The Impact of Antidepressant Discontinuation Versus Antidepressant Continuation on 1-Year Risk for Relapse of Bipolar Depression: A Retrospective Chart Review

Lori Altshuler, M.D.; Lindsay Kiriakos, M.D.; Jeff Calcagno, M.D.; Robyn Goodman, B.A.; Michael Gitlin, M.D.; Mark Frye, M.D.; and Jim Mintz, Ph.D.

Background: Current treatment guidelines recommend discontinuation of an antidepressant within 3 to 6 months after remission of depression in patients with bipolar illness. Yet few studies directly compare the impact of antidepressant discontinuation versus antidepressant continuation on the risk for depressive relapse in patients with bipolar disorder who have been successfully treated for a depressive episode.

Method: In a retrospective chart review, patients with DSM-IV bipolar disorder who were treated for an index episode of depression by adding antidepressant medication to ongoing mood stabilizer medications were identified. The risk of depressive relapse in 25 subjects who stopped antidepressant medications after improvement was compared with the risk of depressive relapse in 19 subjects who continued antidepressants after improvement.

Results: Termination of antidepressant medication significantly increased the risk of a depressive relapse. Antidepressant continuation was not significantly associated with an increased risk of mania.

Conclusion: While this study may have been limited by the retrospective nature of the chart review, nonrandomized assignment of treatment, and reliance on unstructured progress notes, it suggests that antidepressant discontinuation may increase the risk of depressive relapse in some patients with bipolar disorder. Further research is needed to clarify whether maintenance antidepressant treatment may be warranted in some patients with bipolar disorder, especially in those with frequent recurrent depressive episodes.

(J Clin Psychiatry 2001;62:612–616)

Received Mar. 21, 2000; accepted Jan. 24, 2001. *From the Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles (all authors); and the Department of Psychiatry, VA Greater Los Angeles Healthcare System, West Los Angeles Healthcare Center, West Los Angeles, Calif. (Drs. Altshuler, Calcagno, and Mintz).*

Reprint requests to: Lori Altshuler, M.D., VA Medical Center (B116AA), West Los Angeles, 11301 Wilshire Blvd., Los Angeles, CA 90073 (e-mail: LAltshuler@mednet.ucla.edu).

For patients with bipolar disorder, guidelines on treating bipolar depression recommend that antidepressants be discontinued within the first 3 to 6 months after remission of depressive symptoms.[1–3] These recommendations are based on a small literature of both controlled[4–9] (Table 1) and uncontrolled[10] studies, as well as on clinician survey,[1,2] where concern exists that continued treatment with antidepressants might induce cycle acceleration or switches into mania.[11,12] The appropriateness of these recommendations, however, remains uncertain as few studies have directly compared the impact of antidepressant discontinuation versus antidepressant continuation on the risk for depression relapse in patients with bipolar disorder who are successfully treated for an acute depressive episode.[4,7] We sought to evaluate this clinical decision in the current retrospective study.

METHOD

A waiver was obtained through the Human Subjects Protection Committee to review the outpatient records of patients treated for bipolar disorder at the West Los Angeles Veterans Affairs (VA) Mental Health Clinic and the University of California, Los Angeles (UCLA) Mood Disorders Clinic. Charts from 155 outpatients who had a DSM-IV diagnosis of bipolar disorder were reviewed. For each of the patients, the diagnosis of bipolar disorder was made by a treating psychiatrist after a 1½-hour interview. Notes from the interview were reviewed by study personnel to verify a DSM-IV diagnosis. The chart of any outpatient with bipolar disorder who was successfully treated with an antidepressant for an acute depressive episode while being maintained on a standard regimen of a mood stabilizer and whose monthly progress notes were detailed enough to assign a Clinical Global Impressions for bipolar illness (CGI-BP)[13] scale score was included in our study.

