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RESEARCH ARTICLE

Long-term worsening of bipolar disorder related with frequency of antidepressant exposure

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BACKGROUND: The aim of this study of 53 persons with bipolar disorder (BD) was to evaluate the relationship between history of exposure to antidepressants (AD) and mood stabilizers (MS) and the percentage of time spent ill.

METHODS: BD outpatients with more than 12 months of prospective follow-up were included. Outcome was documented using a life charting technique. Current and previous exposure to AD and MS were assessed using a scale that provides a quantitative measure of exposure to psychotropic medications. Regression models were used to correct for possible confounders.

RESULTS: Previous treatment with AD was an independent predictor of polarity changes ($P < .001$) and mixed symptoms ($P = .01$). In contrast, "years of exposure to MS" was an independent predictor of time spent asymptomatic ($P = .019$). The ratio between exposure to AD vs MS was associated with less weeks asymptomatic ($P = .03$), more mixed symptomatology ($P = .019$), and more polarity changes ($P = .001$).

CONCLUSIONS: Antidepressant exposure was a major predictor of mood instability in the long-term outcome of BD. The ratio used of previous exposure to AD vs MS was associated with poor outcomes, suggesting that the harmful effect of AD may be additive and related to how much they are used.

KEYWORDS: bipolar disorder, mood instability, switch, antidepressants, mood stabilizers

INTRODUCTION

Antidepressants (AD) are the drugs most frequently prescribed to persons with bipolar disorder (BD),[1] despite ongoing intense debate about the impact of AD on the disorder's long-term evolution. Previous randomized[2-4] and observational studies[5-7] have found a destabilizing effect by AD, but other short-term trials have not.[8-11] More recently, 2 large randomized studies designed to evaluate AD affectivity in bipolar depression showed no therapeutic advantage for AD added to mood stabilizers (MS) compared with MS alone, but contradictory results about antidepressants´ risk to induce instability in BD outcomes.[11,12] Resolving this issue is critical, given that mood stability and control of depressive symptoms are the main psychopathological factors in helping persons with BD achieve good vocational and social outcomes.[13] Taken together, these data suggest that a prolonged follow-up period might be needed to assess the potential affective instability induced by AD.

Almost all previous studies of AD use in depression have defined efficacy by response rates, and short- and long-term security by switches into a manic or hypomanic episode. Over the long term, however, in addition to the risk of switching into mania or hypomania, exposure to AD might increase affective instability, cycling rates, and perhaps mixed mood states, and decrease asymptomatic periods. Rating a continuum of mood states ranging from both depressive and manic subsyndromal symptoms to full severe episodes might be more useful to assess instability associated with exposure to AD. Moreover, although MS have been shown to reduce the risk of AD-induced mania or hypomania, they might be less effective in reducing other risks associated with AD exposure, such as cycle acceleration or relapse into depression.[14,15]

Beyond this, some basic questions remain unaddressed: If AD cause mood instability, does the effect persist even after they are stopped? Is frequency of exposure quantitatively related to antidepressants' effects on long-term stability? How much mood stabilization is needed to counteract current or previous AD exposure? To assess antidepressants' instability effects during the course of illness, it may be useful to extend follow-up beyond the period of exposure.

The aim of this study was to evaluate in persons with BD the relationship between history of exposure to AD and MS and the percentage of time spent ill. Based on findings of previous studies, we hypothesized that a history of high exposure to MS would be associated with more time spent asymptomatic, whereas a history of high exposure to AD would be related with a poor clinical course, characterized for high manic or mixed symptomatology and changes of polarity.

METHODS

For this retrospective outpatient study, we used the following inclusion criteria: 1) diagnosis of bipolar I disorder (BDI) or bipolar II disorder (BDII), based on the Structured Clinical Interview for DSM-IV (SCID)[16]; 2) age between 18 and 65; 3) >12 months of treatment in our program; 4) no interruptions in this treatment; 5) and the patient provided consent to participate in this research. Exclusion criteria were: substance abuse or dependence within 12 months prior to entry; past treatment with electroconvulsive therapy; history of any neurologic disease; and medical disorders that were not stable.

