Short communication

Antidepressant-associated chronic irritable dysphoria (ACID) in STEP-BD patients

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Abstract

Background: It has been proposed that antidepressants can induce a chronic, dysphoric, irritable state in bipolar patients (called ACID for antidepressant-associated chronic irritable dysphoria). This phenomenon has only been described in case series format, and has not been prospectively validated.

Methods: Prospective data from the first 1500 patients (62.7% with bipolar I, 30.1% with bipolar II, and 7.2% with NOS) treated in the STEP-BD database were examined and those who were euthymic for at least one month at study entry, subsequently developed a depressive episode, and were then followed for one year were identified. Outcome of those who received an antidepressant for this depressive episode (n=27) was compared to those who did not (n=56), with particular attention given to the presence of the proposed symptom triad of ACID, namely dysphoria, irritability, and middle insomnia.

Results: Patients treated with antidepressants were ten times more likely to develop ACID than those who were not (Hazard ratio=9.95, CI=1.103–89.717, P=0.04). However, the hazard ratio dropped to 1.05 (P=0.99) when corrected for significant covariates, notably past antidepressant-related manic switch and sex.

Discussion: This study does not support the existence of ACID as an independent phenomenon. Rather, ACID appears to be part of a broader spectrum of antidepressant treatment-emergent affective switches.

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Bipolar disorder is associated with episodes of mania/hypomania and depression. However, whereas the manic and hypomanic episodes define the illness, the depressive episodes typically dominate the clinical course and, on average, people with bipolar disorder spend between one third to one half of their lives with depressive symptoms (Ghaemi et al., 2000; Judd et al., 2002, 2003; Post et al., 2003a,b). For example, in a prospective study of weekly symptoms in 146 people with a history of mania (i.e., bipolar I disorder), only 15% of the time was spent in mania/hypomania/cycling as compared to 32% of the time spent with syndromal or subsyndromal depressive symptoms (Judd et al., 2002). A similar study of 86 people with bipolar II disorder found that only 3% of the time was occupied by hypomania or cycling, compared to 50% of the time spent with depressive symptoms (Judd et al., 2003). Subjectively, bipolar subjects are more likely to complain of depression and are more commonly prescribed antidepressants than mood stabilizers (Ghaemi et al., 2000). Moreover, several groups have found that the psychosocial impairments and vocational disability associated with bipolar disorder are much more closely linked to the depressed pole of the illness than the manic or hypomanic episode (Altshuler et al., 2006; Simon et al., 2004).

The role of antidepressants in the treatment of bipolar illness continues to be defined. Interestingly, while antidepressants added to a mood stabilizer do not appear to be better than a mood stabilizer alone, antidepressant monotherapy (Amsterdam 1998; Amsterdam et al., 1990) or cotherapy with an atypical antipsychotic (Tohen et al., 2004) appear to be effective, suggesting that either mood stabilizers maximize the antidepressant benefit, or they have an interfering effect that renders antidepressants less effective (El-Mallakh, 2007). Some authors interpret the data as supporting the use of antidepressants in depressed bipolar patients (Gijsman et al., 2004), but an increasing number of randomized studies are failing to find antidepressants effective in bipolar depression (Sachs et al., 2007; Post et al., 2003; Nemeroff et al., 2001) and most experts arguing that antidepressants complicate matters by induction of mania and rapid cycling (El-Mallakh and Karippot 2002; Ghaemi and Goodwin 2005) with the risk appearing higher with multimodal antidepressants (Post et al., 2006; Nemeroff et al., 2001).

Recently, El-Mallakh and Karippot (2005) described a new potential complication of long-term antidepressant treatment. In a case series of six patients on antidepressant for an average of 9.7 years, a clinical picture of a chronic, irritable, dysphoric state was noted (El-Mallakh and Karippot 2005). These patients also had a sleep disturbance that manifested specifically as middle insomnia (disturbed sleep or multiple awakenings). None met full criteria for either depression or (hypo)mania. Invariably, there was significant social and occupational dysfunction. The continuous nature of the dysphoria was clearly different from the pre-antidepressant exposure course of episodic depressions. All antidepressant classes were used by these patients and most received concurrent mood stabilizer and/or atypical antipsychotic medication. Discontinuation of antidepressant treatment, as the only intervention, was associated with remission of most of these symptoms and resolution of the dysfunction in all subjects. A symptomatic triad of dysphoria, irritability, and middle insomnia, was common to all subjects and believed to be the core of this syndrome. Because of the chronic nature of these symptoms and their apparent relationship to antidepressants, the phenomenon was labeled antidepressant-associated chronic irritable dysphoria (ACID).

Due to the case series nature of that initial report, the true nature of the relationship to antidepressant treatment could not be fully elicited. Furthermore, the existence of ACID as a true complication of antidepressant therapy could not be confirmed in the original case series. To examine this phenomenon, we studied subjects who participated in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study. We compared one-year outcome in depressed bipolar subjects who received antidepressants with those who had never been exposed to antidepressants. We found that ACID appears to be associated with antidepressant treatment, but cannot be distinguished from other forms of antidepressant destabilization.

