Impact of Antidepressant Continuation After Acute Positive or Partial Treatment Response for Bipolar Depression: A Blinded, Randomized Study

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Objective: To assess long-term outcome in bipolar disorder, subjects were prospectively followed after receiving acute treatment for bipolar depression.

Method: Eighty-three outpatients with DSM-IV bipolar depression who were enrolled between March 1996 and November 2002 and were treated in a 10-week acute double-blind antidepressant treatment trial agreed to participate in a 1-year double-blind continuation of their medication. In the acute antidepressant treatment trial, subjects were treated with a mood stabilizer plus 1 of 3 randomly assigned antidepressants. Sixty-one subjects had attained an acute positive antidepressant response (50% improvement on the Inventory for Depressive Symptomatology [IDS] or 2-point improvement on the Clinical Global Impression for Bipolar Disorder [CGI-BP]) and 22 subjects achieved only acute partial improvement at the end of the 10-week acute trial. In the blinded continuation phase immediately following the acute trial, subjects continued on the same medications and were rated monthly for up to 1 year using the IDS, CGI-BP, and the Young Mania Rating scale.

Results: At study endpoint, 42 (69%) of the 61 acute positive responders maintained positive response and 32 (53%) achieved remission. Compared to the acute positive responders, 6 (27%) of the 22 acute partial responders had achieved positive treatment response at study endpoint ($p < .001$). Eight acute positive responders (13%) and 5 acute partial responders (22%) developed mania.

Conclusion: Patients who achieve a positive acute antidepressant response to 10 weeks of antidepressant treatment adjunctive to a mood stabilizer will probably maintain response with the same continued treatment. Patients who achieve only a partial acute antidepressant response are less likely to further improve when the same treatment is sustained. The switch rate into mania for patients being treated with an antidepressant adjunctive to a mood stabilizer is not higher than the reported rate for patients on mood stabilizer monotherapy.

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Recent randomized data have demonstrated that the use of antidepressant medication in combination with a mood stabilizer does not confer an advantage over mood stabilizer monotherapy when treating an acute episode of bipolar depression.[1,2] Thus, mood stabilizer monotherapy is considered a first-line treatment strategy for acute bipolar depression. Many patients with an acute bipolar depression, however, will not respond to mood stabilizer monotherapy for an acute depressive episode. Others with bipolar disorder will experience a breakthrough depression despite ongoing mood stabilizer treatment. In both of these types of cases, the addition of an antidepressant to an ongoing mood stabilizer regimen can sometimes result in a substantial improvement in depression.[3–9]

Once the depression resolves with this combination regimen, the ideal maintenance strategy remains to be determined. Published treatment guidelines for bipolar depression recommend discontinuing antidepressants within the first 3 to 6 months after remission of depression[10–14] because concern exists that long-term antidepressant exposure, even in combination with a mood stabilizer, might induce a mania or cycle acceleration.[12,15–19] However, the likelihood that a person who has not switched into mania during the acute treatment phase will switch into a mania during the continuation phase of antidepressant treatment is not well studied and therefore not clearly known.

Prior retrospective maintenance studies by our group[20,21] and others[22] have reported no greater switch rates into mania over the course of up to 1-year follow-up in patients who, after an acute positive treatment response, either continue or do not continue antidepressant treatment in combination with a mood stabilizer. Additionally, some of these reports indicate that those who discontinue antidepressant treatment have a significantly increased risk for depressive relapse within 1 year compared to those who continue adjunctive treatment with antidepressants.[20,21] To our knowledge, only 1 prospective study[23] has been published that assessed risk for relapse or switch in subjects continued on antidepressant medications after acute treatment. Thus, the impact of continued antidepressant treatment on outcome after acute treatment is not clearly known.

We recently reported acute antidepressant response and switch rates from a cohort of prospectively followed subjects with bipolar depression who were randomly assigned to treatment for 10 weeks with 1 of 3 antidepressants added to their mood stabilizer regimen.[3] We now report prospective, blinded, follow-up results in subjects from that study who agreed to participate in a double-blind, longitudinal continuation phase of the acute trial for up to 1 year. This cohort represents a "real world" sample in that it assesses a group of patients who improved acutely on an antidepressant and elected to remain on this treatment.

