Anger Attacks in Bipolar Depression: Predictors and Response to Citalopram Added to Mood Stabilizers

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Background: Of the 2 reports in the literature on anger attacks in bipolar depression, one found them to be uncommon (12%) compared with the rate in bipolar mixed states and unipolar depression (40%–60%), whereas the other found them to be common (62%). We examined anger attacks among participants in an 8-week trial of open-label citalopram added to mood stabilizer for the treatment of bipolar depression. We also examined trait anger, hypomanic symptoms, and depressive symptoms as predictors of anger attacks. We hypothesized that if anger attacks were related to hypomanic symptoms they would respond unfavorably to citalopram, whereas if they were related to trait anger or depressive symptoms they would respond favorably.

Method: In 45 participants with a DSM-IV diagnosis of bipolar I or II depression, anger attacks, hypomanic symptoms, and depressive symptoms were assessed using a modified Anger Attacks Questionnaire, Young Mania Rating Scale, and Hamilton Rating Scale for Depression, respectively. Trait anger was measured using the State-Trait Anger Inventory. Posttreatment data were collected at the end of 8 weeks of treatment with citalopram or at dropout from the trial. The first participant study visit was in November 1998, and the final participant study visit was in December 2000.

Results: Before treatment with citalopram, 17 (38.6%) of 44 participants reported anger attacks (data on anger attacks were missing for 1 participant before treatment and 4 after treatment). Significantly fewer participants reported anger attacks after treatment (6 of 41, 14.6%; McNemar test, $p < .05$, 2-tailed). At pretreatment and posttreatment, trait anger was the only significant predictor of anger attacks ($p < .05$).

Conclusions: These findings suggest that in bipolar depression anger attacks are common, may respond favorably to acute treatment with citalopram added to mood stabilizer, and are better predicted by trait anger than hypomanic or depressive symptoms. Further studies are needed to clarify the diagnostic and treatment implications of anger attacks in bipolar depression.

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Anger attacks are characterized by a rapid onset of intense anger and a crescendo of autonomic arousal that occur following provocations described as trivial by the individual.[1] They are an important symptom because of their association with verbal and physical aggression, which in turn contributes to worry over anger attacks, avoidance of interactions to prevent having anger attacks, and interpersonal problems at home and work.[1–3] In unipolar depression, anger attacks have been reported in 40% to 60% of different samples.[4] In contrast to the attention paid to anger attacks in unipolar depression, we are aware of only 2 reports about anger attacks in bipolar depression.

Jain and colleagues[5] found that 2 (12%) of 17 participants with bipolar depression had anger attacks compared with 19 (62%) of 31 having a bipolar mixed episode and 19 (41%) of 47 with unipolar depression. On the basis of these results, the authors concluded that the presence of anger attacks during a depressive episode may suggest a diagnosis of unipolar depression or a mixed bipolar state rather than bipolar depression. Perlis and colleagues[6] found that 18 (62%) of 29 bipolar depressed participants had anger attacks compared with 13 (26%) of 50 with unipolar depression. These authors concluded that anger attacks during a depressive episode suggest the presence of bipolar disorder, given their finding that anger attacks predicted bipolarity (odds ratio [OR] = 5.8, 95% confidence interval [CI] 2.0 to 16.9) in their combined sample of unipolar and bipolar depressed participants. Here, we have taken an empirical approach, because there are in-

adequate data to make data-based hypotheses on anger attacks in bipolar depression.

