Bipolar Rapid Cycling: Focus on Depression as Its Hallmark

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The phenomenon of frequent cycling in bipolar disorder was first recognized by Emil Kraepelin in 1913. More recently, rapid cycling has been reported to be a predictor of nonresponse to treatment. At the time of presentation, most patients with DSM-IV–defined rapid cycling appear to be in the depressed phase of their illness. Frequent and more severe episodes of depression appear to be the hallmark of rapid cycling. Reported in this article are recent preliminary data suggesting that the combination of lithium and divalproex sodium administered continuously over 6 months appears to result in marked acute and continuation antimanic efficacy in 85% of patients and marked antidepressant efficacy in 60%. However, only one half of patients experienced bimodal stabilization. Comorbid alcohol, cannabis, and/or cocaine abuse and/or dependence did not appear to directly affect the spectrum of efficacy of lithium and divalproex or response rates in compliant patients. Comorbidity appeared to alter prognosis by increasing the prevalence of poor compliance. The majority of patients receiving lithium and divalproex who required additional treatment were depressed, suggesting that the frequent recurrence of depression is the primary unmet need in patients with rapid cycling. The use of antidepressants in this population has been discouraged because of concerns about the possibility of cycle acceleration. There exists a need for a pharmacotherapy that not only possesses marked acute antidepressant properties, but that does so without inducing switching or cycle acceleration. A double-blind, placebo-controlled trial of lamotrigine monotherapy in bipolar I depression has demonstrated efficacy without causing switching at a rate exceeding placebo; however, this initial study excluded patients with rapid cycling. To explore the efficacy of lamotrigine in rapid cycling, a recent multicenter study has examined lamotrigine as a maintenance therapy for this population. The results indicate that lamotrigine may be a useful treatment for patients with rapid-cycling bipolar II disorder and that this drug has begun to address this unmet need.

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Over the last 10 years, the phenomenon of a rapid-cycling course has become widely accepted and primarily associated with bipolar disorder.[1–4] The earliest reports of the prevalence of this subtype of bipolar disorder described the variant of illness as being present in 20% of patients with bipolar I disorder in a tertiary care setting.[5] However, more recent reports have documented its presence in up to 24% of patients,[6] and even higher prevalences have been reported when minimum duration criteria are dropped and patients with ultra-fast rapid cycling are included.[7,8] The earliest clinical reports evaluating treatments for patients with rapid-cycling bipolar disorder noted that patients with this variant of illness did not respond adequately when treated with lithium.[5,9] Subsequently, open prospective preliminary data from studies employing divalproex sodium, as either monotherapy or in augmentation, suggested that this patient population responded to treatment with divalproex, especially for the hypomanic/manic phase of the illness (Table 1).[1,2] These early observations were based on either small, controlled, lithium-treated samples of mixed-patient populations including both rapid cyclers and non–rapid-cycling patients[5] or larger open samples prospectively evaluating the effect of divalproex on a cohort of prospectively defined patients with rapid-cycling bipolar disorder.[1,2]

In 1992, the National Institute of Mental Health Psychobiology of Depression Program retrospectively evalu-

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Table 1. Spectrum of Marked Responses to Divalproex Sodium in Rapid-Cycling Bipolar Disorder (N = 101)[a]

Cycle	Acute	Prophylactic[b]
Dysphoric hypomania/mania	87	89
Elated hypomania/mania	64	77
Depression	21	38

[a]Data from Calabrese et al.[1,2] Diagnoses were made using DSM-IV criteria in a post hoc analysis.
[b]Mean follow-up was 15 months after acute treatment.

ated the phenomenology of rapid cycling in a large mixed sample (N = 919) of openly treated patients with either bipolar (N = 243) or unipolar (N = 676) disorder.[4] Rapid cycling was rare in patients with unipolar disorder, whereas the prevalence rate was 18.5% for those with bipolar disorder. The prevalence of rapid cycling was consistent with prior reports, but these authors were the first to note that this course specifier was transient, with the prevalence decreasing to only 5% over 5 years of follow-up. The data from this report suggested that rapid cycling migrated in and out of the natural history of bipolar disorder, was most commonly seen in women with bipolar II disorder, was not familial, and had a negative impact on prognosis only when it was present within the last 12 months. It was not until Bauer and colleagues[10] performed a 4-site meta-analysis comparing 120 patients with a lifetime history of rapid cycling with 119 patients without such a history that rapid cycling became widely recognized as a distinct course modifier and was included in DSM-IV.

