The Effect of Dermatologic Precautions on the Incidence of Rash With Addition of Lamotrigine in the Treatment of Bipolar I Disorder: A Randomized Trial

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Objective: Prescribing recommendations specify that lamotrigine should ordinarily be discontinued at the first sign of rash, regardless of its type and severity, unless the rash is clearly not drug related. This practice helps to ensure that lamotrigine is discontinued in instances of serious rash (an event occurring in up to 0.13% of cases in bipolar clinical trials) but may lead to unnecessary discontinuation of lamotrigine for cases of nonserious rash arising from nondrug causes. Measures aimed at reducing overall occurrence of dermatologic reactions might reduce the incidence of nonserious rash leading to premature lamotrigine discontinuation. This study assessed the impact of specific instructions designed to decrease risk of dermatologic reactions, including nonserious rash, during initiation of and early treatment with lamotrigine in patients with bipolar I disorder.

Method: Outpatients with DSM-IV–diagnosed bipolar I disorder ≥ 13 years of age at 188 sites were randomly assigned to receive Usual Care Precautions (UCP; precautions from the patient instructions in the prescribing information for reducing risk of rash including nonserious rash) or Dermatologic Precautions (DP; precautions as above [UCP] plus additional precautions intended to decrease risk of any dermatologic reaction including nonserious rash) during 12 weeks of adding open-label lamotrigine to concomitant medications. Patients with comorbid medical and psychiatric problems were not excluded unless, in the opinion of the investigators, these problems were sufficiently severe to preclude participation. Investigators and patients were blinded to which precaution group patients were randomly assigned. The primary outcome measure was the rate of rash during the treatment period. Secondary outcome measures included clinical response to lamotrigine, assessed with the investigator- and self-rated Clinical Global Impressions-Bipolar version (CGI-BP) and the Clinical Global Impressions-Efficacy Index (CGI-EI). Data were collected from August 2003 to August 2004.

Results: 867 (74%) of 1175 patients completed the study. Only 182 (15%) of 1175 patients had an adverse event leading to discontinuation of study medication or withdrawal, including 62 (5.3%) of 1175 due to nonserious rash. No serious rashes were reported during the study in either group. The incidence of nonserious rash was similarly low in patients with UCP and DP (8.8% and 8.6%, respectively). CGI-BP-Severity and -Improvement scores indicated mood improvement when lamotrigine was added to existing therapy, and CGI-EI scores at weeks 5 and 12 reflected a favorable balance between control of mood symptoms and tolerability. At both weeks 5 and 12, investigators reported that therapeutic effects of additional lamotrigine outweighed side effects in 74% of subjects.

Conclusion: UCP and DP yielded low, similar nonserious rash rates, which were marginally lower than nonserious rash rates in prior clinical trials that did not utilize DP but marginally higher than that in a prior open case series using DP. Nevertheless, the results are encouraging: in this large study reflecting real-world use, lamotrigine was well tolerated with no serious rash and low incidences of nonserious rash and discontinuation due to rash, and lamotrigine therapy was associated with clinical improvement in a heterogeneous cohort of patients with bipolar I disorder.

(J Clin Psychiatry 2006;67:400–406)

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GlaxoSmithKline funded the study described in this manuscript. Drs. Graham and Thompson and Messrs. Roberts and Nanry are employees of GlaxoSmithKline.

Portions of this article were previously presented as an abstract for the joint annual meeting of the American Epilepsy Society and the American Clinical Neurophysiology Society in Washington, D.C., December 2–6, 2005.

Financial disclosure appears at the end of the article.

The authors acknowledge Jane Saiers, Ph.D., of The Write Medicine, Inc., Chapel Hill, N.C., for editorial assistance with this manuscript.