Clinically, it is not always easy to distinguish between unipolar and bipolar depression at cross-sectional evaluations, and failure to make the distinction can have adverse clinical consequences as it can result in treatment of bipolar disorder with antidepressants rather than mood stabilizers.[7–9] Because the differential diagnosis between unipolar and bipolar depression has important implications for treatment, clinical features that could help with making the diagnosis are important. If anger attacks are uncommon in bipolar depression as reported by Jain and colleagues,[5] it is possible that anger attacks would make the clinician consider a diagnosis of unipolar depression or a bipolar mixed state rather than bipolar depression. On the other hand, Perlis and colleagues[6] found that anger attacks were more common in bipolar depression compared with unipolar depression and that anger attacks were a predictor of bipolarity in the sample they studied. Therefore, they suggested that anger attacks during a depressive episode may suggest bipolarity. It is noteworthy, however, that the rate of anger attacks in unipolar depression in the report by Perlis and colleagues (13 of 50, 26%) is low compared with the 40% to 60% rates in other unipolar samples.[4]

Akiskal and Benazzi[10] raised the possibility that problems with anger during a major depressive episode may be a marker for a subtle bipolar mixed state, also called a depressive mixed state. A depressive mixed state is defined as a major depressive episode with concurrent hypomanic symptoms that do not meet DSM-IV criteria for a bipolar mixed state, and these authors reported that it is more common in type II bipolar depression compared with unipolar major depression. Akiskal and Benazzi[10] also reported that irritability (i.e., decreased threshold for angry responses) was a significant predictor of depressive mixed states in a regression equation that included DSM-IV major depressive, melancholic, atypical, and hypomanic symptoms (OR = 13.8).

In summary then, there have been suggestions that anger attacks in the context of major depression should cause one to consider a diagnosis of bipolar disorder. As our data were gathered from a sample that only included participants with bipolar depression, we cannot directly answer questions regarding the usefulness of anger attacks in differentiating between bipolar and unipolar disorder. Nevertheless, these data could add to the very limited literature on anger attacks in bipolar depression, their response to short-term treatment with antidepressant added to mood stabilizer, and the power of hypomanic symptoms as predictors of anger attacks compared with depressive symptoms and trait anger.

We are not aware of studies in which anger attacks were the main outcome variable in a treatment trial. There are, however, reports showing that anger attacks significantly decrease when antidepressants are used to treat unipolar depressive disorders.[1,11] We know of no reports on the response of anger attacks when bipolar depression is treated. If anger attacks were a reflection of hypomanic symptoms in a subtle bipolar mixed state, one could hypothesize that they may respond poorly to treatment with the antidepressant citalopram. In this article, we define poor treatment response as experiencing worsening or lack of change in the rate of anger attacks and being less likely to remain in the trial due to increased likelihood of worsening symptoms or a manic switch. On the other hand, if anger attacks were related to depressive symptoms or trait anger, one could hypothesize that they may respond favorably to treatment with citalopram. We chose depressive symptoms and trait anger as the other potential predictors of anger attacks because they are both known to be associated with anger and aggression and to respond favorably to treatment with serotonin reuptake inhibitors.[1,11–15] We are not aware of studies examining whether positive treatment response of anger and aggression in bipolar depression is dependent on a decrease of depressive symptoms. However, there are studies showing that anger and aggression respond to antidepressants independent of depressive symptoms in personality disordered individuals,[12] persons with unipolar depression,[16,17] and normal controls.[18] Therefore, we hypothesized that the treatment response of anger attacks in this sample of bipolar depressives would be independent of improvement in depressive symptoms.

In this study of 45 participants with bipolar depression, we examined (1) the rate and characteristics of anger attacks, (2) the response of anger attacks to citalopram added to mood stabilizer, and (3) the role of hypomanic symptoms as predictors of anger attacks, relative to depressive symptoms and trait anger.

METHOD

Methods employed in this study are summarized here. Further details are available in the article by Kupfer and colleagues.[19]

Participant Recruitment

To be eligible for the study, participants had to be 18 to 70 years of age. They also had to meet DSM-IV criteria for bipolar I or II depression, with a 17-item Hamilton Rating Scale for Depression (HAM-D-17)[20] score ≥ 15 or DSM-IV criteria for subsyndromal bipolar I or II depression with a HAM-D-17 score ≥ 10, after at least 4 weeks of treatment with a therapeutic level of lithium, valproic acid, or carbamazepine. Participants also had to have a Young Mania Rating Scale (YMRS)[21] score ≤ 12 (which indicates that the individual does not have mania) and a Global Assessment of Function score ≤ 70 (which indicates impairment from the illness). Participants with bipolar disorder who had current mania, mixed state,

psychosis, or rapid cycling were excluded. Also excluded were those with schizophrenia and other psychotic disorders, dissociative disorders, substance abuse within the last 3 months, and suicidal behavior within the last 3 months. The first participant study visit was in November 1998, and the final participant study visit was in December 2000.