METHOD

Subjects were drawn from an adult sample with bipolar disorder who were enrolled in the Stanley Foundation Bipolar Network (SFBN), as previously described by Leverich et al.[24] and Post et al.[25] All subjects in the SFBN were recruited from network sites located in Bethesda, Md.; Cincinnati, Ohio; Dallas, Tex.; Los Angeles, Calif.; Munich, Germany; and Utrecht, the Netherlands. Upon enrollment into the network, subjects provided written informed consent to participate in the network evaluations, including a naturalistic longitudinal follow-up study (NFS) of the course and treatment of their illness. Subjects who became depressed despite adequate treatment with mood stabilizers during the NFS were offered the opportunity to participate in a randomized 10-week clinical trial (with a 1-year continuation phase) for bipolar depression as described in Post et al.[3] and approved by each local institutional review board. Patients received bupropion, sertraline, or venlafaxine in a blinded fashion as add-on treatment to their ongoing medication regimen. Patients were enrolled from March 1996 to November 2002.

Patients were included in the acute trial if they (1) met DSM-IV[26] criteria for bipolar depressed phase despite adequate treatment with a mood stabilizer, (2) had an Inventory for Depressive Symptomatology (IDS)[27] score of at least 16, and (3) had a Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP)[28] depression severity score of at least 3 (mildly ill) and CGI-BP mania severity score of 1 (not ill). After 10 weeks of treatment, patients underwent final assessments for acute response. A "positive" antidepressant response was operationalized as either (1) a ≥ 50% improvement on their IDS score or (2) a ≥ 2 point improvement on their CGI-BP depression score without a switch into mania.[3]

If patients had an acute positive response, they were invited to enter a blinded continuation study in which they continued to take the same medications as they had in the acute phase. If patients did not have an acute positive antidepressant response, they could be randomly reassigned up to 2 more times to 1 of the 3 blinded antidepressant medications (bupropion, sertraline, or venlafaxine) that they had not yet tried.[23] Alternatively, if a patient felt his or her response was satisfactory (i.e., had partially improved as judged by the patient in conjunction with the study physician but did not meet criteria for a positive response) and the patient preferred to stay on the same blinded medication rather than be randomly reassigned, he or she could enter the blinded continuation phase. Thus, 2 categories of patients entered the continuation phase: acute positive and acute partial responders.

During the continuation phase, patients continued taking the same mood stabilizer(s) and blinded antidepressant to which they had experienced a positive or partial response. Doses of these medications as well as ongoing benzodiazepines were held relatively steady throughout the continuation phase. The minimum blood level guidelines for the mood stabilizers were 0.7 mmol/L for lithium, 50 μg/mL for valproate, and 4 μg/mL for carbamazepine.

Patients were assessed monthly for up to 1 year by using the IDS, the YMRS, and the CGI-BP. The primary outcome variables at study endpoint were (1) degree of depressive symptom improvement and (2) switch into mania. In an identical manner to that used in the acute trial, positive antidepressant response at study endpoint was operationalized as either a (1) ≥ 50% improvement on the IDS from the baseline score at randomization for

Table 1. Composition of Subjects in Each Cycle of the Acute Antidepressant Trials That Entered the Blinded Continuation Phase

Cycle	Total, N	Acute Positive Responders (N = 61), N	Acute Partial Responders (N = 22), N	Acute Positive and Partial Responders (N = 83), N
First	174	54	17	71
Second	45	6	5	11
Third	11	1	0	1

the acute trial or (2) a ≥ 2 point decrease in the CGI-BP score from the baseline score. We additionally evaluated which patients at study entry and endpoint met remission criteria, operationalized in the acute trial as either an IDS score < 12 or a CGI-BP depression severity score of 1 (normal, not ill). A "switch" was operationalized as the need to discontinue antidepressant medication because of the emergence of manic symptoms.

