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Brief report

Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial

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ABSTRACT

Background: The use of antidepressants in rapid-cycling bipolar disorder has been controversial. We report the first randomized clinical trial with modern antidepressants on this topic.
Methods: As part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, we analyzed, as an a priori secondary outcome, rapid cycling as a predictor of response in 68 patients randomized to continue vs. discontinue antidepressant treatment, after initial response for an acute major depressive episode. Outcomes assessed were percent time well and total number of episodes. All patients received standard mood stabilizers.
Results: In those continued on antidepressants (AD), rapid cycling (RC) subjects experienced 268% (3.14/1.17) more total mood episodes/year, and 293% (1.29/0.44) more depressive episodes/year, compared with non-rapid cycling (NRC) subjects (mean difference in depressive episodes per year RC vs. NRC was 0.85 ± 0.37 (SE), df=28, $p=0.03$). In the AD continuation group, RC patients also had 28.8% less time in remission than NRC patients (95% confidence intervals (9.9%, 46.5%), $p=0.004$). No such differences between RC and NRC subjects were seen in the AD discontinuation group (Table 1). Analyses within the rapid-cycling subgroup alone were consistent with the above comparisons between RC and NRC subjects, stratified by maintenance antidepressant treatment, though limited by sample size.
Conclusions: In an a priori analysis, despite preselection for good antidepressant response and concurrent mood stabilizer treatment, antidepressant continuation in rapid-cycling was associated with worsened maintenance outcomes, especially for depressive morbidity, vs. antidepressant discontinuation.

1. Introduction

Rapid cycling in bipolar disorder (BD) is a descriptor that defines a subset of patients that have a large number of episodes over short periods of time. Specifically, rapid cycling is defined as having 4 or more episodes in a 12 months periods, but many patients may have significantly more episodes. The prevalence of rapid cycling in populations of bipolar patients varies with different studies. In large International multi-site studies (e.g., The Stanley Bipolar Network), or in European countries (the EMBLEM study) the rates are somewhat low at 17.6% and 17.3%, respectively (Kupka et al., 2005; Cruz et al., 2008). However, the rates are higher in the United States, comprising 25.8% of patients in the Collaborative Depression Study (Coryell et al., 2003), and 34.7% of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (Baldassano et al., 2005). In a non-selected American community sample, the prevalence of rapid cycling is approximately 33% of all patients with any BD (Nierenberg et al., 2010). Individuals with rapid cycling generally have a younger age of onset, greater disease burden, and greater exposure to antidepressants (Kilzieh and Akiskalk, 1999; Azorin et al., 2008). Excess representation in women (Baldassano et al., 2005; Nierenberg et al., 2010; Kilzieh and Akiskalk, 1999), and increased suicidal risk are not consistent finding (Nierenberg et al., 2010;

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Kilzieh and Akiskalk, 1999). Rapid cycling does not appear to be a separate entity, and does not breed true (Kilzieh and Akiskalk, 1999). Rather, it appears to be a state that starts and stops, with an average duration of some two years (Coryell et al., 2003). What causes rapid cycling is of significant importance.

Whether or not antidepressants (AD) cause rapid cycling in bipolar disorder (BD) is a controversial issue, with some studies supporting (Kukopulos et al., 1983; Ghaemi et al., 2004; Schneck et al., 2008), and others opposing (Lewis and Winokur, 1982; Coryell et al., 2003), a causal relationship. Antidepressants are the most commonly prescribed class of medication in BD (Baldessarini et al., 2008). If they cause or worsen rapid-cycling, found in about 25% of patients with BD (Goodwin and Jamison, 2007), this presents a major public health problem. Safely and effectively treating rather than exacerbating mood episodes in the most severely ill among this patient population is a priority.

In the past, there have been no randomized clinical trials (RCT) relevant to this question with new generation antidepressants; all other studies have been naturalistic or observational in nature. We report here an analysis from the first RCT of modern antidepressants that addresses this topic (Ghaemi et al., 2010).

