Relationship of Prior Antidepressant Exposure to Long-Term Prospective Outcome in Bipolar I Disorder Outpatients

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ABSTRACT

Objective: The long-term impact of prior antidepressant exposure on the subsequent course of bipolar illness remains controversial.

Method: 139 outpatients (mean age, 42 years) with bipolar I disorder diagnosed by *DSM-IV* criteria had a detailed retrospective examination of their prior course of illness on the National Institute of Mental Health Life Chart Method. Number of prior antidepressant trials and total duration of antidepressant exposure were assessed. Prospective long-term response (for at least 6 months) to naturalistic treatment in the network from 1996 through 2002 was the primary outcome measure as it related to prior antidepressant exposure (and other illness variables) by logistic regression, with $P < .05$ used for statistical significance in this post hoc analysis.

Results: Greater number of antidepressant trials, but not duration of antidepressant exposure, was related to prospective nonresponse ($P = .0051$) whether or not antidepressants were covered by concurrent treatment with a mood stabilizer or atypical antipsychotic. Poor prospective response was also independently related to having had an anxiety disorder and 20 or more prior affective episodes.

Conclusions: That the number of antidepressant trials, but not duration of antidepressant treatment, was associated with prospective nonresponse suggests that it is the repeated use of antidepressants to treat episodes of depression that is related to poor prospective response to naturalistic treatment. The direction of causality is unclear as to whether more antidepressant trials led to this increased treatment resistance or whether a difficult course of illness with more episodes and anxiety comorbidity engendered more attempts at antidepressant treatment.

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Considerable controversy continues to surround the use of unimodal antidepressants in the treatment of bipolar patients. While the data analyzed by Davis et al[1] and Geddes et al[2] are definitive on the efficacy of prophylactic effects of antidepressants in the recurrent unipolar disorders after acute response, no such consensus exists about antidepressants in bipolar illness.

Recent large randomized studies of the use of antidepressants as adjuncts to mood stabilizers in bipolar disorder have not been positive,[3–5] and some evidence continues to suggest that antidepressants may increase the risk of manic induction, cycle acceleration,[6–9] and depressive occurrences in rapid cyclers[5] or negatively influence long-term outcome, for example, to lithium responsiveness.[10] A new meta-analysis by Sidor and MacQueen[11] has found no evidence of significant improvement upon addition of antidepressants versus placebo to mood stabilizers in bipolar depression for 4 to 16 weeks.

In a randomized double-blind trial, low switch rates were observed with the adjunctive use of bupropion and the highest rates with the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine, particularly in those with a history of prior rapid cycling, while the selective serotonin reuptake inhibitor (SSRI) sertraline was intermediate.[12] These data are convergent with the observations of Vieta et al,[13] who found that venlafaxine had a higher switch rate than did the SSRI paroxetine. Previously, Sachs et al[14] had shown a higher switch rate with the noradrenergic-selective tricyclic desipramine compared with the dopamine-active bupropion. Taken together, these 3 studies suggest an increased vulnerability to switching into mania with antidepressants with high noradrenergic potency.

Meta-analyses suggest that switches are more likely to occur in younger patients[15] and on the older tricyclics compared with the newer second-generation antidepressants.[16] Bipolar depressed patients with minor hypomanic symptomatology concurrent with their depressive episode also appear to be at increased risk of switching.[17,18]

In the small subgroup of about 15% of bipolar depressed patients who are good acute responders to adjunctive antidepressants for 2 months or more, observational studies by Altshuler et al[19,20] and Joffe et al[21] and the randomized study by Ghaemi et al[5] suggest that antidepressant continuation compared to antidepressant discontinuation may decrease the incidence of or latency to depressive relapse without increasing switches into mania. However, in those with a history of prior rapid cycling, Ghaemi et al[5] found earlier relapse and 3 times more time depressed when antidepressants were continued as opposed to discontinued.