Maj and colleagues also reported data that supported the recognition of rapid cycling as a distinct course specifier[11] and again observed that patients with rapid cycling were overrepresented in populations of patients who did not respond adequately to lithium.[12] Of 247 lithium-treated patients with bipolar disorder followed for 5 years, no rapid-cycling patient experienced marked prophylactic efficacy, whereas 26% to 27% of those had partial responses or no response. Although one report viewed rapid cycling as a predictor of positive outcome to treatment with carbamazepine,[13] other reports have refuted this hypothesis.[14–16] Overall, this variant of illness appears to predict nonresponse to most treatments.

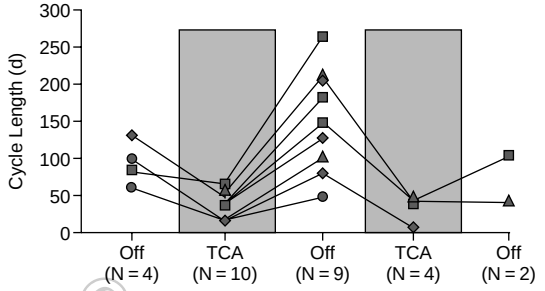
Importantly, when a homogeneous cohort of prospectively defined rapid-cycling subjects is randomly assigned to 2 treatment conditions, a more meaningful understanding of selective efficacy can be ascertained. Such studies are underway (J.R.C., M.D.S., C.L.B., et al., unpublished data) and were designed to evaluate the prophylactic efficacy of lithium monotherapy, divalproex monotherapy, and the combination in rapid-cycling patients with and without alcohol and drug abuse. This article will include a discussion of preliminary open stabilization data from these ongoing maintenance studies, a summary of the results from a recent double-blind placebo-controlled prophylaxis study of lamotrigine in rapid-cycling bipolar disorder,[3] and discussion of the prevalence of depressive symptoms in patients with rapid-cycling bipolar disorder.

PROMINENCE OF DEPRESSIVE SYMPTOMS IN RAPID CYCLING

Kukopulos and colleagues[9] first postulated that the depression associated with rapid cycling appeared to be more severe as compared with depressive episodes associated with patients who were not currently exhibiting rapid cycling. These observations were consistent with data included in a small placebo-controlled study performed by Dunner et al.[17] in which the spectrum of prophylactic efficacy of lithium in patients with bipolar II disorder (both rapid cyclers and non–rapid cyclers) was evaluated over a 16-month maintenance phase. These investigators reported that lithium significantly decreased the mean number of hypomanic episodes compared with placebo (0.32 vs. 1.66), but not depressive episodes (4.54 vs. 1.97), in a small subgroup of patients with rapid cycling. The latter data actually suggested that lithium increased the number of depressive episodes in rapid cycling, but the observed differences did not achieve statistical significance in this small sample. These observations were reaffirmed by us in 1990[1] and then again in 1993[2] in a larger sample, when we observed that the acute and prophylactic treatment with divalproex (alone or in combination) resulted in marked antimanic effects, particularly in those patients with dysphoric hypomania but poor-to-moderate efficacy in the depressed phase of the illness (see Table 1). These preliminary data prompted us to hypothesize that the frequent recurrence of depression was a common feature of most patients with rapid cycling and that the greatest unmet need in this patient population was the management of the depressed phase of the illness. Our preliminary reports of the efficacy of divalproex suggested that the management of the hypomania/mania associated with rapid cycling was not a difficult clinical challenge, but that treatment-refractory depression frequently remained and tended to be a major source of human suffering.

