

Review

## New data on the use of lithium, divalproate, and lamotrigine in rapid cycling bipolar disorder

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### Abstract

The rapid cycling variant of bipolar disorder is defined as the occurrence of four periods of either manic or depressive illness within 12 months. Patients suffering from this variant of bipolar disorder have an unmet need for effective treatment. This review examines two major studies in an attempt to update understanding of the current therapies available to treat rapid cycling patients. The first trial compares lamotrigine versus placebo in 182 patients studied for 6 months. The second is a recently completed, 20-month trial comparing divalproate and lithium in 60 patients. Both trials had a double-blind, randomized parallel-group design. The data from the latter study indicate that there are no large differences in efficacy between lithium and divalproate in the long-term treatment of rapid cycling bipolar disorder. In addition, lamotrigine has the potential to complement the spectrum of lithium and divalproate through its greater efficacy for depressive symptoms. © 2005 Elsevier SAS. All rights reserved.

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### 1. Introduction

In accordance with DSM-IV criteria, rapid cycling bipolar disorder is the occurrence of four or more episodes of illness, either manic or depressive, within a 12-month period. Rapid cycling tends to appear late in the course of bipolar disorder, and occurs more frequently among female patients [4]. Between 14% and 53% of bipolar disorder patients are rapid cycling, and its prevalence appears to differ within bipolar I and II disorder. Calabrese et al. [2] indicated rapid cycling prevalence appears to be as low as 4% in bipolar I disorder and as high as 31% in bipolar II disorder.

A poor treatment response to lithium was found in 72–82% of rapid cycling bipolar disorder patients. A substantial percentage of this poor response appeared to be attributable to rapid cycling [2]. In an attempt to investigate alternative treatments for patients with rapid cycling bipolar disorder, we previously evaluated the spectrum of acute and prophylactic effi-

cacy of divalproate [1]. A total of 55 patients receiving divalproate underwent a 17-month open-label trial; 20 patients received monotherapy, and 35 received combination therapy.

Moderate to marked acute antidepressant responses were seen in 47% of the patients, prophylactic antidepressant responses in 76%, acute antimanic responses in 91%, prophylactic antimanic responses in 94%, acute responses in mixed states in 85%, and prophylactic responses in mixed states in 93%. To summarize, the data suggest that while divalproate might have marked antimanic and mixed state efficacy, it has minimal to moderate antidepressant properties.

As patients with this variant of bipolar disorder are often refractory to treatment, efforts to optimize prescription in this group of patients are paramount. In an attempt to update awareness, the following section discusses two major double-blinded data sets, one recently completed trial and another published trial in the treatment of rapid cycling bipolar patients. The first study compares the mood stabilizing medications divalproate and lithium, and was developed in response to the encouraging results of the preliminary study [5]. Its aim was to test the hypothesis that divalproate was moderately more effective than lithium in the long-term treat-

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ment of rapid cycling bipolar disorder. The second trial compares the anticonvulsant, lamotrigine versus placebo [3].

## 2. Long-term treatment of rapid cycling bipolar disorder: lithium versus divalproate [5]

### 2.1. Trial objectives and design

A randomized, 20-month, double-blind, parallel-group comparison of divalproate and lithium was conducted to test the hypothesis that divalproate was more effective than lithium in the long-term treatment of rapid cycling bipolar disorder. The trial included 254 bipolar patients aged between 18–65 years with rapid cycling, as determined by DSM-IV criteria. Participants were required to be outpatients with no other major health problems. Patients who had drug or alcohol dependence in the last 6 months were excluded from the trial. A combined treatment of  $\geq 0.8$  mEq/l lithium and  $\geq 50$   $\mu\text{g/ml}$  divalproate was given to the participants during the initial open-label stabilization phase, which lasted for up to 6 months, prior to the 20-month randomized phase.

The outcome of the stabilization phase found that, 25% were non-responders (73% resistant depression and 27% resistant hypomania/mania) and 19% had intolerable adverse events. Other outcomes such as substance abuse accounted for 4% of the sample. Poor compliance was exhibited in 28%. The remaining 60 (24%) patients who stabilized were entered into the double-blind phase of the trial.