Given these ongoing ambiguities about efficacy and the potential adverse effects of antidepressants on the subsequent course of bipolar illness, we examined the relationship of the prior retrospective use of antidepressants (number of trials and duration of use) to the long-term outcome in bipolar I disorder outpatients (mean age, 42 years) treated naturalistically, rated prospectively, and assessed for good to excellent response lasting a minimum of 6 months in what might be considered effectiveness research.

Clinical Points

- Increased prior use of antidepressants in the 18 years leading up to network entry in bipolar I disorder outpatients (mean age, 42 years) was associated with a poor long-term (≥ 6 months response) outcome to prospective naturalistic treatment.
- The number of prior antidepressant trials (whether or not they were covered by mood stabilizers) was independently related to prospective nonresponse, as was a history of greater number of prior mood episodes and a comorbid anxiety disorder.
- Given the emerging data on the lack of efficacy of antidepressants in bipolar depression and possible adverse effects of antidepressants on the course of the disorder described here and in the literature, it would appear advisable that other treatment options should initially be explored, and cautious use of antidepressants deferred to later in the treatment sequence.

METHOD

Patients were enrolled in the Stanley Foundation Bipolar Network from 1996 through 2002, now continuing as the Bipolar Collaborative Network. They gave informed consent for participation in the network as approved by local institutional review boards and completed a variety of assessments, including a detailed patient questionnaire and retrospective and prospective graphing of the longitudinal course of their illness on the National Institute of Mental Health-Life Chart Method (NIMH-LCM).[22]

The details of the network methodology are presented elsewhere, but it included naturalistic treatment during most of patients' time in the network[23,24] and daily ratings on the prospective NIMH-LCM performed by trained clinicians, social workers, and research assistants.[24,25] Of these patients, 139 were included in the present report because they had a diagnosis of bipolar I disorder and a complete retrospective graphic depiction on the retrospective NIMH-LCM of their course of illness and types of pharmacologic treatment prior to network entry.[8,9]

For the purpose of this article, all classes of antidepressants were included under a single category, antidepressants. The number of separate antidepressant trials was recorded as well as the total duration of antidepressant treatment.

The antidepressant trials were also divided on the basis of whether they were given with or without "coverage" of a mood stabilizer for a minimum of 75% of the time an antidepressant was used. Included under this mood stabilizer classification was lithium, a mood-stabilizing anticonvulsant (ie, carbamazepine, valproate, or lamotrigine), and any typical or atypical antipsychotic. Only bipolar I disorder patients were included in this analysis because previous work has shown that antidepressants, when covered by mood stabilizers (and perhaps even in monotherapy[26]), are less likely to be associated with a manic or hypomanic episode in bipolar II compared to bipolar I disorder patients.[27,28]

The number and duration of "covered" and "uncovered" antidepressant trials were then related to the primary outcome measure of prospective response to naturalistic treatment and to other course of illness variables that had been previously linked to antidepressant responsiveness in the literature.[8,25,29–31]

Prospective response was considered a good to excellent long-term (for a minimum of 6 months) response in the network.[23,24,32,33] This was ascertained by a depiction of the daily prospective ratings of mania and depression of "much improved" or "very much improved" on the Clinical Global Impressions scale modified for bipolar disorder (CGI-BP). Those who were rated only "mildly improved," "not changed," or "worse" on the CGI-BP were considered nonresponders.

The responders (37.1%) were treated with a mean ± SD of 2.98 ± 2.18 drugs and required a mean of 1.5 years in the network to achieve the beginning of this 6 months of stability after trying and discontinuing an additional 2.04 drugs prior to the response. The nonresponders (58.9%) were similarly treated with a mean of 2.96 drugs at any one time, but they were exposed to a mean of 7.29 drugs in an attempt to achieve stabilization. Their mean ± SD duration of time in treatment in the network was 32.6 ± 18.0 months, while the responders were in the network for a mean ± SD of 38.9 ± 18.0 months.

