was ascertained using Fisher's exact test. To test if rapid cycling status moderated the superiority of venlafaxine over lithium (26, 27), response was regressed on rapid cycling status, treatment condition, and the interaction between rapid cycling status and treatment condition. The effects of rapid cycling on change over time on the HRSD were assessed using generalized estimating equations (GEE) with an autoregressive correlation matrix (AR(1)). In these models, the HRSD scores were regressed on time (the log of the number of weeks from baseline + 1), treatment condition (-0.5 = lithium, 0.5 = venlafaxine), rapid cycling status, rapid cycling by treatment, and the interaction between rapid cycling, treatment condition and time interaction. The baseline HRSD scores, as well as the baseline score by time interaction, were also controlled for in these models. For change over time on the YMRS, the GEE models used a log-link function because the YMRS scores tended to conform to a Poisson distribution.

We compared the proportion of subjects who met any of the definitions of treatment-emergent hypomania by cycling status using Fisher's exact test. To test whether the association between cycling status and hypomanic symptoms differed between venlafaxine and lithium, the definitions of treatment-emergent hypomanic episodes were regressed on rapid cycling status, treatment condition, and the interaction between rapid cycling status and treatment condition.

RESULTS

Enrollment

Acute Phase—One-hundred twenty-nine subjects were enrolled: 60 (46.51%) rapid cycling and 69 (55.49%) non-rapid cycling (see Figure 1). Beyond the expected group difference in the number of prior depressive and hypomanic episodes, the only significant baseline demographic group difference was a younger age at first hypomanic episode ($p=0.002$) and a younger age at study enrollment ($p=0.039$) for rapid cyclers (Table 1).

Continuation Phase—Fifty-nine acute phase responders were available for participation in continuation monotherapy. Of these, 19 were rapid cyclers (45.2%); a similar proportion in the venlafaxine ($n=11$; 45.2%) and lithium ($n=8$; 47.1%) conditions ($p=1.00$, Fisher's exact test). At the start of continuation monotherapy, rapid cyclers had a younger age of illness onset, a shorter duration of the current depressive episode, and were less likely to be non-Caucasian (table 2). Four responders (1 rapid cyler and 1 non-rapid cyler in each treatment condition) withdrew consent to participate in continuation monotherapy with a final continuation phase sample of 55 subjects (17 rapid cycling).

Premature Treatment Discontinuation

Acute Phase—Although more lithium subjects (42.2%) versus venlafaxine subjects (15.4%) discontinued treatment prematurely ($p=0.0009$, Fisher's exact test), rapid cyclers (31.7%) were no more likely than non-rapid cyclers (26.1%) to do so ($p=0.56$, Fisher's

Exact Test). Of subjects randomized to lithium, 42.9% of rapid cyclers versus 41.7% of non-rapid cyclers prematurely discontinued treatment ($p=1.00$). Similarly, for subjects randomized to venlafaxine, 21.9% of rapid cyclers versus 9.1% of non-rapid cyclers prematurely discontinued treatment ($p=0.19$, Fisher's Exact Test). There was no significant interaction of rapid cycling status and treatment condition in predicting premature discontinuation of therapy ($\chi^2(df=1)=1.19$, $p=0.28$).

Continuation Phase—Somewhat more venlafaxine subjects (22.5%) versus lithium subjects (6.7%) prematurely discontinued continuation treatment ($p=0.26$, Fisher's Exact Test). However, rapid cyclers (20.8%) were no more likely than non-rapid cyclers (16.1%) to prematurely discontinue therapy ($p=0.73$, Fisher's Exact Test). One rapid cyclist and no non-rapid cyclist dropped out of continuation treatment during lithium; whereas 23.5% rapid versus 21.7% non-rapid cyclers dropped out of continuation venlafaxine ($p=1.00$). Finally, There was no significant interaction of rapid cycling status and treatment condition in predicting premature discontinuation of continuation therapy ($\chi^2(df=1)=0.0$, $p=1.00$).

