ORIGINAL ARTICLE

Antidepressant treatment-emergent affective switch in bipolar disorder: a prospective case-control study of outcome

Ciclagem afetiva associada a tratamento com antidepressivo no transtorno bipolar: estudo caso-controle prospectivo

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Abstract

Objective: *Treatment-emergent affective switch has been associated to cycle acceleration and poorer outcome, but there are few studies addressing this issue. The aim of this study was to prospectively compare the outcome of patients presenting treatment-emergent affective switch with patients with spontaneous mania, regarding presence and polarity of a new episode and time to relapse.* ***Method:*** *Twenty-four patients with bipolar disorder according to the DSM-IV were followed for 12 months. Twelve patients had treatment-emergent affective switch and twelve had spontaneous mania. Patients were evaluated weekly with the Young Mania Rating Scale and the Hamilton Depression Scale until remission of the index episode, and monthly until completion of the 12-month follow-up.* ***Results:*** *Eleven patients with treatment-emergent affective switch had a recurrence on follow-up, all of them with major depressive episodes. In the group with spontaneous mania, six patients had a recurrence: two had a depressive episode, and four had a manic episode ($p = 0.069$ for new episode, $p = 0.006$ for polarity of the episode). Patients with treatment-emergent affective switch relapsed in a shorter period than patients with spontaneous mania ($p = 0.016$).* ***Conclusions:*** *In this first prospective study, treatment-emergent affective switch patients were at greater risk of relapses, especially depressive episodes, and presented a shorter duration of remission when compared with patients with spontaneous mania.*

Descriptors*: Bipolar disorder; Clinical protocol; Antidepressive agents; Treatment outcome; Affective symptoms*

Resumo

Objetivo: *A ciclagem para mania associada ao antidepressivo tem sido relacionada à aceleração do ciclo e pior evolução, mas há poucos estudos na literatura sobre este assunto. O objetivo deste estudo foi comparar prospectivamente a evolução de pacientes com mania associada a antidepressivo com pacientes com mania espontânea, em relação a tempo para recaída e polaridade do novo episódio.* ***Método:*** *Vinte e quatro pacientes com transtorno bipolar, de acordo com os critérios diagnósticos do DSM-IV, foram seguidos por 12 meses: 12 pacientes com mania associada a antidepressivo e 12 pacientes com mania espontânea. Os pacientes foram avaliados semanalmente com a Escala para Mania de Young e a Escala para Depressão de Hamilton até remissão do episódio inicial e, mensalmente, até completar o período de seguimento de 12 meses.* ***Resultados:*** *Onze pacientes com mania associada ao antidepressivo tiveram uma recorrência no seguimento, sendo todos os episódios depressivos. No grupo de mania espontânea, seis pacientes apresentaram recorrência, sendo dois episódios depressivos, e quatro episódios de mania ($p = 0,069$ para novo episódio e $p = 0,006$ para polaridade do episódio). Pacientes com mania associada a antidepressivo recaíram em um menor período de tempo que os pacientes com mania espontânea ($p = 0,016$).* ***Conclusões:*** *Neste estudo prospectivo, os pacientes com mania associada a antidepressivo apresentaram maior risco de recorrência, especialmente episódios depressivos, e com menor duração de remissão quando comparados aos pacientes com mania espontânea.*

Descritores: *Transtorno bipolar; Protocolos clínicos; Antidepressivos; Resultado do tratamento; Sintomas afetivos*

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Financing: Fundação de Amparo à Pesquisa do Estado de São Paulo (# 99/02079-4).
Conflict of interests: None
Submitted: July 13, 2006
Accepted: August 1, 2006

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Introduction

Antidepressants have been associated with induction of mania and cycle acceleration. Case series and observational studies report an incidence of induction of mania between 0 to 94.5% depending on the study design and class of the antidepressant utilized.[1-5] Controlled studies have suggested that treatment-emergent affective switch (TEAS) is less severe than spontaneous mania.[6-7] Furthermore, the severity of mania may be associated with the class of the antidepressant utilized.[8]

Antidepressants may also change the course and outcome of bipolar disorder. Many authors have observed and reported the induction of cycle acceleration and rapid cycling after antidepressant use, with a rate ranging from 2 to 67%.[9-12]

Kukopulos et al. followed 434 bipolar patients, from which 115 (26.5%) presented a continuous course, without periods of euthymia. From this group, 59 patients (51%) had this course changed after using an antidepressant.[11] In another study, Kukopulos et al. observed that patients who experienced antidepressant-induced rapid cycling had an increase in the frequency of episodes from 0.8 per year to 6.5 per year.[13] Pickar et al. suggested that antidepressants could modify the course of the disorder by sensitization, that is, the exposure to an antidepressant would make the patient more sensitive to the next exposure to an antidepressant.[14]

There is only one prospective and controlled study about cycle acceleration, published by Wehr et al. in 1988.[12] The authors followed 51 patients who were their own controls. In this study, half of the patients presented with rapid cycling and the investigators concluded that the cycling persisted because of the use of tricyclic antidepressants. Some patients had antidepressant-associated mania, and within weeks they had a depressive relapse, although they were still taking antidepressants.

