Do Antidepressants Induce Rapid Cycling? A Gender-Specific Association

Aysegul Yildiz, M.D., and Gary S. Sachs, M.D.

Received March 26, 2002; accepted Nov. 7, 2002. From Dokuz Eylul Medical School, Department of Psychiatry, Izmir, Turkey (Dr. Yildiz); and Harvard Medical School, Massachusetts General Hospital, Bipolar Program, Boston (both authors).

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Corresponding author and reprints: Aysegul Yildiz, M.D., 9109 Sokak No. 12/6 Halil Nevzat Sen Apt. PK: 35370 Yesilyurt, Izmir, Turkey (e-mail: agul_yildiz@hotmail.com).

Objective: To investigate the influence of antidepressant use and gender in the genesis of rapid-cycling bipolar illness.

Method: The charts of bipolar patients treated at the Massachusetts General Hospital Bipolar Clinic (Boston, Mass.) were reviewed for gender, presence or absence of rapid cycling, and antidepressant use prior to first mania.

Results: Data were obtained for 129 bipolar patients (55% women), 45% of whom had experienced a rapid-cycling course. Overall, there was no significant difference in the rates of rapid cycling between the subjects who were exposed to antidepressants prior to their first manic/hypomanic episode and those who were not. Additional analysis carried out separately by gender found a significant association between rapid cycling and antidepressant use prior to first mania/hypomania for women but not for men. A logistic regression analysis with rapid cycling as dependent variable revealed a significant interaction between antidepressant use prior to first mania/hypomania and gender.

Conclusion: We found a gender-specific relationship between antidepressant use prior to first manic/hypomanic episode and rapid-cycling bipolar illness. When antidepressants are prescribed to depressed women who have a risk of bipolar disorder, the risk of inducing rapid cycling should be considered. Differing proportions of women and men in previous studies may account for conflicting results reported in the literature for the relationship of antidepressants and rapid cycling. However, this naturalistic trial was uncontrolled, and controlled research is required to confirm our findings.

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Rapid cycling has been included in the DSM-IV as a course specifier for bipolar mood disorders.[1] It is not known, however, what factors account for some bipolar patients' developing a rapid-cycling course. Risk factors include female gender, early age at onset, longer duration of illness, and use of antidepressant drugs.[2,3] Among these, use of antidepressant drugs is of critical importance since this factor can be controlled if needed. Therefore, we set out to determine whether the use of antidepressants is associated with the genesis of rapid cycling.

There have been various reports of association between antidepressants and rapid cycling. Kukopulos et al.[4] have found that the prevalence of rapid cycling has increased significantly since the introduction of antidepressant drugs. In their longitudinal study of 434 bipolar patients, Tondo et al.[5] reported that 40 out of 67 patients who became rapid cyclers had protracted use of antidepressants. Fujiwara et al.[6] reported that 20% of the rapid-cycling courses of bipolar patients were induced by antidepressants. Wehr et al.[7] reported that at the time of onset of rapid cycling, 73% of the 51 rapid-cycling bipolar disorder patients were taking antidepressant drugs and that the continuation of rapid cycling was associated with antidepressant drug therapy in 51% of the patients. Bauer et al.[8] reported that 20% of their rapid-cycling patients have developed rapid cycling within 2 weeks of reaching therapeutic doses of antidepressants. Altshuler et al.[9] reported that 35% of their patients had a manic episode possibly

induced by antidepressants, and cycle acceleration was found to be associated with antidepressant treatment in 26% of the patients assessed.

While these reports show variations in the rate of rapid cycling associated with antidepressant treatment, there are others challenging the view that antidepressants can precipitate rapid cycling. In a prospective study, Coryell et al.[10] noted that the use of antidepressants did not anticipate rapid cycling after statistical control for the presence of major depression. They comment that "major depression in context of a bipolar illness may anticipate a period of rapid cycling and provoke treatment with antidepressants leading to a falsely apparent causal connection between the 2 events."[10(p129)] Two large studies of prophylaxis in bipolar disorders[11,12] compared patients taking lithium and imipramine with those taking lithium only. In both studies, no statistically significant association between imipramine therapy and appearance of rapid-cycling course was observed. In brief, evidence implicating antidepressants in the genesis of rapid cycling is inconsistent.

In investigating the association between use of antidepressants and rapid cycling, there are several methodological concerns, which may have relevance to the inconsistency of available data. One concern regards the inconsistencies of defining rapid cycling as either present in the entire course of the previous illness or during a specific time of evaluation (e.g., the year before the study). There are a number of patients who, at one point in their clinical course, progress from regular cycling to rapid cycling and vice versa. Hence, if the study period is short, a tendency for rapid cycling may not be taken into account. By considering this issue, the present study is designed to define the rapid-cycling group by the subjects who meet the criterion for rapid cycling either currently or ever through the course of illness.