Forty-five participants were enrolled from 5 academic centers in the United States. Of these, 12 were dropped from the study for noncompliance (N = 4), switching to mania (N = 2), requiring hospitalization for worsening depression (N = 2), and post hoc recognition that they did not meet all study entry criteria (N = 4). Four of the dropped participants did not meet the following study entry criteria: 2 were taking agents that were not permitted (i.e., lamotrigine and gabapentin, in addition to the mood stabilizers required for study entry), 1 had depression that had lasted for longer than a year, and 1 disclosed at the fifth visit that she had posttraumatic stress disorder (PTSD) (an exclusion criterion that she had denied at the start of the study during the Structured Clinical Interview for DSM-IV Axis I Disorders, patient edition [SCID-I]).[22] Consistent with an intent-to-treat approach, all 45 enrolled participants were included for analyses in this article. Including all participants in the analyses maximized the sample size and minimized bias from excluding those who were dropped from the study. The study was approved by the institutional review board of each institution, and written informed consent was secured from each participant.

Participant Characteristics

The participants had a mean age of 42.2 (SD = 11.5) years, and 30 (66.6%) were male. Thirty participants (66.6%) had bipolar disorder type I, and the rest were type II. Thirty-one participants (68.8%) had a diagnosis of major depression, and the remainder had subsyndromal depression. At enrollment, 23 participants were taking lithium, 18 valproic acid, 4 carbamazepine, and 3 lithium and valproic acid. In addition to these mood stabilizers, 11 participants were taking an antipsychotic medication and 20 were taking an anxiolytic or a hypnotic agent. The antidepressants used by participants (venlafaxine, bupropion, and trazodone) were stopped 1 week prior to starting citalopram. The 1 participant whose venlafaxine was discontinued developed withdrawal symptoms with characteristic physical symptoms. This participant reported improvement in mood and anger during the withdrawal syndrome. Thus, the rate of anger attacks prior to starting citalopram was most likely unrelated to antidepressant withdrawal.

Assessment Procedures

After an initial screening visit, eligible participants entered an 8-week period of acute phase treatment with citalopram. At the end of the acute phase, the 21 participants who showed treatment response took part in a 16-week continuation phase of treatment. Treatment response for the acute phase was defined as a 50% decrease of the HAM-D-17 score without meeting criteria for mania, hypomania, or a mixed episode. Anger attacks were assessed at the start and the end of the 8-week acute phase (i.e., time 1 [T1] and time 2 [T2], respectively). The T2 assessment was conducted at the termination visit for those who were dropped from the study prior to the end of the acute phase. The data reported here are for the acute phase, except for the survival analyses, which were conducted for both the acute and continuation phases. The other questions were not examined in the continuation phase due to the small sample sizes.

Psychiatric diagnoses were made by trained raters using the SCID-I for DSM-IV. Hypomanic symptoms were rated by interviewers using the YMRS, and depressive symptoms were rated using the HAM-D-17. Trait anger was measured by self-report using the State-Trait Anger Inventory.[23]

Anger attacks were assessed by self-report using a modified Anger Attacks Questionnaire (AAQ), based on the original AAQ developed by Fava and colleagues.[24] Anger attacks were defined as follows: anger or irritability in the last month, overreacting with anger or rage in the last month, self-reports of having anger attacks in the last month, and at least 1 of the anger attacks being accompanied by 4 or more of the 13 autonomic and behavioral symptoms listed in the original AAQ. (A summary of the changes we made to the AAQ is provided in Appendix 1.)