Statistics

The effect of number of antidepressant trials (variables 1 [total], 2 [covered], 3 [uncovered]) and duration of antidepressant use (variables 4 [total], 5 [covered], 6 [uncovered]) on long-term treatment response was assessed by Mann-Whitney *U* test and then by logistic regression. The 18.3% of patients who entered the network well (very much or much improved on the CGI-BP) and remained so for an additional 6 months or more were included in a separate series of Kruskal-Wallis tests. Demographic variables (see Table 1) that showed a significant relationship with antidepressant use (by Mann-Whitney *U*) were included in a general linear regression (employing a Poisson family variance function and a log link) to determine their relationship to our antidepressant utilization variables. For the retrospective antidepressant trials, the data were mildly overdispersed, and the scale parameters were estimated by using the Pearson residuals.

Retrospective Antidepressants and Prospective Treatment Outcome

The relationship between the 6 antidepressant utilization variables (1–6 noted above) and prospective treatment outcome was examined with a logistic regression including as predictor variables a variety of demographic characteristics thought to be related to poor prognosis in bipolar disorder. This set of variables was free of both specification errors

Table 1. Demographic and Retrospective Course of Illness Variables in Bipolar I Disorder Outpatients

Variable	Ill and Well Patients at Entry (N = 139)	Ill Patients at Entry (n = 108)
Age at onset, mean ± SEM, y	23.5 ± 0.77	23.1 ± 0.84
Age, mean ± SEM, y	42.3 ± 0.94	42.0 ± 1.1
Duration of illness mean, y	18.8	18.9
Treatment response, n		
Responder[a]	60	60
Nonresponder[b]	48	48
Well at entry[c]	31	
Female patients, n (%)	70 (50)	58 (54)
US patients, n (%)	36 (26)	23 (22)
Rapid cyclers, n (%)	58 (43)	50 (47)
Anxiety disorder comorbidity, n (%)	35 (25)	30 (28)
Substance abuse comorbidity, n (%)	48 (35)	36 (33)
History of physical or sexual abuse, n (%)	43 (31)	34 (43)
Unable to work, n (%)	69 (51)	34 (52)
≥ 20 mood episodes, n (%)	58 (43)	53 (51)
History of psychosis, n (%)	102 (78)	79 (77)
Positive history of antidepressant exposure, n (%)	104 (75)	86 (80)

[a]Responders for at least 6 months.
[b]Did not achieve responder status.
[c]Well at network entry and then maintained this response for at least another 6 months.
Abbreviation: SEM = standard error of mean.

and multicolinearity. Analyzing total trials with covered or uncovered trials in a single regression was impossible due to the colinearity; hence, each of the 3 models was examined separately. The goodness of fit achieved by total, covered, or uncovered trials was found to be very close (log likelihood: total, $\chi^2 = 29.21$; uncovered, $\chi^2 = 26.11$; covered, $\chi^2 = 25.21$). In addition, regardless of the model used, the number of antidepressant trials, a history of a comorbid anxiety disorder, and number of prior mood episodes were found to be significant predictors, at least at the trend level, while the duration of antidepressant use was not. The odds ratios for total, uncovered, and covered antidepressant trials were nearly identical (total, OR = 1.42, $P = .007$; covered, OR = 1.55, $P = .041$; uncovered, OR = 1.56, $P = .029$), suggesting that the 3 variables predicted prospective treatment response equally well. As such, only the total number of antidepressant trials, the best-fitted model, is presented in the logistic regression results and Figure 1.

RESULTS

The demographic and illness variables of the 139 bipolar I disorder patients included in this analysis are listed in Table 1 (middle column). Those listed in the right column are the 108 patients who entered the network ill and required additional prospective treatment in order to achieve the response (for ≥ 6 months) or nonresponse categorization. As listed in Table 2, on the basis of the median values in this univariate analysis, there was a highly significant association of nonresponse and both number of antidepressant trials and longer duration of antidepressant treatment (whether or not antidepressants were covered by mood stabilizers).

