Rash in Multicenter Trials of Lamotrigine in Mood Disorders: Clinical Relevance and Management

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Background: The rate of lamotrigine-associated rash in patients with mood disorders has not been well characterized. The objective of this report was to determine rash rates in clinical trials of lamotrigine in DSM-IV unipolar depression or bipolar disorder.

Method: A retrospective analysis was conducted of rates of lamotrigine-related rash in 12 multicenter studies, including 1 open study, 7 randomized controlled acute trials, and 4 randomized controlled maintenance trials from 1996 to 2001.

Results: A total of 1955 patients were treated with lamotrigine in open-label settings (open-label phases preceding or following randomization and 1 stand-alone open-label study); 1198 patients received lamotrigine in controlled settings, and 1056 patients received placebo. In controlled settings, rates of benign rash were 8.3% and 6.4% in lamotrigine- and placebo-treated patients, respectively. Rates of serious rash were 0% with lamotrigine, 0.1% (N = 1) with placebo, and 0% with comparators. In the open-label setting, the overall rate of rash for lamotrigine was 13.1% (N = 257) and of serious rash, 0.1% (N = 2). One mild case of Stevens-Johnson syndrome not requiring hospitalization occurred in a patient treated with lamotrigine. There were no cases of toxic epidermal necrolysis in any setting.

Conclusion: Serious drug eruptions associated with lamotrigine were rare. Although rash is a potentially life-threatening reaction, the risk of serious rash due to lamotrigine should be weighed against more common risks associated with untreated or undertreated bipolar depression.

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Several double-blind, placebo-controlled trials have demonstrated the acute and prophylactic antidepressant activity of lamotrigine in bipolar disorder.[1–4] Its acute antidepressant efficacy has most clearly been demonstrated in patients with bipolar I disorder.[1,3] Its prophylactic efficacy has been demonstrated in patients with rapid-cycling bipolar II disorder,[2] recently manic patients with bipolar I disorder,[4] and recently depressed patients with bipolar I disorder (J.R.C., C.L.B., G.S.S., manuscript submitted). In 2 placebo-controlled acute mania studies, lamotrigine failed to show efficacy,[5] but in 1 small double-blind comparison with lithium, preliminary evidence of acute antimanic efficacy was observed.[6] In 3 placebo-controlled studies, lamotrigine failed to show acute efficacy in recurrent major depressive episodes,[7] but there are anecdotal reports of efficacy in treatment-refractory patients with recurrent major depression.[8]

In prior trials of patients with epilepsy who received lamotrigine as an add-on or as monotherapy, the spectrum

of side effects reported included dizziness, headache, diplopia, nausea, and ataxia.[9,10] In controlled monotherapy trials of patients with mood disorders, lamotrigine has been associated with headache, changes in sleep habits (e.g., somnolence or insomnia), and gastrointestinal side effects (e.g., nausea, vomiting).[11] Although the prevalence of rash in randomized mood disorder trials did not exceed that of placebo, rash is perceived as the side effect most likely to complicate the drug's clinical use. In open-label and placebo-controlled clinical trials involving 3501 epilepsy patients,[12] rash was observed in 10% of lamotrigine-treated patients and 5% of placebo-treated patients. Rash led to drug discontinuation for 3.8% and to hospitalization for 0.3% of lamotrigine-treated patients; these reports included cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. The risk of rash was increased by the coadministration of valproic acid or by exceeding the current recommended initial dose or rate of dose escalation of lamotrigine[12] and was also heightened in patients younger than 12 years.[13] The manufacturer's dosage recommendations changed in 1994.[14] Recent data suggest that about 80% of patients have been started on lamotrigine treatment at or below the current recommended daily dose since 1994, compared with 43% prior to 1994.[15] There is now recognition of the importance of a slow initial rate of titration to minimize serious rash. Since this change, the rate of serious rash appears to have decreased, whereas that of nonserious rash has remained the same.[15]

To explore the prevalence and clinical significance of rash in lamotrigine-treated mood disorder patients, we summarize here rash data from 12 multicenter trials.

