Variables as Mediators or Moderators in Predicting Relapse to Any Type of Mood Episode in a Bipolar Maintenance Study

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ABSTRACT

Objective: Post hoc mediator/moderator analyses were designed to identify risk factors and their relationships in predicting relapse in olanzapine- or lithium-treated bipolar patients with an index manic or mixed episode. The aim was to identify moderators that precede and influence other variables to affect relapse and mediators that explain how or why a second variable affects relapse.

Method: We examined *DSM-IV*–diagnosed bipolar I disorder patients who met symptomatic remission criteria of an index manic or mixed (6.3%) episode after acute (6–12 weeks), open-label, combined therapy with olanzapine (5–20 mg/d; mean dose = 13.5 mg/d) plus lithium (300–1,800 mg/d; mean dose = 1,003.3 mg/d) followed by double-blind randomization to lithium (n = 214) or olanzapine (n = 217) for up to 52 weeks. The study started on August 5, 1999, and finished on June 14, 2002. Mediator/moderator analyses with α cut at .05 were used to understand how variables work together to impact rate of relapse.

Results: For lithium-treated patients, variables identified for relapse were country of residence, smoking status, previous episode history, and previous lithium use. For olanzapine-treated patients, risk factors included smoking status, previous episode history, amount of time patients had a 21-Item Hamilton Depression Rating Scale (HDRS-21) score ≤ 8 at pre-randomization, and HDRS-21 score at randomization. For lithium-treated patients, no mediators/moderators were identified among relapse variables. For olanzapine-treated patients, several baseline variables—such as previous number of mood episodes (manic or depressive)—operate through severity of depressive symptoms prior to remission (mediator) to affect relapse rate. On the other hand, the effect of the patient's pre-remission depressive symptoms on outcome is moderated by the polarity of the first episode, whether manic, depressive, or mixed.

Conclusions: Mediators and moderators may provide valuable information in the treatment planning of patients with bipolar disorder and potentially influence treatment outcomes.

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Bipolar disorder is a severe mental illness characterized by repeated relapses of mania, depression, or mixed episodes. Recurrence is frequent even after a first episode, and rates of recurrence can reach 51% at 1 year and 23% more at 4 years in multiple episodes.[1,2] Lithium and olanzapine have been shown to be effective for the treatment of acute manic episodes and for the long-term prevention of relapse, but a significant number of patients continue to experience relapse despite ongoing treatment.[3,4] In a randomized, double-blind, 12-month clinical trial[5] of olanzapine versus lithium in the prevention of relapse/recurrent mood episode (manic, mixed, or depressive), patients with an index manic or mixed episode were stabilized on a combination of olanzapine and lithium. No statistically significant differences were observed between olanzapine-treated patients and lithium-treated patients on risk of symptomatic overall relapse (any mood episode). However, olanzapine-treated patients had a significantly lower risk of symptomatic relapse to manic and mixed episodes. The goal of these post hoc analyses is to identify potential variables and their relationships in predicting relapse in olanzapine-treated or lithium-treated bipolar mania/mixed patients using mediator/moderator analyses.

Moderators and mediators are both variables. According to classical Baron and Kenny guidelines,[6] moderator variables specify when certain effects will hold, while mediators speak to how or why such effects occur. On the other hand, according to MacArthur guidelines,[7,8] to be considered a moderator, a variable must precede and influence other variables to affect outcome, and a mediator should explain how or why a second variable affects the outcome. In this study, we identify variables related to relapse to any mood episode in bipolar patients with an index manic or mixed episode and the relationship among these variables (ie, which moderators precede and influence other variables to affect relapse to any mood episode and which mediators explain how or why another variable affects the relapse to any mood episode) using the method recommended by the MacArthur group.[7,8]