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The adverse-event profile of lamotrigine monotherapy or adjunctive therapy has been shown to be generally similar to that of placebo in 8 placebo-controlled clinical studies of up to 18 months' duration in patients with bipolar disorder.[1] The incidence of rash in placebo-controlled clinical studies of patients with bipolar disorder was also similar between lamotrigine (9% of 827 patients) and placebo (8% of 685 patients).[1–3] These numbers reflect both serious and nonserious cases

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of rash including phenomena reported as rash, urticaria, erythema multiforme, maculopapular rash, bullous eruption, pustular rash, or Stevens-Johnson syndrome. Rash is of interest because of the previous finding in early epilepsy clinical studies that lamotrigine was associated, albeit infrequently (0.3% incidence in adults), with serious rash, defined as any rash associated with hospitalization and discontinuation of lamotrigine or rash reported as Stevens-Johnson syndrome or toxic epidermal necrolysis.[4–6] In these early clinical trials in patients with epilepsy, cases of serious rash typically occurred in the initial 2 to 8 weeks of therapy and were associated with high initial doses of lamotrigine, rapid dose escalation, and concomitant valproate use.[4–6] In light of these findings, specific lamotrigine dosing recommendations intended to decrease the risk of serious rash were employed in controlled clinical trials of lamotrigine in bipolar disorder.[6] These recommendations involved initiating lamotrigine at a lower initial dose and employing slower titration to an effective dose than in earlier epilepsy trials. Additionally, adjustments to the lamotrigine dose were made depending on concomitant medications including valproate, which doubles plasma lamotrigine concentrations.

These dosing recommendations were supported by the finding that serious rash as defined above was not observed with lamotrigine in placebo-controlled clinical trials in patients with bipolar disorder (0 of 827 lamotrigine-treated patients compared with 1 of 685 placebo-treated patients, or 0.15%).[1] Across all controlled and uncontrolled bipolar disorder studies in the lamotrigine development program, serious rash was reported among 3 (0.13%) of 2272 patients treated with lamotrigine.[1]

The seriousness of rash arising during initiation of lamotrigine therapy cannot be reliably predicted on the basis of its initial appearance. Therefore, the prescribing information recommends that lamotrigine should ordinarily be discontinued at the first sign of rash unless the rash is clearly not drug related.[6] This practice helps to ensure that lamotrigine is discontinued in patients with serious rash but may result in unnecessary interruption or discontinuation of lamotrigine due to benign dermatologic reactions arising from other causes. Measures that reduce the occurrence of dermatologic reactions from nondrug causes might reduce the frequency of discontinuation of lamotrigine for nonserious rash and rash arising from other causes and thereby help to optimize therapy with lamotrigine. However, every intervention has costs as well as potential benefits. It is important to test hypotheses about the value of information before adding educational burdens, including the staff time and effort involved in providing information about rash, patient time and effort learning, and implementing what is learned.

In a prior open, uncontrolled, single-center case series,[7] 100 adult patients (mean age = 40.5 years, 55% female, 88% white) with bipolar disorder (type I, N = 27; type II, N = 60; not otherwise specified, N = 13) were instructed NOT to ingest other new medicines or new foods or to utilize new cosmetics, conditioners, deodorants, detergents, or fabric softeners and to avoid sunburn or poison ivy/oak exposure for the first 3 months after adding lamotrigine to concomitant medications. Lamotrigine was not started within 2 weeks of having a rash, viral syndrome, or vaccination. In addition, lamotrigine was titrated more slowly than recommended in the prescribing information, such that an average of about 9 weeks (rather than 5 weeks) was required to reach 200 mg per day. Patients were monitored for rash and clinical phenomena using the Systematic Treatment Enhancement Program for Bipolar Disorders (STEP-BD) Clinical Monitoring Form.[8] No patient had serious rash. Five patients (5%) experienced nonserious rash, which resolved uneventfully both in patients who discontinued lamotrigine (N = 3) and in those who continued it (N = 2). Two patients with rash were found not to have been adherent to dermatology precautions. Among the remaining patients, only 3 of 98 (3.1%) had nonserious rash. The observed rate of rash was lower than the approximately 10% incidence in other clinical studies. The authors suggested that adhering to dermatology precautions with slower titration might yield a low incidence of rash with lamotrigine and noted that controlled assessment of this strategy is needed. The design of this study confounded efforts to determine the relative contributions of slower titration versus dermatology precautions to the low observed rate of nonserious rash.