METHOD

Table 1 summarizes the designs of 11 GlaxoSmithKline-sponsored multicenter, randomized controlled trials of lamotrigine in bipolar disorder and recurrent major depression and 1 open-label study (Study 601[16]), which is included because of the occurrence of 1 case of serious rash. Lamotrigine-related rash rates as of March 22, 2002, were calculated for the controlled setting (N = 1198) and the open-label setting (N = 1955), which included Study 601 as well as the open-label phases preceding and following randomization in controlled maintenance trials.

Study 601 was a 48-week open-label, prospective trial of lamotrigine in 75 patients with treatment-refractory bipolar I or bipolar II disorder. Lamotrigine was used as monotherapy in 15 patients and as adjunctive therapy in 60 patients. Dosages for patients receiving lamotrigine as monotherapy or add-on therapy were set per current manufacturer guidelines, except those for patients who were receiving valproate; these patients received 25 mg of lamotrigine every other day for weeks 1 and 2 instead of the recommended 12.5 mg every day for weeks 1 and 2.

In controlled studies, lamotrigine was compared with lithium in bipolar disorder trials and with desipramine in unipolar depression trials when an active treatment group was included in the study methodology. Rash-related adverse events were recorded on a case report form that included demographic information, patient history, laboratory evaluations, and concurrent medications. The investigator or consulting dermatologist was also asked to identify the rash-related event with one of the following descriptors: urticaria, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity, morbilliform rash (maculopapular rash, with flat discolored areas [macules] or solid, red, elevated areas [papules] that later become confluent), unknown, or other. "Serious rash" was defined as any rash resulting in drug discontinuation and hospitalization. In these studies, lamotrigine was assessed as acute monotherapy, adjunctive therapy, or continuation phase therapy in recurrent unipolar depression, bipolar I disorder, bipolar II disorder, and rapid-cycling populations. Dosing in all trials was in accordance with current manufacturer recommendations. When used as monotherapy or in the absence of enzyme inhibitors or enhancers, lamotrigine was usually prescribed at 25 mg/day during weeks 1 and 2, 50 mg/day during weeks 3 and 4, and then with weekly increases to 100 mg/day and then 200 mg/day as clinically tolerated.

RESULTS

Rash in Controlled Settings

Table 2 shows benign and serious rash rates for 2681 patients treated with lamotrigine (N = 1198), placebo (N = 1056), lithium (N = 280), or desipramine (N = 147) in controlled clinical trials. Benign rash (e.g., isolated, self-limited eruptions without internal organ involvement) occurred in 8.3% (95% confidence interval [CI] = 6.8% to 10.1%) of patients receiving lamotrigine, 6.4% (95% CI = 5.0% to 8.1%) receiving placebo, 4.3% (95% CI = 2.2% to 7.4%) receiving lithium, and 9.5% (95% CI = 5.3% to 15.5%) receiving desipramine. The most common kinds of rash occurring with lamotrigine were morbilliform or exanthematic (red or discolored) eruptions.

During the controlled phases of these trials, no cases of serious rash occurred in lamotrigine-treated patients. One case of serious rash (i.e., requiring discontinuation of medication and hospitalization) occurred in placebo-treated patients (0.1%): a 35-year-old female patient receiving placebo augmentation of valproate and topiramate for treatment of rapid-cycling bipolar disorder (Study 611) developed erythema nodosum, with small tender reddened nodules under the skin, fever, and transient arthritic pains, and was withdrawn from the study.

Overall rash rates varied somewhat by study type. Rash rates with lamotrigine were 9.6% (95% CI = 7.5%

Table 1. Multicenter Trials of Lamotrigine in Mood Disorders[a]