Table 2. Greater Prior Number of Antidepressant Trials and Duration of Antidepressant Treatment Are Associated With Poorer Prospective Outcome in Bipolar I Disorder Outpatients[a]

	Total Antidepressant Use					Antidepressants Covered by Mood Stabilizers					Antidepressants Uncovered by Mood Stabilizers				
Prospective Outcome:	Well at Entry[b]	Responders (C)[c]	Nonresponders (D)[d]	*P*, Overall[e]	*P*, C vs D[f]	Well at Entry[b]	Responders (C)[c]	Nonresponders (D)[d]	*P*, Overall[e]	*P*, C vs D[f]	Well at Entry[b]	Responders (C)[c]	Nonresponders (D)[d]	*P*, Overall[e]	*P*, C vs D[f]
No. of antidepressant trials															
Mean	2.7	2.2	4.1			1.4	1.3	2.1			1.3	1	2		
Median	1	2	3	<.000	<.001	0	0	2	<.001	<.01	0	0	1	<.003	<.003
Antidepressant trial duration, d															
Mean	793.1	826.3	968.1			419	398.3	511			374	428	457.1		
Median	30	210	427	<.003	<.08	0	0	150	<.003	<.04	0	0	151	<.006	<.009

[a]Mean number of antidepressant trials and mean duration of antidepressant treatment in days are listed only for clinical reference, as the statistics were performed on the median values.
[b]Patients who entered the study well and remained so for ≥ 6 months; n = 31.
[c]Patients who scored "very much" or "much improved" on CGI-BP for > 6 months; n = 61.
[d]Patients who scored "minimal," "not improved," or "worse" on CGI-BP; n = 44.
[e]Kruskal-Wallis test.
[f]Mann-Whitney test.
Abbreviation: CGI-BP = Clinical Global Impressions scale modified for bipolar illness.

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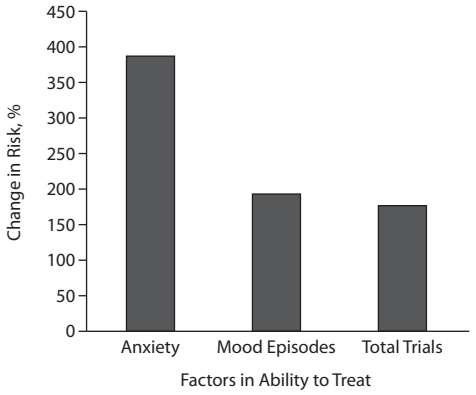
Figure 1. Percentage Change in Risk of Inability to Prospectively Treat



However, in the regression analysis (below), the duration of antidepressant treatment was not an independent predictor of outcome.

We then eliminated the 31 patients in the well group and focused on the group of 108 bipolar I disorder patients (right column of Table 1), who were ill at entry,[24] in order to specifically examine the potential impact of prior antidepressant use on whether or not these patients responded to prospectively observed and rated naturalistic treatment. In an effort to see how the prior use of antidepressants was associated with other retrospective illness variables, we examined the relationship of the number of antidepressant trials and duration of antidepressant exposure to other variables previously associated with a less favorable long-term response in the literature.[32] This was done initially in a univariate analysis. Having had 20 or more prior episodes was associated with more total antidepressant trials and longer duration of antidepressant use (whether or not these were covered or uncovered by a mood stabilizer or antipsychotic). A history of physical or sexual abuse was associated with fewer total and uncovered antidepressant trials and shorter duration of antidepressant use. A history of having been psychotic was associated with a lesser total duration and uncovered duration of antidepressant use. Patients who were studied in the United States, as opposed to the Netherlands or Germany,[12,32] had a greater duration of total antidepressant use and amount of time that antidepressants were covered by a mood stabilizer.

In the general linear regression analysis, the number of antidepressant trials was significantly predicted by the following variables. For total trials, those with more than 20 prior mood episodes had 2.1 times more antidepressant trials ($P = .005$), and a history of physical/sexual abuse in childhood was associated with a trend ($P = .058$) for having 0.65 times fewer antidepressant trials. For covered antidepressant trials, only those with ≥ 20 mood episodes were significantly ($P = .018$) related to 2.4 times more covered antidepressant trials. For antidepressant trials uncovered by mood stabilizers, only trend-level relationships were observed. Those with ≥ 20 mood episodes had 1.86 times more uncovered antidepressant trials ($P = .061$), and those with a history of physical/sexual abuse were 0.57 times as likely to have uncovered antidepressant trials ($P = .066$).