The characteristics of the lithium versus divalproate trial group are outlined in Table 1. As expected, given the epidemiology of rapid cycling in bipolar patients, approximately two thirds of the group was female and two thirds had bipolar II disorder.

The 60 patients who were entered for randomization were stratified for bipolar I and II disorder. A rigorous definition of response was set: patients were required to have a level of  $\geq 0.8$  mEq/l lithium or  $\geq 50$   $\mu\text{g/ml}$  divalproate. The cohort also needed to have a 24-item Hamilton Rating Scale for Depression (HAM-D [24]) score of  $\leq 20$ , Young Mania Rating Scale (YMRS) score of  $\leq 12.5$ , and Global Assessment Scale (GAS) score of at least 51 for 4 continuous weeks.

During the randomized phase patients received either lithium or divalproate monotherapy and were studied for

20 months. The key outcome measures were in study survival: time to any mood episode; time to relapse for depression; time to relapse for mania; time to dropout for any reason; the proportion relapsing; and, completer analysis.

Prior to study initiation, it was estimated that a minimum of 30 patients per arm would detect a minimum hazard ratio of 0.36 at a power of 80% and an alpha of 0.05. The study was not powered to detect small changes and no interim analysis was conducted. Kaplan–Meier curves were generated for the time-to-event data, and differences between treatment groups were tested using log-rank tests.

### 2.2. Results

The rate of relapse into a mood episode was 56% on lithium and 51% on divalproate. The number of patients relapsing into mania/mixed states was 22% for both lithium and divalproate.

The proportion discontinuing prematurely due to side-effects was 16% on lithium and 4% on divalproate (not significant). The median time to the initiation of additional pharmacotherapy to treat emerging symptoms was 18 weeks on lithium and 45 weeks on divalproate. However, this magnitude of difference did not achieve statistical significance ( $P = 0.390$ ) due to the small sample size (Fig. 1).

Median survival was 26 and 14 weeks, respectively (Fig. 2; not significant).

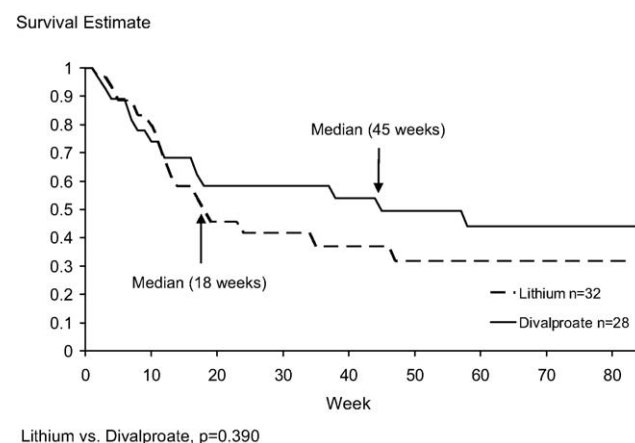


Fig. 1. Time to intervention for a mood episode.

Table 1  
Participant characteristics

	Lithium (n = 32)	Divalproate (n = 28)
Mean age in years (S.D.)	37.2 (9.0)	37 (8.2)
Female (%)	59	43
Bipolar II (%)	59	61
Previous suicide attempt (%)	44	29
Psychiatric hospitalization (%)	53	41
Lifetime psychosis (%)	47	39
Median number of mood episodes in last year (S.D.)	7.9 (4.7)	9.7 (6.5)
Depression (S.D.)	4.0 (2.4)	4.9 (3.2)
Hypomania/mania/mixed states (S.D.)	4.0 (2.4)	4.8 (3.3)

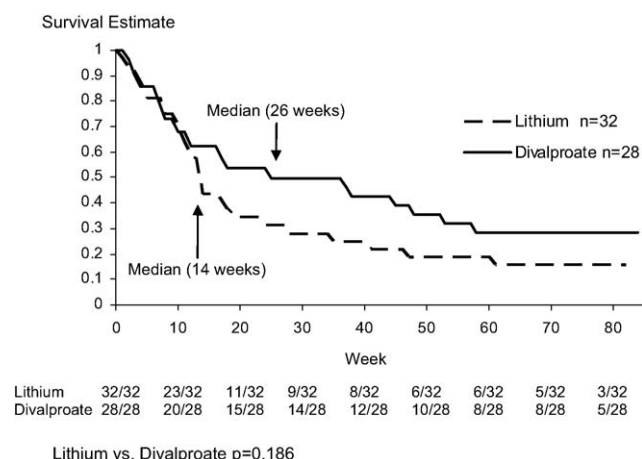


Fig. 2. Time to drop out for any reason.

