Dermatology Precautions and Slower Titration Yield Low Incidence of Lamotrigine Treatment-Emergent Rash

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Objective: To assess treatment-emergent rash incidence when using dermatology precautions (limited antigen exposure) and slower titration during lamotrigine initiation.

Method: We assessed rash incidence in 100 patients with DSM-IV bipolar disorder instructed, for their first 3 months taking lamotrigine, to avoid other new medicines and new foods, cosmetics, conditioners, deodorants, detergents, and fabric softeners, as well as sunburn and exposure to poison ivy/oak. Lamotrigine was not started within 2 weeks of a rash, viral syndrome, or vaccination. In addition, lamotrigine was titrated more slowly than in the prescribing information. Patients were monitored for rash and clinical phenomena using the Systematic Treatment Enhancement Program for Bipolar Disorder Clinical Monitoring Form. Descriptive statistics were compiled.

Results: No patient had serious rash. Benign rash occurred in 5 patients (5%) and resolved uneventfully in 3 patients discontinuing and 2 patients continuing lamotrigine. Two patients with rash were found to be not adherent to dermatology precautions. Therefore, among the remaining patients, only 3/98 (3.1%) had benign rashes.

Conclusion: The observed rate of benign rash was lower than the 10% incidence in other clinical studies. The design of this study confounds efforts to determine the relative contributions of slower titration versus dermatology precautions to the low rate of rash. Systematic studies are needed to confirm these preliminary findings, which suggest that adhering to dermatology precautions with slower titration may yield a low incidence of rash with lamotrigine.

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Adverse effects are commonly encountered in the management of bipolar disorders and vary across medications.[1] From a systems perspective, perhaps the most commonly encountered problems involve gastrointestinal (nausea, vomiting, diarrhea, constipation) and central nervous system (cognitive difficulties, sedation, tremor, ataxia, extrapyramidal symptoms) side effects. Although challenging, such difficulties are common enough across medication classes that psychiatrists have the benefit of substantial direct clinical experience to help address concerns in individual patients treated with specific medications by adjusting dosage or symptomatically treating side effects.

Arguably, this is less the case for dermatologic adverse effects, particularly for agents associated with (albeit rare) serious rashes.[2] For example, the anticonvulsants carbamazepine[3] and lamotrigine[4] are effective in bipolar disorders and yield common (about 10%) benign rashes as well as rare (0.1% or less) serious rashes.[5,6] Although gradual initial titration markedly decreases the risk of serious rash with lamotrigine,[7] benign rashes are still common enough to yield considerable anxiety (for both clinicians and patients), expense (for medical evaluations), and treatment discontinuations. However, there are few data regarding ways to manage the risks of benign or unrelated rashes.

One heuristically appealing approach to limiting the risk of benign or unrelated rashes that are primarily en-

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countered in the first 3 months of treatment is to limit exposure to other new antigens during that time and avoid starting the medication of interest in the setting of immune system activation. In addition, using even slower titration than that described in the prescribing information could further decrease the risk of rash. We report the findings of using such dermatology precautions and slower titration in efforts to decrease the incidence of lamotrigine treatment-emergent rash.

METHOD

In 100 outpatients with DSM-IV bipolar disorder treated at the Stanford Bipolar Disorders Clinic, Stanford, Calif., data were collected from Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Affective Disorders Evaluations and Clinical Monitoring Forms.[8] Patients received verbal and written instructions for dermatology precautions for the first 3 months taking lamotrigine (Appendix 1). Thus, patients were instructed to avoid other new medicines and new foods, cosmetics, conditioners, deodorants, detergents, and fabric softeners, and to avoid sunburn and exposure to poison ivy/oak. Lamotrigine was not started within 2 weeks of a rash, viral syndrome, or vaccination.

Lamotrigine was added to prior treatment (including no prior treatment) and initiated even more gradually than the rate recommended in the prescribing information[9] in efforts to minimize the risk of rash (Appendix 2). Thus, in patients not taking enzyme inducers or inhibitors, lamotrigine was started at 25 mg/day for 2 weeks, increased to 50 mg/day for 2 weeks, and thereafter increased weekly by 25 mg/day as necessary and tolerated. The commonly targeted dose was 200 mg/day, but it could ultimately be increased gradually up to 500 mg/day. Due to pharmacokinetic drug-drug interactions, in patients taking divalproex, lamotrigine doses were halved, and in patients taking carbamazepine, lamotrigine doses could be doubled.

