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Early improvement of psychotic symptoms with lithium monotherapy as a predictor of later response in mania

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Abstract

Although lithium has been the first line agent in the treatment of bipolar disorder (BD), few studies have evaluated lithium's efficacy in mania with psychosis and its association with later response. Furthermore, given the widespread concern about antipsychotic side effects, answering a question about whether lithium alone can manage to treat both psychotic and non-psychotic mania seems a very relevant one. The present study addresses the antipsychotic efficacy of lithium monotherapy in acute mania and early improvement of psychotic symptoms as a predictor of later response of manic symptoms. Forty-six patients presenting a manic episode (32 with psychotic features and 14 subjects without psychotic features) were treated for 4 weeks with lithium monotherapy and evaluated weekly using the Young Mania Rating Scale (YMRS). Subjects with rapid cycling, substance abuse/dependence, or mixed episodes were excluded. The overall antimanic efficacy of lithium in psychosis vs. non-psychosis groups was evaluated. In addition, early improvement of psychotic symptoms and its prediction of subsequent response (>50% decrease in total YMRS scores) or remission were evaluated. Lithium showed a similar efficacy in both psychosis and non-psychosis mania. Early improvement of psychotic symptoms was associated with clinical response and remission at endpoint.

Keywords

Psychosis; Mania; Bipolar disorder; Lithium; Early improvement; Monotherapy

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1. Introduction

Psychotic symptoms are present in about half of the manic episodes in bipolar disorder (BD) (Pope and Lipinski, 1978; Coryell et al., 2001; Keck et al., 2003). Psychosis in BD has been associated with poorer cognitive functioning (Bora et al., 2010), longer periods of active illness (Coryell et al., 2001), and higher relapse rates (Tohen et al., 1990). Although lithium is considered a first line agent for treating acute mania (Yatham et al., 2009), only a few studies have systematically evaluated lithium's efficacy for the treatment of mania with psychosis (Prien et al., 1972; Small et al., 1995; Swann et al., 2004) and none have addressed the time course of action onset. This seems to be mostly due to the widespread practice of combining antipsychotics with mood stabilizer agents within the first weeks of treatment (McElroy et al., 1996), which has been recommended for both psychosis and non-psychosis mania (Goodwin, 2009; Malhi et al., 2009; Yatham et al., 2009).

Few studies have evaluated early improvement in bipolar mania as a predictor of outcome (Houston et al., 2010; Kemp et al., 2011a; Ketter et al., 2010). It has been shown that improvement of psychotic (Ketter et al., 2010) and manic symptoms (Houston et al., 2010; Kemp et al., 2011a) in the first week predicts later response with second-generation antipsychotics. However, only a few predictors of response with lithium are available (Grandjean and Aubry, 2009) and no study has evaluated early improvement of psychotic symptoms with lithium and its potential role as a predictor of later response.

The present study aims to evaluate: 1) lithium's efficacy in mania with psychosis. Results were subsequently compared with a comparison group of concurrently-recruited, mania without psychosis treated with lithium; 2) whether or not lithium induces early improvement of psychotic symptoms, and 3) whether early improvement of psychotic features of mania is associated with later response and remission.

2. Materials and methods

This study is a post-hoc analysis from a larger 4-week, randomized, double-blind, trial in bipolar mania comparing the efficacy of lithium plus placebo vs. lithium plus other drugs (Machado-Vieira et al., 2008). The present analysis is performed in the lithium plus placebo arm of the original trial. Forty-six inpatients, aged 18–65 years, with a diagnosis of manic episode with psychosis ($n = 32$) or without psychotic features ($n = 14$; comparison group) by means of the Structured Clinical Interview for Axis I DSM-IV-TR Disorders, Research Version, Patient Version (First et al., 2001) were evaluated. All patients were enrolled between September 2003 and September 2006 at the Bipolar Disorder Research Center, Espirita Hospital of Porto Alegre, Brazil. Subjects were required to present a score of greater than or equal to 22 on YMRS (Young et al., 1978) at baseline. All subjects were in good physical health (determined by medical history, physical examination and blood tests) and free of comorbid substance abuse or dependence for at least 5 weeks prior to screen. Patients had not taken any psychopharmacologic treatment for at least 4 weeks before admission. Other exclusion criteria included rapid cycling, mixed episode, previous history of refractoriness to lithium, or other current axis I psychiatric disorder.