Clinical and symptomatic assessment

All participants were outpatients from the bipolar disorder program of the Neuroscience Institute of Favaloro University in Buenos Aires. Clinical and demographic information obtained from clinical charts and direct patient interviews included age, sex, age at illness onset, length of illness, and previous manic/hypomanic and depressive episodes. Latency to diagnosis was calculated as the period of time between when a patient first contacted the health system with symptoms of BD and when this diagnosis was provided. Where possible, we attempted to verify these historical data with outside reports from family or others sources, including previous physician records.

For each patient treated in our program, the course of illness usually is documented by his/her psychiatrist using a modified life chart technique based on the US National Institute of Mental Health (NIMH) life-charting method and anchored with scores from the Hamilton Depression Rating Scale (HDRS)[17] and Young Mania Rating Scale (YMRS)[18] (**FIGURE**). Our group used this life chart technique in a previous study,[19] and it was developed without the knowledge or purpose of the present study. High interrater reliability was obtained for scores in YMRS (interclass correlation coefficient [ICC = 0.96]) and HDRS (ICC = 0.95). The main investigators (S.S., D.M.) reviewed all life charts in this study.

FIGURE
Criteria used for assigning mood state scores in life charts

	January				February				
+4									Severe mania (YMRS ≥26)
+3									Moderate mania (YMRS ≥16 and ≤25)
+2									Mild mania (YMRS ≥9 and ≤15)
+1									Subclinical mania (YMRS ≥4 and ≤8)
0									Euthymic (YMRS ≤4 and HDRS ≤4)
-1									Subclinical depression (HDRS ≥5 and ≤9)
-2									Mild depression (HDRS ≥10 and ≤15)
-3									Moderate depression (HDRS ≥16 and ≤25)
-4									Severe depression (HDRS ≥26)

Course of illness was documented weekly (in this example in January and February) during follow-up using a modified life chart technique based on the National Institute of Mental Health life-charting method and anchored with scores from the Hamilton Depression Rating Scale (HDRS)[17] and Young Mania Rating Scale (YMRS).[18]

For this report, we considered: syndromic mood states (depressive or manic) as the time spent with clinical symptoms (mild, moderate, or severe); symptomatic mood states (manic or depressive) as the time spent with clinical and subclinical symptoms; mixed symptomatology when patients had simultaneously significant clinical symptoms of any polarity and at least subclinical symptomatology of opposite polarity; and changes of polarity when patients switched from at least mild depression to at least mild mania/mixed states or from at least mild mania/mixed states to mild depression or more.

Psychopharmacological assessment

Exposure to AD, MS, antipsychotics, and benzodiazepines was assessed by the Clinical Scale of Intensity, Frequency, and Duration of Psychopharmacological Treatment (IFD).[20] This scale provides a quantitative measure in a 0- to 5-point range of exposure to different groups of psychotropic medications during a treatment period (0 = no medication, 1 = sporadic low dose, 2 = continued low dose, 3 = middle dose, 4 = high dose, and 5 = very high dose); exposure during treatment of previous episodes (0 = no medication, 1 = very occasionally, 2 = occasionally, 3 = half the time, 4 = almost all the time, and 5 = all the time); and total years of exposure. Over the follow-up period, patients were naturalistically treated by their psychiatrists, who prescribed all psychotropic medications according to published guidelines.

Data analysis

Spearman bivariate correlations were computed to assess the relationship between different measures of follow-up and clinical and pharmacological variables. We used multivariate regression models to address the hypothesis that history of exposure to AD and MS would account for a significant amount of variance in the percentage of time spent ill beyond clinical variables and current psychotropic medications.

We first entered clinical variables (age at illness onset, length of illness, clinical subtype, and number of previous manic/hypomanic and depressive episodes) into the model, followed by current exposure to psychotropic medications, and then other variables such as total years of exposure and treatment of previous episodes with AD and MS. This order of variables allowed us to examine the independent contribution of history to exposure to AD and MS in the prediction of measures of follow-up, while also correcting for the influence of clinical variables and current exposure to psychotropic medications.