The current study used a double-blind, randomized, controlled design to assess the impact of providing patients with specific instructions designed to decrease the risk of non–drug-related dermatologic reactions on the incidence of nonserious rash in a real-world setting. Patients initiated treatment with the standard titration rate described in the product information with open-label lamotrigine as monotherapy or adjunctive therapy.

METHOD

The protocol for this prospective, multicenter, parallel-group U.S. study (GlaxoSmithKline protocol SCA40917) was approved by institutional review boards for each of the 188 study sites. All patients provided written informed consent prior to entry into the study. Data were collected from August 2003 to August 2004.

Patients

Male or female adults (≥ 18 years of age) or adolescents (13–17 years of age) who had been diagnosed with bipolar I disorder meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[9] criteria based on unstructured clinical interview and review of available medical records were eligible for the

Table 1. Usual Care Precautions (UCP) and Dermatologic Precautions (DP) to Reduce Risk of Rash in Patients With Bipolar Disorder Receiving Add-On Lamotrigine (N = 1175)

Precautions	UCP	DP
To be eligible for the study, the patient could not:		
Have received lamotrigine before study enrollment	✓	✓
Be pregnant or have intentions of becoming pregnant during the study	✓	✓
Intend to breastfeed or currently be breastfeeding	✓	✓
At screening, the patient was advised to notify the investigator if the patient was being treated with valproate or carbamazepine	✓	✓
The patient was advised not to exceed the recommended initial dose or dose-escalation schedule for lamotrigine during the study	✓	✓
The patient was advised that, if a rash developed during the study, the patient was to:		
Contact the investigator immediately and arrange to be evaluated	✓	✓
Discontinue lamotrigine immediately unless instructed to do otherwise by the investigator	✓	✓
The patient was advised that during the study he or she should not:		
Ingest other new medicines[a] or new foods		✓
Use new cosmetics, conditioners, deodorants, detergents, or fabric softeners		✓
Stimulate the immune system through excessive sun exposure		✓
Participate in activities that might lead to exposure to poison oak or poison ivy		✓
Receive any immunizations		✓

[a]Both groups were instructed per protocol to not add new psychotropic medications.

study. If patients were currently being treated for bipolar disorder, they were required to have been on a stable regimen of psychotropic medications for at least the previous 2 months and not to have received lamotrigine before study entry. Patients the investigators judged to have confounding medical conditions or severe psychiatric symptoms that could interfere with participation in the study were excluded. Women were excluded if they were pregnant or breastfeeding or capable of bearing children and not using adequate contraception.

Procedures

The study comprised a 12-week, open-label treatment period, which included a lamotrigine initiation/titration phase lasting 5 weeks and a continuation phase lasting 7 weeks. A 12-week treatment period was considered to be of sufficient duration to capture most clinically relevant incidents of rash, which in epilepsy clinical trials were most often observed between 2 and 8 weeks after initiation of lamotrigine.[4,5] Clinic visits occurred at screening/baseline and after 5 weeks and 12 weeks of lamotrigine therapy.

During the baseline visit, patients eligible for the study were instructed in the use of an interactive voice response system (IVRS), which was used to assess self-reported clinical status throughout the study, and were dispensed titration dose packs of lamotrigine for the 5-week titration period. Patients were randomly assigned through a call center to groups that would receive either Usual Care Precautions (UCP) (precautions from the patient instructions in the prescribing information for reducing risk of rash including nonserious rash) or Dermatologic Precautions (DP) (UCP plus additional specific precautions intended to decrease the risk of any dermatologic reaction including nonserious rash) during 12 weeks of open-label lamotrigine therapy (Table 1). Call center personnel administered and explained the precautions to patients via scripted instructions. Patients were not told to which group they had been randomly assigned and were instructed not to communicate any precautions information to investigators. Thus, investigators were blinded to patients' precautions group. Precautions for both groups of patients specified that patients developing a rash should immediately arrange to be evaluated in the clinic and discontinue lamotrigine unless directed by the investigator to continue lamotrigine.