On the first day, patients were started on lithium carbonate 600 mg/day, and subsequent dosage adjustments were allowed at a flexible fashion, aiming to achieve therapeutic levels in the plasma (0.6–1.2 mmol/L), and then adjusted according to clinical improvement. Diazepam up to 20 mg/day was allowed as supplementary medication for agitation during the 4-week study period, except for the day prior to clinical assessment with the YMRS; physical restraint was used when necessary. In accordance with the Declaration of Helsinki,

the local institutional review board approved the study and all subjects and/or family members provided written informed consent before entry into the study.

2.1. Outcome measures

Subjects were assessed with the YMRS on a weekly basis from baseline to week 4. Statistical analyses were made for baseline, 1-week, and 4-week (endpoint) measures, using the last observation carried forward (LOCF) or linear mixed model when data were missing. Psychosis in mania was defined as the presence of delusions and hallucinations, i.e., YMRS item-8 (Content) score = 8 (maximum score). Early improvement in psychotic symptoms (early improvers) was defined as improvement of delusions and hallucinations after 1 week of treatment, based on a decrease ≥25% in the YMRS item-8 (Content) score. Clinical response was defined as a decrease of 50% or more in the YMRS at the endpoint (week 4). Remitters were those who had YMRS ≤12 at endpoint. An additional analysis using a more stringent criterion at endpoint (YMRS score ≤7) was also performed.

2.2. Statistical analysis

Demographic and clinical characteristics of psychosis and non-psychosis mania at baseline were compared with the Chi-square test for categorical data. A linear mixed model was used to examine the time course of improvement with lithium treatment in mania with and without psychosis and to compare diazepam use between groups. Also, Student's *t* test (normal) or Manne-Whitney (non-normal distribution) tests were used for continuous variables. Wilcoxon signed ranks test was used to compare YMRS scores at baseline and endpoint. Spearman test was used to correlate decrease in the YMRS item-8 and total scores. Statistical significance was set at $p < 0.05$ (two-tailed). All statistical analyses were conducted in the SPSS 16.0 software. In the psychosis mania group, additional analyses were conducted in order to determine the prognostic value of early improvement in psychotic symptoms at week 1 in predicting endpoint (week 4) response or remission. Sensitivity, specificity, and positive and negative predictive values (see Kemp et al., 2011a for further details) were calculated.

3. Results

3.1. Clinical and demographical data

Demographic and clinical data for the psychosis and non-psychosis mania groups are summarized in Table 1. There were no differences between groups except for a larger number of women in the mania without psychosis group.

3.2. Mania with and without psychosis has similar severity and also similar improvement with lithium treatment

YMRS total scores did not show significant differences between mania with and without psychosis ($F = 0.27$, df 1, 42, $p = 0.87$), nor significant interaction between group and time ($F = 1.16$, df = 3, 110, $p = 0.33$) (Fig. 1). When baseline was included as a time point in the mixed model, also no significant difference between YMRS total scores of mania with and without psychosis was found ($F = 1.76$, df = 1, 46, $p = 0.19$) and no significant interaction between group and time ($F = 0.88$, df = 4, 151, $p = 0.48$). There were no significant differences between psychosis and non-psychosis groups in YMRS single items, except for greater YMRS-item 11 scores in the psychosis group (data not shown).