Another concern arises from the fact that the majority of the bipolar patients have been exposed to antidepressant drugs at some time during the course of their illnesses. Within the framework of long-term effects of antidepressant drugs,[13] particularly after discontinuation, it is a methodological problem to find antidepressant-naive patients when investigating cycle-accelerating effects of these drugs. In an attempt to overcome this concern, in this study we determined antidepressant use prior to first manic/hypomanic episode. Finally, although there appear to be significant gender differences in the course of bipolar illness (such as rapid cycling being more common in bipolar females[1–3] and psychotic bipolar males having an earlier age at onset[14]), none of the studies mentioned above systematically examined the possibility of gender influence on the relationship of antidepressant use and rapid-cycling course. Therefore, this study aims to investigate the relationship between rapid cycling, antidepressant use, and gender.

METHOD

The charts of all consecutive patients evaluated at the Massachusetts General Hospital (MGH) Bipolar Clinic (Boston, Mass.) in the years 1990 through 1999 were reviewed. Formal Structured Clinical Interview for DSM-IV (SCID)[15] diagnoses were made using the mood modules of the SCID. These diagnoses were not made retrospectively at the time of chart review, but prospectively by psychiatrists working at the MGH Bipolar Clinic with expertise in bipolar disorders at the time of the clinical interview. Subjects were included in the analysis if the chart documented the type of bipolar illness, the presence of rapid cycling either current or ever through the course of bipolar illness, and the presence or absence of antidepressant use prior to first manic/hypomanic episode, as well as gender. Rapid cycling was defined as 4 or more episodes (or 2 complete cycles) in a year as in DSM-IV. Patients who were diagnosed as bipolar not otherwise specified were excluded from the analysis, since evaluation of the rapid cycling can be valid only for bipolar I or bipolar II patients by definition in DSM-IV. Subjects with unreliable information for the presence or absence of rapid-cycling course and/or antidepressant use prior to first mania/hypomania were also excluded from the analysis.

Finally, to carry out further analysis of the data, we reviewed the charts for the type of first affective episode. Subjects were included in this secondary analysis only if the chart documented first affective episode sufficient for diagnosis of major depression or mania/hypomania.

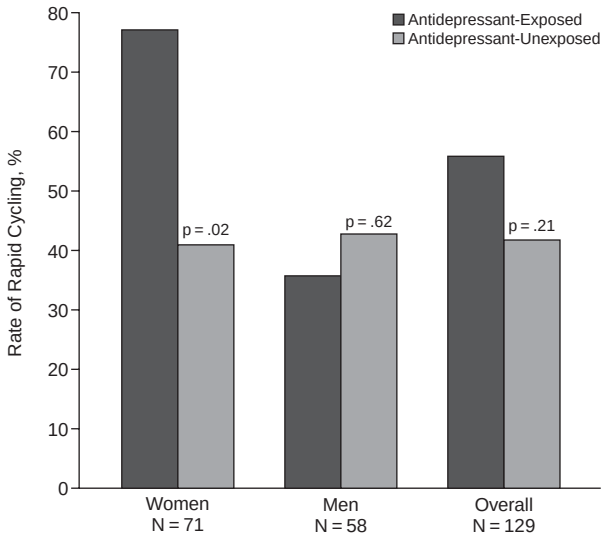
For identifying current or lifetime histories of rapid cycling, the presence of antidepressant use prior to first mania/hypomania, and the type of first affective episode, we reviewed the Affective Disorders Evaluation Form and Clinical Monitoring Form.[16] Both forms are routinely completed for each bipolar patient and include a modified version of SCID modules. Furthermore, we collect information on the presence of rapid-cycling course as well as on the history of antidepressant use. Data included in these assessment forms came from clinical interviews with the patient and from outside reports from the family or other sources, including hospital charts and previous physician records.

Massachusetts General Hospital Institutional Review Board approved the study. Statistical analysis of data was performed using the chi-square and logistic regression tests as appropriate. All reported p values are 2-sided. Significance level was set at $p < .05$.

