An Open-Label Study of Lamotrigine Adjunct or Monotherapy for the Treatment of Adolescents With Bipolar Depression

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ABSTRACT

Objective: The treatment of pediatric bipolar depression has not been well studied. The authors wished to prospectively study the efficacy of lamotrigine as adjunctive or monotherapy in adolescents with bipolar disorder who were experiencing a depressive episode. **Method:** This was an 8-week open-label trial of lamotrigine with 20 adolescents ages 12–17 years (mean age 15.8; 7 boys, 13 girls) with diagnoses of bipolar disorder I, II, or not otherwise specified, who were experiencing a depressive episode. Lamotrigine was begun at 12.5 to 25 mg/day. Primary response criteria was a 1 or a 2 on the Clinical Global Impression-Improvement at week 8. A secondary criterion was at least a 50% decrease in Children's Depression Rating Scale-Revised scores. **Results:** Nineteen subjects completed the trial. The mean final dose was 131.6 mg/day. Seven subjects were taking other psychotropic medications. Sixteen subjects (84%) responded by primary criteria, and 12 (63%) responded to our secondary criteria. Eleven subjects (58%) were considered in remission at week 8. Young Mania Rating Scale and Overt Aggression Scale-Modified scores also decreased significantly during the trial. There was no significant weight change, rash, or other adverse effects during the trial. **Conclusions:** Adolescents with bipolar depression appeared to respond to lamotrigine treatment, whether as adjunctive therapy or monotherapy, with decreases in depression, mania, and aggression. Larger, placebo-controlled studies of lamotrigine are needed in this population. *J. Am. Acad. Child Adolesc. Psychiatry*, 2006;45(3):298–304. **Key Words:** lamotrigine, bipolar disorder, depression, adolescents, trial.

Adolescents with bipolar disorder (BD) commonly present with mixed mania and continuous rapid cycling of mood states, including depression, irritability, and less commonly euphoria (Findling et al., 2001; Geller et al., 2000). Although there have been multiple reports published regarding the treatment of manic symptoms in children and adolescents, albeit mostly open studies, the efficacy of agents to treat bipolar depression in this population has not been adequately studied.

Nevertheless, there exist many possible treatments for patients with bipolar depression. Studies have found lithium, divalproex, tricyclic antidepressants, serotonin reuptake inhibitors (SRIs), lamotrigine, olanzapine, olanzapine/fluoxetine combination, quetiapine, and pramipexole effective in treating adults with bipolar depression (Ketter et al., 2004). Although antidepressants have historically been the first-line treatment, concern over the propensity for antidepressants to cause manic switching or cycle acceleration has led to questioning of this approach (Ghaemi et al., 2003). Based on existing data, an international consensus group recently recommended lithium or lamotrigine as the first line treatment of adult bipolar depression, closely followed by olanzapine or olanzapine/fluoxetine combination (Calabrese et al., 2004). Specifically, lamotrigine has been found efficacious in treating (Calabrese et al., 1999b) as well as preventing (Goodwin et al., 2004) adult bipolar depression.

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Although adult data in this area may inform where there is a lack of child data, it may be prudent not to extrapolate blindly. For example, tricyclic antidepressants are effective for depression in adults but not children (Emslie and Judge, 2000). Fortunately, there are some emerging data on the naturalistic treatment of pediatric bipolar depression. In a retrospective chart review, 42 children with BD who were prescribed SRIs were seven times more likely to improve in depressive symptoms than children with BD who were not prescribed any other medication (Biederman et al., 2000). However, children prescribed SRIs were also three times more likely to experience a subsequent manic episode, a finding not shared by prescription of a mood stabilizer. Through this and more anecdotal evidence, including retrospective chart reviews, SRIs are thought to increase the risk of manic switching in pediatric BD (Cicero et al., 2003; Faedda et al., 2004), although not all reports agree with this conclusion (Craney and Geller, 2003).