Data Analysis

Simple descriptive statistics were used to characterize the anger attacks. Response to treatment was examined using the McNemar test to compare anger attacks at T1 and T2 and also by using Kaplan-Meier survival analysis. For the survival analyses, a poor treatment outcome event was coded in 2 ways: (1) dropout for any reason and (2) an adverse mood outcome (dropout due to manic switch or worsening depression, or new onset of anger attacks in a subject without anger attacks at T1). Separate survival analyses were conducted using these definitions. In addition to the adverse outcomes of the 12 participants who were dropped from the study (see Participant Recruitment), other adverse outcomes included new-onset anger attacks at T2 (N = 2), noncompliance in the continuation phase (N = 2), and worsening depression in the continuation phase (N = 2). There were no manic switches or new-onset anger attacks in the continuation phase.

The relative roles of hypomanic symptoms, depressive symptoms, and trait anger as predictors of anger attacks were examined using logistic regression. Due to right skew of YMRS scores at T2, they were dichotomized as

Table 1. Characteristics of Anger Attacks[a,b]

Characteristics	Time 1 N	Time 1 %
Aggressive impulses and acts		
Feel like yelling	16	94.1
Verbally attacking	14	77.8
Feel like physically attacking	13	76.5
Physically attacking	3	17.6
Destroying/throwing objects	5	29.4
Anger attacks typical of self		
No	6	35.3
Somewhat	8	47.1
Yes	3	17.6
Guilt or regret after attacks		
Yes	9	52.9
Yes, not always	8	47.1
No	0	0
Worry about anger attacks		
Very much	4	23.5
Moderately	6	35.3
Somewhat	5	29.4
Very little	2	11.8
Try to prevent anger attacks		
Yes	7	41.2
Sometimes	10	58.8
No	0	0

[a]Anger attacks were reported by 17 of 44 participants at the beginning of the 8-week treatment phase (time 1).
[b]Compared with those without anger attacks, those with anger attacks reported significantly more irritability (mean rank 17.31 vs. 29.18, Mann-Whitney U test, $p < .01$) and more overreaction with anger or rage to minor annoyances (mean rank 14.98 vs. 34.44, Mann-Whitney U test, $p < .01$).

follows: "0" for the 24 participants with a score of zero and "1" for the other 19 who had a score greater than zero. Data on anger attacks were missing for 1 participant at T1 and for 4 at T2. All significance tests were 2-tailed.

RESULTS

Rate and Characteristics of Anger Attacks

At T1, 17 (38.6%) of 44 participants reported anger attacks. This rate is significantly higher than the 12% rate reported by Jain et al.[5] (binomial test, $p < .01$), but not significantly different from the 62% rate reported by Perlis et al.[6] (binomial test, $p > .1$). The rates of anger attacks were similar among those with type I and type II bipolar disorder (11 of 30 vs. 6 of 14, χ^2 test nonsignficant). Table 1 shows some of the characteristics of the anger attacks at T1, in order to illustrate features such as associated aggression, worry and guilt over anger attacks, and attempts to prevent anger attacks.

Response to Treatment With Citalopram Added to Mood Stabilizer

At T2, 6 (14.6%) of 41 participants reported anger attacks, significantly less than the rate at T1 (McNemar test, $p < .05$, 2-tailed). Among the participants for whom these data were available, 11 (73.3%) of the 15 participants who had anger attacks at T1 did not have them at T2, whereas only 2 (8.7%) of the 23 participants without anger attacks at T1 reported having them at T2 (McNemar test, $p = .02$). For participants with type I bipolar disorder, 8 (80%) of 10 who had anger attacks at T1 did not have them at T2, whereas 2 (11.8%) of 17 without anger attacks at T1 reported having them at T2 (McNemar test, $p = .11$). For participants with type II bipolar disorder, 3 (60%) of 5 who had anger attacks at T1 did not have them at T2, whereas 0 (0%) of 8 without anger attacks at T1 reported having them at T2 (McNemar test, $p = .25$).