RESULTS

Fifty-three patients were included [37 female (69.8%)], and 22 (41.5%) had BDI. Mean age was 45.34 (SD = 14.66) years; mean age of onset was 30.40 (SD = 11.03) years; mean length of illness was 14.48 (SD = 9.83) years; and they had 2.83 (SD = 2.29) previous manic/hypomanic episodes and 3.89 (SD = 2.53) previous depressive episodes. We followed this sample for a mean of 86.38 (SD = 34.32) weeks; the percentage of time spent ill is shown in **TABLE 1**. Exposure to different groups of psychotropic medications during the study period, treatment of previous episodes, and years of exposure are shown in **TABLE 2**. Patients had an average latency to BD diagnosis of 8.46 (SD = 5.95) years; latency in diagnosis correlated with a higher number of previous depressive episodes (R = 0.450, $P = .001$) and with less treatment of previous episodes with MS (R = –0.488, $P < .001$).

Results of bivariate correlations between different measures of follow-up and clinical and pharmacological variables are summarized in **TABLE 3**. We conducted a logistic regression to adjust for possible confounders, especially clinical variables and current treatment. The only 3 variables that independently predicted the time asymptomatic during follow-up were length of illness

(β = –0.57, t = –3.95, $P < .001$), current treatment with AD (β = –0.28, t = –2.29, $P = .027$), and years to exposure to MS (β = 0.35, t = 2.44, $P = .019$), accounting for approximately 36% of variance (adjusted $R^2 = 0.356$; $F[3] = 9.48$, $P < .001$). It might not be surprising—taking into account that depressive symptomatology was more prevalent during the follow-up—that the same variables contributed to explain 34% of time spent with depressive symptomatology (adjusted $R^2 = 0.340$; $F[3] = 8.89$, $P < .001$): length of illness (β = .54, t = 3.72, $P = .001$), current treatment with AD (β = 0.28, t = –2.26, $P = .029$), and years to exposure to MS (β = –0.38, t = –2.62, $P = .012$). Contrarily, any variable predicted time spent with manic symptomatology.

On the other hand, the clinical subtype (β = 0.32, t = 2.30, $P = .026$) was the only variable that predicted changes of polarity during follow-up, explaining 8% of variance (adjusted $R^2 = 0.084$; $F[1] = 5.29$, $P = .026$). The addition of current psychotropic treatments did not significantly improve the model (adjusted $R^2 = 0.097$; $F[1] = 5.94$, $P = .019$), whereas with the addition of previous exposure to AD and MS the model accounted for approximately 28% of variance (adjusted $R^2 = 0.277$; $F[1] = 18.63$, $P < .001$), with treatment of previous episodes with AD being the only independent predictor (β = 0.54, t = 4.31, $P < .001$). It is interesting to note that with the addition of treatment of previous episodes with AD, clinical subtype no longer remained a significant predictor (β = 0.11, t = 0.79, $P = .42$). Similarly, treatment of previous episodes with AD (β = 0.35, t = 2.53, $P = .015$) was the only independent predictor of time spent with mixed symptoms, explaining 10% of variance (adjusted $R^2 = 0.105$; $F[1] = 6.41$, $P = .015$).

We also constructed an index of previous exposure of AD to MS that correlated with latency of diagnosis ($R = 0.464$, $P = .001$) and number of previous depressive episodes ($R = 0.348$, $P = .017$). After correcting for these clinical variables, the ratio of AD to MS was related to asymptomatic weeks (β = -0.46, t = -3.19, $P = .03$), mixed symptomatology (β = 0.38, t = 2.44, $P = .019$), and changes of polarity (β = 0.49, t = 3.51, $P = .001$).

TABLE 1
Percentage of time that patients spent ill

	Mean (SD)
Symptomatic	41.93 (25.73)
Asymptomatic	58.07 (25.68)
Depression symptomatic	29.98 (21.25)
Depression syndromic	14.74 (15.17)
Subclinical depression	15.24 (13.02)
Mild depression	8.92 (9.08)
Moderate depression	5.09 (7.63)
Severe depression	0.73 (2.53)
Manic symptomatic	7.06 (8.83)
Manic syndromic	2.38 (3.52)
Subclinical mania	4.68 (6.49)
Mild mania	1.51 (2.14)
Moderate mania	0.59 (1.48)
Severe mania	0.28 (1.03)
Mixed syndromic	4.89 (7.22)
Changes of polarity (raw-score)	1.64 (1.95)

SD: standard deviation.