Patients were instructed to report any rash and were prospectively queried regarding occurrence of rash at clinical visits that varied in frequency (weekly to monthly) depending on clinical acuteness. Although patients were commonly prospectively reminded of dermatology precautions and queried regarding adherence (and routinely claimed to be adherent), data regarding some aspects of adherence (such as avoiding new foods, cosmetics, conditioners, deodorants, detergents, and fabric softeners, as well as sunburn and poison oak) were not systematically coded on the Clinical Monitoring Forms. However, evidence for adherence was prospectively recorded for other important components of dermatology precautions, such as not starting lamotrigine within 2 weeks of having a rash, viral syndrome, or vaccination and not ingesting other new medicines, which were prospectively systematically queried and recorded on the Clinical Monitoring Forms. In addition, patients who developed rash were systematically queried regarding adherence to all of the above aspects of dermatology precautions, and the nature of the eruption and additional medical records were reviewed regarding the nature and course of the rash. The above data were reviewed for the first 100 patients treated with the above regimen to assess the incidence of rash, and descriptive statistics were compiled.

RESULTS

Patients had a mean ± SD age of 40.5 ± 14.7 years; 55% were female (N = 55), and 88% were white (N = 88). Twenty-seven percent of patients (N = 27) had bipolar I disorder, 60% (N = 60) had bipolar II disorder, and 13% (N = 13) had bipolar disorder not otherwise specified, with a mean onset age of 20.9 ± 11.2 years and mean illness duration of 19.7 ± 13.3 years. Patients were taking a mean of 2.2 ± 1.6 prescription psychotropic medications and 0.9 ± 1.4 other prescription medications when lamotrigine was started. Twenty-nine patients were taking lithium (mean dose 802 ± 346 mg/day), 26 were taking divalproex (mean dose 899 ± 595 mg/day), and 5 were taking carbamazepine (mean dose 480 ± 179 mg/day) when lamotrigine was started. Twenty patients were taking other anticonvulsants (14, gabapentin; 4, topiramate; 1, oxcarbazepine; 1, zonisamide), 30 were taking antipsychotics, 50 were taking antidepressants, and 31 were taking hypnotics/benzodiazepines when lamotrigine was started. Seventy-four patients (74%) had depressive (35 syndromal and 39 subsyndromal) symptoms, 14 patients (14%) had hypomanic (3 syndromal and 11 subsyndromal) symptoms, and 12 patients (12%) were recovered when lamotrigine was started.

Histories of immunologic and dermatologic disturbances were present in 36 patients (36%) and included prior (primarily antibiotic-related) drug allergies/rashes in 22% (N = 22), environmental allergies in 6% (N = 6), and eczema in 6% (N = 6). Seven patients (7%) reported a history of asthma.

Patients were seen a mean of 2.7 ± 2.3 times in the 3 months before starting lamotrigine and 4.3 ± 2.5 times during the first 3 months taking lamotrigine. Eighty-nine patients (89%) completed the first 3 months of lamotrigine therapy, with a mean final lamotrigine dose of 94 ± 41 mg/day in patients taking, and 178 ± 80 in those not taking, concurrent divalproex. Eleven patients (11%) did not complete the first 3 months of lamotrigine therapy and had a mean duration of 6.8 ± 4.0 weeks of lamotrigine, with a mean final lamotrigine dose of 18 ± 11 mg/day in patients taking, and 122 ± 84 in those not taking, concurrent divalproex. Lamotrigine was discontinued during the first 3 months for benign rash in 3/100 patients (3%), and for reasons other than rash in 8/100 patients

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(8%), including 3 for inefficacy, 1 for nonadherence, and 4 for other reasons.

No patient developed serious rash. Benign rash occurred in 5/100 patients (5%). At the time rash developed, mean duration of lamotrigine treatment was 74 ± 12 (range, 58–84) days, and lamotrigine dose was 50 mg/day in 1 patient taking, and 188 ± 63 (range, 100–250) mg/day in 4 patients not taking, concurrent divalproex. All rashes resolved uneventfully after discontinuation of lamotrigine in 3 patients and despite continuation of lamotrigine in 2 patients.

Among patients who developed rash, 2 were found to be not adherent to dermatology precautions. One of these patients was taking lamotrigine 100 mg/day, olanzapine 10 mg/day, and clonazepam 0.5 mg/day and developed a pruritic erythematous eruption on the trunk and extremities considered related to lamotrigine that resolved uneventfully with discontinuation of lamotrigine (without dermatologic consultation). The other patient was taking lamotrigine 200 mg/day, olanzapine 5 mg/day, isocarboxazid 100 mg/day, liothyronine 0.05 mg/day, zolpidem 20 mg/day, gabapentin 1200 mg/day, and propranolol 80 mg/day and had inguinal intertrigo, candidiasis, and bacterial folliculitis considered not related to lamotrigine that resolved uneventfully despite continuation of lamotrigine (after dermatologic consultation).