Since there was a significant gender difference between psychosis and non-psychosis groups, additional linear mixed model analyses were performed in female patients and showed no significant differences in YMRS total scores between psychosis and non-psychosis groups, respectively ($F = 0.21$, df = 1, 27, $p = 0.65$ and $F = 1.2$, df = 1, 30, $p =$

0.28) and no significant interaction between group and time ($F = 0.86$, $p = 0.46$; $F = 0.73$ $p = 0.57$). Diazepam use and side effects were not significantly different between psychosis and non-psychosis groups (data not shown).

Lithium treatment was associated with a significant improvement of manic symptoms in the psychosis group from baseline to endpoint (YMRS: 35.1 ±8.6 vs. 14.8 ± 12.5, respectively, $p < 0.001$). At endpoint, in the psychosis mania group ($n = 32$), 63% achieved clinical response, and 50% remitted (YMRS ≤ 12). Also, 34% remitted using more stringent criteria (YMRS ≤ 7). In the non-psychosis group ($n = 14$), lithium also showed a significant improvement of manic symptoms from baseline to endpoint (YMRS: 31 ± 8.6 vs. 12.6 ± 12.7, respectively, $p = 0.002$). Sixty four percent showed both response and remission (YMRS ≤ 12) at the endpoint, while half of patients presented remission accordingly to the more stringent criteria.

Changes from baseline to endpoint of psychotic symptoms in YMRS item-8 (Content) correlated with improvement of YMRS total scores ($p < 0.001$) in psychotic mania (Fig. 2).

3.3. Early improvement in psychotic symptoms predicts later response and remission

Sixteen (50%) subjects in psychosis mania group presented an early improvement of delusions and hallucinations after one week of lithium treatment. Among early improvers, 15 achieved clinical response (PPV = 94%), 12 remitted (PPV = 75%, YMRS ≤ 12), and 8 presented remission (PPV = 50%) at endpoint with a more stringent criteria (YMRS ≤ 7) (Table 2). Among the 16 patients having no early improvement in psychotic symptoms after one week of treatment, 11 did not respond (NPV = 69%), 12 did not have remission (NPV = 75%, YMRS<13), while 13 failed to achieve remission with a more stringent criteria (NPV = 81%) at endpoint. Sensitivity, specificity, and positive and negative predictive values are summarized in the Table 2.

4. Discussion

Lithium monotherapy showed similar efficacy in both mania with and without psychosis in patients without rapid cycling or mixed states. To the best of our knowledge, this is the first study showing that early improvement of psychotic symptoms predicts later outcome with lithium monotherapy. Our results are in line with other studies showing the efficacy of lithium or divalproex monotherapy (Swann et al., 2004), and lithium plus carbamazepine (Small et al., 1995) for treating psychotic symptoms in mania.

Specifically, the response rates found in our study for both psychosis (63%) and non-psychosis mania (64%) are slightly higher than those observed in previous studies with lithium monotherapy. Improvement of psychotic symptoms in bipolar mania with lithium monotherapy was studied by Swann et al. (2002), who found lithium treatment significantly better than placebo for improving mania in a psychotic subtype (derived from a previous cluster analysis). In addition, lithium was compared to first and second-generation neuroleptics in mania with psychosis. Prien et al. (1972) found chlorpromazine superior to lithium in suspiciousness measured by Brief Psychiatric Rating Scale (BPRS) and Keck et al. (2009) found aripiprazole, but not lithium, more effective than placebo in psychotic symptoms by Positive and Negative Syndrome Scale (PANSS) scale. Bowden et al. (2005) found lithium and quetiapine similarly effective and superior to placebo in the treatment of psychosis by PANSS positive subscale. In summary, the different results found may be explained by the use of different methodology and scales to compare lithium and antipsychotics for treating mania with psychosis.