DISCUSSION

The main finding of this study was that previous exposure to AD was a major predictor of mood instability in the long-term outcome of BD. In fact, treatment of previous episodes with AD was the only independent predictor of switches and mixed symptomatology. We also found that the ratio of previous AD exposure to MS use was associated with poor outcomes, suggesting that the harmful effect of AD and the positive effect of MS may be additive and related to how much they are used. These results were corrected for severity of illness (such as number of previous episodes, age of onset, length of illness, and clinical subtype) and current treatment regimens.

Our results agree with some[2-7,11,14] but not all[8-10,12] previous studies on this topic. Some methodologic issues might explain the disagreement: first, prior observational studies did not use regression analysis to correct for confounding by indication (perhaps clinicians prescribed more AD for patients with more depression in their evolution) or other confounding factors (such as severity of illness). Other studies were randomized but with short follow-up.[8,9] One commonly cited meta-analysis is focused on acute depression efficacy and thus is not relevant to the long-term impact of AD.[21] It is relevant that another meta-analysis of long-term outcomes with AD was consistent with our results, finding no long-term depression benefit and increased long-term manic morbidity with AD.[22]

Randomized maintenance studies in BD usually only assess switches into a manic episode—not rapid

TABLE 2
Exposure to different psychotropic medications as assessed during follow-up with the Clinical Scale of Intensity, Frequency, and Duration of Psychopharmacologic Treatment (IFD)

	Previous episodes, mean (SD)	Follow-up treatment period, mean (SD)	Total years, mean (SD)
Benzodiazepines	3.28 (1.48)	1.30 (1.11)	6.73 (6.24)
Antidepressants	2.68 (1.59)	1.30 (1.40)	4.18 (4.65)
Mood stabilizers	2.62 (1.33)	3.98 (0.68)	4.66 (5.17)
Antipsychotics	2.04 (1.76)	1.04 (1.02)	3.49 (5.39)

The IFD scale provides a quantitative measure in a 0- to 5-point range of exposure to different groups of psychotropic medications during a treatment period (0 = no medication, 1 = sporadic low dose, 2 = continued low dose, 3 = middle dose, 4 = high dose, and 5 = very high dose); previous episodes (0 = no medication, 1 = very occasionally, 2 = occasionally, 3 = half the time, 4 = almost all the time, and 5 = all the time); and total years of exposure.[20]

SD: standard deviation.

cycling, increased mood stability, or euthymic duration, as in this study. In most studies, manic switch occurs in the first few months of AD treatment, Thus, other long-term poor outcomes (such as rapid cycling or decreased euthymic periods) are not often assessed.[23] Only a randomized study that assessed long-term mood instability and rapid cycling with AD did find worsened outcome.[3] Finally, this is the only study in which AD and MS exposure was assessed using an instrument specially designed to quantitatively assess drug exposure.

These results raise the hypothesis that the mood destabilizing effect of AD persists even after their discontinuation. Previous exposure to both AD and MS appear to affect the course of illness, independent of current treatments. These data are consistent with a prior study[24] that found that the main predictor of manic switch was the number of previous AD trials, and with other long-term prospective observational studies of AD-related outcomes in BD.[5-7] The ratio between prior exposure to AD and MS also correlated with stability. This concept may be clinically useful, suggesting that clinicians should enhance their use of MS relative to AD in managing BD.

The result that years of exposure to MS was a predictor of more asymptomatic remission is consistent with many previous studies[25,26] and perhaps validates the general findings of this study. It is interesting that the benefit of MS exposure still may be reduced by the negative effects of length of illness, because both were independent predictors of outcome. Curiously, although treatment of previous episodes with AD negatively affected the illness course, we found that years of exposure to AD did not. This apparent contradiction may be explained by the approximately 20% of patients with BD who show a sustained antidepressant response without mood switching during long-term treatment.[11] These patients may benefit from long-term AD exposure. In a larger subgroup of patients with BD, however, AD treatment might induce affective instability even after AD discontinuation. This pattern may be the opposite in the case of MS, with years of exposure more than treatment of previous episodes having a benefit in the long-term outcome.