2. Methods

This report presents an a priori secondary analysis of an open randomized clinical trial within the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study cohort (Ghaemi et al., 2010). Subjects ($n=68$) were diagnosed with DSM-IV BD types I, II, or NOS and achieved clinical recovery (at least two months of euthymia) from an index episode of acute BD major depression while treated with an AD and a mood-stabilizer. They were then randomized to AD-continuation ($n=31$) or AD-discontinuation ($n=37$) and their mood-stabilizer was continued for up to three years. Full details of the patient population can be found in the primary paper (Ghaemi et al., 2010). Overall, 17 rapid-cycling subjects were treated; with lithium ($n=11$), lamotrigine ($n=8$), and valproate or carbamazepine ($n=3$ each); 8 subjects received two mood stabilizers. Other currently prescribed psychotropic agents (excluding any non-study antidepressants) could continue and be used or changed at the discretion of each patient's prescribing physician, as in standard clinical practice (8 received neuroleptics: two each for quetiapine, risperidone, ziprasidone, and aripiprazole; 4 received novel anticonvulsants: two each for topiramate and gabapentin). The study procedures and consent forms were approved by the Institutional Review Boards of the collaborating sites. Data on one patient was missing for some of the outcome variables, leaving 67 subjects for these analyses.

Results are presented in both *between-group* and *within-group* analyses. *Between-group* analyses assessed outcomes in rapid cycler (RCs) vs. non rapid cycler (NRC) subjects in two groups: those who were randomized to AD discontinuation, vs. those randomized to AD continuation. These between-group analyses used the entire sample of RC and NRC subjects. *Within-group* analyses are limited to the RC subgroup of 16 subjects, and assess outcomes based on randomization to AD continuation or not only in this subset.

Results were assessed using modeling effect estimates (beta values or odds ratios) for each predictor stratified by randomization to antidepressant discontinuation or not.

Outcomes assessed were percent of time in remission (time well) and number recurrent episodes. Number of recurrent episodes was assessed in two ways, as mean number of depressive episodes per year, mean of manic/hypomanic episodes, and total number of episodes (either manic or depressive) for study duration.

Descriptive statistics are provided, with effect estimates and confidence intervals. For mean differences between groups, *t*-test with unequal variance was applied. *P*-value assessments from this test, should be interpreted in the context of the a priori nature of this secondary outcome of rapid-cycling status. This analysis was the first analysis conducted after the primary outcome in this study (depressive morbidity). Interpretation of statistical significance for the first outcome measures, in an a priori fashion, after the primary outcome involves much lower rates of false positive results than for post-hoc analyses (Friedman et al., 1998). False negative results are possible with small samples, as in the rapid-cycling alone group. Thus, the main analysis used the entire sample, stratifying by rapid-cycling status. As a sensitivity analysis, the sample was reduced to rapid cyclers only, stratified by antidepressant status.

3. Results

The overall sample, 54% of which was female, had a mean age of 43.4 ± 13.1 years, experienced 1.1 ± 1.35 total episodes/year, most of which were depressive (0.8 ± 1.05). Diagnostic subtype was type I bipolar disorder in 69% and type II in 31%. Mean follow-up duration of the sample was 1.66 ± 0.99 years, and subjects spent $72.9\% \pm 23.1\%$ of follow-up time well (not meeting DSM-IV syndromal criteria for mood episodes). In the overall sample of 68 patients, 28% were rapid cyclers ($n=18$).

Between-group analyses (Table 1; comparing RC vs. NRC in the AD continuation group; and separately analyzing RC vs. NRC in the AD discontinuation group) found that in the AD continuation group, RC subjects experienced 268% (3.14/1.17) more total mood episodes/year, and 293% (1.29/0.44) more depressive episodes/year, compared with NRC subjects. Differences in depressive episodes were statistically significant in this a priori secondary outcome (Mean difference in depressive episodes per year RC vs. NRC was 0.85 ± 0.37 (SE), df=28, $p=0.03$). In the AD continuation group, RC patients also had 28.8% less time in remission than NRC patients, a highly statistically significant a priori outcome (95% confidence intervals (9.9%, 46.5%), $p=0.004$). No such differences between RC and NRC subjects were seen in the AD discontinuation group (Table 1).

Within-group analyses was limited to the rapid cyclers only ($n=16$ overall), randomized to antidepressant continuation or not, and found similar results as in the between-group analyses, but with smaller subsample sizes (Table 2).

Though these data are part of a randomized clinical trial, the rapid-cycling (Rasmussen) subsample is small. To address the question whether a few patients might have skewed the mean results, we examined the distributions of the data for any glaring differences. In subjects randomized to stop antidepressants, the

Table 1
Between-group outcomes comparing rapid cyclers and non-rapid cyclers.