The prominence of frequent episodes of depression in patients with rapid cycling and their apparent association with a recent use of unimodal antidepressants have prompted some to hypothesize that rapid cycling can be induced by antidepressant use through cycle acceleration.[18,19] In 14 open-label reports (N = 64), 2% to 67% of patients have been reported to exhibit the induction of rapid cycling following the use of monoamine oxidase inhibitors or tricyclic antidepressants.[9,10,20–31] These open reports have been replicated by one placebo-controlled, prospective double-blind study.[18] In that report, 17 patients who were currently rapidly cycling on treatment with antidepressants were crossed over to placebo. Ten patients were blindly observed while receiving antidepressants and placebo. Rapid cycling was associated with antidepressants in 70%

Figure 1. Tricyclic-Induced Shortening of Bipolar Cycle Length (N = 10)[a]



[a]Adapted from Wehr and Goodwin.[18] Abbreviation: TCA = tricyclic antidepressant.

of patients and appeared to subside after cross over to placebo (Figure 1). Therefore, the most systematic of these assessments of the phenomenology of antidepressant-induced rapid cycling have reported induction rates of 20%,[10] 26%,[31] and 73%.[18] These placebo-controlled data were sufficient to stimulate controversy, but have not been replicated with placebo-controlled study designs. In addition, there is inadequate consensus as to the definition of drug-induced rapid cycling and the best methods to document it. As well, the likelihood of this phenomenon when mood stabilizers are also being used remains to be clarified. This scientific area remains a significant source of controversy, since patients who present with rapid cycling are frequently treated with antidepressant medication and quite commonly do not respond adequately.[3,32]

LITHIUM AND DIVALPROEX IN RAPID-CYCLING BIPOLAR DISORDER WITHOUT ALCOHOL OR DRUG ABUSE COMORBIDITY

We evaluated the spectrum of efficacy of combined lithium and divalproex treatment over 6 months in a prospectively defined cohort of 215 patients with rapid-cycling bipolar I or II disorder. These preliminary data come from the open stabilization phase of an ongoing and still blinded 20-month maintenance study (J.R.C., M.D.S., C.L.B., et al., unpublished data) designed to compare the efficacy of lithium monotherapy with divalproex monotherapy after 6 months of treatment with both medications concurrently. Consistent with the findings of Kukopulos and colleagues,[9] each of the treatments was more efficacious in the hypomanic/manic phases of the illness than the depressed phase.

To be included in this study, patients were required to meet criteria for rapid cycling and to have had an episode of hypomania or mania within the 3 months prior to study entry. Table 2 shows the baseline characteristics of subjects in 2 ongoing rapid-cycling maintenance trials. Patients enrolled in the first study were mostly women with bipolar II disorder presenting in the depressed phase of their illnesses. The median number of affective episodes meeting DSM-IV criteria in the 12 months prior to study entry was 8. (The definitions of response are included in the footnotes of Tables 3 and 4.) In addition, patients were required to have minimum therapeutic concentrations of 0.8 mEq/L of lithium and 50 µg/mL of valproate. Both intent-to-treat analyses and responder analyses on completers were carried out. Table 3 summarizes intent-to-treat outcome of combined lithium and divalproex in 2 populations of patients with rapid-cycling bipolar disorder (with and without alcohol or drug abuse comorbidity). Table 4 describes the responder analyses on the subgroup of patients who were compliant, did not have intolerable side effects, and completed the open stabilization phase of this study. In the study that excluded individuals with comorbid substance abuse, of 55 patients who failed to be randomly assigned because they were nonresponsive to

Table 2. Baseline Characteristics of Subjects in 2 Ongoing Rapid-Cycling Maintenance Trials[a]

Characteristic	Without ADA[b] (N = 215)	With ADA[c] (N = 56)
Mean age, y	37	38
Female	64	36
White/African American	87/13	77/23
Bipolar I	31	59
Bipolar II	69	41
Circular continuous cycling	92	91
Index episode		
Depressive	61	50
Hypomanic	32	23
Manic	3	13
Mixed	3	11
Euthymic	1	4

[a]J.R.C., M.D.S., C.L.B., et al., unpublished data. All values shown as percentages unless otherwise specified. Abbreviation: ADA = alcohol/drug abuse.
[b]No alcohol/drug abuse within 6 months.
[c]Abuse or dependence on alcohol, cannabis, and/or cocaine within 6 months.

Table 3. Outcome During 6 Months of Combined Lithium and Divalproex Treatment in Bipolar Rapid Cycling[a]

Variable	Without ADA[b] (N = 215)	With ADA[c] (N = 56)
Mood stabilization[d]	25	21
Early full remission of ADA	N/A	25
Premature discontinuation		
Poor compliance	29	38
Refractory depression	20	21
Refractory hypomania/ mania/mixed states	6	8
Side effects	18	11

[a]J.R.C., M.D.S., C.L.B., et al., unpublished data. All values shown as percentages. Abbreviation: ADA = alcohol/drug abuse.
[b]No alcohol/drug abuse within 6 months.
[c]Abuse or dependence on alcohol, cannabis, and/or cocaine within 6 months.
[d]Four weeks with Young Mania Rating Scale score ≤ 12, Hamilton Rating Scale for Depression score ≤ 20, and Global Assessment Scale score ≥ 50.