Altshuler et al. suggested that TEAS may be a marker for a greater vulnerability to cycle acceleration induced by antidepressants.[15] They retrospectively analyzed the life charts of 51 bipolar refractory patients and observed that 46% of the patients with antidepressant-associated mania and 14% with spontaneous mania presented with cycle acceleration. In this study, cycle acceleration was associated with younger age at first treatment, and was more likely to occur in women and bipolar II patients.

Other risk factors have been implicated in antidepressant-induced cycle acceleration: female gender, patients with predominantly manic episodes, previous history of rapid cycling, cyclothymic temperament, bipolar disorder type I, and hypothyroidism.[11,16-21] It is important to note that those studies were open and retrospective.

These studies suggest that antidepressants can induce cycle acceleration in patients with bipolar disorder and in some cases of rapid cycling. As most of the studies were open, retrospective and non-controlled, the results must be carefully considered.

In this report, we prospectively followed patients with spontaneous mania and antidepressant-associated mania to compare the risk, polarity, and timing of mood relapses. To the best of our knowledge, this is the first prospective case-control study of the outcome of patients with treatment-emergent mania.

Method

Twenty-four patients with bipolar disorder according to DSM-IV were divided into two groups: 12 consecutively admitted patients with spontaneous mania and 12 consecutively admitted patients with antidepressant-induced mania. Patients were recruited from the Bipolar Disorder Research Program at the Institute of Psychiatry of Universidade de São Paulo Medical School.

Inclusion criteria were patients between 18 and 60 years of both genders with bipolar disorder according to the DSM-IV,[22] with a manic, hypomanic or mixed episode, and a Young Mania Rating Scale (YMRS)[23] index score of 12 points or more. Patients with rapid cycling in the last year according to the DSM-IV, current diagnosis of abuse and/or addiction to alcohol or drugs, or organic cerebral disease were excluded.

Patients with antidepressant-associated mania were included only if they had received an antidepressant for at least three consecutive days within the previous two weeks. Patients with spontaneous mania were included if they had not received antidepressants in the preceding two months.

The diagnosis was made using the Structured Clinical Interview for the DSM-IV, Patient Version (SCID-P). Twenty-four subjects were rated with the YMRS and the Hamilton Depression Scale (HAM-D).[24] Response to treatment was defined as a 50% reduction in the YMRS index score and remission as a score of 6 or less on the YMRS. Patients were evaluated once a week until remission and monthly thereafter.

During follow-up, it was considered a new episode when it occurred after a period of at least two months of euthymia. Mania, hypomania, depression or mixed episodes were diagnosed according to the DSM-IV plus a score of 12 or more on the YMRS for a manic or hypomanic episode, 16 or more on the HAM-D for a depressive episode, and both scores for a mixed episode.

Data was analyzed using the SPSS software version 10.0 (Statistical Package for the Social Science). Chi-square or Fisher's exact tests were used to compare categorical data. All p values were based on two-tailed tests with a significance level of 0.05. Time to relapse was analyzed using Kaplan-Meyer Survival analysis and log-rank test.

This study was approved by the Ethic Commitee of the Hospital das Clínicas of the Universidade de São Paulo Medical School (process number 188/99).

Results

Patients with TEAS were older, had a longer duration of illness, more previous episodes, higher prevalence of subclinical hypothyroidism, and reported more previous episodes of mania associated with antidepressant use. TEAS was less severe, with a lower incidence of psychotic symptoms, a lower YMRS index score, and rarely required hospitalization. The interval from intervention to response and remission was similar in both groups. These baseline results were reported in detail elsewhere.[7]

All 24 patients had bipolar disorder, 23 had type I, and one had type II. Twenty-two patients had had at least one previous episode of depression. Eight patients with spontaneous mania and one patient with antidepressant-associated mania required hospitalization. Criteria for discharge from the hospital were not standardized. Patients with TEAS presented manic symptoms in average 12 weeks after starting an antidepressant (range: 3-26 weeks). The antidepressants used were sertraline (n = 4), venlafaxine (n = 1), fluoxetine (n = 2), paroxetine (n = 4), nortryptiline (n = 1), imipramine (n = 1), and amitryptiline (n = 1). Antidepressants were stopped in all patients with antidepressant-associated mania. Two patients