Lamotrigine was titrated in a manner consistent with the prescribing information and as appropriate for specific concomitant medications to a target dosage of 200 mg/day (range, 100–400 mg/day). Standard titration packs supplied lamotrigine 25 mg/day for the first 2 weeks, 50 mg/day for the third and fourth weeks, and 100 mg/day for the fifth week. Patients taking divalproex or carbamazepine (or phenytoin, primidone, and phenobarbital) were given special titration packs with these dosages halved and doubled, respectively. At the end of the 5-week titration period, patients returned to the clinic to complete assessments and to receive drug supplies for the remainder of the treatment period. Patients not receiving divalproex or carbamazepine took lamotrigine 200 mg/day beginning with week 6. The dosage could subsequently be gradually increased further (by no more than 100 mg weekly increments) as high as 400 mg/day. At the investigator's discretion, rate of titration and/or dosage of lamotrigine could be slowed during the 5-week titration period for patients intolerant of dose escalation. Addition of new medications for bipolar disorder was not permitted (resulting in incorporation of this component of dermatology precautions in both the UCP and DP groups), and dosages of concomitant medications were not to be increased to treat mood symptoms. However, dosages of concomitant medications could be decreased to control side effects. If the investigator deemed that other intervention for mood symptoms (such as adding a new medication)

was necessary, the patient was discontinued from the study.

Measures and Statistics

Patients used the IVRS to complete the self-rated Clinical Global Impressions-Bipolar[10] version (CGI-BP, which includes both severity and improvement components of manic, depressive, and overall symptoms) at baseline, at the end of the titration phase at the end of week 5, and at the end of the treatment period at the end of week 12 or at the time of early discontinuation. At the week 5 and week 12 clinic visits, investigators completed the CGI-BP and the Clinical Global Impressions-Efficacy Index (CGI-EI).[11] The CGI-EI was measured by the following groups: therapeutic effect outweighs side effects (scores 01, 02, 05, 06, 09, 10), therapeutic effect equals side effects (scores 03 and 13), and side effects outweigh therapeutic effect (scores 04, 07, 08, 11, 12, 14, 15, 16).

At all clinic visits, patients were assessed for and queried by the investigator about adverse events, defined as any untoward medical occurrences regardless of suspected cause.

The primary endpoint was the rate of rash (including nonserious rash) during the 12-week treatment period. Rash, as the primary endpoint, was predefined to include events coded by any of the adverse event verbatim terms: rash; bullous dermatitis; erythema; heat rash; erythematous, macular, maculopapular, papular, pruritic, and pustular rash; and urticaria. The difference between the UCP group and the DP group in the rate of rash was tested using a logistic regression model including terms for center grouping, age, and gender. A sample size of 1026 (513 per group) was determined to provide 90% power to detect the difference between a rate of rash of 10% for the UCP group (the observed rate in prior clinical trials that did not utilize DP) and 5% for the DP group (the observed rate in a prior open trial that used DP with slower titration) with a 2-group continuity-corrected χ^2 test with a 1-sided 0.05 significance level.

Secondary endpoints included mean changes from baseline to week 5 and to week 12 in self-rated and investigator-administered CGI-BP-Severity scores, mean CGI-BP-Improvement scores at week 5 and week 12, percentages of patients in each CGI-EI response category at week 5 and week 12, and the incidence of adverse events over the 12-week study period. Response rate was defined as the percentage of patients with week 12 (last observation carried forward [LOCF]) CGI-BP-Improvement overall scores (1 or 2) indicating very much improved or much improved, respectively. Remission rate was defined as the percentage of patients with week 12 (LOCF) CGI-BP-Severity overall scores of 1 or 2 and at least 2 points lower than baseline. Data on CGI-BP-Severity, CGI-BP-Improvement, and CGI-EI were summarized descriptively with pooled data from the UCP group and the DP group. The data were pooled because the type of precaution was not expected to impact these data on clinical response. Data on CGI-BP-Severity, CGI-BP-Improvement, and CGI-EI were summarized using both observed data and LOCF scores. The results of the observed-case and LOCF summaries were comparable, and only the LOCF data are reported.