Forty-four patient charts (39 bipolar I, 5 bipolar II; 29 men, 15 women) were eligible to be included in the analysis. Demographic variables including gender, age at onset of illness, duration of illness, age at index episode of de-

Table 1. Double-Blind Studies of Maintenance Treatment of Bipolar Patients With or Without Antidepressants

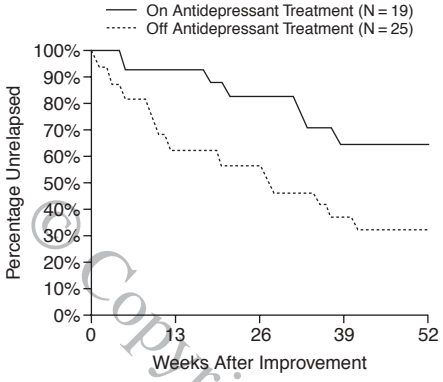
Study	N	Design	Mood at Randomization	Length of Follow-Up	% of Bipolar Patients Who Relapsed Into Mania	% of Bipolar Patients Who Relapsed Into Depression	Comments
Prien et al, 1973[4]	44 bipolar disorder 78 unipolar disorder	Double-blind, randomized; lithium monotherapy; imipramine monotherapy; placebo	Euthymic after recent admission and stabilization of a depressive episode	2 y	12% lithium 67% imipramine 33% placebo	12% lithium 0% imipramine 55% placebo	Median imipramine dose = 125 mg/d, lithium level between 0.4–1.4, mEq/L
Quitkin et al, 1981[5]	75 bipolar I disorder	Double-blind, randomized; lithium/placebo; lithium/imipramine	Euthymic on lithium treatment (no recent index episode necessary)	4.5 y	10.5% lithium/placebo 24% lithium/imipramine	10.5% lithium/placebo 8% lithium/imipramine	Depression relapses so low in all groups authors state in their discussion section "unable to draw conclusion about the advantage of adding imipramine to lithium as a prophylactic regimen"
Kane et al, 1982[6]	22 bipolar II disorder 27 unipolar disorder	Double-blind, randomized (Ns for bipolar disorder patients); lithium monotherapy (N = 4); imipramine monotherapy (N = 5); lithium + imipramine (N = 6); placebo (N = 7)	Remission for ≥ 6 mo	2 y	0% lithium 20% imipramine 0% lithium + imipramine 14% placebo	25% lithium 40% imipramine 17% lithium + imipramine 57% placebo	6 bipolar depressive relapses; not stated what group think they are from; maximum imipramine dose = 150 mg/d
Prien et al, 1984[7]	117 bipolar disorder 150 unipolar disorder	Double-blind, randomized; lithium monotherapy; imipramine monotherapy; lithium + imipramine; placebo (unipolar disorder patients only)	Euthymic after recent treatment for acute depression or mania and stable for 2 mo	2 y	26% lithium 53% imipramine 28% lithium + imipramine	29% lithium 28% imipramine 22% lithium + imipramine	Lithium + lithium/imipramine significantly better than imipramine alone; lithium level, 0.6–0.9 mEq/L; imipramine dose 150 mg/d
Johnstone et al, 1990[8]	13 bipolar disorder 27 unipolar disorder	Double-blind, randomized; lithium + placebo; lithium + amitriptyline	Stable after an episode. Time to enter study after recovery varied	3 y	0% lithium + placebo 0% lithium + amitriptyline	Not reported	Mean amitriptyline dose = 91 ± 36 mg/d

pression, lifetime episodes of mania/depression, history of substance abuse, and history of psychosis were abstracted from the records. The index depressive episode was operationally defined as the first depressive episode that was successfully treated with antidepressants while the patient was an outpatient in the clinic. The antidepressant class, start date, type, dose, taper date, and stop date were recorded, as was the length of follow-up. The distribution of antidepressants according to class was as follows: 17 selective serotonin reuptake inhibitors (SSRIs), 14 tricyclic antidepressants (TCAs), 9 bupropion, and 4 monoamine oxidase inhibitors (MAOIs).