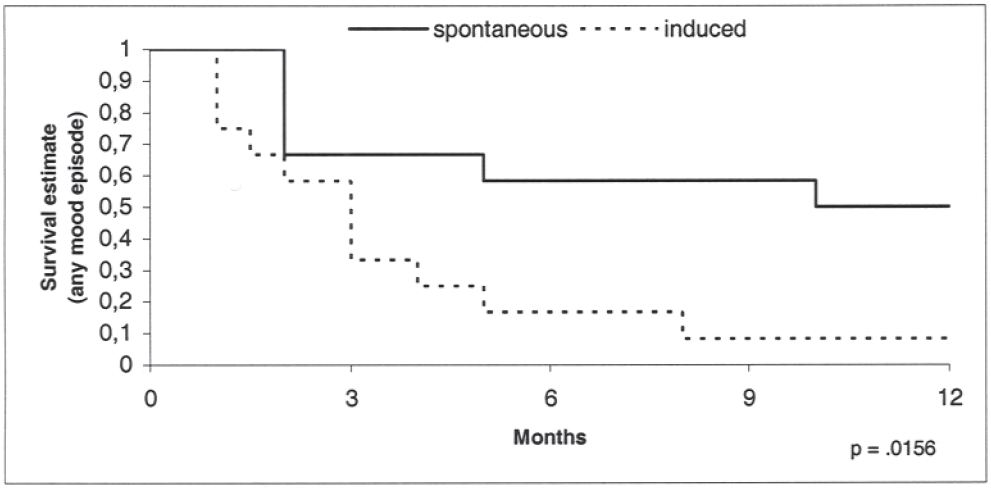

Figure 1 – Survival estimate of any mood episode

were receiving only antidepressants in the index episode and a mood stabilizer was introduced during their treatment. Nine patients received a combination of two antipsychotics and four received a combination of two mood stabilizers.

During follow-up, six patients in the group with spontaneous mania had a new episode: four had a manic episode and two had a depressive episode. In the TEAS group, 11 patients had a new depressive episode. Although the proportion of patients who had a new episode in each group did not reach statistical significance ($p = 0.069$), there was a significant difference between groups for polarity of the new episode ($p = 0.006$).

Kaplan-Meyer method and log-rank test indicated that patients with TEAS had significantly shorter duration of remission compared to patients with spontaneous mania ($p = 0.016$) (Figure 1).

Four patients in the TEAS group had cycle acceleration after the index episode and met criteria for rapid cycling. No patients presented rapid cycling during follow-up in the spontaneous mania group ($p = 0.093$ – Fisher's Exact Test).

Discussion

Our study suggests that patients with TEAS have a poorer outcome, a higher rate of recurrence and a shorter duration of remission when compared to patients with spontaneous mania. These findings are in agreement with a study by Kukopulos et al.,[13] who observed an increased number of episodes after antidepressant use. Altshuler et al. observed that 46% of the patients with antidepressant-associated mania presented cycle acceleration. In our study, 33.3% developed rapid cycling.[15]

All patients with TEAS were discontinued from antidepressants and experienced a depressive relapse some weeks later. This relapse could be associated with early antidepressant discontinuation, or it may be due simply to a greater severity of the illness of TEAS patients. Altshuler et al. suggested that early antidepressant discontinuation is associated with a fourfold increase in the risk of depressive relapses in some patients with bipolar disorder type I.[25] Ghaemi et al. suggest that antidepressants should be maintained only in those who repeatedly relapse after antidepressant discontinuation, a minority that they estimate represents 15-20% of bipolar depressed patients.[26] However, in our study these patients represented the majority of cases of TEAS (66.7% of the patients presented previous TEAS).

Although the impact and necessity of antidepressants in the treatment of bipolar patients have been largely discussed, there is still no agreement about their use.[27-28] Some authors suggest that antidepressants may destabilize mood and should be used only in severe depression,[29] while others believe that treatment guidelines are too restrictive concerning the use of antidepressants in bipolar patients.[30]

Our study has limitations. The small sample may limit the generalization of the data, although it is important to note that, even with this small sample, significant differences were found between the groups. Patients were assigned to each outcome group on a non-random basis. Medication use was not controlled. Nevertheless, our study is unique in comparing prospectively antidepressant-associated mania and spontaneous mania during a 12-month follow-up.

Acknowledgements

Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP (# 99/02079-4) provided a two-year scholarship to the corresponding author.

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