Table 4. Responder Analyses on Completers After 6 Months of Combined Lithium and Divalproex in Bipolar Rapid Cycling[a]

Effect	Without ADA[b] (N = 109)	With ADA[c] (N = 28)
Mood stabilization[d]	50	43
Time required (mo)	4.7	5.4
Marked antimanic effect[e]	88	86
Cycling into depression (N)	42	12
Marked antidepressant effect[f]	61	57
Cycling into hypomania/ mania/mixed states (N)	13	4

[a]J.R.C., M.D.S., C.L.B., et al., unpublished data. All values shown as percentages unless otherwise specified. Abbreviations: ADA = alcohol/drug abuse, GAS = Global Assessment Scale, HAM-D = Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.
[b]No alcohol/drug abuse within 6 months.
[c]Abuse or dependence on alcohol, cannabis, and/or cocaine within 6 months.
[d]Four weeks with YMRS score ≤ 12, HAM-D score ≤ 20, and GAS score ≥ 50.
[e]Four weeks with YMRS score ≤ 12.
[f]Four weeks with HAM-D score ≤ 20.

combined treatment, 76% were experiencing refractory depression and 24% were experiencing refractory hypomania/mania/mixed states.

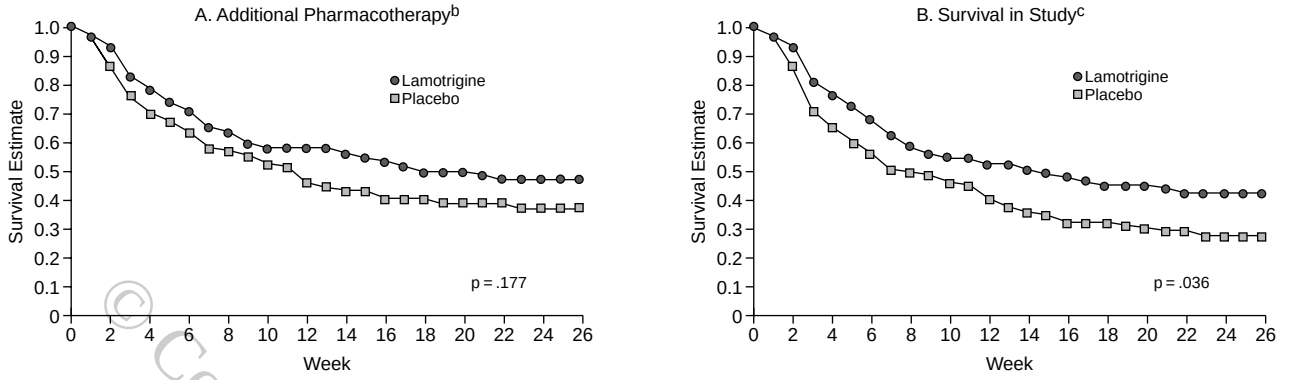
The definition of a marked antidepressant response was designed to be permissive, since treatment-refractory depression was expected and more rigorous criteria would have prevented an adequate number of patients from being enrolled into the randomized phase of this maintenance study, thus not allowing the study to be reflective of treatment as it usually occurs. The Hamilton Rating Scale for Depression (HAM-D) score that was used is consistent with the upper limits of mild severity of depression; the Young Mania Rating Scale score defining a marked response is consistent with subsyndromal presentations of hypomania. Of the 109 completers, only one half met criteria for a marked bimodal response and were randomly assigned to the maintenance phase of the study; 61% of patients met criteria for a marked antidepressant response, and 88% met criteria for a marked antimanic response (see Table 4).