Of the 6 participants with anger attacks at T2, 4 reported anger attacks at T1 and 2 denied having them at T1. One of the 2 participants with new-onset anger attacks at T2 had been dropped from the study due to not disclosing at recruitment the diagnosis of PTSD, which was an exclusion criterion. The other participant with bipolar disorder type I had nonresponse of depressive symptoms after 8 weeks of taking citalopram (HAM-D-17 score at T1 was 11 and at T2 was 8) and an increase in YMRS score from 2 to 8 (which is within the range for euthymia on the YMRS, i.e., ≤ 12).

Treatment response of depression and anger attacks were unrelated to each other as follows. Those who achieved clinical response (defined as 50% reduction of depressive symptoms) compared with those who did not were equally likely to have anger attacks at T2 (2 of 21 vs. 4 of 20, χ^2 nonsignificant). Similarly, those who achieved remission (defined as a HAM-D-17 score ≤ 7) compared with those who did not were equally likely to have anger attacks at T2 (2 of 6 vs. 13 of 35, Fisher exact test nonsignificant). Similarly, the participants whose anger attacks responded to treatment compared with those whose anger attacks did not respond to treatment were equally likely to have achieved clinical response of depressive symptoms as follows: 5 of 11 versus 2 of 4 with clinical response defined as 50% reduction of symptoms, and 3 of 11 versus 2 of 4 with remission defined as a HAM-D-17 score ≤ 7 (Fisher exact test nonsignificant for clinical response and remission of depressive symptoms).

As noted, survival analyses were conducted for 2 types of outcome: dropout and adverse mood events. Those with and without anger attacks at T1 were equally likely to continue (i.e., not dropout) in both the acute phase and the combined acute and continuation phases of the study (log-rank test statistic, $p > .1$). These results were the same including and excluding the participants dropped for not meeting study entry criteria. Also, survival analyses showed that those with and without anger attacks at T1 were equally likely to have an adverse mood outcome as defined previously (i.e., dropout due to manic switch or worsening depression and new onset of anger attacks) during both the acute and continuation phases of the study. (The rates of occurrence of each adverse outcome were described previously.)

Table 2. Descriptive Data for Predictors of Anger Attacks

	Total Sample			Anger Attacks Present[a,b]			Anger Attacks Absent			Prediction of Anger Attacks		
Parameter	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Odds Ratio[c]	95% Confidence Interval
YMRS												
Time 1	45	3.33	3.2	17	4.77	4.1*	27	2.56	2.3	44	1.6	0.7 to 3.3
Time 2	42	2.71	5.1	6	4.00	3.8	35	1.80	3.2	39	1.5	0.1 to 22.5
HAM-D-17												
Time 1	45	16.60	4.0	17	18.11	4.1	27	15.89	4.0	44	1.6	0.5 to 5.7
Time 2	42	10.00	6.0	6	9.83	5.8	35	9.78	5.9	39	0.2	0.02 to 2.0
Trait anger												
Time 1	44	19.39	7.4	17	24.29	7.0**	27	16.30	6.0	44	3.0*	1.3 to 7.1
Time 2	39	16.05	5.5	6	22.83	7.5**	33	14.82	4.2	39	20.1*	1.6 to 258.7

[a]Significance tests in this column are for comparisons between those with and without anger attacks; all are t tests except Mann-Whitney U test for YMRS at time 2 due to nonparametric distribution.
[b]Those with anger attacks had significantly more threshold symptoms compared with those without anger attacks at time 1 (mean rank 26.32 vs. 20.09, Mann-Whitney U, $p < .05$) but not at time 2 (mean rank 24.67 vs. 20.37).
[c]Logistic regression odds ratio.
*$p < .05$.
**$p < .01$, 2-tailed, for differences between those with and without anger attacks.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.

Predictors of Anger Attacks

Table 2 shows descriptive statistics for the predictors at T1 and T2. The mean YMRS scores at T1 and T2 were substantially lower than both the standard definition for euthymia (≤ 12) and a more strict definition (≤ 7).[25] The HAM-D-17 scores at T1 and T2 were in the moderate and mild ranges, respectively.[26] Compared with a normative group, the mean trait anger scores for the whole sample was at the 63rd percentile at T1 and the 35th percentile at T2 (as the normative data were gender keyed, mean trait anger scores were gender weighted for the comparisons with normative data).[23]

Table 2 shows that at both T1 and T2 only trait anger was a significant predictor of anger attacks when YMRS scores, HAM-D-17 scores, and trait anger scores were simultaneously entered as independent variables into a logistic regression equation.