Effectiveness

Acute Phase—Overall, 66 (51.2%) of subjects met criteria for response. Venlafaxine produced a higher rate of response relative to lithium (67.7% versus 34.4%, respectively ($p<0.001$, Fisher's exact test). Rapid cycling status did not predict overall response, with 30 rapid cyclers (50.0%) and 36 non-rapid cyclers (52.2%) meeting criteria for response ($p=0.86$, Fisher's Exact Test). A similar proportion of rapid cyclers (59.4%) versus non-rapid cyclers (75.8%) responded to venlafaxine ($p=0.19$, Fisher's Exact Test). A similar proportion of rapid cyclers (39.3%) versus non-rapid cyclers (30.6%) responded to lithium, ($p=0.60$, Fisher's Exact Test). Thus, rapid cycling status did not statistically moderate the effect of treatment on response (Odds ratios (OR)=0.32, SE=0.76, ($\chi^2(df=1)=2.28$, $p=0.13$). Similarly, change over time in HRSD scores was not predicted by rapid cycling ($\beta=-0.73$, SE=1.30, $\chi^2(df=1)=0.32$, $p=0.58$), irrespective of the treatment condition ($\beta=2.26$, SE=2.28, $\chi^2(df=1)=0.98$, $p=0.32$).

Continuation Phase—Seven subjects (12.7%) relapsed during continuation monotherapy with venlafaxine ($n=3$, 7.5%) showing a clinically meaningful, albeit non-significant, superiority over lithium ($n=4$, 26.7%) in preventing depressive relapse (OR=0.22, $\chi^2(df=1)=3.21$, $p=0.07$). Rapid cyclers were no more likely to relapse ($n=3$; 12.5%) than non-rapid cyclers ($n=4$; 12.9%, $p=1.00$, Fisher's Exact Test). Moreover, a similar proportion of rapid cyclers (5.9%) versus non-rapid cyclers (8.7%) relapsed during venlafaxine ($p=0.27$, Fisher's Exact Test). Similarly, a similar proportion of rapid cyclers (28.6%) versus non-rapid cyclers (25.0%) relapsed during lithium ($p=0.19$, Fisher's Exact Test). Thus, rapid cycling status did not moderate the effect of treatment on relapse (OR=0.55, SE=1.73, $\chi^2(df=1)=0.12$, $p=0.73$). Finally, rapid cycling status was not associated with the overall rate of sustained response ($\chi^2(df=1)=0.10$, $p=0.75$) or with the rate of sustained response in venlafaxine ($\chi^2(df=1)=1.23$, $p=0.27$) or lithium ($\chi^2(df=1)=0.02$, $p=0.90$) (see Figure 2).

Treatment-emergent hypomanic symptoms

Acute Phase—During treatment, approximately one-third of subjects (34.6%) experienced an increase in YMRS score relative to their baseline score. However, rapid cycling status was not a significant predictor of increase over time in YMRS scores ($\beta=-0.71$, $SE=0.50$, $\chi^2(df=1)=2.05$, $p=0.15$), irrespective of the treatment condition ($\beta=1.50$, $SE=1.00$, $\chi^2(df=1)=3.46$, $p=0.14$). Rapid cycling status did not predict the frequency or duration of treatment-emergent syndromal or sub-syndromal hypomanic episodes (Table 3), irrespective of treatment condition ($p<0.31$). Thus, the rate of any treatment-emergent syndromal or sub-syndromal episodes was comparable ($p=0.58$) in non-rapid cyclers on venlafaxine (28.1%) or lithium (25.0%) as well as rapid cyclers on venlafaxine (31.2%) or lithium (15.6%).