Statistical Analyses

Demographic and illness characteristics of those patients who chose to enter the continuation phase were compared with the patients who chose not to participate by using independent samples t tests for continuous variables and χ^2 tests for categorical variables. All reported χ^2 values are based on the likelihood ratio χ^2. The patients were compared on the basis of their status at the time of entering the acute trial.

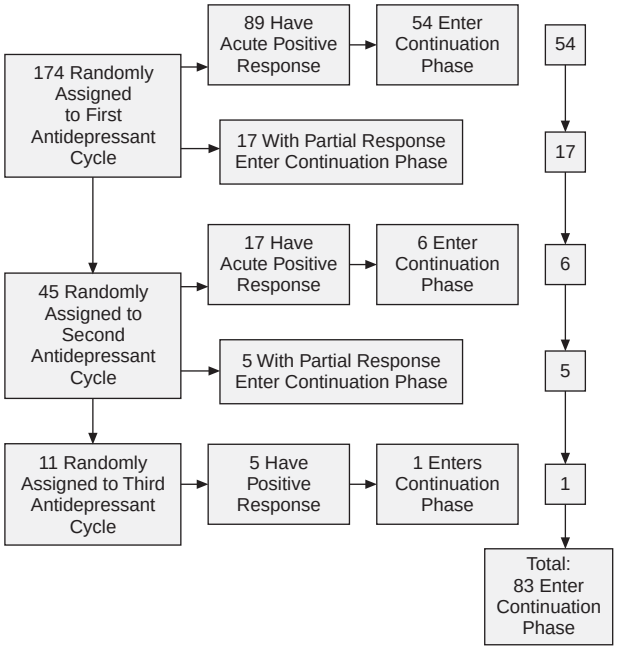
For the continuation phase data, we compared response rates at study endpoint of those who had positive versus partial acute antidepressant response before they entered the continuation phase using the likelihood ratio χ^2. A follow-up χ^2 analysis was performed to evaluate treatment response as a function of antidepressant medication used.

RESULTS

Patient Participation

Table 1 and Figure 1 show the number of subjects of each acute response type (positive or partial) who agreed to participate in the continuation phase at each of the 3 randomization cycles. In the first randomization cycle of the acute trial, 174 patients with bipolar depression were randomly assigned to bupropion, sertraline, or venlafaxine as adjunctive treatment to 1 or more mood stabilizers. Of these 174 subjects, 89 (51%) had an acute positive antidepressant response after 10 weeks[3] and 54 of these responders chose to enter the continuation phase. Additionally, 17 partial responders to this first antidepressant randomization decided, in conjunction with their physician, to enter the continuation phase. Thus, 71 subjects entered the continuation phase after the first randomization of the acute trial.

Figure 1. Subject Flow Through 3 Randomization Cycles of the Acute Phase Trial



Forty-five subjects (of the original 174) who did not respond to the first antidepressant trial agreed to be randomly reassigned to a different antidepressant medication in a second antidepressant randomization cycle. Of these 45, seventeen (38%) had an acute positive antidepressant response to the second antidepressant, and 6 of these responders chose to enter the continuation phase. Five partial responders chose to participate in the continuation phase as well. Thus, 11 subjects entered the continuation phase after the second randomization of the acute trial.

Eleven subjects who did not respond to the second antidepressant trial agreed to a third randomization cycle. Of these 11, five (45%) had a positive response, and 1 positive responder chose to enter the continuation phase. No partial responder chose to participate in the continuation phase. Thus, 1 subject entered the continuation phase after the third randomization of the acute trial.

In summary, of those 174 subjects who participated in 1 or more acute blinded antidepressant trials, 83 subjects (71 from the first randomization cycle, 11 from the second, and 1 from the third) chose to enter a double-blind longitudinal continuation phase. Fifty-six subjects met DSM-IV diagnostic criteria for bipolar I disorder, 24 for bipolar II disorder, 2 for bipolar disorder not otherwise specified and 1 for schizoaffective disorder. Only 1 subject (1%) met criteria for the rapid cycling specifier. There were no significant differences in age, gender, duration of illness, or number of prior depressive or manic

Table 2. Demographic Acute Baseline[a] Characteristics of Subjects Who Had an Acute Positive or Acute Partial Response