METHOD

We examined a total of 431 *DSM-IV*–diagnosed bipolar I disorder patients who met symptomatic remission criteria of an index manic or mixed (6.3%) episode after acute (6–12 weeks), open-label, combined therapy with olanzapine (5–20 mg/d; mean dose of 13.5 mg/d) plus lithium (300–1,800 mg/d; mean dose of 1,003.3 mg/d) followed by double-blind randomization to lithium (n = 214) or olanzapine (n = 217) monotherapy for up to 52 weeks. Details on the design and outcome of the study have been published elsewhere.[5] The study started on August 5, 1999, and finished on June 14, 2002. Symptomatic remission was defined as having a Young Mania Rating Scale (YMRS)[9] total score ≤ 12 and a 21-Item Hamilton Depression Rating Scale (HDRS-21)[10] total score ≤ 8, and symptomatic relapse of bipolar

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Clinical Points

- Identification of variables as mediators or moderators is important for the prediction of relapse and may aid in the selection of specific treatments.
- Identification of mediators and moderators may provide valuable information in the treatment planning of patients with bipolar disorder. Each mediator or moderator should also be taken into account when planning personalized treatment for bipolar disorder patients in order to reduce the risk of relapse to any mood episode.

disorder was defined as having symptomatic relapse of either mania or depression. In addition, symptomatic relapse of mania was defined as reaching a YMRS total score of 15 or greater after having met the criteria for symptomatic remission, and symptomatic relapse of depression was defined as reaching an HDRS-21 total score of 15 or greater after having met the criteria for symptomatic remission.[11]

The candidate variables evaluated for relapse to any mood episode for both lithium- and olanzapine-treated patients included weight gain from screening to end of open-label phase, age (years), gender (male), country of residence (developed countries [Austria, Australia, Belgium, Canada, Switzerland, Germany, Denmark, Finland, Great Britain, Ireland, Italy, Netherlands, Norway, New Zealand, and Sweden] versus developing countries [Bulgaria, Czech Republic, Croatia, Hungary, Israel, Lithuania, Poland, Romania, Russia Federation, Slovenia, Slovakia, Turkey, and South Africa]), onset age of bipolar disorder (first symptoms of mania, depression, or both), polarity of first episode (whether the first episode is manic, depressive, or mixed), age at onset for different first episode polarity types, years of illness, previous episode history (total number of previous mania episodes lifetime/past 12 months, number of episodes lifetime/past 12 months), number of episodes per year, previous lithium use, previous valproate use, previous hospitalization, smoking status (each patient's smoking history was assessed by measuring the average number of cigarettes, cigars, and pipes smoked daily), substance abuse, type of mania (mixed or pure), severity of depressive symptoms throughout pre-randomization period (ie, time to achieve HDRS-21 score ≤ 8 plus time with HDRS-21 score ≤ 8 before randomization), depressive symptom improvement during pre-randomization, HDRS-21 score at randomization, and YMRS score at randomization. In this study, we adopted the criteria defined by the United Nations (UN) to classify a country as "developing" or "developed." The UN classifies the countries according to the Human Development Index,[12] which measures the average achievements in a country based on 3 dimensions: a long and healthy life, knowledge, and a decent standard of living. The UN classification also considers quality of medical practice as one of the criteria for classification.

Figure 1 shows the candidate variables arranged chronologically. The variables associated with relapse to any mood episode were identified by using Spearman correlation test ($P < .05$). The specific variable candidates selected at study entry were chosen because they were the only ones identified at the time. The variable candidates from the open-label treatment phase were selected based on efficacy of treatment (lithium + olanzapine). Our analyses did not identify variables other than those shown in Figure 1.

Mediators and moderators were identified based on results from the logistic regression model, correlation of the variables and the chronological order of the variables, according to the guidelines defined by the MacArthur group.[7,8] Analytic criteria are used to empirically demonstrate whether an eligible variable actually functions as a moderator or mediator. Mediator/moderator analyses with α cut at .05 were used to identify mediators and moderators among the variables identified by Spearman correlation test.