Finally, the latency to diagnosis of 8.5 years in our sample is similar to other reports.[27-29] Latency to diagnosis was associated with more previous depressive episodes, less MS use, and indirectly more AD use. Given a mean duration of illness of 14.5 years, notable exposure to AD occurred before the BD diagnosis was made. Because the first years of bipolar illness may represent a critical period that might substantially influence future course,[19,30] these data suggest that many BD patients may become treatment-resistant as a result of misdiagnosis and AD use long before MS are tried. Some data[31] suggest delay in starting MS treatment as the only independent predictor of poor outcome in BD.

As in all research, our results should be interpreted in the context of study design. First, our study was observational, not randomized, and retrospective. Thus confounding bias cannot be excluded; unlike most psychiatric studies of this type, however, we corrected for some confounding factors (such as severity of illness and bipolar subtypes) in our regression models. Importantly, the possibility of confounding by indication can be excluded by our regression models' adjusting for severity of illness. Second, our measure of exposure to psychopharmacological treatments does not discriminate among different AD and MS, although the potential negative or positive effects of each drug within those groups may not be equivalent. On the other hand, unlike almost all previous studies, the IFD scale we used provided a measure of dose exposure to different groups of psychotropic medications in current treatment. Third, although we did not control for the effects of antipsychotic and benzodiazepine treatments during follow-up, those agents were used infrequently.

Another limitation is the sample size of 53; these data are therefore not definitive and require replication with

TABLE 3
Spearman bivariate correlations between measures of follow-up and clinical and pharmacological variables

	Asymptomatic	Depression symptomatic	Mania symptomatic	Mixed symptomatic	Changes of polarity
Age at illness onset	-0.102	0.138	0.060	-0.015	0.138
Length of illness	-0.445[a]	0.471[a]	0.148	0.163	0.182
Number of previous manic episodes	-0.115	0.024	0.343[b]	0.118	0.233
Number of previous depressive episodes	-0.291[b]	0.193	0.378[b]	0.207	0.355[b]
Clinical subtype	-0.161	0.197	-0.036	0.054	0.282[b]
Current exposure to AD	-0.424[a]	0.422[a]	0.029	0.274	0.364[a]
Current exposure to MS	-0.312[b]	0.305[b]	0.209	0.100	0.280[b]
Previous treatment AD	-0.322[b]	0.325[b]	0.073	0.382[a]	0.553[c]
Previous treatment MS	0.336[b]	-0.318[b]	0.005	-0.276	-0.246
Years of exposure to AD	-0.299[b]	0.326[b]	0.068	0.226	0.437[a]
Years to exposure to MS	0.322[a]	-0.253	0.087	-0.246	-0.182

The Spearman correlation coefficient determines the strength of the relationship between 2 variables. Significant correlations were included in multivariate regression models to address the hypothesis that history of exposure to AD and MS would account for a significant amount of variance in the percentage of time spent ill beyond clinical variables and current psychotropic medications.

[a]$P < .01$.
[b]$P < .05$.
[c]$P < .001$.

AD: antidepressants; MS: mood stabilizers.

larger samples. Further research would employ additional indices of mood instability such as impulsivity or affective instability during periods of clinically significant depression. Thus, though not definitive, these results advance the psychiatric literature and at least provide some evidence for clinical practice as opposed to the mostly anecdotal basis for current opinions regarding long-term AD use in BD.

CONCLUSIONS

In summary, these data suggest mood-destabilizing effects of antidepressants in BD that endure long term after AD treatment ends. Corrected for confounding by indication, the frequency of AD use, as well as its relative ratio with the amount of MS use, correlate with mood instability. In contrast, as expected, greater MS exposure was the sole treatment predictor of remission. Finally, because delay to diagnosis was associated with greater AD use and poorer outcome, this study provides more evidence about the need for timely diagnosis of BD. ■

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