1. Methods

1.1. Study overview

Data as were collected from participants in the STEP-BD study. STEP-BD is a prospective, longitudinal, naturalistic outcome multicenter study (10). Participants had to be at least 15 years of age, and had to meet diagnostic and statistics manual (DSM-IV) criteria for either bipolar I, bipolar II, cyclothymia, bipolar NOS, or schizoaffective disorder, manic or bipolar types. The diagnosis is made after a Mini-International Neuropsychiatric Interview (MINI) (11) and history and illness characteristics were made with an Affective Disorder Evaluation (ADE) (12) by a trained rater. For this report, participants were drawn from the first 1500 patients to enter STEP-BD.

1.2. Participants

Of the 1500 patients evaluated, 59% were women, and 92.6% were Caucasian (3.4% African–American, 1.1%
Asian–American, 0.4% Native American, and 2.8% as other including mixed race). At study entry, mean age was 40.6±SD 12.7 years and mean duration of bipolar illness was 13.1±12.9 years. Seventy one percent were type I, 24% were type II, four were not otherwise specified, and the remaining 1% were schizoaffective or cyclothymic.

### 1.3. Assessments

The primary treating clinician used a Clinical Monitoring Form (CMF) (12) to elicit information used to quantify the severity of selected symptoms, and assign as clinical global impression score (CGI) and a general assessment of function score (GAF) during every visit. These visits occurred as clinically indicated rather than a fixed schedule. All treating psychiatrists had to be certified in the use of the CMF and were periodically monitored to ensure that rating standards were maintained (10). Over the first year, participants completed 9.34±SD 7.31 CMFs.

All of the first 1500 subjects in STEP were followed for up to two years after study entry. All subjects who initiated their involvement in STEP-BD in a euthymic state (defined by ADE), subsequently developed a depression, and then recovered, were evaluated for the study (as defined by CMF). Excluding patients with ongoing depression was necessary so that ACID could be reliably identified. Similarly, all patients who switched to mania, hypomania, or mixed states were excluded. Characteristics of the excluded subjects were not recorded. This was not a randomized, nor a controlled study. Treatment received by the participants was naturalistic, and patients who did not receive an antidepressant may have received a non-antidepressant treatment for their depression. While the data were collected prospectively, the analysis is post hoc.

There were 83 patients who fulfilled criteria. These were classified into two groups: those who used an antidepressant during the depressive episode, and those who were never exposed to an antidepressant throughout the observation period of one year.

Outcome was evaluated over the time subsequent to the resolution of the depressive episode. Individuals who experienced significant irritability (>30% of the time), significant dysphoria (>30% of the time), and a significant reduction in sleep (<−1 on CMF scale), and who were not either depressed, manic, hypomanic, or mixed were defined as having an ACID-like state.

Comparisons of the baseline characteristics across the groups were conducted by chi-square test for character variables, and ANOVA for continuous variables. Survival analysis to the time of developing ACID was performed. Cox proportional hazards models were used to analyze the effects of antidepressant use on time to the first appearance of ACID with and without adjustment for the covariates (covariates examined are listed in Table 1). This method was chosen before it was known how many subjects might have developed ACID.

### 2. Results

Table 1 summarizes the characteristics of the 83 subject sample at study entry. Fifty-two (62.7%) had bipolar I, 25 (30.1%) had bipolar II, and the remaining 6 (7.2%) were either cyclothymic or not otherwise specified. The average age of onset of illness was 19.8±SD 9.0 years of age. Women were more likely to receive an antidepressant (43.5%) than men (19.4%) (*P*=0.02). The average age of the patients was 43.8±13.1 years.

Four patients receiving antidepressants (14.8%) met the proposed criteria ACID, as compared to only one (1.8%) patient who did not receive an antidepressant. Fig. 1 is the Kaplan–Meier survival curve to time of onset of ACID. Patients receiving antidepressants developed ACID significantly earlier than those not receiving antidepressants (*P*=0.012).

The odds ratio of developing ACID when receiving an antidepressant is 6.8 compared to 0.15 for those not receiving an antidepressant. In terms of relative risk, patients prescribed antidepressants were nearly 10 times more likely to develop ACID than those who did not take antidepressants (estimate hazard ratio 9.95, CI 1.103, 89.717; *P*=0.04). However, the maximum likelihood dropped to 1.05 when the model included the significant covariates (*P*=0.99). While the regression analysis suggested that the risk for developing ACID was almost entirely explained by a history of at least one antidepressant-induced affective switch and female sex, this test is