The main outcome variable—ability to achieve a good prospective long-term response—was significantly predicted in the logistic regression (log likelihood $\chi^2_{11} = 29.21$, $P = .0051$). Only 3 variables were found to predict prospective long-term treatment response. As illustrated in Figure 1, it was found that the odds of being unable to achieve a successful prospective long-term treatment response were 178.5% higher for those with 1 SD higher prior total number of antidepressant trials (right column), 194.1% higher for those with ≥ 20 prior mood episodes (middle column), and 388.4% higher for those with a prior lifetime history of a comorbid anxiety disorder (left column).

DISCUSSION

These data suggest a relationship between a greater amount of antidepressant use in bipolar I disorder patients in the 18 years prior to network entry at a mean age of 42 years and a less favorable long-term outcome to prospectively rated naturalistic treatment with a mean of 3 medications. In the initial univariate analysis, both the number of antidepressant trials and the duration of antidepressant exposure, whether or not the antidepressants were covered by a mood stabilizer or atypical antipsychotic, were related to a less favorable long-term outcome during naturalistic treatment in the network (Table 2). Fewer prior antidepressants had been used in those who were well at network entry and in the responders (who were improved for at least 6 months in the network). Conversely, a greater number of antidepressant trials and duration of prior antidepressant use were seen in the prospective long-term nonresponders.

In the logistic regression illustrated in Figure 1, the total number of antidepressant trials remained independently related to a poor long-term outcome in the network (ie, nonresponse), as did patients having had ≥ 20 prior mood episodes or a history of a comorbid anxiety disorder. Moreover, the relationship of prior number of antidepressant trials remained an independent predictor of long-term treatment response/nonresponse whether the antidepressants had been covered by a mood stabilizer or an atypical antipsychotic. Even though we selected variables most likely to influence the relationship between antidepressant use and treatment outcome, as in any observational study, there could be other meaningful confounding factors that we did not account for or examine leading to residual confounding bias in our results.

The finding that having 1 standard deviation higher percentage of prior total number of antidepressant trials increased the chance of being a prospective nonresponder by 178.5% is novel. The relationships of nonresponse to having ≥ 20 prior episodes or a lifetime history of a comorbid anxiety disorder[34–39] are both consistent with a substantial literature. This is the first analysis to suggest that both anxiety disorder comorbidity and exposure to a greater number of

antidepressant trials are each independent predictors of prospective long-term nonresponse (even when prior number of mood episodes is taken into account). In contrast to the univariate analyses (Table 2), the duration of time antidepressants were used did not survive as an independent predictor of prospective outcome in the regression analysis.

The nature of these associations and the causal directions of these relationships remain uncertain. A greater retrospective number of antidepressant trials were given to those with a greater number of prior mood episodes, and both number of antidepressant trials and having ≥ 20 prior episodes were independently related to a poor outcome. Thus, antidepressants could have been used more in an effort to treat and moderate an already difficult prior course of illness, or, conversely, antidepressant use could have contributed to an adverse course of illness and ultimately to treatment nonresponsiveness.

In a recent survey, Baldessarini et al[40] suggested that approximately 50% of patients with a new diagnosis of bipolar illness were still being treated with antidepressants, often in the absence of mood stabilizers or atypicals, which is not in accord with conventional wisdom and most treatment guidelines. Therefore, uncovered use of antidepressants continues at a very high rate in bipolar illness despite growing evidence that antidepressants (even when covered by mood stabilizer or atypical antipsychotic) have a less than desirable efficacy profile and a possible association with an increased rate of switching into hypomania or mania or of cycle acceleration (as reviewed in the Introduction).