	Antidepressant continuation		Antidepressant discontinuation	
Episodes/year (mean ± SD)	RC ($n=7$)	NRC ($n=23$)	RC ($n=9$)	NRC ($n=28$)
Total	3.14 ± 2.73	1.17 ± 1.90	2.44 ± 2.60	1.36 ± 1.74
Depressive	1.29 ± 1.25	0.44 ± 0.73*	0.82 ± 1.12	0.78 ± 1.30
Manic	0.43 ± 0.53	0.25 ± 0.86	0.22 ± 0.44	0.07 ± 0.26
% Time well	52.4 ± 25.3	80.6 ± 19.2**	64.0 ± 24.0	73.1 ± 22.6

* Mean difference in depressive episodes per year RC vs. NRC was 0.85 ± 0.37 (standard error), df=28, $p=0.03$.

** Mean difference 28.8, 95% confidence intervals (9.9, 46.5), $p=0.004$. Other differences were not statistically significant.

Table 2
Within-group outcomes comparing antidepressant continuation (ADC) and antidepressant discontinuation (ADD) in subjects with rapid cycling.

	RAPID CYCLERS	
Episodes/year (mean ± SD)	ADC ($n=7$)	ADD ($n=9$)
Total	2.00 ± 1.63	1.33 ± 1.22
Depressive	1.29 ± 1.25	0.78 ± 1.30
Manic	0.43 ± 0.53	0.22 ± 0.44
% Time well	52.4 ± 25.3	64.0 ± 24.0

No differences were statistically significant.

distribution for depressive episodes was similar in RC vs. NRC groups: 22/28 (79%) NRC subjects vs. 7/10 (70%) RC subjects had 0 or 1 episodes; only 3/28 (11%) NRC subjects vs. 1/10 (10%) RC subjects had 4 or more episodes. In subjects randomized to continue antidepressants (ADc), the distributions for depressive episodes in NRC vs. RC groups were clearly different: 15/25 (60%) NRC subjects vs. 1/7 (14%) RC subjects had 0 episodes – a four-fold difference (RR=4.2, 95% confidence intervals 0.67, 26.5). Only 1/25 (4%) NRC subjects vs. 3/7 (43%) RC subject had 4 or more episodes – a 91% decreased rate (RR=0.09, 95% confidence intervals 0.01, 0.76). In summary, in all groups except the rapid cyclers maintained on antidepressants, distributions were skewed toward zero, meaning most patients had few if any depressive episodes. In the RC group maintained on antidepressants, the distribution was normal, meaning most patients had 2–4 depressive episodes.

4. Discussion

In this sample, long-term continuation of antidepressants was associated with more mood episodes in patients with rapid-cycling bipolar disorder, particularly with three-fold increased rate of depressive episodes in the first year of follow-up. These data represent the first randomized data with new generation antidepressants, and they confirm the only other randomized study, conducted with tricyclic antidepressants.

This sample consists of a selected population of patients who had responded to antidepressants for acute bipolar depression, without manic switch. Thus, this was an "enriched" sample of antidepressant-responsive patients. Even so, there appeared to be worsening of depressive episodes over time in subjects with a history of rapid-cycling bipolar disorder. This result is important because it demonstrates that antidepressant-related worsening of rapid-cycling is a separate (but related) phenomenon from a simple switch in mood state from acute depression to acute mania or hypomania.

Further, all patients took baseline mood stabilizers, indicating that mood stabilizers were not protective against such antidepressant-related worsening of mood episodes in rapid-cycling bipolar disorder, at least in the depressive pole.

In contrast to these consistent results with the two RCTs of this topic, observational studies have yielded inconsistent findings of AD effects in RC patients (Kukopulos et al., 1983; Ghaemi et al., 2004; Schneck et al., 2008; Lewis and Winokur, 1982; Coryell et al., 2003). One observational study found more recurrences in patients taking TCAs or other non-SRI antidepressants than in patients not taking these ADs (Kukopulos et al., 1983), and another found that SRIs generally did not have lower rates of negative outcomes than TCAs (Ghaemi et al., 2004). A small study found that bupropion may not be associated with rapid cycling (Haykal and Akiskal, 1990).

As is a basic axiom of evidence-based medicine, randomized data are more valid than observational data, because of the many confounding factors that can influence observational results. Thus, despite different outcomes in some observational studies, our data and those with other RCT with TCAs likely represent the most valid data on this topic.