Variable	All (N = 83)	Acute Positive Responders (N = 61)	Acute Partial Responders (N = 22)	Test	p Value
Female gender, %	58	54	68	$\chi^2 = 1.34$, df = 1	.25
Age, mean ± SD, y	41.8 ± 11.5	43.2 ± 11.9	37.9 ± 9.4	t = 1.89, df = 81	.06
Age at illness onset,				t = 0.91, df = 80	.36
mean ± SD, y[b]	18.8 ± 10.0	19.4 ± 10.4	17.1 ± 8.7		
N	82	60	22		
Time ill at start of study,				t = 1.01, df = 80	.29
mean ± SD, y[b]	22.9 ± 11.3	23.7 ± 11.5	20.7 ± 10.8		
N	82	60	22		
Bipolar I, N (%)	56 (67)	39 (64)	17 (77)		
Bipolar II, N (%)	24 (29)	19 (31)	5 (23)		
Bipolar NOS, N (%)	2 (3)	2 (3)	0		
Schizoaffective, N (%)	1 (1)	1 (2)	0	$\chi^2 = 2.68$, df = 3	.44
Prior depression history[b]					
No. of episodes,				t = 0.33, df = 72	.74
mean ± SD	18.7 ± 11.4	18.9 ± 11.8	17.9 ± 10.4		
N	74	55	19		
No. of hospitalizations,				t = 0.85, df = 71	.40
mean ± SD	1.4 ± 2.0	1.3 ± 1.8	1.7 ± 2.6		
N	73	54	19		
Prior mania history[b]					
No. of episodes,				t = 1.26, df = 72	.21
mean ± SD	15.8 ± 11.9	14.8 ± 12.0	18.8 ± 11.5		
N	74	55	19		
No. of hospitalizations,				t = 1.14, df = 69	.26
mean ± SD	2.1 ± 4.6	1.7 ± 3.4	3.1 ± 6.8		
N	71	52	19		
Severity of depression scores at baseline, mean ± SD[a]					
IDS	30.9 ± 10.7	32.0 ± 10.2	27.7 ± 11.8	t = 1.62, df = 81	.11
YMRS	1.78 ± 2.4	1.5 ± 2.1	2.73 ± 2.73	t = 2.21, df = 81	.03
CGI-BP depression severity	4.28 ± 0.93	4.41 ± 0.92	3.91 ± 0.87	t = 2.22, df = 81	.03
CGI-BP mania severity	1.08 ± 0.29	1.05 ± 0.22	1.18 ± 0.40	t = 1.94, df = 81	.06

[a]Baseline refers to beginning of acute antidepressant trial.
[b]Some demographic and/or illness history data were not available for a few subjects.
Abbreviations: CGI-BP = Clinical Global Impressions Scale for Bipolar Disorder, IDS = Inventory for Depressive Symptomatology, NOS = not otherwise specified, YMRS = Young Mania Rating Scale.

episodes between the 83 subjects who agreed to participate in the continuation phase and the 91 subjects from the acute trials who chose not to participate in the blinded continuation phase after acute treatment. Thus, the data indicated no evidence of a selection bias for subjects entering the continuation phase based on demographics or course duration.

Table 2 displays the demographic and illness characteristics of the 2 treatment groups who entered the continuation phase (61 subjects who met the criteria for positive antidepressant response and 22 subjects who did not meet these criteria).

Patient Outcome as a Function of Acute Antidepressant Response

Table 3 presents the outcome for all 83 subjects who entered the continuation phase. The mean time in the continuation phase was not significantly different between groups. Forty-two (69%) of the 61 acute positive responders continued to have a positive response at the end of the continuation trial. Only 6 (27%) of the 22 acute partial responders achieved a positive antidepressant response at the end of the continuation trial. This difference was significant ($\chi^2 = 11.5$, $p < .001$; see Table 3). There were no significant differences in continuation phase outcome as a function of a specific antidepressant medication in either the positive responders ($\chi^2 = 0.92$, df = 2, $p = .63$) or partial acute responders ($\chi^2 = 1.28$, df = 2, $p = .53$).