LITHIUM AND DIVALPROEX IN RAPID CYCLING COMORBID WITH ALCOHOL, CANNABIS, AND/OR COCAINE ABUSE OR DEPENDENCE

More recently, we commenced evaluation of the spectrum of efficacy of combined treatment with lithium and divalproex in a cohort of 56 patients with rapid-cycling bipolar I or II disorder comorbid with a current history of either abuse of or dependence on alcohol, cannabis, and/or cocaine. These preliminary data are derived from the open stabilization phase of an ongoing and still blinded 6-month maintenance study designed to compare the efficacy of lithium monotherapy with the combination of lithium and divalproex after 6 months of open stabilization with the combination. To be included in this study, patients were also required to meet criteria for rapid cycling, to have had an episode of hypomania or mania within the 3 months preceding study entry, and to meet DSM-IV criteria for abuse of or dependence on alcohol, cannabis, and/or cocaine. All patients were required to attend a 12-step–based intensive outpatient chemical dependency treatment program (see Table 2 for the baseline characteristics of subjects enrolled in this study). Patients enrolled in this study were mostly men with bipolar I disorder presenting in the depressed phase. However, manias and mixed states were more commonly observed at study entry as compared with the cohort of noncomorbid patients with rapid cycling. The median number of affective episodes meeting DSM-IV criteria in the 12 months prior to study entry was also 8. Of 28 subjects who were not randomly assigned because they were nonresponsive to lithium and divalproex treatment, 74% were experiencing refractory depression and 26% refractory hypomania/mania/mixed states (see Tables 3 and 4). Twenty-five percent of patients met DSM-IV criteria for an early full remission to their alcohol or drug abuse disorder at the end of open stabilization. The responder analyses indicated that of 28 completers, only 43% met criteria for a marked bimodal response and were randomly assigned to the maintenance phase of the study; 57% of patients met criteria for a marked antidepressant response, and 86% met criteria for a marked antimanic response.

In summary, these two 6-month combination therapy data sets suggest that the majority of patients presenting with a recent history of rapid cycling present (either with or without drug abuse) in the depressed phase of the illness and that combined treatment with lithium and divalproex possesses marked efficacy in the treatment of hypomania and mania, but only moderate efficacy in the treatment of depression. These data also suggest that combined treatment with lithium and divalproex leaves a large number of patients with this illness still suffering even after 6 months, and usually with symptoms of depression. The similar designs employed by these 2 studies permit comparisons of treatment response to combination lithium and divalproex between rapid-cycling patients with and without alcohol and drug abuse. Bipolar I disorder (59% vs. 31%), men (64% vs. 36%), DSM-IV mixed states (11% vs. 3%), and poor compliance (38% vs. 29%) were more common in the dual-diagnosis population compared with the non–substance abusing population. Common to these 2 populations was a similar frequency of cycling in the 12 months prior to study entry and a similar prevalence of circular continuous cycling. For both populations, the most common mood state at the time of study entry was depression, and most patients not responding to the combination of lithium and divalproex experienced treatment-refractory depression. These findings are also consistent with earlier observations by Kukopulos and colleagues[9] and tend to suggest that the hallmark of rapid cycling is the frequent recurrence of depression.

Figure 2. Survival Curves Indicating Length of Study Participation for the Overall Study Population of Patients Treated With Lamotrigine Compared With Patients Treated With Placebo[a]



[a]Reprinted from Calabrese et al.,[3] with permission.
[b]Patients who withdrew when they required additional pharmacotherapy for emerging mood symptoms.
[c]Patients who prematurely withdrew from the study for any reason (including additional pharmacotherapy for emerging mood symptoms).

LAMOTRIGINE IN RAPID-CYCLING BIPOLAR DISORDER

Lamotrigine is an established anticonvulsant of the phenyltriazine class that was shown to have positive effects on mood during its clinical development for epilepsy.[33] More recently, several clinical studies of patients with bipolar disorder, including some with treatment-resistant forms of depression and rapid cycling, have suggested that lamotrigine might have antidepressant and mood-stabilizing properties.[34–37] Therefore, a study was designed to examine the safety and efficacy of lamotrigine as monotherapy for the long-term prophylaxis of affective episodes in patients with rapid-cycling bipolar disorder, and the results are reported in detail in a recent edition of the *Journal*.[3]