RESULTS

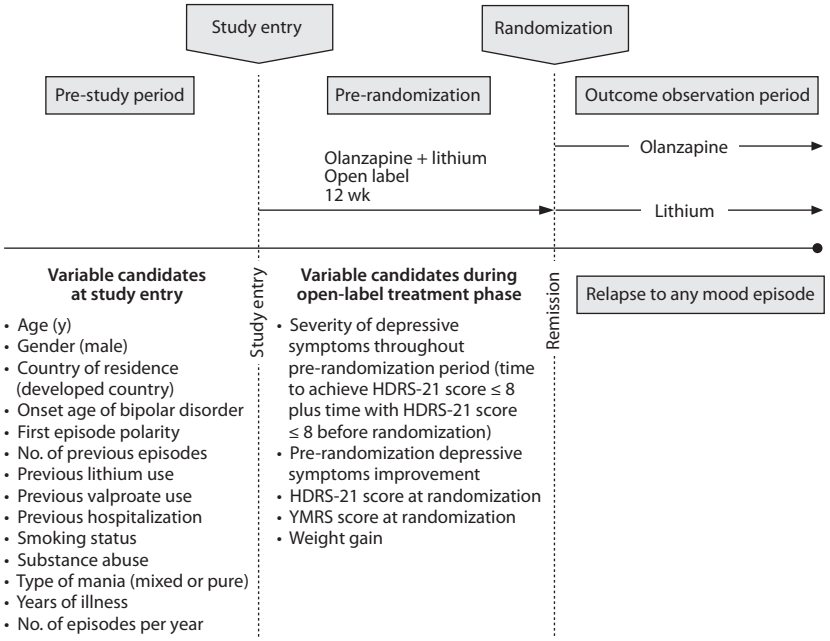
Baseline Characteristics of Patients

At baseline, 93% of the patients had a manic index episode, and 26% were experiencing psychotic features. Among patients randomly assigned to a treatment condition, 72.2% were hospitalized for treatment of their index episode at the time they entered into the open-label cotreatment phase (lithium = 74.8%; olanzapine = 69.6%). Both treatment groups were comparable for demographic and clinical characteristics as described elsewhere.[5]

Identification of Variables Associated With Prediction of Relapse to Any Mood Episode

For lithium-treated patients, the variables identified for relapse to any mood episode were country of residence ($r = 0.2106$, $P < .005$), smoking status ($r = 0.1567$, $P < .05$), previous episode history (total number of previous mania episodes lifetime and past 12 months and number of episodes lifetime and past 12 months all had a significant or borderline significant correlation with outcome, but only the statistics for total lifetime number of previous episodes are shown here: $r = 0.1703$, $P < .05$), and previous lithium use ($r = 0.1419$, $P < .05$). Positive r indicates positive association between the variable and relapse to any mood episode. For olanzapine-treated patients, the variables identified included smoking status ($r = -0.2347$, $P < .0005$), previous episode history (again, several measures of the previous number of episodes were significantly or borderline significantly associated with outcomes of interest; only the statistics for total lifetime number of previous episodes are presented here: $r = 0.1541$, $P < .05$), length of time that patients stay in HDRS-21 score ≤ 8 stage at pre-randomization ($r = -0.1652$, $P < .05$), and HDRS-21 score at randomization ($r = 0.1460$, $P < .005$). Our findings show that among olanzapine-treated patients, smokers are less likely to relapse to any mood

Figure 1. Study Design of Olanzapine Versus Lithium in Relapse Prevention in Bipolar Disorder



Abbreviations: HDRS-21 = 21-Item Hamilton Depression Rating Scale, YMRS = Young Mania Rating Scale.

episode ($r = -0.2347$), indicating that the more olanzapine-treated patients smoke, the less they will relapse to any mood episode.