DISCUSSION

Our analyses showed that 38.6% of a sample of 45 bipolar depressed study participants reported anger attacks. This was significantly higher than the rate of 12% reported by Jain et al.[5] in bipolar depression but not significantly different from the 62% rate reported by Perlis et al.[6] Also, this rate of 38.6% is similar to the 40% to 60% rate of anger attacks reported in unipolar depression.[4]

The rate of anger attacks in this sample significantly decreased after short-term treatment with open-label citalopram added to mood stabilizer. The rates of dropout and adverse mood events (i.e., dropout due to manic switch or worsening depression and new-onset anger attacks) during the study intervention were similar for those with and without anger attacks, suggesting that those with anger attacks were not more susceptible to events resulting in dropout from the study. This finding was in contrast to the hypothesis that if anger attacks were a manifestation of a subtle or subthreshold mixed bipolar state, those with anger attacks would be less likely to complete the trial due to adverse mood events (i.e., manic switches, worsening depression, and new-onset anger attacks).

Lastly, our regression analyses showed that trait anger was a significant predictor of anger attacks at both T1 and T2, whereas neither hypomanic symptoms nor depressive symptoms were significant predictors. This finding, along with the positive response of anger attacks to citalopram, suggests that anger attacks may not be a manifestation of hypomanic symptoms.

From a clinical standpoint, these findings suggest that anger attacks may not be a useful way of distinguishing between bipolar and unipolar depression, and between bipolar depression and subthreshold mixed states. Our findings also suggest that anger attacks in bipolar depression may respond in the short term to serotonin reuptake inhibitors added to mood stabilizers, and that such treatment response may occur independent of response of depressive symptoms.

Those with type I and type II bipolar disorder had similar rates of anger attacks at T1. Though the rate of anger attacks after treatment at T2 for those with type I and type II disorder was similar to the rate for the whole sample, response of anger attacks to treatment was not statistically significant when considering type I and type II disorder separately. Most likely, this lack of statistical significance was because of the small sample sizes.

Consistent with other studies,[1,11,27,28] we found that though anger attacks tend to respond positively to treatment, there is a small minority of individuals who endorse anger attacks at the end of the treatment trial after denying them at the outset. New-onset anger attacks have also been found in response to placebo.[11] A review of this literature and the 2 cases of new-onset anger attacks in this

study did not reveal an explanation for this phenomenon. Nevertheless, it may be useful to monitor for the onset of anger attacks in clinical practice.

The following features of our study limit the generalizability of our findings. First, our small sample size limited the number of hypotheses we could examine. For instance, it would have been useful to examine whether bipolar depressives with anger attacks and any threshold manic symptoms are a distinct subgroup. Second, though we compared the rate of anger attacks in this sample with the rates reported by Jain et al.[5] and Perlis et al.,[6] the latter studies do not represent true control groups but were used as historical control groups. Comparison is further limited because unlike the studies by Jain et al.[5] and Perlis et al.,[6] this sample was recruited for a clinical trial and was not a convenience sample. This study used a modified AAQ that assessed for anger attacks in the last month rather than the last 6 months as on the original AAQ, and this study excluded individuals with rapid cycling. Also, generalizability to clinical samples is limited by the relatively small sample size and the inclusion criteria for the treatment trial.