Regarding full remission, 43 of the 61 acute positive responders had achieved remission at the end of the acute phase (and thus had entered the continuation phase in remission) and 18 had not. Of these 43, twenty-six (61%) remained in remission at study endpoint. Of the 18 acute positive responders who were not in remission at the end of the acute trial, only 5 (28%) had achieved remission at study endpoint ($\chi^2 = 5.6$, $p < .02$).

Switch Rates Into Mania

Eight (13%) of the 61 acute positive responders and 5 (22%) of the 22 acute partial responders discontinued the study over the 1-year longitudinal follow-up due to a switch into mania or hypomania ($\chi^2 = 1.1$, df = 1, $p = .29$).

Table 3. Patients With Acute Positive Antidepressant Response Versus Partial Response and Outcome at End of Continuation Phase (N = 83)

Response	Acute Positive Responders (N = 61)[a]	Acute Partial Responders (N = 22)[b]	χ^{2c}	p Value	OR
Positive antidepressant response (IDS or CGI-BP improvement), N (%)	42 (69)	6 (27)	11.5	< .001	5.89
IDS (50% improvement), N (%)	31 (50.8)	5 (22.7)	5.2	< .025	3.51
CGI-BP (at least 2 points of improvement), N (%)	38 (62.2)	6 (27.3)	7.9	< .01	4.41
Discontinued because of switch into mania or hypomania, N (%)	8 (13.1)	5 (22.7)	1.13	NS	0.51
No. of days in continuation phase, mean ± SD	189 ± 128	180 ± 125	0.27[d]	NS	0.07[e]

[a]Acute responders from the first, second, or third acute randomization cycle who went into the continuation phase; acute antidepressant positive response operationalized as 50% IDS improvement or 2-point CGI improvement.
[b]Acute partial responders from the first, second, or third acute randomization cycle who went into the continuation phase; acute antidepressant partial response operationalized as not meeting acute positive response criteria but improvement viewed as satisfactory by patient and study physician.
[c]N = 83.
[d]t Test; df = 81.
[e]Cohen d.
Abbreviations: CGI-BP = Clinical Global Impressions Scale for Bipolar Disorder, IDS = Inventory of Depressive Symptomatology, NS = not significant.

DISCUSSION

Our study has 3 major findings. First, in subjects who attain only a partial acute positive response after 10 weeks of acute treatment for bipolar depression, continued antidepressant treatment is not associated with a high likelihood of further improvement. Second, in subjects who achieve an acute positive response with an antidepressant as adjunctive treatment to a mood stabilizer (that alone did not treat the depression), continued antidepressant treatment for up to 1 year is associated with a high (69%) likelihood of continued positive antidepressant response. Further, in those subjects who do obtain an acute positive response, those who obtain remission in the acute phase have the best 1-year outcome. Third, continued 1-year antidepressant treatment in those patients who achieve an acute positive response is associated with a relatively low risk of switch into mania.

Partial Versus Positive Acute Response and Long-Term Antidepressant Outcome

Our first finding suggests that a person who has a less than optimal acute antidepressant response is significantly less likely to improve over time with the same sustained treatment. To our knowledge, no other published study has addressed the long-term outcome in bipolar depressed subjects as a function of the degree of acute antidepressant response. However, a reanalysis of a recent study[23] published by our group sheds some light on the issue. In that study, life chart data were obtained prospectively to measure antidepressant response rates in patients across multiple treatment trials (a subset of these trials are included in the current study).[23] While the published analysis indicated that only a minority of trials resulted in sustained longitudinal positive antidepressant response, the analysis did not take into account the degree of acute antidepressant response. A reanalysis of these data as a function of the degree of the acute antidepressant response achieved revealed similar results to the current analysis. Of the acute trials that ended with subjects rated as "much or very much improved" on the CGI-BP improvement scale, 72% of subjects maintained a positive response in the continuation phase. Of the acute trials in which subjects scored only "minimally improved" or less on the CGI-BP, only 39% were "much or very much improved" at the end of the longitudinal follow-up. Thus, this reanalysis by degree of acute response corroborates our current findings. These findings suggest that those patients who respond less well acutely may not improve substantially with further continuation of the same treatment, and an alternative treatment strategy should be sought soon after either an unsuccessful or partially successful 10-week trial. Future studies assessing the impact of long-term antidepressant treatment response should take into consideration the degree of acute response.