Continuation Phase—Thirteen subjects (22.4%) experienced an increase in YMRS scores during continuation monotherapy. No non-rapid cyclist experienced a treatment-emergent syndromal or sub-syndromal hypomanic episodes (0.0%). By contrast, rapid cyclers experienced type I hypomanic episode ($n = 1$, 4.2%) ($p=0.44$, Fisher's Exact Test); type II hypomanic episodes ($n = 3$, 12.5%) ($p=0.08$, Fisher's Exact Test); and type III hypomanic episodes ($n = 2$, 8.3%) ($p=0.19$, Fisher's Exact Test). Thus, it appears that rapid cycling *per se* was associated with treatment-emergent sub-syndromal hypomanic episodes ($n=6$, 25%, $p=0.005$, Fisher's Exact Test), irrespective of the treatment group (see Table 4). Among rapid cycling subjects, lithium produced a higher percentage of treatment-emergent sub-syndromal hypomanic episodes ($n=3$, 42.9%) relative to venlafaxine ($n=3$, 17.6%), but this difference was not statistically significant ($p=0.31$, Fisher's Exact Test).

DISCUSSION

Few studies have specifically examined the comparative effectiveness and safety of antidepressant versus mood stabilizer monotherapy in rapid and non-rapid cycling bipolar II subjects (6, 23–25). While antidepressant use in bipolar I disorder has generally been associated with mood conversion episodes and rapid cycling (2, 14, 15, 17), the presence of antidepressant-induced manic symptoms and rapid cycling in bipolar II disorder has been more controversial (4, 17, 19, 36, 37). In the acute phase of the current study, rapid cycling status was neither associated with treatment effectiveness nor with treatment-emergent hypomanic symptoms. Results from the current study replicate observations from prior studies of venlafaxine versus lithium carbonate, suggesting that venlafaxine may provide greater relapse-prevention relative to lithium (26, 32, 38–40) as well as the observations that this effectiveness is unaffected by cycling status (23–25).

Rapid cycling status was associated with a higher frequency of sub-syndromal hypomanic episodes during continuation therapy. However, these symptoms occurred during both treatments and were not limited to, or even associated with, antidepressant use *per se*. Given that these findings emerged in the context of a randomized trial, prior work from observational data suggesting a link between antidepressants and rapid cycling could be understood to reflect reverse causality. That is, antidepressants use in rapid cyclers may be contemporaneous, and seem related to, the onset of hypomania because rapid cycling

patients are more likely to be depressed and subsequently cycle into hypomania, irrespective of whether they are prescribed antidepressants or not.

Several other randomized studies of rapid cycling bipolar II disorder have suggested that antidepressant monotherapy may be as effective as mood stabilizer monotherapy, without precipitating more treatment-emergent mood conversion episodes or rapid cycling syndrome relative to mood stabilizer monotherapy. For example, a 12-week, open-label comparison of venlafaxine versus lithium monotherapy in 27 rapid and 57 non-rapid cycling bipolar II depressed subjects showed greater effectiveness for venlafaxine versus lithium that was independent of rapid cycling status and not associated with a greater risk of mood conversion episodes during venlafaxine (25). A prospective, 12-week, open-label study of fluoxetine monotherapy in 42 rapid cycling versus 124 non-rapid cycling bipolar II depressed subjects showed a faster onset of antidepressant action in rapid cycling subjects with no clinically meaningful or statistically significant difference in hypomanic switch rates between groups (23). In the continuation phase of that trial, there was no significant difference in the proportion of rapid versus non-rapid cycling subjects with depressive relapse, in either treatment condition (24). Similarly, there were no significant differences by rapid cycling status, in either treatment condition, in the onset of hypomanic symptoms.

Important limitations should be considered before interpreting the present findings. This study was exploratory in nature and not specifically powered to detect statistically significant differences in effectiveness or mood conversion rates between rapid and non-rapid cycling groups. Thus, the study may have been underpowered to detect differences in hypomanic and subthreshold hypomanic episodes, especially if those differences were small. The sample size during the continuation phase of the study, especially in the lithium condition, was small. Thus, larger samples are needed to determine whether there are small differences in effectiveness or mood conversion rates for patients that are randomly assigned to mood stabilizer vs. antidepressant monotherapy. While the fact that this study is underpowered is a significant limitation, at the very least, the present findings do not support a view that the use of antidepressants in patients with rapid cycling bipolar depression should be avoided entirely. Moreover, analyses addressing the effectiveness of the monotherapies, particularly in the acute phase of treatment, had the benefit of a larger sample. Finally, we employed several different sensitive metrics of treatment-emergent hypomania using repeated measurements. The findings obtained from these analyses are especially important given that they were obtained in the context of an experimental design where many third variable confounds are controlled for.