Progress notes from the index depressive episode and each subsequent follow-up clinical visit were abstracted. CGI-BP scores were generated for each progress note. The CGI-BP has been used extensively in the past 5 years in bipolar illness research protocols to rate the clinical progress of patients with bipolar disorder. Validity and high interrater reliability have been demonstrated.[13] Improvement was operationalized as 2 months of euthymia (defined as a CGI-BP score ≤ 2 [minimally ill] on the severity index for depression) on 2 consecutive monthly visits and the absence of meeting criteria for major depressive disorder. Relapse into depression was defined as at least 2 weeks of DSM-IV depressive symptoms with a CGI-BP score ≥ 4 (moderately ill) on the severity index for depression or antidepressant initiation in association with at least 2 weeks of a CGI-BP score ≥ 3 (mildly ill). Relapse into mania was defined as at least 1 week of DSM-IV manic symptoms with a CGI-BP score ≥ 4 on the severity index for mania or mood stabilizer increase in association with at least 1 week with a CGI-BP score ≥ 3. Time to relapse was defined as the date of relapse minus the date of improvement (the date after 2 months of euthymia). Progress notes were reviewed until either criteria for relapse were met or the last follow-up visit in the clinic occurred.

The impact of stopping antidepressant treatment on the risk for depression relapse and mania relapse was analyzed using the method of proportional hazards regression with a time-dependent covariate (SAS Proc PHREG). The dependent variable was time to relapse or last known status. A graphical display of the survival results was created

Figure 1. One-Year Depression Relapse in Bipolar Disorder Patients Who Continued or Discontinued Antidepressant Treatment After Improvement



using the product moment method, but basing the cumulative survival estimates on the actual effective sample sizes at each timepoint.

RESULTS

The 44 patients were followed in the clinics from 0.27 years to 4.6 years (median = 306 days). Twenty-five patients stopped taking antidepressants during the follow-up (median duration of treatment after date of improvement = 42 days), and 19 continued on antidepressant treatment throughout follow-up. No significant differences existed between the 2 study groups in age at onset of bipolar disorder, duration of illness, prior number of episodes of depression, prior number of episodes of mania, history of psychosis, history of substance abuse, or age at index depression ($p > .1$ on t and nonparametric Wilcoxon tests).

The regression analysis indicated that termination of antidepressant medication treatment was significantly associated with an increased risk of depression relapse (odds ratio = 3.13, $\chi^2 = 7.41$, df = 1, $p = .0065$). The product-limit survival curve (Figure 1) indicated that at 1 year, 68% of patients taken off antidepressant treatment had experienced a depressive relapse compared with only 32% of patients maintained on antidepressant treatment. (None of the 5 bipolar II patients relapsed into depression regardless of whether the antidepressant was continued or discontinued.) When patients who discontinued antidepressant treatment were stratified according to length of continuation after improvement of symptoms, those who continued on treatment at least 6 months post-"improvement" (that is, for 8 months of euthymia) were significantly less likely to suffer depressive relapse than those whose antidepressant regimen was stopped between 2 and 6 months ($\chi^2 = 5.37$, df = 1, $p = .02$).

The regression analysis also indicated that continuation of antidepressant medication was not significantly associated with an increased risk of mania relapse (odds ratio = 1.92, $\chi^2 = 0.88$, df = 1, $p = .348$). The product-limit survival curves indicated that at 1 year, 25% of patients taken off antidepressant treatment had experienced a mania relapse compared with 20% of patients maintained on antidepressant treatment.

DISCUSSION

The present study has several limitations. First, this was a retrospective chart review including patients whose diagnoses were made on the basis of clinical interviews rather than with the use of structured clinical interview tools (e.g., the Structured Clinical Interview for DSM-IV [SCID]). Furthermore, there was no randomized assignment to a continuation or discontinuation group. Nevertheless, the present study is unique in that it compares antidepressant continuation with antidepressant discontinuation in a group of patients with bipolar disorder recently treated for depression, and it raises the issue that continued treatment for both mania and depression may be warranted for some bipolar patients to prevent depressive relapse.