Third, the lack of differences in the survival curves of those with and without anger attacks and the positive treatment response to citalopram may have been because this was a short-term treatment trial. As noted by Ghaemi and colleagues,[29] studies of longer duration may be needed to detect the adverse consequences of antidepressants in bipolar disorder. Fourth, we are not able to tease apart the relationship between trait anger and bipolar disorder. Specifically, it would be useful to know whether trait anger in samples such as this is an enduring personality trait independent of the mood disorder, a subthreshold bipolar symptom preceding the onset of major mood episodes, or a residual symptom persisting between acute episodes.[9,30–32] Though traits are considered to be enduring individual differences, trait anger in this study declined over the course of the 8-week trial, consistent with changes of trait-like individual differences in response to antidepressant treatment among both healthy[33] and depressed groups.[17] This, too, suggests the usefulness of a more detailed examination of trait anger and its relationship to mood symptoms as noted here. Fifth, as we did not assess for personality, we were unable to examine the relationship between anger attacks and personality. This would have been useful as affective lability and anger dyscontrol are core symptoms of cluster B personality disorders, and these disorders are known to be associated with anger attacks.[34]

In the modified AAQ, we reduced the reference period for the questions from 6 months to 1 month, and we changed the original dichotomous (yes/no) answers to provide more response options. Studies have shown that reducing the reference period and providing more response options cause respondents to assume the researcher is inquiring about more frequent behaviors of lesser severity and about behaviors within a normal range.[35,36] Thus, it is possible that our modifications may have increased the likelihood of participants endorsing questionnaire items. Nevertheless, those reporting anger attacks in this study reported significantly more irritability and overreaction with anger compared with those without anger attacks (Table 1). Also, those reporting anger attacks reported high levels of aggressive impulses and acts during the anger attacks and worry and guilt over anger attacks (Table 1). In this regard, it is noteworthy that Morand et al.[28] questioned the boundaries of anger attacks and raised the possibility that the criteria proposed by Fava[4] may "underestimate the true prevalence of anger attacks."(p44) Thus, it may be useful to develop empirically derived criteria to define anger attacks. Also, assessing anger attacks for the last month may have underestimated treatment response in this 8-week trial, as only those whose anger attacks responded within the first 4 weeks would be assessed as not having anger attacks at T2. Thus, in future studies a longer trial and enumeration of the frequency of anger may be needed to get a better estimate of treatment response.

In summary, our results suggest that anger attacks in bipolar depression are related to trait anger rather than hypomanic symptoms. Thus, further studies are required to clarify the diagnostic usefulness of anger attacks in bipolar depression. Such studies would need to examine the relationship between trait anger and bipolar disorder and whether trait anger is causally related to anger attacks. Also, it would be useful to examine the relative contributions of trait anger and hypomanic symptoms to anger attacks in studies of bipolar depression where the upper limit of hypomanic symptoms is not constrained as in this study. Lastly, this study showed that anger attacks in a sample of bipolar depressives responded positively to short-term open-label citalopram added to mood stabilizer. Given the interpersonal morbidity associated with anger attacks, it may be worthwhile to examine ways of treating anger attacks in bipolar depression.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Tegretol, and others), citalopram (Celexa and others), gabapentin (Neurontin), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), trazodone (Desyrel), valproic acid (Depakene), venlafaxine (Effexor).

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Appendix 1. Modifications to the Anger Attacks Questionnaire (AAQ)

We modified the original AAQ by providing more response choices for answers that were dichotomous, using response choices such as "almost always" rather than "always," adding to or expanding items in the list of anger attacks symptoms (to get a more detailed picture of anger attacks, but without affecting the scoring procedures), and changing the reference period for symptoms from 6 months to 1 month (because we were working with bipolar disorder, in which symptoms change frequently).

Changes we made in the AAQ were as follows:

1. Three symptoms of anger attacks in question 5 of the original questionnaire were each expanded into 2 separate symptoms so that they could be rated individually by participants. When anger attacks were scored, the items in each pair were treated as a single item, to ensure that a positive response to both items was counted as only 1 symptom.
2. The responses to questions on "overreaction with anger or rage to minor annoyances," "guilt after anger attacks," and "whether anger attacks are characteristic of the self" were expanded to provide 3 possible responses rather than just "yes" or "no."
3. We inquired if the respondent was worried about having anger attacks and whether the respondent did things to try to prevent having anger attacks. The possible implications of these modifications for our results are addressed in the Discussion section of the article.