Similar to the case in adults with BD, lamotrigine may be a better choice than antidepressants as a first-line treatment in children and adolescents with bipolar depression. One open study that included seven adolescents found lamotrigine effective in treating bipolar depression (Kusumakar and Yatham, 1997). A case series also reported on the usefulness of lamotrigine adjunct and monotherapy in nine adolescents with refractory depressive disorders (six with bipolar depression; Carandang et al., 2003). In this series, eight patients responded well to a mean dose of 142 mg/day, as determined by a 1 or a 2 on the Bipolar scale of the Clinical Global Impressions. However, lamotrigine carries a U.S. Food and Drug Administration–mandated box warning cautioning the increased risk of rash in children under age 16 years. This warning was the result of reports of a 10-fold incidence of serious rash, including Stevens-Johnson syndrome, in children compared with adults treated with lamotrigine. Before 1997, a few fatalities had also been reported in children taking lamotrigine, mostly caused by toxic epidermal necrolysis, which carries a higher rate of mortality than Stevens-Johnson syndrome (Guberman et al., 1999). Because of these data, many clinicians may have been reluctant to use this medication in pediatric populations. However, these data were acquired before current slower titration guidelines were recommended, including slower titration when valproate is given concomitantly. More recent data suggest a much lower rate of rash, especially serious rash, in pediatric patients (Messenheimer, 2002).

Therefore, we wished to study the efficacy, safety, and tolerability of lamotrigine in adolescents with BD who were experiencing a depressive episode. Because of the paucity of data, we conducted an open study of lamotrigine in adolescents with BDs.

METHOD

This was an 8-week open-label trial of lamotrigine monotherapy or adjunct therapy in adolescents with bipolar depression or mixed mania. Informed written and verbal consent was obtained from the parent or legal guardian of the subjects, and written and verbal assent was obtained from the subjects. The protocol was approved by the Stanford University Panel on Human Subjects in Medical Research.

Inclusion criteria were males or females, 12–17 years old, with a diagnosis of BD I, II, or not otherwise specified (NOS) by the WASH-U-KSADS (Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia; Geller et al., 1996). We used *DSM-IV* definitions of BD I and II: BD I required a full manic episode (at least 7 days of elevated, irritable, or expansive mood, with 3 concurrent "B" symptoms of mania and 4 if the mood was irritable and not elevated). BD II required a hypomanic episode (4–6 days of meeting symptom criteria for a manic episode) as well as a history of a major depressive episode. For the purposes of this study, BD NOS was defined as having a period of significant elevated, irritable, or expansive mood for at least 2 days, with at least 2 other symptoms of mania during that time (3 if the predominant mood was irritable). Comorbid conditions of attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, separation anxiety, social phobia, and generalized anxiety disorder were allowed. Subjects also were required to be experiencing a depressive episode by *DSM-IV* criteria and needed to have a score of 36 or greater on the Children's Depression Rating Scale-Revised (CDRS-R; Poznanski et al., 1984, 1985) before beginning lamotrigine treatment.

If patients were taking an antidepressant, then the medication was tapered and discontinued for 2–4 weeks before reassessing the subject for entry criteria. Other mood stabilizers, (lithium, valproate, carbamazepine), antipsychotics (olanzapine, risperidone, quetiapine, ziprasidone, or aripiprazole), and ADHD treatments (including psychostimulants and atomoxetine) were allowed to be continued as long as there had been no dose changes within 1 month of the study. Psychotherapy was not allowed to be started within 1 month before the study.

Exclusion criteria included prior exposure to lamotrigine, substance dependence or use within 2 months before the study, acute active suicidal ideation (i.e., plan or intent) or recent (within 6 months) suicide attempt, diagnosis of autism or Asperger's disorder, mental retardation (suspected IQ <80), or concomitant seizure disorder.

Physical examinations, including height and weight assessment, were performed and laboratory tests, including complete blood count, renal panel, thyroid-stimulating hormone, β-human chorionic gonadotropin, and mood stabilizer serum levels, were performed at baseline and at week 8. The rating scales used weekly were the CDRS-R, the Young Mania Rating Scale (YMRS; Young et al., 1978), the Overt Aggression Scale-Modified (Coccaro et al.,

2000), the CGI Severity scale (CGI-S), and the CGI Improvement scale (CGI-I). The primary measure for response was a "1" or a "2" on the CGI-I at week 8. The secondary measure for positive response was defined as at least a 50% decrease in the CDRS-R score from baseline to week 8.

Lamotrigine was gradually added to any current medication regimens (if any; mood stabilizers, stimulants, antipsychotics) of subjects experiencing a depressive or mixed episode. The dose of lamotrigine in subjects not taking adjunct valproate was titrated as follows: 25 mg/day lamotrigine for 2 weeks, 50 mg/day for 2 weeks, then 100 mg/day. Dose was then increased by 25 mg/week according to clinical need. The target dose of lamotrigine for subjects not taking valproate was 100 to 200 mg/day (Table 1). The three subjects taking valproate, which usually doubles or triples the serum levels of lamotrigine, were started on 12.5 mg/day and titrated to a final target dose of 50 to 100 mg/day. Three other subjects not taking valproate were started at 10 mg/day for 1 week because of their young age (mean 4.0 ± 0.4 years) and the parent's increased concern about the child's sensitivity to past medications. Lamotrigine was given once or twice daily.