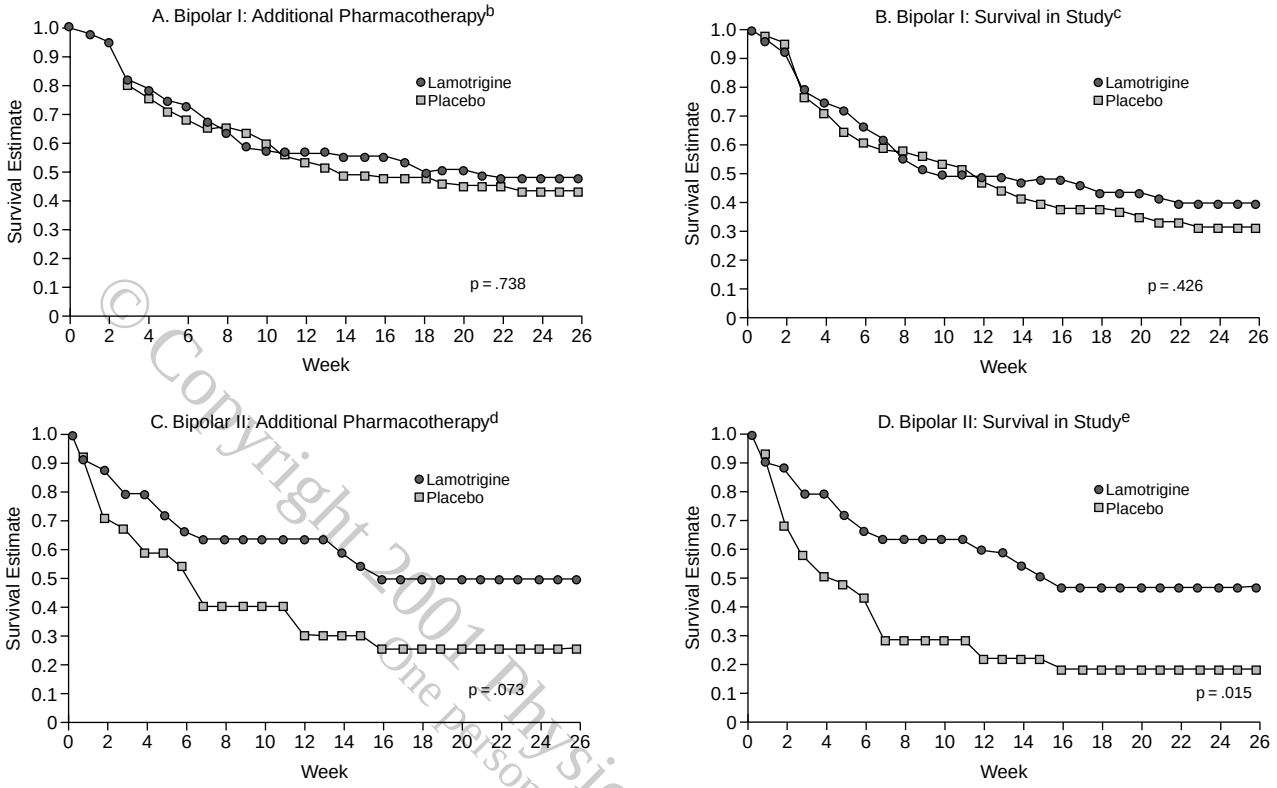
Lamotrigine was added to patients' current psychotropic regimens and titrated to clinical effect during an open-label treatment phase. Stabilized patients were tapered off treatment with other psychotropics and randomly assigned to lamotrigine or placebo monotherapy (in a 1:1 ratio) for 6 months after being stratified for bipolar I or II disorder. Time to additional pharmacotherapy for emerging symptoms of a mood episode was the primary outcome measure. Secondary outcome measures included survival in study, percentage of patients stable without relapse for 6 months, and changes in scores on the Global Assessment Scale (GAS) and the Clinical Global Impressions-Severity of Illness scale (CGI-S).

Three hundred twenty-four patients meeting DSM-IV criteria for rapid-cycling bipolar disorder received open-label lamotrigine, and 182 patients were randomly assigned to the double-blind maintenance phase. For patients entering the open stabilization phase, the mean age was 38 years, the percentage of women was 59%, the percentage of bipolar I subtype was 69%, and the percentage of patients receiving thyroid supplements for diagnosed hypothyroidism was 7%. At study entry, 57% of patients were depressed, 20% were hypomanic or manic, 18% were euthymic, and 5% had mixed states. The mean number of mood episodes in the 12 months prior to study entry was 6.3. The lifetime prevalence of psychosis was 27%, and the percentage of patients with prior suicide attempts was 36%. Prior lifetime exposures to psychotropics included lithium (68%), carbamazepine (27%), divalproex (57%), lamotrigine (< 1%), antidepressants (82%), and antipsychotics (27%). Concomitant psychiatric medications at study entry included lithium (19%), divalproex (19%), carbamazepine (4%), antidepressants (30%), and antipsychotics (7%). Although the most commonly prescribed lifetime medications at the time of study entry were antidepressants, only 36% of patients reported having responded to them positively.