Prospective use of antidepressants (as recommended as an adjunct to a mood stabilizer or atypical antipsychotic in treatment guidelines) was also observed at a very high rate in bipolar patients treated naturalistically in our network[24,32] and in the Systematic Treatment Enhancement Program for Bipolar Disorder.[41,42] As previously reported,[24] more antidepressants were utilized prospectively in the nonresponders (a mean 1.96 antidepressant trials/patient) than in the responders (1.29 trials/patient), and antidepressants in general had a low overall success rate of 17.8%, ie, being involved in the regimen that achieved a good long-term response for 6 months or more. In contrast, lithium, for example, had the highest success rate; 49.3% of the time it was used in the treatment regimens that achieved this good long-term response.[32]

The same potential ambiguity for causality exists for this prospective use of antidepressants more often in the nonresponders than in responders, as previously discussed, for the retrospective antidepressant data. Antidepressants could have been used more often prospectively in the nonresponders in an effort to establish an effective treatment regimen, although the opposite perspective is also possible. Greater use of antidepressants prospectively contributing to nonresponse would be in accord with the randomized findings of Ghaemi et al[5] that antidepressant continuation in good acute responders leads to a great number of depressive episode recurrences and more morbidity in those with a prior history of rapid cycling but not in those with non–rapid cycling bipolar disorder. Forty-seven percent of the 108 patients in our study who were ill at network entry were classified as a rapid cycler in the year prior to entry and thus potentially prone to the antidepressant destabilizing effects seen by Ghaemi et al[5] in this subgroup.

While the prior number of antidepressant trials was associated with a poor long-term response to prospective naturalistic treatment independent of the experience of ≥ 20 prior episodes or having a comorbid anxiety disorder, it appears that only randomized clinical trials can address the issues of whether antidepressants compared to placebo or compared to other mood-stabilizing or atypical antipsychotic drugs may have a direct adverse effect on the course of bipolar illness. These trials should evaluate the effects of antidepressants on rate of switching into mania, cycle acceleration, the occurrence of greater number of episodes, and, ultimately, long-term clinical nonresponse to prospective naturalistic treatment as reported here.

It is problematic that such randomized clinical trials (which could even be accomplished in comparative effectiveness studies or practical clinical trials using open rather than double-blind randomization) have not been conducted in patients with bipolar illness sufficiently to address this key therapeutic question. The antidepressants have been available for use in unipolar disorder and only by extrapolation in bipolar illness for more than 50 years, and the lack of adequate data about their effectiveness and safety in the acute and long-term treatment of bipolar depression is further evidence of the continued clinical neglect of treatment-related studies in bipolar disorder.[43–45] Until such randomized clinical trials of antidepressants compared to other treatment options are conducted in acute bipolar depression and long-term prophylaxis, the much needed systematic database to answer questions about the appropriate role of antidepressants in the treatment of bipolar depression will continue to be lacking.[43,46]

Randomized trials so far give the suggestion that the SNRI antidepressant venlafaxine may be more likely to induce switch than SSRIs or buproprion[12,13] and antidepressant continuation in good acute responders is not indicated in the subgroup of rapid cyclers,[5] but further studies of antidepressants in comparison to other options (such as in the study by McElroy and colleagues[47] comparing paroxetine to the atypical quetiapine) in acute bipolar depression treatment and then in long-term prophylaxis are needed.

Our findings reveal an association between the greater previous use of antidepressants (especially the number of antidepressant trials) and a subsequent, less successful, prospective long-term outcome (response for at least 6 months) during naturalistic treatment in adult outpatients with bipolar I disorder. However, whether greater antidepressant use was causally involved in this adverse outcome or merely reflected attempts at treating a more difficult course of illness (as suggested by the independent relationship to patients with ≥ 20 prior episodes and a comorbid anxiety disorder) remains to be further clarified. Given the emerging evidence of inadequate acute and long-term response to antidepressants in the treatment of bipolar depression and the direct or indirect

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association of prior antidepressant exposure to an adverse course of bipolar disorder described here, it would appear clinically advisable that other treatment options be explored prior to the cautious use of adjunctive antidepressants in bipolar I disorder.

Drug names: bupropion (Aplenzin, Wellbutrin, and others), carbamazepine (Carbatrol, Equetro, and others), desipramine (Norpramin and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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