In the present study, lithium monotherapy produced early improvement of psychotic symptoms in half of the patients after 1-week treatment. Early improvement of psychotic symptoms (delusions and hallucinations) in the first week of treatment yielded high specificity and positive predictive value for later clinical response at endpoint (week 4). Likewise, Ketter et al. (2010) found that early improvement (i.e., improvement after 4 days) on ziprasidone predicted remission at 21 days according to the Schedule for Affective Disorders and Schizophrenia-Change (SADS-C). Another study looked at early improvement of manic symptoms but did not evaluate improvement of psychosis. Kemp et al. (2011a) found that patients without improvement in overall manic symptoms at week 1 (<25% decrease in YMRS total score) with risperidone and olanzapine were less likely to reach response and remission at week 3.

Furthermore, our results are in agreement with other studies in different psychiatric conditions. Early improvement was found to predict later outcome in studies with atypical antipsychotics in schizophrenia (Kinon et al., 2008), antidepressants in unipolar depression (Szegedi et al., 2009), and mood stabilizers and atypical antipsychotics in bipolar depression (Kemp et al., 2011b).

Limitations include the exclusion of subjects with mixed episodes and rapid cycling, gender differences between psychosis and non-psychosis groups, and the lack of a specific rating scale for quantifying psychotic symptoms (e.g., BPRS, PANSS).

In conclusion, lithium monotherapy showed similar efficacy in both mania with and without psychosis.

To our knowledge, this is the first report to describe early improvement of psychotic symptoms having a high positive predictive value and significant specificity for later response with lithium therapy. The present findings reinforce the role of lithium in the treatment of classic mania with psychotic features as well as the importance of assessing improvement of psychosis in the first week of treatment as a predictor of subsequent outcome. Further studies are necessary to confirm these preliminary findings.

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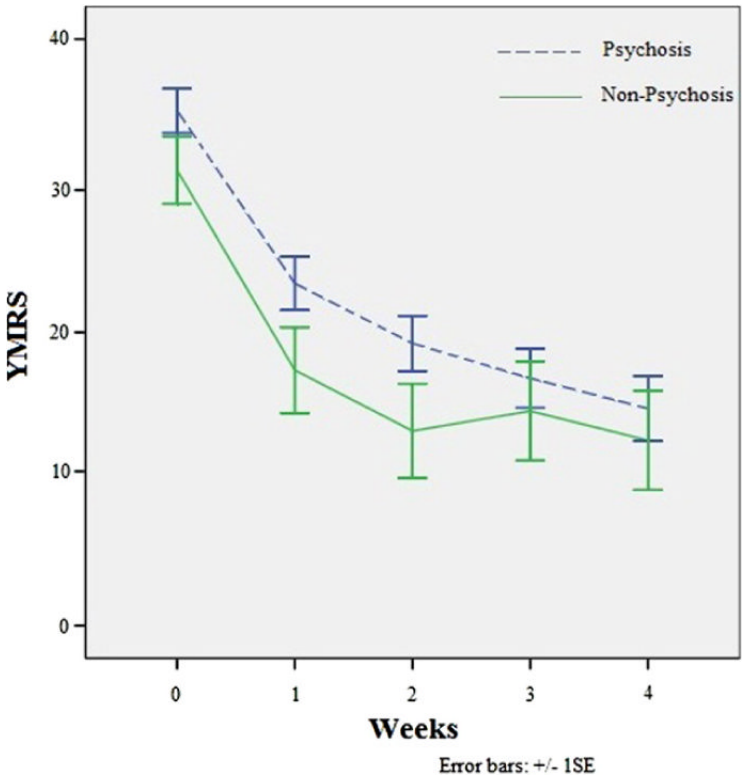

Fig. 1.
Course of overall manic symptoms (total YMRS) with lithium treatment in psychosis and non-psychosis mania.