Treatment groups during the randomized phase (N = 182) were similar with respect to age, sex, race, medical history, psychiatric history, prior treatments, response to treatments, and current psychiatric state. The majority of patients were classified as having bipolar I disorder (71%). A comparison of bipolar I and II patients showed no differences on key parameters. Compared with bipolar II patients, bipolar I patients had a greater prevalence of suicide attempts (40% vs. 28%) and average number of lifetime hospitalizations (2.3 vs. 0.7). The average daily lamotrigine dose was 288 ± 94 mg, and the range was 100 to 506 mg/day.

Forty-nine placebo patients (56%) and 45 lamotrigine patients (50%) required additional pharmacotherapy for emerging symptoms of a mood episode. The difference between the 2 general treatment groups in time to additional pharmacotherapy did not achieve statistical significance (Figure 2A). The median survival times were 18 weeks for lamotrigine and 12 weeks for placebo. When survival in

Figure 3. Survival Curves Indicating Length of Study Participation for Bipolar I (N = 125) and II (N = 52) Subtypes Treated With Lamotrigine Compared With Placebo[a]

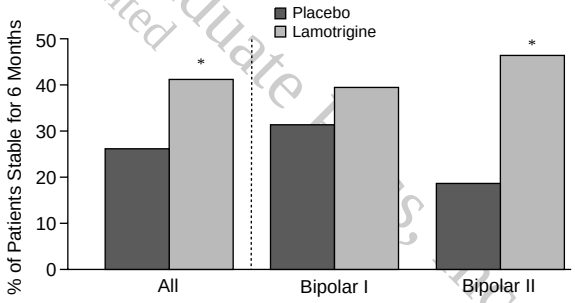


[a]Reprinted from Calabrese et al.[3] with permission.
[b]Bipolar I patients who withdrew when they required additional pharmacotherapy for emerging mood symptoms.
[c]Bipolar I patients who prematurely withdrew from the study for any reason (including additional pharmacotherapy for emerging mood symptoms).
[d]Bipolar II patients who withdrew when they required additional pharmacotherapy for emerging mood symptoms.
[e]Bipolar II patients who prematurely withdrew from the study for any reason (including additional pharmacotherapy for emerging mood symptoms).

study (any premature discontinuation, including for additional pharmacotherapy) was evaluated, the difference between the treatment groups was significant (p = .04; Figure 2B). For survival in study, the median survival times were 14 weeks for lamotrigine and 8 weeks for placebo. Time to additional pharmacotherapy and survival in study did not yield significant differences between lamotrigine and placebo in patients with bipolar I disorder (Figure 3). When time to additional pharmacotherapy was evaluated, a trend toward significance (p = .07) was found in the separation between placebo and lamotrigine. Median survival time without additional pharmacotherapy for the bipolar II subtype was 17 weeks for lamotrigine and 7 weeks for placebo. The overall survival in study analysis yielded a significant separation between treatment groups (p = .01). Median overall survival was 15 weeks for lamotrigine and 4 weeks for placebo. The majority of those patients (80%) requiring additional pharmacotherapy were treated for depressive symptoms; 20% were treated for emerging manic, hypomanic, or mixed symptoms.

The percentage of patients who completed the 6-month randomized phase clinically stable on monotherapy without evidence of relapse into hypomania, mania, or depression was significantly greater in the lamotrigine group than in the placebo group (Figure 4). Of the 60 patients who were stable for 6 months of monotherapy, 37 (41%) of 90 were in the lamotrigine group compared with 23 (26%) of 87 in the placebo group (p = .03). The difference

Figure 4. Percentage of Patients Stable Without Relapse for 6 Months Receiving Lamotrigine or Placebo[a]



[a]Reprinted from Calabrese et al.[3] with permission.
*p < .05.