Our results suggest that antidepressant discontinuation in patients recently treated for depression is associated with a significant (approximately 3-fold) increase in the odds of depressive relapse in patients with bipolar disorder. Further, those continued on antidepressant treatment for at least 8 months of euthymia fared better when antidepressants were discontinued than those whose antidepressants were stopped before 8 months of sustained euthymia. In our sample, there was no increased risk for mania in the first year of follow-up posttreatment for an acute depressive episode in those who remained on treatment with antidepressants compared with those who discontinued antidepressants. These findings, if replicated, should lead to reconsideration of the current recommendation to discontinue treatment of bipolar depression within 3 to 6 months of resolution of depressive symptoms.[1–3] That is, guidelines more similar to recommendations for acute, continuation, and maintenance treatment for a unipolar depressive episode may be in order[14,15] but require further study. As the majority of our patients had bipolar I disorder, these results suggest that antidepressant continuation—as opposed to discontinuation—may provide better clinical outcomes (less depression and no increased risk for mania) for some patients with bipolar I disorder. This study suggests a need for further exploration of the role of maintenance antidepressant treatment in some persons with bipolar disorder, especially those with recurrent depressive episodes.

To our knowledge, few prospective studies exist that shed light on whether it is better clinical practice to continue or discontinue antidepressant treatment in patients with bipolar disorder who recently have been successfully

treated for depression. In the 4 controlled double-blind trials involving subjects with bipolar I disorder randomly assigned to either lithium plus a TCA or lithium as monotherapy,[5–8] those on lithium monotherapy were no more likely to have depressive relapses than those on lithium plus the TCA. However, in 3 of these studies,[5,6,8] patients were followed when euthymic, but not necessarily soon after a successfully treated depressive episode (and thus not at a time when they were most vulnerable for risk of relapse), and in 2 of the studies[7,8] subtherapeutic doses of antidepressants were used. In only 1 study were patients randomly assigned to receive lithium plus placebo or lithium plus imipramine after inpatient treatment for an acute bipolar depressive episode.[7] The combination of lithium with imipramine was no better than lithium alone at preventing depressive relapse. (Twenty-nine percent of patients on lithium monotherapy versus 22% on lithium/imipramine combination therapy had a depressive relapse within 2 years of follow-up.) Patients, however, were treated with relatively low doses of imipramine (75–150 mg/day).

While our current study did not reveal an increased risk for mania with continued antidepressant use, we as well as other researchers have reported that antidepressants induce switches into mania.[4,11,12] Our earlier study,[12] however, involved subjects with refractory bipolar disorder, which may have represented a group more vulnerable to switching than the current group of bipolar subjects who were not refractory to treatment. Nonetheless, if antidepressant continuation decreased the risk for acute depressive relapse, the benefit of decreased risk for acute depressive relapse would have to be weighed against the potential risk of precipitating mania. During a 2-year follow-up, Prien and colleagues[4] found that 67% of patients with bipolar illness on imipramine monotherapy had manic episodes compared with 33% on placebo and 12% on lithium therapy. Clearly, antidepressant monotherapy in patients with bipolar depression can increase the risk of mania. A later 2-year follow-up study by Prien and colleagues[7] again demonstrated a high risk for mania in subjects with bipolar illness on imipramine monotherapy (53%), but no difference in risk for mania in bipolar subjects on lithium plus imipramine therapy (22% switch rate) versus those on lithium therapy alone (29% switch rate). Another study[5] comparing lithium monotherapy (lithium plus placebo) with lithium plus an antidepressant, however, demonstrated an increased risk for mania in the lithium plus imipramine group (24%) compared with the lithium monotherapy group (10.5%). While the rate of manic relapses was 2 times greater for the lithium/imipramine combination than for lithium alone, this was not a statistically significant difference in the study. Notwithstanding the lack of statistical significance, this study raises clinical concern that, for some subjects, antidepressants may be associated with increased risk for manic relapses despite prophylaxis with a mood stabilizer. It may further be the case that TCAs are more likely to induce a switch than some other antidepressant classes. In a recent study, Sachs et al.[16] found that both TCAs and bupropion (combined with mood stabilizers) were effective treatments for acute bipolar depression, but switch rates into mania occurred more frequently in those subjects taking TCAs. The fact that in our current study only 14 patients were treated with a TCA and, of those continued on antidepressants, only 3 were taking a TCA may have contributed to our finding a low switch rate into mania as well.