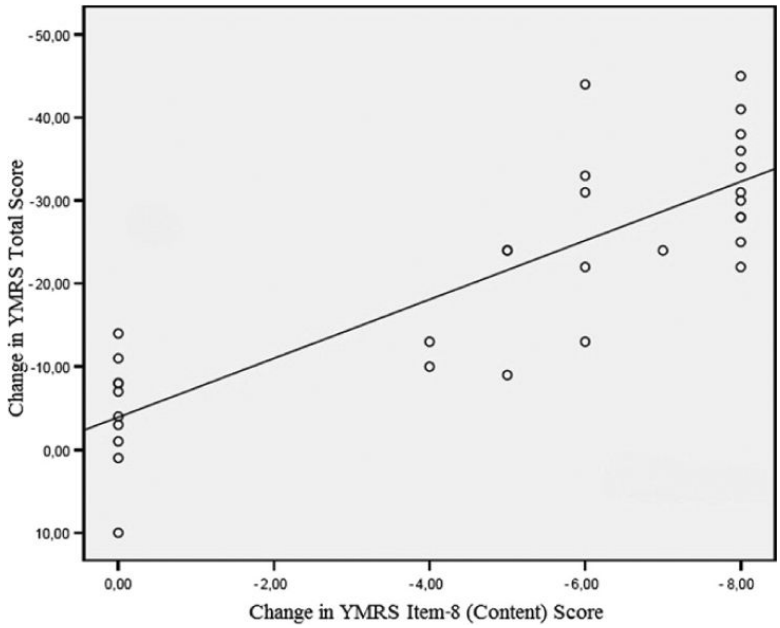

Fig. 2.

Relationship between change in YMRS item-8 (content) and YMRS total scores from baseline to endpoint in psychotic Mania. YMRS – Young Mania Rating Scale.

Table 1

Demographic variables and clinical characteristics of psychosis and non-psychosis groups compared.

YMRS item	Psychosis (*n* = 32)	Non-psychosis (*n* = 14)	*p*
Gender			
Male/female, *n* (%)	16(50)/16(50)	1(7)/13(93)	0.006*,[a]
Age			
Age, year (SD)	28.8 (8.5)	30.7 (8.7)	0.36
Race			
White, *n* (%)	27 (84)	11 (79)	0.63[a]
Black, *n* (%)	5 (15)	3 (21)	
Age at onset, year (SD)	22.7 (3.9)	20.9 (3.8)	0.16[b]
Duration of illness, year (SD)	8 (7.7)	7.9 (6.9)	0.97[b]
Number of mood episodes, year (SD)	4.5 (3.5)	5.6 (3.2)	0.35[b]
Number of manic episodes (SD)	2.7 (2.2)	4.1 (3)	0.06[c]
Type of first episode			
Mania, *n* (%)	16 (50)	9 (64)	0.65[a]
Depression, *n* (%)	12 (37)	4 (29)	
Mixed, *n* (%)	4 (13)	1 (7)	
Number of past hospitalizations (SD)	2.8 (2.7)	3.5 (3)	0.52[c]
Suicidal attempts (SD)	1.6 (2.1)	0.7 (1.6)	0.17[c]
Familiar history of bipolar disorder	16 (50)	8 (57)	0.65[a]
Present, *n* (%)			
Serum lithium at endpoint, mEq/L (SD)	0.96 (0.2)	0.93 (0.19)	0.91[c]
Diazepam use, mg (SD)	184.7 (122)	134.3 (127)	0.81[d]

YMRS – Young Mania Rating Scale. SD – standard deviation.

*Significantly different.

[a]Chi-square.

[b]Student's *T* test.

[c]Mann–Whitney test.

[d]Linear mixed model.

Table 2

Analyses of early improvement in psychotic symptoms (delusions and hallucinations within the first week) in the psychosis group as a predictor of endpoint outcome.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Response	75	92	94	69
Remission (YMRS ≤ 12)	75	75	75	75
Remission (YMRS ≤ 7)	73	62	50	81

Values displayed as percentages. YMRS – Young Mania Rating Scale. Response is defined as ≥50% improvement in YMRS total score from baseline to endpoint.