Data on the primary endpoint of rate of rash and on adverse events were summarized for all patients who were randomly assigned and received at least 1 dose of study medication (safety population). Data on clinical response to lamotrigine were analyzed for all patients who were randomly assigned and received at least 1 dose of study medication and provided at least 1 on-treatment assessment of clinical response (intent-to-treat population).

RESULTS

Patients

The number of randomly assigned patients was 1191, of whom 1175 patients (98.7%) received at least 1 dose of study medication (safety population; UCP, N = 591; DP, N = 584). Of these 1175, 1139 patients (96.9%) provided at least 1 on-treatment assessment of clinical response (intent-to-treat population; UCP, N = 571; DP, N = 568). Demographic characteristics were comparable between the UCP group and the DP group (Table 2). The majority of the sample was ≥ 18 years (96.6%), female (64%), and white (90%). Patients' mean ± SD age was 42.2 ± 13.1 years. The most frequent mood states (DSM-IV criteria) at study screen/baseline were depressed: moderate (21%), mixed: moderate (13%), and depressed: mild (9%). The CGI-BP-Severity overall mean ± SD score at baseline was 3.4 ± 1.32. Patients were taking a mean ± SD of 2.38 ± 1.45 (2.40 for UCP and 2.37 for DP) prescription psychotropic medications at baseline when lamotrigine was started. The most common concomitant psychiatric medications were lithium, valproate, and bupropion (Table 2). Of the 1175 patients in the safety population, 867 (74%) completed the study. The mean ± SD doses of lamotrigine for completers at week 12 were: 184.1 ± 43.93 for the 646 patients not receiving divalproex or carbamazepine (or phenytoin, primidone, and phenobarbital); 101.1 ± 30.43 for the 179 patients receiving divalproex; and 304.3 ± 108.7 for the 41 patients receiving carbamazepine (or phenytoin, primidone, and phenobarbital). The most common reasons for premature withdrawal were adverse events, being lost to follow-up, and voluntary withdrawal (i.e., patient's decision) (Table 2).

Incidence of Rash

There were no reports of serious rash. Rates of rash (as the primary outcome measure, serious and nonserious rash) and the rates of individual adverse event verbatim

Table 2. Demographics, Concomitant Psychiatric Medication Use, and Patient Disposition (safety population) of Patients With Bipolar Disorder Receiving Add-On Lamotrigine

Characteristic	UCP (N = 591)	DP (N = 584)	All Patients (N = 1175)
Demographic			
Age, mean (SD), y	42.5 (12.9)	41.9 (13.3)	42.2 (13.1)
Female, N (%)	386 (65)	371 (64)	757 (64)
Ethnicity, N (%)			
American Hispanic	17 (3)	25 (4)	42 (4)
Black	34 (6)	25 (4)	59 (5)
White	530 (90)	525 (90)	1055 (90)
Other	10 (2)	9 (2)	19 (2)
Most common concomitant psychiatric medications, N (%)[a]			
Bupropion	122 (21)	127 (22)	
Lithium	142 (24)	125 (21)	
Quetiapine	70 (12)	93 (16)	
Valproate	125 (21)	135 (23)	
Citalopram	74 (13)	68 (12)	
Clonazepam	75 (13)	66 (11)	
Patient disposition			
Completed study, N (%)	434 (73)	433 (74)	867 (74)
Discontinued study prematurely, N (%)			
Adverse event	92 (16)	88 (15)	180 (15)
Voluntary withdrawal (patient's decision)	18 (3)	24 (4)	42 (4)
Lost to follow-up	21 (4)	17 (3)	38 (3)
Protocol violation	15 (3)	13 (2)	28 (2)
Other	11 (2)	9 (2)	20 (2)