for lamotrigine versus placebo was not statistically significant for the bipolar I subtype, but was significant (46% vs. 18%, respectively; p = .04) for the bipolar II subtype. The CGI-S and GAS were used to provide additional measures of clinical stability. For the overall study population and the bipolar I subtype, there were no statistically significant differences between treatment groups in CGI-S change from baseline scores using last observation carried forward (LOCF). For the bipolar II subtype, trends toward statistically significant differences (p < .10) favoring the lamotrigine group were observed in CGI-S scores compared with the placebo group at weeks 6 and 12. No statistically significant differences favoring lamotrigine were observed between groups in GAS change from baseline scores in the general cohort of patients (LOCF). Significant differences favoring lamotrigine were noted at weeks 3, 6, and 12 in the bipolar II subtype; however, no significant differences were noted at any timepoint for the bipolar I subtype. There were no significant differences observed in the change from baseline LOCF analyses at any point for the 17-item HAM-D or the Mania Rating Scale.

The most common adverse events (≥ 10%) observed during the open stabilization phase were headache, infection, influenza, nausea, dream abnormality, dizziness, and rash. In the randomized phase, 122 patients (67% lamotrigine; 68% placebo) experienced adverse events, and the most common adverse events were headache, nausea, infection, pain, and accidental injury. Lamotrigine-related rash occurred in 8% of patients during open stabilization and in no patients in the randomized phase. There were no serious rashes during either phase of the study, and no patients required hospitalization for a rash. From study entry to study endpoint, there was no mean change in body weight for the lamotrigine-treated patients.

DISCUSSION

The available data suggest that only one half of patients with rapid-cycling experience a marked bimodal response to the combined administration of lithium and divalproex at the end of a 6-month treatment period. The spectrum of activity includes marked antimanic and moderate antidepressant properties. Comorbid alcohol and drug abuse does not appear to affect the spectrum of activity or the overall response rates in compliant patients. Rather, the comorbidity appears to alter prognosis by increasing the prevalence of poor compliance. There exists a need for an agent that possesses marked antidepressant properties without causing cycle acceleration. The maintenance study comparing lamotrigine monotherapy with placebo included a large prospective sample of patients with rapid-cycling bipolar disorder. These placebo-controlled data suggest that lamotrigine monotherapy is a useful treatment for rapid-cycling patients with bipolar II disorder. The spectrum of efficacy of lamotrigine appears to complement that of combined lithium and divalproex therapy.

There is now a series of published reports which suggest that the most prominent feature of rapid-cycling bipolar disorder is recurrent depression, and usually treatment-refractory depression: (1) the original observations by Kukopulos and colleagues[9]; (2) the earlier findings of Dunner et al.,[17] which demonstrated that lithium had prophylactic efficacy in hypomania, but not depression; (3) the spectrum of prophylactic efficacy of divalproex (either in monotherapy or in combination)[1,2]; (4) the higher prevalence of depression as the index episode in the lamotrigine maintenance study[3]; and (5) the high prevalence of patients having depression on reaching study endpoint in both treatment arms (37% lamotrigine; 45% placebo) and requiring additional pharmacotherapy in the lamotrigine maintenance study.[3] The higher prevalence of depression as the index episode in the 2 new cohorts of patients with rapid cycling presented in this article, as well as the higher rates of treatment-refractory depression at the end of 6 months of combined treatment with lithium and divalproex, also appears to support the role of depression as the primary clinical challenge in rapid-cycling bipolar disorder. In addition, the Stanley Bipolar Disorders Network data also reflect that the majority of patients initially present in the depressed phase of their illness and that in 11,000 visits involving the treatment of more than 500 patients, more than 50% of the visits were associated with questionable-to-definite depressive symptoms of mild-to-moderate severity (reference 8 and T.S., unpublished data, 2001).

There now exist large data sets which appear to suggest that lamotrigine may complement the spectrum of efficacy of lithium and divalproex when used in rapid-cycling bipolar disorder. In managing patients with this refractory variant of illness, the triple regimen of lithium, divalproex, and lamotrigine may be useful in combination. An urgent need exists to evaluate the spectrum of efficacy and safety of these medications when used in combination in the management of patients with rapid-cycling bipolar disorder, and such a study is ongoing.

Drug names: carbamazepine (Tegretol and others), divalproex sodium (Depakote), lamotrigine (Lamictal).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, carbamazepine and lamotrigine are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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