### Table 1

Characteristics of the study population

<table>
<thead>
<tr>
<th>Character variables (n)</th>
<th>No antidepressant</th>
<th>Received antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) N=50</td>
<td>Age (years) N=33</td>
<td></td>
</tr>
<tr>
<td>44.0±SD 13.4</td>
<td>43.4±12.6</td>
<td></td>
</tr>
<tr>
<td>Female gender (46)*</td>
<td>26 (56.5)</td>
<td>20 (43.5)</td>
</tr>
<tr>
<td>Female gender (46)*</td>
<td>13 (48.1)</td>
<td>14 (51.9)</td>
</tr>
<tr>
<td>Bipolar type I (52)</td>
<td>35 (67.3)</td>
<td>17 (32.7)</td>
</tr>
<tr>
<td>Bipolar type II (25)</td>
<td>18 (72.0)</td>
<td>7 (28.0)</td>
</tr>
<tr>
<td>History of suicide attempt (30)</td>
<td>19 (63.3)</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>Lifetime substance Dep/abuse (36)</td>
<td>24 (66.7)</td>
<td>12 (33.3)</td>
</tr>
<tr>
<td>Current substance Dep/abuse (4)</td>
<td>2 (50.0)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>History psychosis (28)</td>
<td>17 (60.7)</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td>Rapid cycling previous year (7)</td>
<td>5 (71.4)</td>
<td>2 (28.6)</td>
</tr>
</tbody>
</table>

*Only female gender and history of affective switch are statistically related to ACID (*P*=0.02 and 0.005, respectively).
unreliable when the events (i.e., ACID) are few (i.e., <10) (Peduzzi et al., 1995). Viewed differently, the fraction of patients who did not develop ACID after receiving an antidepressant (85.2%) is significantly less that those who did not develop ACID without an antidepressant (98.2%, \( z = 2.01, P < 0.05 \) utilizing a test for proportional data [El-Mallakh et al., 1994]).

3. Discussion

The current study observed that about one in eight patients with bipolar depression will develop a chronic irritable dysphoric state after beginning antidepressant medication. However, while the risk of developing ACID was nearly 10 times higher among the patients prescribed antidepressants for an acute depressive episode (i.e., 14.8% of the antidepressant-treated patients versus 1.8% of those not receiving antidepressants), it was also true that approximately 85% of the patients treated with antidepressants did not develop a chronic irritable dysphoric state.

The risk of developing ACID was almost entirely related to a previous history of antidepressant-induced affective switch and female gender. Without these predisposing factors, there is no increase in the risk of developing ACID. It appears that other factors such as prior sensitization to the destabilizing effect of antidepressants may play a role (Altshuler et al., 1995; Goldberg and Whiteside, 2003).

ACID has been independently described by different investigators a generation apart (Akiskal et al., 1977; El-Mallakh and Karippot 2005). The original description in 1977 (Akiskal et al., 1977) was in first degree relatives of bipolar patients, suggesting that the risk of antidepressant-induced worsening might be shared by relatives of bipolar patients. ACID may explain why long-term antidepressant treatment is associated with more depressed days than avoidance of antidepressants (Bauer et al., 2005). ACID is a syndrome that has been previously defined as occurring in either type I or type II bipolar patients after prolonged antidepressant exposure. It manifests with the triad of irritability, dysphoria, and middle insomnia (El-Mallakh and Karippot, 2005). Almost always, it is associated with social or occupational dysfunction. The chronic nature of these symptoms distinguish ACID from the more episodic major depressive or mixed manic syndromes. Marked improvement in function and the ACID symptoms is seen with antidepressant discontinuation (El-Mallakh and Karippot 2005).

It is important to note that the current study was not designed to capture ACID symptomology. ACID symptoms were gleaned from the CMF data entered by the STEP-BD investigators. Furthermore, the original case series of ACID patients described an average duration of antidepressant treatment of 6.6 years (range 3–7 years) (El-Mallakh and Karippot 2005), in the current study we evaluated ACID symptoms after only one year of antidepressant treatment. The small sample, and the small number of patients with ACID may increase the likelihood of a biased regression coefficient (Peduzzi et al., 1995), thereby precluding sweeping conclusions regarding the effect of antidepressant treatment on the development of chronic irritable dysphoria. Stated simply, while the Cox proportional hazards model appears to be accurate, the analysis of confounding covariates is not reliable.

Additionally, it is not likely that past antidepressant-associated mood switch and female gender are simply confounding factors which negate the validity of ACID as a phenomenon. Rather re-exposure to antidepressants seems relevant with effect modification perhaps mainly in those with past antidepressant exposure (often females) and manic responses to them.

Depression in bipolar illness is a very important syndrome. It occupies a large fraction of the patients’ lives and is related to significant morbidity and mortality. Yet these are very few studies examining its treatment directly. Efficacy and safety of antidepressant treatment, particularly long-term treatment, in bipolar patients needs additional investigation.

Role of funding source

Funding for this project was provided by a grant and a contract from the NIMH. For the STEP-BD contract NIMH had input regarding safety issues in study design. NIMH did not dictate the design of data collection, management, or analysis.
Conflict of interest

No conflict declared.

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References