[a]Patients could have been using more than 1 concomitant medication. Data not calculated for All Patients.
Abbreviations: DP = Dermatologic Precautions, UCP = Usual Care Precautions.

terms considered nonserious rash are summarized in Table 3. Over the 12-week treatment period, the rate of nonserious rash was low and similar between the UCP and DP groups (8.8% and 8.6%, respectively; OR = 0.99, 90% CI = 0.7 to 1.4, p = .486). Rates of nonserious rash reported by investigators as lamotrigine-related were 5.9% (35/591) and 5.7% (33/584) for UCP and DP, respectively. Nonserious rash leading to discontinuation of study lamotrigine or withdrawal was slightly higher for the UCP group (34/591, 5.8%) than DP (28/584, 4.8%). This study enrolled 40 subjects less than 18 years of age and 49 subjects older than 65 years of age. The rate of nonserious rash in the adolescent group was comparable and slightly less than that in the total population (1/14 [7.1%] UCP and 2/26 [7.7%] DP) while the rate was slightly higher in the elderly UCP group (4/24 [16.7%] UCP and 1/25 [4.0%] DP). The sample sizes of these subgroups were much smaller than that of the entire sample.

Clinical Response

In the sample as a whole, CGI-BP-Severity scores (investigator-rated) improved from baseline at both week 5 and week 12 visits (Figure 1). Investigator-administered CGI-BP-Improvement scores also indicated improvement during the course of the treatment period. Improvements were observed for both manic and depressive symptom scores as well as for CGI-BP-Severity and CGI-BP-Improvement overall scores. The response and remission rates (as defined above) with lamotrigine were 50% and 29%, respectively. Clinical response was also observed in the 40 patients < 18 years old, with investigator-rated CGI-BP-Severity overall mean scores decreasing from 3.5 at screen/baseline to 2.6 at week 12.

CGI-EI scores at week 5 and week 12 reflected a favorable balance between clinical response and tolerability in the study sample. At both week 5 and week 12 assessments, investigators indicated that the therapeutic effect of additional lamotrigine outweighed side effects in 74% of patients (Figure 2). In addition, 57% and 58% of patients reported a therapeutic benefit with lamotrigine with no side effects at the week 5 and week 12 assessments, respectively. Repeating the above analyses separately for the UCP and DP groups revealed that lamotrigine yielded similar improvements in clinical response compared with baseline in both groups. In addition, the incidences of overall compliance and withdrawal were similar in the UCP and DP groups, a finding that further confirms the appropriateness of pooling the groups.

Safety

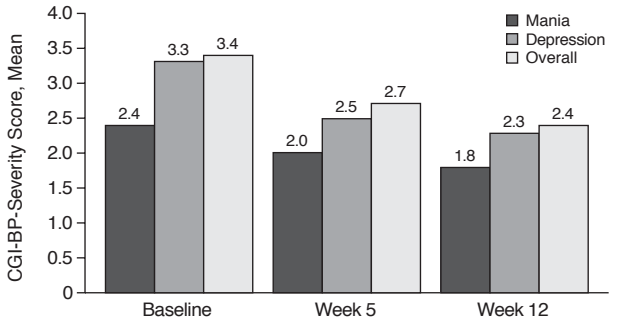
Adverse events were reported in 60% (356/591) of patients in the UCP group and 58% (336/584) in the DP group and were deemed to be drug related in 40% (235/591) and 37% (217/584) of patients, respectively. Adverse events reported in ≥ 5% of patients during the treatment period were headache, insomnia, dizziness, rash (adverse event verbatim term), and nausea. The only adverse event thought to be drug related and reported in ≥ 5% was headache. Adverse events leading to discontinuation of study medication or withdrawal were reported in 16% (92/591)