There were also a greater number of completers in the divalproate group compared to the group treated with lithium, 26% and 16%, respectively. The full outcome of events during the 20-month randomized period is presented in Table 2.

### 2.3. Safety

Significantly more participants experienced tremors in the lithium group (28%) compared to the divalproate group (4%;  $P = 0.011$ ). There was also a significant difference in the presentation of polyuria and polydipsia, 22% versus 0% in the lithium and divalproate groups, respectively ( $P = 0.009$ ). No significant differences were observed in any of the other comparisons for safety between the two treatment arms.

## 3. Long-term treatment of rapid cycling bipolar disorder: lamotrigine versus placebo [3]

### 3.1. Trial objectives and design

A randomized, double-blind, 6-month parallel-group comparison of lamotrigine versus placebo was conducted in 324 patients with rapid cycling bipolar disorder. During a 12-week, open-label stabilization phase, 100–300 mg lamotrigine was added to patients' current psychotropic regimens and titrated to clinical effect while other psychotropic medication was tapered concurrently. The 182 patients who stabilized were then assigned to the double-blind maintenance phase. During the double-blind phase the participants were

Table 2  
Outcome during randomized phase

	Lithium (n = 32)	Divalproate (n = 28)
Completers (%)	16	29
Adverse events (%)	16	4
Medical illness (%)	3	4
Substance abuse (%)	0	4
Non-compliance (%)	9	11
Relapsed (%)	56	50

$P = NS$ .

randomized to 100–500 mg lamotrigine or placebo monotherapy and studied for 6 months.

The primary outcome measure was time to additional pharmacotherapy for emerging symptoms. Secondary outcome measures included: time to premature discontinuation from the trial due to any cause (survival in study); percentage of patients stable without relapse for 6 months; and, changes in GAS and Clinical Global Impressions-Severity scale (CGI-S). Safety was assessed from adverse events, physical examination, and laboratory data.

### 3.2. Results

Within the entire study cohort, the difference between the treatment groups in time to additional pharmacotherapy, did not achieve statistical significance. However, survival in study was statistically improved in the lamotrigine group compared to the placebo group ( $P = 0.036$ ).

In bipolar I disorder patients, time taken before additional pharmacotherapy and time to drop out was marginally different between lamotrigine and placebo. However, bipolar II disorder patients treated with lamotrigine exhibited a longer median time to additional pharmacotherapy (17 weeks) in comparison with placebo (7 weeks;  $P = 0.073$ ; Fig. 3). A longer median time to drop out was also found in the bipolar II disorder patients treated with lamotrigine, 15 weeks compared to 4 weeks in the placebo group ( $P = 0.05$ ; Fig. 4).

Analyses of the entire study found a 6-week difference in median survival time favoring lamotrigine. Within the group of patients treated with lamotrigine, 41% were stable without relapse for 6 months of monotherapy, compared to 26% of patients in the placebo group ( $P < 0.05$ ; Fig. 5). The results demonstrate that the significant improvement in the results for the entire cohort is an outcome of the efficacy within the bipolar II disorder patients.

### 3.3. Safety

Of the 324 patients enrolled into the open stabilization phase of this study and treated with lamotrigine, 11% expe-

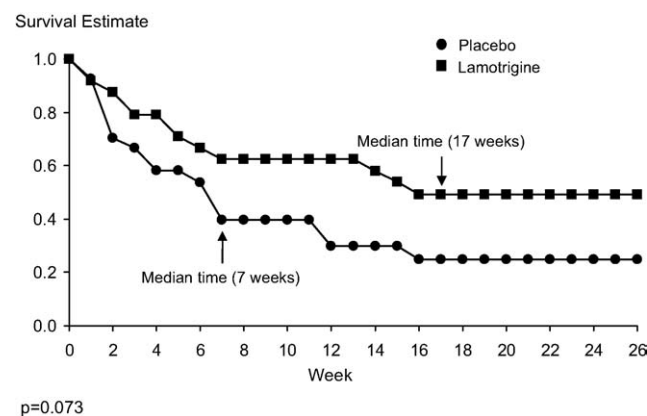


Fig. 3. Time to require additional pharmacotherapy in bipolar II disorder patients.