Long-Term Continued Positive Antidepressant Response

Our second finding suggests that if a positive antidepressant response is obtained acutely by using a treatment approach involving adjunctive antidepressants, continuing treatment with combined antidepressant and mood stabilizer will likely result in a continued antidepressant response. This finding is consistent with a prior nonrandomized longitudinal observational study,[21] in which approximately 70% of the subset of patients who had a good acute antidepressant response and remained on the combination of a mood stabilizer and an antidepressant continued to remain well over the course of a year. Additionally, our current data show that in the group of patients who did have an acute positive response at the end of the acute trial, those patients who experienced remission fared better at 1-year follow-up than those who had experienced an acute positive response without achieving

remission. These data in bipolar subjects comport well with a recent study from Sequenced Treatment Alternatives to Relieve Depression that also demonstrates that the degree of acute response is predictive of longer term outcome.[29] In that study of subjects with unipolar depression, those who achieved remission after acute treatment had a better longitudinal course than those who, after acute treatment, had obtained improvement without remission. Our study supports this concept in the bipolar population.

In the current study, we did not have a group of subjects who were randomly assigned back to a mood stabilizer without adjunctive antidepressants after the acute treatment. It therefore could be suggested that once acutely better with an antidepressant–mood stabilizer combination, these patients might have remained well even with the antidepressant withdrawal at the end of the acute trial. This is certainly possible. However, in prior retrospective studies by our group in which we evaluated patients who either continued or discontinued antidepressants after an acute positive response,[20,21] the groups of patients who discontinued antidepressants after acute positive treatment results were found to have higher rates of depressive relapse than those subjects who remained on antidepressant continuation treatment. A definitive blinded prospective maintenance study remains to be conducted that randomly assigns discontinuation or continuation of the antidepressant in patients who required a mood stabilizer plus an antidepressant to achieve an acute positive response. This study would compare relapse and switch rates between the 2 groups: 1 group maintained on the antidepressant and mood stabilizer, and 1 group maintained on mood stabilizer monotherapy.

Six randomized studies have directly assessed the longitudinal impact of antidepressant medication exposure on risk for recurrence of bipolar depression in subjects with bipolar disorder concurrently treated with a mood stabilizer.[17,23,30–33] In 3 of these studies,[31–33] euthymic patients were followed who had not necessarily been recently treated for an acute depressive episode and thus were not necessarily at a point in their illness course when they were most vulnerable for risk of relapse into depression. Thus, the best prophylactic strategy against recurrence of bipolar depression in those subjects with a recent episode could not be optimally addressed. Two studies have, as in our current study, assessed longitudinal outcome after acute resolution of a depressive episode.[17,30] In 1 blinded randomized study, depressive relapse rates over a 2-year follow-up were found to be similar in a group receiving a combination of lithium and imipramine (22%) compared to a group receiving lithium monotherapy (29%).[17] However, patients entered that study after an index inpatient episode of either mania or depression, and the relationship of treatment effectiveness to the pole of the index episode was not fully reported. In a reanalysis of these data that allowed for relapse rates to be assessed differentially as a function of the initial index episode, Shapiro et al.[34] found that in patients whose index episode was depression, combination treatment of lithium and an antidepressant resulted in less than half the risk of experiencing a relapse over the follow-up period compared to those receiving lithium monotherapy. While these results did not quite reach significance (30 subjects were receiving lithium monotherapy and 18 were receiving the combination), the authors concluded that the combination treatment was the most effective treatment for those patients with bipolar disorder with an index episode of depression.