We assessed hypomanic symptoms on a continuum and considered the presence of sub-syndromal episodes. However, it is possible that even milder hypomanic episodes of shorter duration should have been evaluated, as some investigators suggest these mild mood fluctuations as pathognomonic of bipolar II disorder (41). In this context, we did not employ the DSM definition of rapid cycling, which has been criticized as arbitrary (19, 42) and, instead, employed a definition of rapid cycling based upon a lifetime average of 4 affective episodes per year over the course of the illness. This definition was designed to capture individuals who have more chronic histories of rapid mood cycling. It comports with 'real world' characterization of the rapid cycling syndrome, especially in bipolar II disorder,

given that the symptom course may be either intermittent or continuous for years, but absent in the preceding 12 months. Others have suggested changes to the definition of rapid cycling including that it be expanded beyond one year (2) and some research suggests greater predictive validity of the DSM IV definition of rapid cycling in those with severe manic symptoms (43) or with even more mood switches in the prior year than the DSM IV definition requires (44). A separate, albeit related question, is whether the phenomenon of rapid cycling is best considered as a continuous one (45). Future work should seek to compare the predictive validity of alternative ways of defining the phenomenon of rapid cycling.

It is possible that the frequency of venlafaxine-induced mood conversion episodes during continuation monotherapy in the rapid cycling group may have been higher had a longer treatment duration been employed. While sub-syndromal hypomanic episodes were more frequent in rapid cyclers during continuation treatment in the present study, these observations differ from those of a prior study of continuation fluoxetine monotherapy which found no increase in treatment-emergent mood conversion episodes (24). It is possible that risk for mood conversion generally, or for antidepressant-induced mood conversions, is highly contingent on the nature of the subject sample. The relatively low mood conversion rate observed in this study may have resulted from the inclusion of more mildly ill individuals with a lower propensity for antidepressant-induced hypomanic episodes. To help guide treatment decisions, future work should explore predictors of treatment-emergent hypomania. It is possible that the effectiveness of lithium may have been higher had the dose of lithium been adjusted to maintain even higher steady-state serum levels within the therapeutic range. Finally, other pharmacological agents like lamotrigine may prove to have better antidepressant properties with a more favorable side-effect profile.

In summary, there is a paucity of controlled, prospective studies examining safety and efficacy of antidepressants in rapid versus non-rapid cycling bipolar II disorder. We compared venlafaxine to lithium monotherapy in rapid versus non-rapid cycling subjects with bipolar II major depressive episode during acute and continuation treatment. Rapid cycling status did not predict or moderate the effect of treatment on response, change over time in HRSD scores, or depressive relapse rate during continuation monotherapy. In the acute phase of treatment, rapid cycling status did not predict the onset of hypomanic symptoms, irrespective of how low the threshold for detecting hypomania was. Only during continuation monotherapy were rapid cyclers more likely than non-rapid cyclers to report any type of treatment-emergent subsyndromal hypomanic episodes. This observation, however, was not specific to rapid cyclers on antidepressants, and, in fact, seemed more common among those in the lithium condition. Thus, rapid cycling status appears to be an overall predictor of hypomania. These findings, though not definitive, suggest that, relative to lithium, venlafaxine monotherapy may be an efficacious acute and continuation monotherapy for bipolar II rapid cyclers with major depression, with a similar rate of treatment-emergent mood conversion. Venlafaxine may also be better tolerated than lithium and does not require costly blood level or metabolic monitoring. Our findings of more hypomanic episodes in rapid cyclers during continuation treatment highlight the importance of conducting longer-term follow-up studies of individuals with rapid cycling bipolar II

disorder. Larger, prospective trials on the treatment of rapid cycling bipolar II depression are needed.