Some clinicians have expressed skepticism about these findings (Rasmussen). Such skepticism may reflect insufficient appreciation of the importance of randomized data as opposed to observational data, and insufficient knowledge of prior studies regarding the nature of rapid cycling bipolar disorder, as found in the standard text in the field (Goodwin and Jamison, 2007), prospective outcome studies (Schneck et al., 2008), and comprehensive review articles (Baldessarini et al., 2008). In bipolar disorder—including rapid-cycling—depressive episodes are more frequent and lengthy than manic episodes (e.g., Nierenberg et al., 2010). Our data are consistent with this literature; we observed about two-fold more depressive vs. manic episodes in our rapid cycling subjects. Our study confirms the importance of the concept of "cycling" or "recurrence" (not just polarity) as a key aspect of manic-depressive illness, which is a notion dating back to Kraepelin (Trede et al., 2005). In an illness in which most cycles involve depression more frequently and severely than mania, antidepressants appear to induce not just acute mania, but long-term cycle acceleration with worsening depressive morbidity (Ghaemi et al., 2004; Schneck et al., 2008). This is reflected in recent guidelines that suggest against the use of antidepressants in patients with rapid cycling (Pacchiarotti et al., 2013).

Our data are not definitive, but they are based on the most valid research design we have, and they are consistent with the best available data on modern antidepressants in rapid-cycling bipolar disorder (Schneck et al., 2008).

The mechanism of this effect is not known. However, induction of rapid cycling in bipolar subjects may be related to possession of at least one copy of the long form of the serotonin transporter gene variant (Trede et al., 2005). This same genotype is also associated with an increase in depression in the setting of adversity in non-Asian populations (Trede et al., 2005), and has been purported to predispose to a pro-depressive response to antidepressants (Masoliver et al., 2006). This is consistent with the observation that bupropion may be less problematic in patients with rapid cycling (Kukopulos et al., 1983). Thus, the short form of the serotonin transporter may underlie our observations. We did not genotype the subjects in this study.

4.1. Limitations of the current study

These data must be interpreted in the context of the study design. Sample size is always limited in secondary outcomes of partial datasets. We addressed this problem two ways. First, to avoid a common over-emphasis on *p*-values, which are liable to major false negative risks with small samples, we emphasized descriptive statistics of effect sizes (number of episodes per year). Second, since we predicted and found that only 25% of the sample would have rapid cycling, we planned *a priori*, seven years before the data analysis, to compare the rapid cyclers ($n=17$) to the much larger non-rapid cycling sample ($n=53$) (Ghaemi et al., 2010). The rationale was that, in such an analysis, large descriptive differences, as described above, would be statistically significant when *p*-values were applied (as detailed in the article, namely, about three-fold increased rate of depressive episodes in rapid cyclers vs. non rapid cyclers continued on antidepressants). Finally, we did not examine temperament of these individuals. Cyclothymic temperament has been associated with many of the problematic aspects of cycling (Azorin et al., 2010).

5. Conclusion

Even with pre-selection for good antidepressant response and absence of acute mania related to antidepressants, and despite concurrent mood stabilizer treatment, a priori analysis of rapid cycling status predicted more depressive episode criteria in those who continued antidepressant treatment as opposed to discontinued antidepressant treatment. This decreased efficacy of antidepressants supports previous claims of limited clinical utility and lack of safety in long term treatment of BD patients with ADs.

Role of funding source

The study was funded by a grant from the NIMH, United States. The NIMH approved the design of the study, but was not involved in the data collection, data analysis, or manuscript preparation for the study.

Conflicts of interest

Dr. El-Mallakh currently has research grant support from Merck and is on the speakers' bureau of AstraZeneca, Otsuka, and Sunovion. Dr. Ghaemi currently has a research grant with Takeda Pharmaceuticals North America, and has provided research consultation in the past year to Sunovion. None of the other authors have any conflicts of interest to report.

Contributors' roles

Rif S. El-Mallakh performed some of data collection and paper writing.

Paul A. Vöhringer performed most of data analysis.

Michael M. Ostacher performed much of data collection and some of the writing.

Claudia F. Baldassano performed some of data collection and some of the writing.

Niki S. Holtzman BA assisted with much of the data analysis.

Elizabeth A. Whitham was study coordinator and data maintenance.

Sairah B. Thommi was study coordinator and data maintenance.

Frederick K. Goodwin supervised study design and oversaw writing.

S. Nassir Ghaemi designed study, performed much of data collection and oversaw data analysis and wrote initial draft of paper.

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