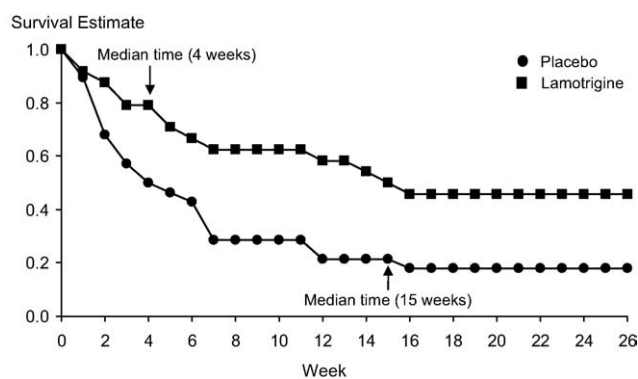


Fig. 4. Time to drop out in bipolar II disorder patients.

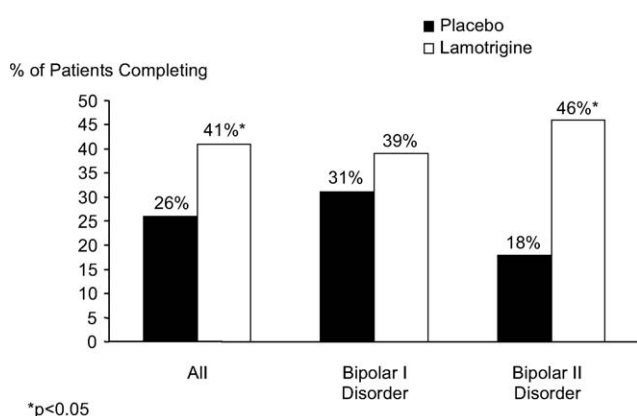


Fig. 5. Study survival according to bipolar I and II disorder. Figs. 3–5 reprinted by permission from: Calabrese JR, Suppes T, Bowden CL, Sachs GS, Swann AC, McElroy SL, et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid cycling bipolar disorder. *The Journal of Clinical Psychiatry*. 61, 841–50, 2000. Copyright 2000, Physicians Postgraduate Press.

rienced intolerable side-effects and were discontinued from the study prior to randomization. Lamotrigine was found to be well tolerated during the randomized phase with an adverse event profile comparable to placebo. The safety data are presented in Table 3: no treatment-related changes in laboratory parameters, vital signs, or body weight were reported and no serious rashes occurred.

#### 4. Discussion

The data suggest that divalproate and lithium are effective in the long-term management of rapid cycling bipolar disorder. In our study, both lithium and divalproate were found to have similar relapse rates (56% versus 50%, respectively). Divalproate exhibited a marginally preferential safety profile

Table 3  
Adverse events: lamotrigine versus placebo

Adverse event	Lamotrigine (n = 92)	Placebo (n = 88)
Headache (%)	23	17
Nausea (%)	14	11
Infection (%)	12	11
Accidental injury (%)	11	5
Pain (%)	10	8
Dizziness (%)	9	3
Influenza (%)	7	9
Rash (%)	3	2

P = NS.

in comparison to lithium monotherapy, and both divalproate and lithium were well tolerated when co-administered [5].

Lamotrigine is also a useful treatment for some patients with rapid cycling bipolar disorder. Its greater potency for antidepressant action has the potential to complement the spectrum of efficacy of divalproate and lithium in patients presenting with more depressive, than manic symptoms [3].

The rapid cycling variant of bipolar disorder is a non-specific weak predictor of poor outcome. The informed use of combined therapy could provide the opportunity for greater adaptation of treatment and dosage according to the symptom range in bipolar disorder. Indeed combining therapies is becoming the most viable option to meet the challenge of improving outcomes in rapid cycling bipolar disorder.

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