We also instructed subjects to follow antigen precautions (Ketter et al., 2005). That is, during the trial, subjects were advised not to ingest other new medicines or new foods or use new cosmetics, conditioners, deodorants, detergents, or fabric softeners. In addition, we made sure that subjects did not start lamotrigine within 2 weeks of having a rash, viral syndrome, or vaccination. Finally, we requested that subjects avoid stimulating their immune system by preventing sunburn or poison oak exposure. These precautions were designed to decrease the incidence of nonserious rashes that were not caused by lamotrigine and to decrease the stimulation of the immune system that could increase immune reactions to drug.

TABLE 1
Demographics of Study Subjects (N = 20)

Mean age, yr (SD)	15.8 (1.7)
Gender, % male	35
Race, no. (%)	
African American	1 (5)
Hispanic	1 (5)
Asian	0 (0)
White	18 (90)
Bipolar diagnoses, no. (%)	
Bipolar I disorder	7 (35)
Bipolar II disorder	6 (30)
Bipolar disorder NOS	7 (35)
Comorbid diagnoses, no. (%)	
ADHD	13 (65)
Anxiety disorder	10 (50)
Oppositional defiant disorder	9 (45)
Psychosis	3 (15)
Concurrent psychotropic medications, no. (%)	
Stimulants	2 (10)
Lithium	1 (5)
Valproate	3 (15)
Antipsychotics	2 (10)
Any	7 (35)

Note: ADHD = attention-deficit/hyperactivity disorder; NOS = not otherwise specified.

TABLE 2
Change in Scores for Relevant Measures from Baseline to Week 8 (N = 19)

	Baseline	Week 8	p
CDRS-R	58.0 (12.7)	28.0 (11.6)	.001
YMRS	16.6 (8.6)	9.8 (8.1)	.001
OAS-Aggression	48.9 (50.2)	16.7 (24.7)	.02
OAS-Irritability	6.4 (1.6)	3.3 (2.5)	<.001
OAS-Suicidality	1.56 (2.1)	0.26 (0.65)	.02
Weight (lb)	159.3 (40.5)	160.2 (42.1)	.34
LTG dose (mg/day)	0.00	131.6 (31.0)	—

Note: CDRS-R = Children's Depression Rating Scale-Revised; YMRS = Young Mania Rating Scale; OAS = Overt Aggression Scale; LTG = lamotrigine.

RESULTS

There were seven subjects with BD I, six with BD II, and seven with BD NOS. Mean age was 15.8 ± 1.7 years, and there were 13 girls and 7 boys. Thirteen children had a comorbid diagnosis of ADHD, 10 had oppositional defiant disorder, 9 had generalized anxiety disorder, 1 had conduct disorder, and 3 had a history of psychotic symptoms. There were seven (35%) subjects taking adjunctive medications: two were on divalproex sodium; one on methylphenidate; one on aripiprazole; one on olanzapine; one on alprazolam, trazodone, and lithium; and one on atomoxetine, OROS-methylphenidate and divalproex sodium. Subjects were predominantly white, with one Asian subject and one African American subject (Table 1).

One subject (female, age 15, with BD NOS) dropped out before week 2 because of suicidality necessitating hospitalization. Her data were included only in the baseline and week 1 data, and she was not included in the responder analyses because she had only had 1 week of lamotrigine treatment at 25 mg/day. The rest of the subjects completed the study, with one other subject being hospitalized at week 8. Mean final dose was 132 ± 31 mg/day. For the three subjects taking divalproex, final lamotrigine doses were 75, 75, and 100 mg/day, respectively.

Of 19 evaluable subjects, 16 (84%) were considered responders by primary criteria (a score of 1 or 2 on the CGI-I), and 12 (63%) responded by secondary criteria (at least a 50% decrease in CDRS-R scores). Remission, considered a score of 28 or less on the CDRS-R and a CGI-S score of 1 or 2, was achieved by 11 of 19 (58%) subjects. Paired-samples t test revealed a significant decrease in CDRS-R score

from baseline to completion of the study (mean change –30.1 ± 11.9; t = 11.1, p < .001; Table 2). There was statistical improvement in CDRS-R scores after 1 week (t = 2.2, df = 19 p = .04; including data from all subjects); however, this significance was lost at week 2 (t = 0.70 , df = 18, p = .49), but regained at week 3 and thereafter (t = 4.1, df = 18, p = .001; Fig. 1).