Identification of Mediators and Moderators Associated With Prediction of Relapse to Any Mood Episode

Mediator/moderator analyses with α cut at .05 were used to understand how the variables work together to impact rate of relapse to any mood episode. For lithium-treated patients, no mediators and moderators were identified among the variables associated with prediction for relapse to any mood episode. In olanzapine-treated patients, the baseline variables identified as variables for relapse were smoking status, type of first episode, amount of time patients had an HDRS-21 score ≤ 8 at the stabilization of mania period (pre-randomization), and HDRS-21 score at time of randomization. Several baseline variables from patient histories were identified as mediators or moderators. For example, the effect of previous number of bipolar episodes (manic/depressive) on the relapse rate was mediated by the severity of depressive symptoms prior to remission (Table 1). In other words, patients who had less severe depressive symptoms showed lower rates of relapse than those with the same number of previous episodes but with more severe depressive symptoms. We also found that the effect of the patient's pre-remission depressive symptoms on outcome was moderated by polarity of the first episode, whether manic, depressive, or mixed (Table 1). This means that patients whose first episode was mania were more likely to relapse given the same depressive score prior to randomization. In addition, depressive symptoms mediated the effect of number of previous episodes on relapse rate.

DISCUSSION

To our knowledge, this is the first study to apply a mediators-and-moderators approach to identify predictors of relapse in patients with bipolar disorder in a controlled relapse-prevention clinical trial. The common variables for relapse to any mood episode for both lithium- and olanzapine-treated patients include smoking status and previous episode history. Smoking is a well-known variable that contributes to poorer outcomes for both physical and mental health.[13] The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) has shown that smoking was associated with more lifetime depressive and manic symptoms as well as greater severity,[14] suggesting that smoking cessation may be an integral component of the treatment regimen of patients with bipolar disorder. However, our findings show that smokers among olanzapine-treated patients are less likely to relapse to any mood episode. It is still unclear why smoking status had a protective effect on olanzapine-treated patients after treatment with olanzapine-lithium followed by remission, and further studies are needed to explore this finding.

No mediators or moderators were identified in lithium-treated patients after remission, while in olanzapine-treated patients after remission, the severity of depressive symptoms prior to remission was identified as a mediator for the effect of previous number of bipolar episodes on relapse rate. In other words, the relapse rates of those patients who have less severe depressive symptoms are lower than those of patients with the same number of previous episodes. In addition, for olanzapine-treated patients, the polarity of the first episode was identified as a moderator of the effect of patients' pre-randomization depressive symptoms on relapse rate. This means that patients whose first episode was mania were more likely to relapse given the same depressive score prior to randomization.

Recurrence in patients with bipolar disorder is common,[1,2,15] and preventing recurrence/relapse is essential. Previous studies have shown a higher rate of manic/mixed recurrence associated with a greater number of prior manic or mixed episodes in patients with bipolar I disorder.[1,15] Olanzapine-treated patients that presented fewer previous numbers of bipolar episodes (manic or mixed) were associated with an overall lower rate of manic or mixed recurrence when compared to lithium-treated patients,[15] which supports the previous number of bipolar episodes as an important variable that can affect the recurrence/relapse rate. In addition, the number of previous mixed mood episodes was shown to be a predictor of functional impairment in patients with bipolar disorders.[1,16]

Table 1. Mediators and Moderators for Relapse to Any Type of Mood Episode in Olanzapine-Treated Patients as Identified by MacArthur Analytic Criteria[a]

		Eligibility		Analysis		
Variable 1	Variable 2	Variable 1 Precedes Variable 2?	Association Between Variables 1 and 2 (*P* value)	Interaction Between Variables 1 and 2 (*P* value)	Main Effect of Variable 2 (*P* value)	Conclusions
Total no. of episodes—lifetime	Time in depressive remission before randomization	Yes	.002	.618	.031	Variable 2 mediates variable 1
Total no. of episodes—past 12 mo	Difference in time to remission (mania or depression)	Yes	.023	.294	.037	Variable 2 mediates variable 1
First episode polarity: mania	Time in depressive remission before randomization	Yes	.526	.045	.002	Variable 1 moderates variable 2
Previous mania episodes—past 12 mo	Difference in time to remission (mania or depression)	Yes	.590	.045	.012	Variable 1 moderates variable 2

[a]Criteria described in Kramer et al.[7,8]