Another concern about long-term use of antidepressants in patients with bipolar disorder is the risk for rapid cycling. As our outcome variable was episode recurrence, the occurrence of rapid cycling (i.e., multiple episode recurrences) with long-term antidepressant use could not be assessed. Our study, therefore, could not thoroughly nor adequately assess the benefit of a reduction in number and/or severity of depressive episodes versus the risk of increased cycling. As such, this study does not allow for definitive support of the long-term use of antidepressants. Rapid cycling has been documented to be increased with antidepressant use in controlled[12] and uncontrolled[5,13] studies. Further controlled prospective studies are encouraged to clarify which patients with bipolar disorder should be considered for ongoing antidepressant therapy for mood stabilization versus which patients would be destabilized by this approach. It is possible that some patients with bipolar disorder would have an overall reduction in illness morbidity if maintenance treatment for both "poles" of their bipolar illness were provided.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin and others).

REFERENCES

1. Frances AJ, Kahn DA, Carpenter D, et al. The expert consensus guidelines for treating depression in bipolar disorder. J Clin Psychiatry 1998; 59(suppl 4):73–79
2. Sachs GS, Printz DJ, Kahn DA, et al. The Expert Consensus Guidelines Series: Medication Treatment of Bipolar Disorder. New York, NY: McGraw Hill; 2000:1–102
3. Yatham L, Kusumakar V, Parikh S, et al. Bipolar depression: treatment options. Can J Psychiatry 1997;42(suppl 2):S87–S91
4. Prien RF, Klett CJ, Caffey EM. Lithium carbonate and imipramine in prevention of affective episodes. Arch Gen Psychiatry 1973;29:420–425
5. Quitkin F, Kane J, Rifkin A, et al. Prophylactic lithium carbonate with and without imipramine for bipolar 1 patients. Arch Gen Psychiatry 1981;38: 902–907
6. Kane JM, Quitkin FM, Rifkin A, et al. Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness: a prospective, placebo-controlled comparison. Arch Gen Psychiatry 1982;39:1065–1069
7. Prien R, Kupfer D, Mansky P, et al. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Arch Gen Psychiatry 1984;41:1096–1104
8. Johnstone E, Owens D, Lambert M, et al. Combination tricyclic antidepressant and lithium maintenance medication in unipolar and bipolar depressed patients. J Affect Disord 1990;20:225–233
9. Wehr TA, Goodwin FK. Rapid cycling in manic-depressives induced by tricyclic antidepressants. Arch Gen Psychiatry 1979;36:555–559

10. Kukopulos A, Reginaldi P, Laddomada G, et al. Course of the manic-depressive cycle and changes caused by treatments. Pharmakopsychiatr Neuropsychopharmakol 1980;13:156–167
11. Wehr T, Goodwin F. Can antidepressants cause mania and worsen the course of affective illness? Am J Psychiatry 1987;144:1403–1411
12. Altshuler L, Post R, Leverich G, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995;152: 1130–1138
13. Spearing M, Post R, Leverich G, et al. Modification of the Clinical Global Impressions (CGI) scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997;73:159–171
14. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder [Revision]. Am J Psychiatry 2000;157(suppl 4):1–45
15. Kupfer DJ. Long-term treatment of depression. J Clin Psychiatry 1991; 52(5, suppl):28–34
16. Sachs GS, Lafer B, Stoll AL, et al. A double-blind trial of bupropion vs desipramine for bipolar depression. J Clin Psychiatry 1994;55:391–393