A very recent randomized open study[30] assessed rates of depressive relapse in subjects taking mood stabilizer and antidepressant versus mood stabilizer monotherapy in a continuation phase. While patients randomly assigned to mood stabilizer and antidepressant had a longer time until relapse into the next depression, rates of depressive relapse were very high in both groups and no overall difference in rates of depressive relapse in a group who continued (N = 32) versus discontinued (N = 38) antidepressant treatment adjunctive to a mood stabilizer for up to 1 year after acute treatment was found.[30] While our current study involved only subjects who did not do well receiving mood stabilizer monotherapy and thus required an adjunctive (antidepressant) treatment, it is not clear if this was the case in the above study.

Risk for Manic Switch

Our third finding demonstrated that approximately 13% of the acute positive responders and 22% of the partial responders who continued taking antidepressants switched into hypomania or mania in the continuation phase. As our sample involved only subjects who had not switched into mania during the acute 10-week antidepressant trial, this finding suggests that the risk for manic switch in the first year after acute treatment in those subjects who do not acutely switch is 13% to 22%. This is similar to prior reports[21,23] showing that approximately 14% to 18% of patients followed after an acute treatment trial with antidepressants will experience hypomania/mania over a 1-year period of continued antidepressant exposure. Whether these switches are due to antidepressant exposure per se, or reflect the natural recurrence rate of mania within 1 year following treatment for an acute depressive episode remains to be studied. Our current study did not have a control group of subjects who were not receiving antidepressants in the continuation phase. Thus, the natural switch/recurrence rate and, therefore, additional risk for switch associated with antidepressants, could not be directly assessed in this study. At least 1 prospective longitudinal study[30] of 38 patients receiving combination therapy (antidepressant plus a mood stabilizer) and 32 patients receiving mood stabilizer monotherapy suggests that similar rates of patients taking

antidepressants (18.8%) versus not taking antidepressants (13.3%) experienced a hypomanic, manic, or mixed state.

CONCLUSION

Recent treatment studies suggest that combining a mood stabilizer with an antidepressant for acute bipolar depression may be no more effective than either mood stabilizer monotherapy[1] or 2 mood stabilizers.[35] Our study does not address the ideal or optimal treatment for acute bipolar depression, but rather the effect of continued antidepressant treatment in combination with a mood stabilizer in those subjects who required both to achieve an acute antidepressant response. This study addresses a very specific subpopulation of patients with bipolar disorder: namely, those who, despite adequate mood stabilizer treatment, have a depression and are treated adjunctively with antidepressants.

Our data suggest that (1) the subgroup of subjects with bipolar depression who respond positively acutely to an antidepressant in addition to a mood stabilizer will likely continue to do well with sustained treatment (e.g., will continue to have a high rate of continued antidepressant response); (2) a patient who has only a partial acute antidepressant response to the combination of an antidepressant added to a mood stabilizer is less likely to improve with the same sustained treatment over the course of a year compared to a person who has a positive acute antidepressant response, so, for the partial responder, the benefit of continued adjunctive antidepressant treatment is low; and (3) switching into mania may occur in 13% to 23% of patients maintained on an antidepressant with a mood stabilizer.

Current guidelines regarding the duration of antidepressant treatment after resolution of an acute episode of bipolar depression are continuing to evolve. Our study suggests that continued antidepressant treatment in those subjects who needed antidepressants to attain an acute positive response is associated with continued antidepressant benefit. Guidelines more similar to those for the maintenance treatment of unipolar depression may ultimately be in order for those bipolar depressed patients who respond well to acute adjunctive antidepressant treatment,[36,37] but further prospective randomized controlled trials are needed. If patients with bipolar depression have only a partial response to acute treatment with an adjunctive antidepressant, then continued treatment with this adjunctive medication may not result in a high likelihood of achieving a good antidepressant response. Other treatment strategies, such as another antidepressant trial, combination mood stabilizer treatment, or lithium/anticonvulsant/antipsychotic combination treatments should be tried to avoid continued morbidity. The switch rate into mania with continued antidepressant treatment may be no different than the natural switch rate over the course of the year if treated with a mood stabilizer alone (i.e., without an antidepressant),[21,22,30] but further prospective studies are needed to confirm this.

Drug names: bupropion (Aplenzin, Wellbutrin, and others), carbamazepine (Carbatrol, Equetro, and others), imipramine (Tofranil and others), lithium (Eskalith, Lithobid, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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