Effect sizes (Cohen's d) were calculated to allow comparison of the magnitude of treatment effect with other similar studies. The overall CDRS-R effect size was 2.47 (Cohen's d), and YMRS effect size 0.81.

Because there were so few nonresponders by primary criteria, we performed exploratory analyses to determine predictors of response and nonresponse according to secondary criteria. Although no subjects were in a mixed episode by *DSM-IV* criteria, several subjects had transient symptoms of mania leading to relatively elevated YMRS scores. Subjects with a baseline YMRS score >20 were less likely to be responders by secondary criteria (Fisher exact test, df = 1, p = .04). Nevertheless, YMRS scores decreased significantly over the course of the study (p = .002; Table 2). At evaluation during week 3, 14 of the 19 (74%) subjects had a significant increase in YMRS score compared with the week before (t = 2.2, df = 18, p = .04). The mean YMRS score at week 3 was 16.3 ± 8.1, which was the highest mean weekly YMRS score after baseline (Fig. 2). Of the 11 responders by secondary criteria, 4 had BD I, 3 had BD II, and 4 had BD NOS. Hence, the type of BD did not predict response. Neither gender (Fisher exact test, df = 1, p = .68) nor age (t = 0.24, df = 17, p = .82) predicted response. The mean baseline CDRS-R score for CDRS-R nonresponders was similar to that of responders (55.7 ± 17.2 versus 59.3 ± 9.9, respectively; F = 0.35, df = 17, p = .56). The presence of a comorbid condition was not different between responders and nonresponders (F = 0.16, df = 17, p = .70).

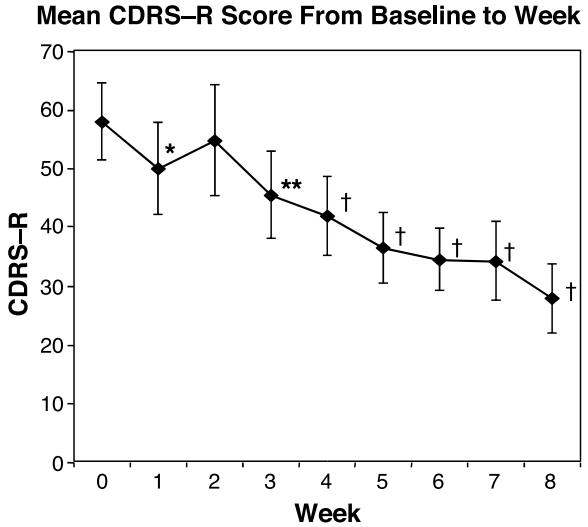

Fig. 1 Mean YMRS score from baseline to week 8 in study completers. Bars represent SD. *p = .04 compared with baseline, **p = .001 compared with baseline, †p < .001 compared with baseline.

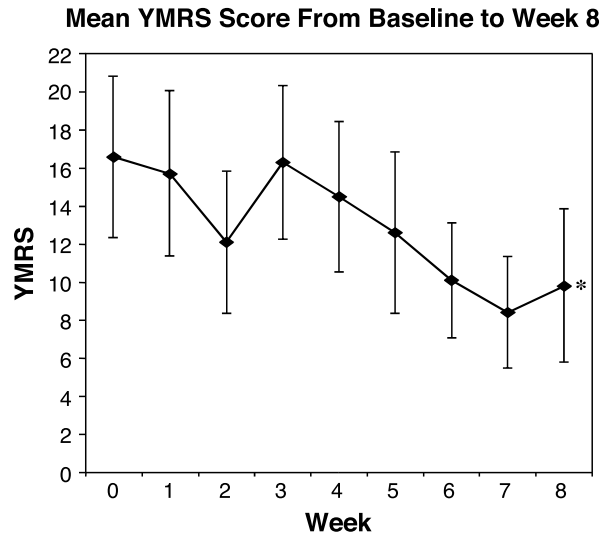

Fig. 2 Mean CDRS-R score from baseline to week 8 in study completers. Bars represent SD. *p < .001 compared with baseline.