RESULTS

Among the 476 charts evaluated, 129 documenting the type of bipolar illness, gender, and the presence or absence of rapid cycling and antidepressant use prior to first

Figure 1. Rates (%) of Rapid Cycling in Antidepressant-Exposed and Antidepressant-Unexposed Bipolar I and II Patients[a]



[a]Rates included current rapid cycling or rapid cycling ever through the course of illness. Antidepressant-exposed patients had a positive history of antidepressant use prior to first mania/hypomania. Antidepressant-unexposed patients had a negative history of antidepressant use prior to first mania/hypomania.

manic/hypomanic episode were included in the analysis. The sample was 55% female and comprised mainly bipolar I patients (89%) and a small number of bipolar II patients (11%). Overall, 45% (N = 58) of the sample had a positive lifetime history of rapid cycling, and 21% (N = 27) had a positive history of antidepressant use prior to the manifestation of first manic/hypomanic episode.

Overall, the rate of rapid cycling was 56% among the patients with a positive history of antidepressant use prior to first manic/hypomanic episode and 42% among the patients with a negative history of antidepressant use prior to first manic/hypomanic episode. This difference was found statistically insignificant ($\chi^2 = 1.549$, df = 1, p = .21). However, additional analysis carried out separately by gender found significance for women, but not for men. The rate of rapid cycling among the female bipolar patients who were exposed to antidepressants prior to their first manic/hypomanic episode was 77%, and the rate of rapid cycling among the female bipolar patients who were not exposed to antidepressants prior to their first manic/hypomanic episode was 41% ($\chi^2 = 5.376$, df = 1, p = .02). On the other hand, the rate of rapid cycling for the male bipolar patients who were exposed to antidepressants prior to first mania/hypomania was 36%, and the rate of rapid cycling for the male bipolar patients who were not exposed to antidepressants prior to first mania/hypomania was 43% ($\chi^2 = 0.244$, df = 1, p = .62) (Figure 1).

To examine the possibility of these findings being an epiphenomenon resulting from greater exposure of bipolar women to antidepressant medications, we investigated the frequencies of antidepressant use prior to first mania in men and in women. Analysis of the sample (N = 129) showed that 18% of the women and 24% of the men were exposed to antidepressants prior to first mania/hypomania, and the female-to-male ratio of the antidepressant-exposed group was 0.93 (13/14) ($\chi^2 = 0.655$, df = 1, p = .42).

To investigate if it is the type of first affective episode determining the rapid-cycling course, we investigated the association between the type of first affective episode and the history of rapid cycling. The type of first affective episode could frankly be identified for 118 among the original 129 subjects. In this sample, 37 women had a first episode of mania and 28 had a first episode of depression. For men, 22 of 53 had a first episode of mania. Overall, the rate of rapid cycling among the patients who experienced depression as the first affective episode was 46%, and the rate of rapid cycling among the patients who experienced mania/hypomania as the first affective episode was 39% ($\chi^2 = 0.555$, df = 1, p = .46). Further analysis of the sample by gender revealed no significant association between the type of first affective episode and the history of rapid cycling either for women or men. The rate of rapid cycling among the female bipolar patients who experienced depression as the first affective episode was 54%, and the rate of rapid cycling among the female bipolar patients who experienced mania/hypomania as the first affective episode was 38% ($\chi^2 = 1.597$, df = 1, p = .21). The rate of rapid cycling among the male bipolar patients who experienced depression as the first affective episode was 39%, and the rate of rapid cycling among the male bipolar patients who experienced mania/hypomania as the first affective episode was 41% ($\chi^2 = 0.026$, df = 1, p = .87).

For investigating the interaction of antidepressant use prior to first mania/hypomania and gender, which was suggested by the univariate analyses in the genesis of rapid cycling, we carried out a logistic regression analysis. Rapid cycling was the dependent variable in the model that includes the type of first affective episode, antidepressant use prior to first mania/hypomania, gender, and the interaction variable between the last 2; this analysis revealed a significant interaction between antidepressant use prior to first mania/hypomania and gender ($\beta = 2.018$, odds ratio = 7.52, p = .04).

DISCUSSION

Present data suggest a gender-specific relationship of rapid cycling and antidepressant use in patients with bipolar illness: bipolar women who were exposed to antidepressant drugs before their first manic/hypomanic episode

had higher rates of rapid cycling than women who were not, whereas there was no such association in bipolar men.