Table 3. Occurrence of Nonserious Rash (NSR)[a] in Patients With Bipolar Disorder Receiving Add-On Lamotrigine (safety population)

Event (Preferred Terms)	UCP (N = 591)	DP (N = 584)
Any NSR, N (%)[a]	52 (8.8)	50 (8.6)
Individual NSR events, N (%)[b]		
Rash[c]	35 (6)	36 (6)
Erythema	3 (< 1)	3 (< 1)
Rash maculopapular	3 (< 1)	3 (< 1)
Urticaria	4 (< 1)	2 (< 1)
Rash papular	2 (< 1)	3 (< 1)
Rash pruritic	2 (< 1)	3 (< 1)
Rash erythematous	1 (< 1)	3 (< 1)
Heat rash	1 (< 1)	1 (< 1)
Rash macular	2 (< 1)	0
Dermatitis bullous	1 (< 1)	0
Rash pustular	1 (< 1)	0

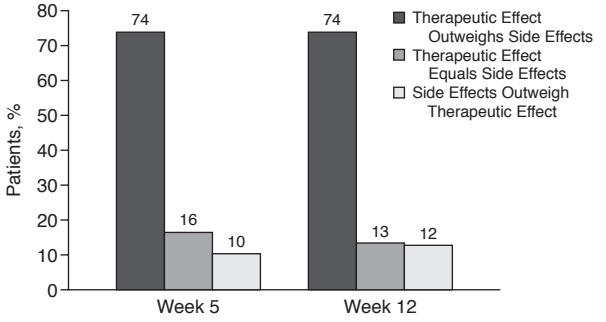
[a]NSR (terminology used since no serious rash was reported) included adverse event verbatim terms: rash; bullous dermatitis; erythema; heat rash; erythematous, macular, maculopapular, papular, pruritic, and pustular rash; and urticaria.
[b]Patients could have more than 1 event.
[c]Adverse event verbatim term of rash (only).
Abbreviations: DP = Dermatologic Precautions, UCP = Usual Care Precautions.

Figure 1. Clinician-Rated Severity of Illness After Lamotrigine was Initiated as Add-On Therapy for Patients With Bipolar Disorder (N = 1139) (LOCF, intent-to-treat population)



Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar version, LOCF = last observation carried forward.

Figure 2. Clinical Response (by CGI-EI; LOCF and intent-to-treat population) and Side Effect Burden After Initiation of Lamotrigine as Add-On Therapy for Patients With Bipolar Disorder (N = 1139)



Abbreviations: CGI-EI = Clinical Global Impressions-Efficacy Index, LOCF = last observation carried forward.

of patients in the UCP group and 15% (90/584) of patients in the DP group. Serious adverse events were reported in 3% (19/591) and 4% (22/584) of patients in the UCP and DP groups, respectively. The most commonly reported serious adverse events were psychiatric problems such as suicidal ideation (N = 5), suicide attempt (N = 5), mania (N = 3), exacerbation of bipolar I disorder (N = 3), abnormal behavior (N = 1), and depression (N = 1). None of these serious adverse events were thought to be related to lamotrigine except for 1 report of mania. No suicides were reported.

There was no significant change in mean weight during the study in either group. The UCP group had a mean ± SD change from baseline to week 12 of 0.0 ± 3.82 kg compared with –0.1 ± 3.54 kg in the DP group (p = NS).

DISCUSSION

Both UCP and specific DP yielded rates of nonserious rash (8.8% and 8.6%, respectively) that were comparable to rates previously reported in clinical trials not utilizing DP, were consistent with the 9% reported in the 8 controlled trials of lamotrigine for bipolar disorder,[1] and were marginally lower than the rate seen in the open-label dose-escalation phase of 2 long-term trials where rash occurred in 11% of patients.[6] Both the UCP and DP groups had a component of dermatology precautions (discontinuing participation if new psychotropic medications were added), a factor that may have contributed to the marginally lower rate of nonserious rash in both groups.