The seven subjects on adjunctive medication did not have a significantly different CDRS-R score compared with those on lamotrigine monotherapy at baseline (t = 0.109, df = 17, p = 091) or week 8 (t = 0.96, df = 17, p = .35). In addition, subjects on adjunctive medication did not respond better than those on monotherapy (Fisher exact test, df = 1, p = .17). The six subjects taking adjunctive mood stabilizers or antipsychotics had a significantly lower mean baseline YMRS score than those not taking these medications (10.5 ± 5.8 versus 19.0 ± 8.2; t = 2.3, df = 18, p = .03). For subjects taking adjunctive mood stabilizers, lithium and valproate serum levels did not change from baseline to week 8 (lithium: 0.7 to 0.7 mEq/L; valproate: 87.7 ± 24.0 to 83.5 ± 22.0 μg/mL).

Scores on the Overt Aggression Scale-Modified also decreased significantly from baseline to week 8 (Table 2). Subjects showed significant decreases in total aggression (48.9 ± 50.2 to 16.7 ± 24.7; t = 2.6, df = 18, p = .02) and subscales of irritability (6.1 ± 1.6 to 3.3 ± 2.5; t = 3.98, df = 18, p < .001) and suicide (1.56 ± 2.1 to 0.26 ± 0.65; t = 2.7, df = 18, p = .02).

There was no significant weight change during the course of the trial (0.42 ± 1.9 kg; $t = 0.98$, $df = 18$, $p = .34$). Adverse effects reported at any time during the study included headache (84%), fatigue (58%), nausea (53%), sweating (47%), and difficulty sleeping (10.5%). Two subjects (10.5%) reported a rash during the study; however, on review, it was decided that these subjects experienced skin irritations, not true rashes. One subject had used an electric razor for the first time and had a subsequent mild erythematous patch on his cheek. The other subject reported vaginal itching after intercourse, and an emergency department physician determined the cause as an ingrown hair. No subject discontinued the study because of any adverse effects, including rash. Furthermore, no subjects had any significant laboratory abnormalities at week 8.

DISCUSSION

Adolescents with BDs and depressive episodes responded well to open-label treatment with lamotrigine both by overall clinical impression as well as by depression scores. The majority of subjects received monotherapy; those who received adjunct therapy did not respond differently. Furthermore, no subject developed a manic episode during the 8 weeks of the study. Lamotrigine was well tolerated, with no rashes deemed drug related or requiring cessation of the drug.

There have been few previous studies of agents in adolescent bipolar depression, so it is difficult to compare our results with existing data. Certainly, our response rate by primary criteria (84%) appears robustly high, especially compared with open studies of agents for acute mania in similar populations, which have reported approximately 42% to 62% response rates (Frazier et al., 2001; Kowatch et al., 2000). It is also somewhat higher than the 68% of depressed adults with BD who improved by CGI-I in an open study of lamotrigine adjunct therapy or monotherapy (Calabrese et al., 1999a).

Our response rate by secondary criteria (63%) approaches response rates seen for open studies of adolescent mania for lithium (66%) and divalproex (65%; Chang and Simeonova, 2004). The discrepancy between our two rates of response (84% and 63%) can be partially attributed to two subjects who failed to show a 50% decrease in CDRS-R scores by only 1 point and had a CGI-I score of 2 at week 8. Thus, although these additional subjects clearly showed good overall clinical response, they did not meet secondary response criteria. In addition, YMRS and Overt Aggression Scale-Modified scores decreased significantly across subjects, indicating overall improvements in symptoms of mania and aggression. These improvements, along with decreases in depression symptoms, likely also contributed to CGI-I ratings indicating improvement and positive response to treatment.

Furthermore, remission was achieved by 58% of subjects in this study. This figure may be more important clinically than the response rate because remission indicated that depressive symptoms were almost nonexistent, and the patient was at most considered "mildly ill." This rate is slightly higher than the 47% of 90 children and adolescents with BD achieving remission in an open study of lithium and valproate combination therapy (Findling et al., 2003). In that study, remission criteria included a CDRS-R score of ≤40, whereas our cutoff was ≤28. Therefore, it is unclear whether these subjects achieved similar low levels of depressive symptoms as did subjects in our study.

There are data to support the use of lamotrigine in adults with rapid cycling BD (Calabrese et al., 1999a). Rapid cycling in adolescents with BD often appears as ultradian cycling (Tillman and Geller, 2003), which can approximate mixed states. Although none of our subjects had a clear episode of mixed mania before entry into the study, many did have periodic manic symptoms that caused relatively elevated baseline YMRS scores. Mania symptoms did decrease overall throughout the study, but nonresponders (by secondary criteria) had higher baseline YMRS scores than responders. This finding suggests that patients with mixed mania may not respond to lamotrigine as well as those with bipolar depression and fewer manic symptoms.