One possible explanation of our findings could be greater use of antidepressants among bipolar women.[17] However, our analysis revealed no significant difference in the frequency of antidepressant use prior to first manic/hypomanic episode between bipolar women and bipolar men. It has been reported that rapid-cycling bipolar patients frequently experience depression as the first affective episode, which may anticipate a period of rapid cycling, provoke treatment with antidepressants, and thereby lead to a falsely apparent causal connection between the 2 events.[7,10] To investigate this possibility, we examined the association between rapid cycling and the type of first affective episode. Contrary to this view, our analysis found no significant association between the 2 events, neither for the population in general nor separately by gender. Consistently, after statistical control for presence of depression as a first affective episode, antidepressant use prior to mania/hypomania, and gender, none of these factors except the interaction between gender and antidepressant use prior to first mania/hypomania was significant in the genesis of rapid cycling. Of course, it still remains possible that the number and type of the episodes as well as timing of antidepressant use have an influence on the subsequent likelihood of rapid cycling, but our limited data do not allow any inference regarding these questions. For instance, we do not know what alterations antidepressants make in bipolar brains and how long these effects last. An ideal clinical study answering these questions would indeed necessitate antidepressant-naive bipolar patients (with a negative history of rapid cycling and similar episode patterns) who would prospectively be assigned to antidepressant treatment in a randomized controlled manner for a certain duration and followed up for the genesis of rapid cycling through the course of antidepressant treatment as well as after the discontinuation. However, designing such a study is difficult given the practical and ethical concerns.

As we found an association between antidepressant use prior to first mania and rapid cycling in women, one would expect women whose first episode is depressive to be more likely than those whose first episode is manic to develop rapid cycling. However, our secondary analysis showed that this is not the case. This finding may reflect the fact that some of the women who had a depressive episode first did not receive treatment.

The present findings suggest that female bipolar patients may be more susceptible than male bipolar patients to cycle-accelerating effects of antidepressants. In previous studies, different proportions of women and men may account for conflicting results reported in literature for the relationship of antidepressants and rapid cycling.

Although several investigators have discussed the likelihood of bipolar women to be at increased risk for antidepressant-induced rapid cycling,[7,9,18,19] ours is the first report investigating this issue systematically. However, it remains to be determined what makes bipolar women more vulnerable to cycle-accelerating adverse effects of antidepressant drugs. In general, sex differences in psychiatric disorders are accounted for by the effects of gonadal steroids on the brain development and/or function.[17] There is some evidence suggesting such a contribution of gonadal steroids on the pathogenesis of mood cycling through their effects on circadian rhythms, by changing the rate and frequency of oscillations in biological systems.[17,20–22]

While there are limitations to a retrospective study, this naturalistic study represents the course of bipolar illness in actual clinical practice for a relatively long period and assesses the relationship between rapid cycling, antidepressant use, and gender by addressing some of the previous methodological concerns. As this study was conducted in a referral center and an outpatient clinic, we do not know to what extent our patients represent the bipolar population in general. However, as far as severity of illness is concerned, these 2 factors (i.e., a referral center and being an outpatient clinic) most likely have opposing effects and therefore may mitigate or even cancel each other.

In an attempt to overcome confounding caused by the long-term effects of antidepressants and antidepressant-induced switch in precipitating cycling, we chose to examine antidepressant use prior to first mania/hypomania. Such an approach, however, leads to the assumption that if a patient never had a manic episode prior to antidepressant use, and rapid cycling developed at any point after the use of antidepressants, then the patient has antidepressant-induced rapid cycling. Conversely, if a patient had a manic episode prior to antidepressant use and then rapid cycling developed subsequently, the antidepressant use and rapid cycling seem to be unrelated. Whether these assumptions represent the reality is yet to be elucidated in future studies. However, it may be the case that there are a number of cumulative factors interacting with each other to provoke either a predisposition toward or an actual appearance of rapid cycling. The present findings indicate that the interaction of female gender and antidepressant use prior to first mania/hypomania represents one of these factors, but not necessarily the only one. There may be a structural tendency to develop rapid cycling, and depending on the severity of such tendency, female gender and antidepressant exposure may interact with each other to rouse actual expression of rapid cycling. In addition, it is possible that timing of the antidepressant exposure (such as upon a stressful life event or at some point in the early/middle/late phases of the illness) may act as another factor that plays a role in the genesis of rapid cycling.

In conclusion, a gender-specific relationship between antidepressant use prior to first manic/hypomanic episode and rapid-cycling bipolar illness was found. When antidepressants are prescribed to depressed women who have a

risk of bipolar disorder, the risk of inducing rapid cycling should be considered. Previous studies investigating the influence of antidepressant drugs individually as well as in general in precipitating rapid cycling should be re-evaluated by controlling for gender. Naturalistic retrospective studies, such as this one, are subject to recall bias. Yet they are still useful in providing evidence with real-world samples that are often excluded from controlled research studies. Nonetheless, controlled research of the matter with carefully planned methodology reflecting on the exceptional aspects of rapid cycling is needed.

Drug name: imipramine (Tofranil and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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