The incidence of nonserious rash in the DP group was marginally higher than the 5% rate observed in a prior open-label, uncontrolled case series.[7] A possible reason for the difference in nonserious rash rates between the 2 studies was the double-blind administration of the UCP and DP in the current study. Although, it is also possible that lack of compliance with the additional precautions in the DP group or unstipulated use by investigators of additional precautions given to the UCP group contributed to the inability of the current study to show a difference between groups or replicate the previous finding. Other reasons might include less emphatic presentation of DP in the current study relative to the case series (i.e., by call center personnel rather than by treating physicians), the infrequent presentation of DP (i.e., only once at screen/baseline) during the current study, and between-study differences in concomitant medications. Another reason for

the difference from the case series may be the use of different adverse event terms for reporting nonserious rash. Additionally, the inherent limitations of the design of an open, uncontrolled case series and the use of an initial titration rate in that case series that was slower than that in the prescribing information for lamotrigine (mean time to 200 mg/day was 9 weeks compared with 5 weeks in the current study [and prescribing information]) may contribute to the difference in the rate of rash compared with the current study. The design of this open case series confounded efforts to determine the relative contributions of slower titration versus dermatology precautions to low observed rate of rash.

Although the current study did not demonstrate a difference between the UCP and DP in reducing the risk of nonserious rash, the results are encouraging: lamotrigine was well tolerated with no serious rash and low incidences of nonserious rash and discontinuation due to rash in a large heterogeneous sample of patients taking an average of 2.4 concomitant prescription psychiatric medications in a real-world setting. Furthermore, the relatively low incidence of nonserious rash is notable in a study that risked overreporting rash given that the study was specifically designed to assess this particular adverse event. The absence of serious rash and low occurrence of nonserious rash in this study supports a previous finding that suggests temporarily stopping the medication and immediately seeking a medical professional for a physical examination at the first sign of rash.[3] Therefore, a serious rash may be ruled out, and so these procedures would potentially decrease unnecessary discontinuation of lamotrigine for cases of nonserious rash.

Overall clinical response to open-label lamotrigine in this study was consistent with results observed in placebo-controlled clinical trials demonstrating the effectiveness of lamotrigine in bipolar disorder.[12–14] CGI-BP-Severity and -Improvement scores indicated clinical improvement over the treatment period, and CGI-EI scores at weeks 5 and 12 reflected a favorable balance between control of mood symptoms and tolerability. Patients' self-reports were similar to clinicians' ratings for mania, depression, and overall. Although measures to assess clinical response were included in this study, the ability to draw conclusions about the data is limited given the open-label administration of lamotrigine, the lack of a placebo control or active comparator, and the relatively brief duration of the study, which lasted 3 months.

In summary, in this large clinical study replicating real-world use of lamotrigine, the incidence of nonserious rash with lamotrigine was low and was similar in patients receiving usual instructions for safe initiation of lamotrigine and in those receiving additional instructions for reducing the risk of dermatologic reactions. No serious rash was reported, and lamotrigine was generally well tolerated.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clonazepam (Klonopin and others), divalproex (Depakote), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), phenytoin (Dilantin, Phenytek, and others), primidone (Mysoline and others), quetiapine (Seroquel).

Financial Disclosures: Dr. Ketter has received grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, Eisai Inc., Elan Pharmaceuticals, Eli Lilly, GlaxoSmithKline, Janssen, Novartis, Shire, Solvay, and Wyeth; is a consultant to Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Corcept, Elan, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Jazz Pharmaceuticals, Novartis, Pfizer, Shire, Solvay, UCB, and Wyeth; and has received lecture honoraria from Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Novartis, Pfizer, and Shire. Dr. Greist is a consultant to and has received grant/research support and honoraria from GlaxoSmithKline. Mr. Roberts is a stock shareholder of GlaxoSmithKline. Dr. Thompson is a major stock shareholder of options in GlaxoSmithKline.

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