The severity of depressive symptoms prior to remission was the only significant mediator identified. Residual depressive symptoms have been consistently associated with poor functioning.[17] Presence of depressive symptoms during manic episodes may also be associated with poor response to psychopharmacologic treatments, and even a modest level of pretreatment depression-related symptoms can be considered predictor of lithium nonresponse.[18] In this study, we found that the previous number of mood episodes (which are shown to be a variable associated with recurrence/relapse) work through the severity of depressive symptoms prior to remission (mediator) to affect rate of relapse to any mood episode. Predominant polarity characterized by more depressive than manic episodes is known to be associated with poorer responses to treatment of acute bipolar depression, particularly in men.[19] Moreover, the polarity of the first episode (whether the patient's first episode was manic, depressive, or mixed) was identified as the only moderator to influence the pre-randomization depressive symptom improvement in predicting relapse to any mood episode. Indeed, patients with a depressive onset are known to experience a higher number of depressive relapses and present an outcome characterized by chronicity and cyclicity.[20] Taken together, these findings suggest that identifying mediators and moderators in the course of illness can provide valuable clinical as well as nosologic information. However, in order to compare our results to other studies, definitions of outcome should become standard.[11]

We applied the new MacArthur model instead of the traditional Baron and Kenny model to identify the mediators and moderators among the variables.[8] The MacArthur model imposes the eligibility criterion of temporal precedence for moderation: a moderator variable 1 must precede variable 2. In this study, the polarity of the first episode is a variable 1 (moderator) that precedes pre-randomization depressive symptom improvement (variable 2), and the moderator influences pre-randomization depressive symptom improvement (variable 2) to affect the relapse to any mood episode (outcome). There was also no association between the polarity of the first episode (moderator) and pre-randomization depressive symptom improvement (variable 2). Moreover, the analytic criteria for mediation should include association between the number of previous bipolar episodes (variable 1) and severity of depressive symptoms prior to remission (variable 2), and the interaction between variable 1 and variable 2 is indicative of mediation and not moderation. In summary, an interaction between the polarity of the first episode (variable 1) that precedes pre-randomization depressive symptom improvement (variable 2) indicates moderation, whereas an interaction between an associated number of previous bipolar episodes (variable 1) and the severity of depressive symptoms prior to remission improvement (variable 2) indicates mediation. In this study, by identifying a patient's disease history as a moderator of the first episode's polarity on relapse to any mood episode rate, the clinician can determine possible outcomes and in some cases the best treatment option to prevent relapse to any mood episode for patients with first episode based on whether they were manic, depressive or mixed. On the other hand, identifying the severity of depressive symptoms prior to remission as mediators in patients known to have previous bipolar episodes can help clinicians to select the best medication to treat depressive symptoms in order to minimize the risk of relapse to any mood episode.

One of the study limitations is that other potential variables (such as family history, degree of lithium response, or psychosocial functioning) were not included since the data were not collected. In addition, the only potential mediators we analyzed were the symptoms and improvement in manic and depressive symptoms (total score measure) from baseline during the acute stabilization phase, which represents a constraint of the available data. Other limitations include that clinical trial data may not be generalized to clinical populations and our findings can be applied only when olanzapine or lithium are given as monotherapy, not with other treatments used as monotherapy or in combination.

In conclusion, our findings suggest that specific treatments may determine the identification of variables as mediators and moderators for prediction of relapse. We used post hoc analyses to identify mediators and moderators that may provide valuable information in the treatment planning of patients with bipolar disorder as well as potentially influence their treatment outcome. Each mediator and moderator should also be taken into account when planning personalized treatment for bipolar disorder patients in order to reduce risks of relapse to any mood episode.

Drug names: lithium (Lithobid and others), olanzapine (Zyprexa).
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Potential conflicts of interest: **Dr Tohen** was an Eli Lilly employee when the study was conducted and has received honoraria from or been a consultant for AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Johnson & Johnson, Sepracor, Otsuka, Merck, Sunovion, Forest, Lundbeck, and Wyeth. His spouse is a current employee and minor stockholder of Eli Lilly. **Ms Wang** is an employee of Eli Lilly. **Dr Leboyer** is a consultant for Eli Lilly. **Dr Jen** was an employee of Eli Lilly when the study was conducted.
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