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REFERENCES

1. Coryell W, Solomon D, Turvey C, Keller M, Leon AC, Endicott J, et al. The long-term course of rapid-cycling bipolar disorder. *Arch Gen Psychiat.* 2003; 60:914–920. [PubMed: 12963673]
2. Koukopoulos A, Sani G, Koukopoulos AE, Minnai GP, Girardi P, Pani L, et al. Duration and stability of the rapid-cycling course: a long-term personal follow-up of 109 patients. *J Affect Disord.* 2003; 73:75–85. [PubMed: 12507740]
3. Schneck CD, Miklowitz DJ, Miyahara S, Araga M, Wisniewski S, Gyulai L, et al. The prospective course of rapid-cycling bipolar disorder: Findings from the STEP-BD. *Am J Psychiat.* 2008; 165:370–377. [PubMed: 18198271]
4. Ghaemi SN. Treatment of rapid-cycling bipolar disorder: Are antidepressants mood destabilizers? *Am J Psychiat.* 2008; 165:300–302. [PubMed: 18316425]
5. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. *Bipolar Disord.* 2003; 5:407–420. [PubMed: 14636364]
6. Parker G, Tully L, Olley A, Hadzi-Pavlovic D. SSRIs as mood stabilizers for bipolar II disorder? A proof of concept study. *J Affect Disord.* 2006; 92:205–214. [PubMed: 16516304]
7. Goldberg J. Antidepressant prescribing and rapid cycling. *Am J Psychiat.* 2008; 165:1048–1049. [PubMed: 18676603]
8. Mattes JA. Antidepressant-induced rapid cycling: another perspective. *Ann Clin Psychiat.* 2006; 18:195–199.
9. Bauer MS, Callahan AM, Jampala C, Petty F, Sajatovic M, Schaefer V, et al. Clinical practice guidelines for bipolar disorder from the Department of Veterans Affairs. *J Clin Psychiat.* 1999; 60:9–21.
10. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiat.* 2013; 170:1249–1262. [PubMed: 24030475]
11. Frances AJ, Kahn DA, Carpenter D, Docherty JP, Donovan SL. The Expert Consensus Guidelines for treating depression in bipolar disorder. *J Clin Psychiat.* 1997; 59:73–79.
12. Ghaemi SN, Rosenquist KJ, Ko JY, Baldassano CF, Kontos NJ, Baldessarini RJ. Antidepressant treatment in bipolar versus unipolar depression. *Am J Psychiat.* 2004; 161:163–165. [PubMed: 14702267]
13. Vázquez GH, Holtzman JN, Tondo L, Baldessarini RJ. Efficacy and tolerability of treatments for bipolar depression. *J Affect Disord.* 2015; 183:258–262. [PubMed: 26042634]
14. Goldberg JF, Ghaemi SN. Benefits and limitations of antidepressants and traditional mood stabilizers for treatment of bipolar depression. *Bipolar Disord.* 2005; 7:3–12. [PubMed: 16225555]
15. Goldberg JF, McElroy SL. Bipolar mixed episodes: Characteristics and comorbidities. *J Clin Psychiat.* 2007; 68:e25.
16. Maj M, Pirozzi R, Formicola AM, Tortorella A. Reliability and validity of four alternative definitions of rapid-cycling bipolar disorder. *Am J Psychiat.* 1999; 156:1421–1424. [PubMed: 10484955]

17. Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PE, 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 Psychiatr*. 2006; 163:232–239. [PubMed: 16449476]
18. Kupfer DJ, Chengappa KNR, Gelenberg AJ, Hirschfeld RMA, Goldberg JF, Sachs GS, et al. Citalopram as adjunctive therapy in bipolar depression. *J Clin Psychiatr*. 2001; 62:985–990.
19. Grunze HC. Switching, induction of rapid cycling, and increased suicidality with antidepressants in bipolar patients: Fact or overinterpretation? *CNS Spectr*. 2008; 13:790–795. [PubMed: 18849898]
20. Wehr TA, Sack DA, Rosenthal NE, Cowdry RW. Rapid cycling affective disorder: contributing factors and treatment responses in 51 patients. *Am J Psychiatr*. 1988; 145:179–184. [PubMed: 3341463]
21. Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatr*. 2004; 161:1537–1547. [PubMed: 15337640]
22. Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *New Engl J Med*. 2007; 356:1711–1722. [PubMed: 17392295]
23. Amsterdam JD, Luo L, Shults J. Effectiveness and mood conversion rate of short-term fluoxetine monotherapy in patients with rapid cycling bipolar II depression versus patients with nonrapid cycling bipolar II depression. *J Clin Psychopharm*. 2013; 33:420–424.
24. Amsterdam JD, Luo L, Shults J. Efficacy and mood conversion rate during long-term fluoxetine v. lithium monotherapy in rapid- and non-rapid-cycling bipolar II disorder. *Brit J Psychiatr*. 2012; 202:301–306.
25. Amsterdam JD, Wang C-H, Shwarz M, Shults J. Venlafaxine versus lithium monotherapy of rapid and non-rapid cycling patients with bipolar II major depressive episode: A randomized, parallel group, open-label trial. *J Affect Disord*. 2009; 112:219–230. [PubMed: 18486235]
26. Amsterdam JD, Lorenzo-Luaces L, Soeller I, Li SQ, Mao JJ, DeRubeis RJ. 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. *J Affect Disord*. 2015; 185:31–37. [PubMed: 26143402]
27. Amsterdam JD, Lorenzo-Luaces L, Soeller I, Li SQ, Mao JJ, DeRubeis RJ. Effectiveness and mood conversions in short-term venlafaxine versus lithium monotherapy of bipolar type II major depressive episode: A randomized, double-blind, prospective study. *Brit J Psychiatr*. In press.
28. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. 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.
29. Williams JBW. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatr*. 1988; 45:742–747. [PubMed: 3395203]
30. International Conference on Harmonisation Working Group. *Wiley Encyclopedia of Clinical Trials*. Wiley-Blackwell; 1994. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH).
31. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Brit J Psychiatr*. 1978; 133:429–435.
32. Amsterdam JD, Wang G, Shults J. Venlafaxine monotherapy in bipolar type II depressed patients unresponsive to prior lithium monotherapy. *Acta Psychiatr Scand*. 2010; 121:201–208. [PubMed: 19694630]
33. Guy W. ECDEU assessment manual for psychopharmacology: US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs. 1976
34. Altshuler LL, Post RM, Helleman G, Leverich GS, Nolen WA, Frye MA, et al. Impact of antidepressant continuation after acute positive or partial treatment response for bipolar depression: A blinded randomized study. *J Clin Psychiatr*. 2009; 70:450–457.