Among the remaining patients, 3/98 (3.1%) had benign rash. One of these patients was taking lamotrigine 50 mg/day, divalproex 2000 mg/day, lithium 1200 mg/day, risperidone 2 mg/day, sertraline 200 mg/day, buspirone 30 mg/day, and modafinil 200 mg/day and developed erythema multiforme minor (confirmed by biopsy) on 1 lower extremity that was considered related to lamotrigine, yet resolved uneventfully despite continuation of lamotrigine (after dermatologic consultation). Another patient was taking lamotrigine 200 mg/day and developed seborrheic dermatitis on the scalp and extremities considered not related to lamotrigine that resolved uneventfully after discontinuation of lamotrigine (after dermatologic consultation). Another patient was taking lamotrigine 250 mg/day, lithium 450 mg/day, bupropion 450 mg/day, and levothyroxine 0.075 mg/day and developed a papular eruption on the trunk and extremities considered related to lamotrigine that resolved uneventfully after discontinuation of lamotrigine (after dermatologic consultation).

CONCLUSION

We found a low incidence of lamotrigine treatment-emergent rash. Among 100 patients advised to follow dermatology precautions and slower titration, 5% developed lamotrigine treatment-emergent benign rash, and 3% discontinued lamotrigine due to rash. Excluding 2 patients with rash who were found to be not adherent to dermatology precautions, only 3.1% developed treatment-emergent rash. The observed rate of benign rash was lower than the 10% incidence in other clinical studies.[6] Rash resolved uneventfully in 3 patients discontinuing and 2 patients continuing lamotrigine. No patient developed serious rash, as would be expected by the limited sample size and the low incidence of serious rash with this drug.

This study has noteworthy strengths and limitations. The sample was derived from a heterogeneous cohort of patients with bipolar disorder with diverse clinical presentations, comorbidities, and medication regimens,[8] suggesting more generalizability than might be inferred from controlled trials with restrictive inclusion and exclusion criteria. In particular, lamotrigine was added to an average of 2.2 psychotropic and 0.9 other medications, reflecting the sort of combination pharmacotherapies used in clinical settings. However, the findings of this study need to be approached with considerable caution in view of important limitations, including a relatively small (100-patient) sample size and the lack of a control condition. In addition, although patients were commonly prospectively reminded of dermatology precautions and queried regarding adherence (and routinely claimed to be adherent), data regarding some aspects of adherence (such as avoiding new foods, cosmetics, conditioners, deodorants, detergents, or fabric softeners, as well as sunburn and poison oak) were not systematically coded (unless the patient developed rash), so that the frequencies of rash in adherent compared to nonadherent patients could not be assessed. However, evidence for adherence was prospectively recorded for other important components of dermatology precautions, such as not starting lamotrigine within 2 weeks of having a rash, viral syndrome, or vaccination, and not ingesting other new medicines. Although the approach of utilizing dermatology precautions might be considered heuristically appealing, there are few clinical data regarding the efficacy of such a strategy in general, and few basic data regarding potential mechanisms of action. Finally, the design of this study confounds efforts to determine the relative contributions of slower titration versus dermatology precautions to the low rate of rash.

Nevertheless, our observations support the contention that more research is indicated. Specifically, systematic studies appear warranted to confirm these preliminary findings suggesting that dermatology precautions and slower titration may yield a low incidence of rash with lamotrigine.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Tegretol, and others), clonazepam (Klonopin and others), divalproex (Depakote), gabapentin (Neurontin and others), isocarboxazid (Marplan), lamotrigine (Lamictal), levothyroxine (Synthroid, Levo-T, and others), liothyronine (Triostat and Cytomel), lithium (Eskalith, Lithobid, and others), modafinil (Provigil), olanzapine (Zyprexa), oxcarbazepine (Trileptal), propranolol (Inderal, Innopran, and others), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax), zolpidem (Ambien), zonisamide (Zonegran).

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Appendix 1. Stanford Dermatology Precautions Given to Patients as Written Instructions at Lamotrigine Initiation

Stanford University Bipolar Disorders Clinic Dermatology Precautions and Rashes

We recommend that patients taking lamotrigine (Lamictal) adhere to dermatology precautions. That is, during the initial three months of lamotrigine treatment, patients are advised to NOT ingest other new medicines or new foods, or utilize new cosmetics, conditioners, deodorants, detergents, or fabric softeners, and we request that patients not stimulate their immune system by developing sunburn or poison oak exposure. In addition, we recommend patients do not start lamotrigine within two weeks of having a rash, viral syndrome, or vaccination.

Any patient developing a rash accompanied by eye, mouth, or bladder discomfort must immediately go to the emergency room for dermatological assessment, as such symptoms could herald the onset of a serious rash. Rashes with more benign presentations must be evaluated as soon as possible (and before taking the next dose of lamotrigine) to assess the risk of continuing lamotrigine treatment.

Appendix 2. Slower Titration Used During Lamotrigine Initiation

In patients not taking enzyme inducers or inhibitors, lamotrigine was initiated at 25 mg/day for 2 weeks, increased to 50 mg/day for 2 weeks, and thereafter increased weekly by 25 mg/day. Thus, compared to the titration in the prescribing information, in this study it took 80% longer to reach the target dose of 200 mg/day (63 rather than 35 days). In patients taking divalproex, lamotrigine doses were halved, and in patients taking carbamazepine, lamotrigine doses could be doubled.

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