Lamotrigine was well tolerated in this study, with no serious adverse events, including weight gain or rash. Rash remains possibly the largest concern that clinicians have in using this medication in children, as lamotrigine carries a boxed warning on the package insert cautioning increased incidence of rash in children under 16 years of age. This U.S. Food and Drug Administration requirement was the result of studies before March 1998 reporting a 10-fold increase in risk of serious rash (defined as necessitating hospitalization or discontinuation of treatment)

in children compared with adults taking lamotrigine, including Stevens-Johnson syndrome (1.0% versus 0.3%; Guberman et al., 1999). More recent data suggest that the risk of serious rash has been reduced (Messenheimer, 2002). This reduction is thought to be secondary to a more gradual titration schedule that is now recommended by the manufacturers, including halving the dose for patients who are also taking valproate, which can double or triple serum levels of lamotrigine (Guberman et al., 1999; Messenheimer, 2002). We may also have prevented rash not caused by lamotrigine by using antigen precautions developed specifically for this purpose.

Lack of weight gain, as seen in this study, is a significant advantage of a mood-stabilizing medication in this population. Other commonly used mood stabilizers (predominantly used for manic symptoms), including divalproex, lithium, olanzapine, risperidone, and quetiapine, all have been reported to be associated with mild, moderate, or even severe weight gain in children (Chang and Simeonova, 2004; Cheng-Shannon et al., 2004).

Limitations

Foremost, this was an open study and thus susceptible to rater bias. Lack of a placebo-control arm prevents further understanding of how much improvement was the result of other factors, such as receiving weekly evaluation and treatment at an academic research center. Our subject pool was slightly heterogeneous in including adolescents with BD I, II, and NOS, although it may be more representative of typical patients who present as outpatients to mental health clinicians. Our sample size, however, was somewhat small and contained predominantly white subjects and more females than males, limiting the ability to generalize these findings to all adolescents with bipolar depression. Finally, because some patients were taking other medications, including mood stabilizers and atypical antipsychotics, it is unclear whether lamotrigine was particularly effective because of an undetected synergistic effect with another medication.

Clinical Implications

Depressive symptoms commonly occur either as part of a first depressive mood episode or as part of a mixed episode. Four-year follow-up of a cohort of 86 youths with BD found that polarity switch into a depressive episode occurred 1.1 times per year (Geller et al., 2004). Suicidality appears at any given time in up to 25% of children with BD (Geller et al., 2000). Thus, effective and safe treatments for pediatric bipolar depression are greatly needed. SRIs have been reported through retrospective case reviews to cause or exacerbate manic symptoms in children and adolescents with BD (Biederman et al., 2000; Faedda et al., 2004). Most of these manic reactions occurred within 1 month of beginning antidepressant treatment. In this study, lamotrigine was an efficacious treatment for adolescents with bipolar depression without causing worsening of manic symptoms over the course of 2 months. Full resolution of depressive symptoms (a CDRS-R score of $\leq$28) was seen as early as 1 month in 4 subjects and by 2 months in 11 of 19 subjects (58%), with effective doses ranging from 100 to 175 mg/day.

By gradual titration of lamotrigine and implementation of antigen precautions, the risk of serious rash may be largely minimized. This is in contrast to reports before 1998, in which children were commonly prescribed lamotrigine beginning at relatively high doses (e.g., 100 mg/day) and increasing the dose quickly. This quick titration may have led to the prior high rate of rash necessitating cessation of lamotrigine therapy. Current guidelines for children and adolescents, based on epilepsy data, recommend much more gradual titration (see Guberman et al., 1999 for details), especially in the presence of adjunctive valproate therapy. Nevertheless, it is still recommended that any child or adolescent with a new rash appearing within the first 2 months of initiation or a dose increase of lamotrigine be evaluated, with probable subsequent discontinuation of lamotrigine therapy if there is no alternate reason for the rash. Most rashes caused by lamotrigine appear to be benign and resolve upon lamotrigine discontinuation. Any child with a serious rash, especially involving mucous membranes, should be immediately referred to an emergency treatment center for further treatment.

This is the first prospective trial of an agent for the treatment of adolescent bipolar depression. Given the robust efficacy of lamotrigine in adults with bipolar depression and these promising open data, further controlled studies should be conducted in this population as well as in younger children with bipolar depression.

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