35. Fournier JC, DeRubeis RJ, Shelton RC, Gallop R, Amsterdam JD, Hollon SD. Antidepressant medications v. cognitive therapy in people with depression with or without personality disorder. *Brit J Psychiat*. 2008; 192:124–129.
36. Parker G, Parker K. Which antidepressants flick the switch? *Australian and New Zealand Journal of Psychiatry*. 2003; 37:464–468. [PubMed: 12873332]
37. Koukopoulos A, Serra G, Zazzara F, Koukopoulos A, Sani G. Rapid cycling of bipolar patients. *Bipolar Psychopharmacotherapy: Caring for the Patient, Second Edition*. 2011:411–422.
38. Amsterdam JD, Shults J. Comparison of short-term venlafaxine versus lithium monotherapy for bipolar II major depressive episode: a randomized open-label study. *J Clin Psychopharm*. 2008; 28:171–181.
39. Amsterdam JD, Shults J. Efficacy and mood conversion rate of short-term fluoxetine monotherapy of bipolar II major depressive episode. *J Clin Psychopharm*. 2010; 30:306–11.
40. Amsterdam JD, Shults J. Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: a randomized, double-blind, placebo-substitution study. *Am J Psychiat*. 2014:792–800.
41. Akiskal HS, Bourgeois ML, Angst J, Post R, Möller H-J, Hirschfeld R. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J Affect Disord*. 2000; 59:S5–S30. [PubMed: 11121824]
42. Bauer M, Beaulieu S, Dunner DL, Lafer B, Kupka R. Rapid cycling bipolar disorder-diagnostic concepts. *Bipolar Disord*. 2008; 10:153–162. [PubMed: 18199234]
43. Bowden CL, Calabrese JR, McElroy SL, Rhodes LJ, Keck PE Jr, Cookson J, et al. The efficacy of lamotrigine in rapid cycling and non-rapid cycling patients with bipolar disorder. *Biological Psychiatry*. 1999; 45:953–958. [PubMed: 10386176]
44. Kupka RW, Luckenbaugh DA, Post RM, Suppes T, Altshuler LL, Keck PE Jr, et al. Comparison of rapid-cycling and non-rapid-cycling bipolar disorder based on prospective mood ratings in 539 outpatients. *Am J Psychiat*. 2014; 162:1273–1280. [PubMed: 15994709]
45. Thase ME. Antidepressants and rapid-cycling bipolar II disorder: dogma, definitions and deconstructing discrepant data. *The British Journal of Psychiatry*. 2013; 202:251–252. [PubMed: 23549940]

Significant outcomes

- In the acute phase of treatment, rapid cycling status was not associated with antidepressant effectiveness or treatment emergent hypomanic symptoms during venlafaxine versus lithium monotherapy.
- During the continuation phase of treatment, all treatment-emergent hypomanic symptoms occurred in rapid cycling subjects.
- Treatment-emergent hypomanic symptoms were no more likely to occur during venlafaxine than during lithium monotherapy.

Limitation

- The study was not powered to detect small differences in effectiveness or treatment-emergent hypomanic symptoms between rapid and non-rapid cycling groups.
- Limited effectiveness of lithium during acute treatment resulted in a smaller than anticipated sample size for the lithium group during continuation treatment.

Figure 1.
CONSORT diagram for subjects with rapid or non-rapid cycling bipolar II depression
randomized to monotherapy with venlafaxine versus lithium

Figure 2.

Effectiveness of venlafaxine monotherapy vs. lithium monotherapy in the acute and continuation treatment of bipolar II major depression by rapid cycling status

Note. Acute phase treatment response = 50% reduction in baseline 17-item HRSD score plus a final Clinical Global Impression / Severity (CGI/S) score 3. Sustained treatment response = treatment response in the acute phase without relapse or discontinuation in the six-month follow-up. Acute treatment phase N = 129 (65 on venlafaxine, 64 on lithium). Continuation study phase N = 55 (40 on venlafaxine, 15 on lithium).

Table 1

Baseline demographic and clinical characteristics of all subjects by cycling status.

	All subjects (n=129)		Rapid cycling (n=60)		Non-rapid cycling (n=69)		p value
	N	%	n	%	n	%	
Female ^a	73	56.6	37	61.0	36	52.2	0.29
Non-Caucasian ^a	26	20.2	10	16.7	16	23.2	0.39
Inter-episode Recovery ^{a, b}	28	21.7	13	21.7	15	21.7	1.00
	Mean	SD	Mean	SD	Mean	SD	
Age ^c	42.9	13.6	40.20	13.5	45.2	13.5	0.04
Age 1 st MDE ^c	17.9	7.3	18.4	6.8	17.8	7.6	0.66
Age 1 st hypomanic episode ^c	20.5	9.3	19.1	6.3	23.8	9.5	0.01
# prior MDEs ^c	24.0	37.4	40.4	49.1	9.8	10.4	<0.001
# prior hypomanic episodes ^c	44.2	81.7	81.7	107.2	11.5	17.1	<0.001
HRSD ^c	20.1	3.8	19.2	5.0	20.0	4.7	0.16
YMRS ^c	0.5	0.4	0.5	1.5	0.5	1.4	0.95
Median duration of depressive episode (mo.) ^d	6.0	--	4.2		6.5		0.39

^a p value from Fisher's exact test,^b data were missing for three patients,^c p value for comparison of means from independent samples t-test;^d p value for comparison of medians from independent samples.

HRSD = Hamilton Rating Scale for Depression. YMRS = Young Mania Rating Scale. mo.= months.

Table 2
Demographic and clinical characteristics of subjects at start of continuation monotherapy by cycling status.

	All subjects (n=59)			Rapid cycling (n = 32)			Non-rapid cycling (n = 27)			p value
	N	%		n	%		n	%		
Female ^a	32	54.2		16	59.3		16	50.0		0.60
Non-Caucasian ^a	10	16.9		1	3.7		9	28.1		0.02
Inter-episode Recovery ^{a, b}	16	28.1		7	26.9		9	29.0		1.00
	Mean	SD		Mean	SD		Mean	SD		
Age ^c	42.2	12.5		38.6	13.23		45.3	11.1		0.04
Age 1 st MDE ^c	18.5	7.1		17.3	5.4		19.6	8.1		0.21
Age 1 st hypomanic episode ^c	20.8	6.9		18.2	4.5		23.3	8.0		0.01
# prior MDEs ^c	29.8	49.8		53.1	65.9		10.2	11.6		0.001
# prior hypomanic episodes ^c	41.9	61.4		74.9	76.0		14.0	21.4		<0.001
HRSD ^c	4.3	3.0		3.9	2.6		4.7	3.2		0.30
YMRS ^c	0.2	0.6		0.2	0.5		0.2	0.7		0.67
Median duration of depressive episode (mo.) ^d	4.0	--		2.0	--		6.0	--		0.02

^a p value from Fisher's exact test,

^b data were missing for three patients,

^c p value for comparison of means from independent samples t-test;

^d p value for comparison of medians from independent samples.

HRSD = Hamilton Rating Scale for Depression. YMRS = Young Mania Rating Scale. mo.= months.

Frequency and duration (in days) of treatment-emergent hypomanic symptoms during acute monotherapy.

Table 3

	Rapid cycling		Non-rapid cycling		<i>P</i>
	<i>n</i>	%	<i>n</i>	%	
Hypomania ^a	3	5.0	4	5.8	1.00
Type I ^a	4	6.7	2	2.9	0.42
Type II ^a	6	10.0	7	10.0	1.00
Type III ^a	6	10.0	8	11.6	1.00
Any hypomania ^a	15	25.0	17	24.6	1.00
Duration	Mean	SD	Mean	SD	<i>P</i>
Hypomania ^b	10.0	7.0	9.3	5.0	0.87
Type I ^b	2.5	0.6	3.5	0.7	0.13
Type II ^b	14.3	11.9	10.2	6.6	0.47
Type III ^b	2.0	1.3	3.1	1.9	0.23
Any hypomania ^b	7.5	9.5	9.9	9.8	0.49

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

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

Table 4 Frequency and duration (in days) of treatment-emergent hypomanic symptoms during continuation monotherapy.

	Rapid Cycling		Non-rapid cycling		<i>P</i>
	<i>n</i>	%	<i>n</i>	%	
Hypomania ^a	0		0		
Type I ^a	1	4.2	0.0	0.0	0.44
Type II ^a	3	12.5	0.0	0.0	0.08
Type III ^a	2	8.3	0.0	0.0	0.19
Any hypomania ^a	6	25.0	0.0	0.0	0.005
Duration	Mean	SD	Mean	SD	<i>P</i>
Hypomania ^b	--	--	--	--	--
Type I ^b	1.0	--	--	--	--
Type II ^b	9.0	5.0	--	--	--
Type III ^b	3.0	1.4	--	--	--
Any hypomania ^b	5.7	5.0	--	--	--

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

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