Trial	Mood State[b]	Study Design[c]	Treatment Arms	Duration (wk)	Outcome
601[16]	BP I and II hypomania, mixed episode, or depression	Open	LTG add-on (N = 75)	48	68%–84% responded
602[1]	BP I depression	Acute, monotherapy	LTG, 200 mg/d (N = 63), LTG, 50 mg/d (N = 66), PBO (N = 65)	7	HAM-D: NS, MADRS: LTG > PBO, CGI: LTG > PBO
603[d]	BP I and II depression	Acute, monotherapy	LTG, 100–300 mg/d (N = 103), PBO (N = 101)	10	NS
605[e]	BP I depression, index episode	Controlled monotherapy continuation following open stabilization	LTG, 50–400 mg/d (N = 219), LI (N = 120), PBO (N = 121)	76	LTG > PBO, LI > PBO
606[4]	BP I mania, index episode	Controlled monotherapy continuation following open stabilization	LTG, 100–400 mg/d (N = 59), LI (N = 46), PBO (N = 70)	76	LTG > PBO, LI > PBO
609[f]	BP I mania	Acute, monotherapy	LTG, 50 mg/d (N = 84), LI (N = 36), PBO (N = 95)	3	NS
610[g]	BP I mania	Acute, add-on	LTG, 200 mg/d (N = 74), LI (N = 78), PBO (N = 77)	6	LI > PBO
611[h]	BP I and II rapid cycling	Prophylaxis, add-on	LTG, 100–500 mg/d (N = 68), PBO (N = 69)	32	NS
613[7]	Unipolar depression	Acute, monotherapy	LTG, 200 mg/d (N = 145), desipramine (N = 147), PBO (N = 145)	8	HAM-D: NS, MADRS: NS, CGI: LTG > PBO
614[2]	BP I and II rapid cycling	Controlled monotherapy continuation following open stabilization	LTG, 100–300 mg/d (N = 92), PBO (N = 88)	26	LTG > PBO for BP II
20022[i]	Unipolar depression	Acute, monotherapy	LTG, 200 mg/d (N = 74), PBO (N = 75)	7	NS
20025[j]	Unipolar depression	Acute, monotherapy	LTG, 200 mg/d (N = 151), PBO (N = 150)	7	NS
Total			LTG (N = 1273), LI (N = 280), desipramine (N = 147), PBO (N = 1056)		

[a]Abbreviations: BP = bipolar disorder, CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, LI = lithium, LTG = lamotrigine, MADRS = Montgomery-Asberg Depression Rating Scale, NS = no significant difference observed, PBO = placebo. Symbol: >, superior to. [b]Mood states were DSM-IV diagnosed. [c]Study 601 was a stand-alone open-label trial. All other studies were controlled trials (N = 1198). [d]GlaxoSmithKline, unpublished study. [e]J.R.C., C.L.B., G.S.S., manuscript submitted. [f]GlaxoSmithKline, unpublished study. [g]GlaxoSmithKline, unpublished study. [h]GlaxoSmithKline, unpublished study. [i]GlaxoSmithKline, unpublished study. [j]GlaxoSmithKline, unpublished study.

to 12.1%) in the monotherapy studies, 7.7% (95% CI = 3.9% to 13.4%) in the add-on studies, and 6.2% (95% CI = 4.0% to 9.2%) in the monotherapy continuation phases (Table 3). No cases of Stevens-Johnson syndrome or toxic epidermal necrolysis related to lamotrigine were reported in the randomized phases of placebo-controlled trials.

Rash in the Open-Label Setting

There were 1955 patients treated with lamotrigine in an open-label setting: 1629 in the open-label stabilization phases preceding randomization in controlled maintenance trials, 251 in the open-label follow-up phases after the completion of the randomized phase of controlled maintenance trials, and 75 in a stand-alone open-label study. Overall, the lamotrigine-related rash rate was 13.1% (95% CI = 11.7% to 14.7%). Two cases of lamotrigine-related serious rash (0.1%) occurred (see Table 3). One case of mild Stevens-Johnson syndrome was reported in a patient with multiple risk factors while on lamotrigine treatment during the preliminary phase of Study 605 (J.R.C., C.L.B., G.S.S., manuscript submitted). The patient did not require hospitalization and recovered uneventfully.

A case of serious rash (i.e., rash requiring discontinuation and hospitalization) occurred during the open-label

Table 2. Occurrence of Rash in Controlled Clinical Studies of Lamotrigine in Mood Disorders[a]

Trial	Treatment Arm	No. of Cases of Rash: Benign	Serious	SJS/TEN
602	LTG, 200 mg/d	6	0	0
	LTG, 50 mg/d	9	0	0
	PBO	7	0	0
603	LTG, 100–300 mg/d	17	0	0
	PBO	12	0	0
605	LTG, 50–400 mg/d	16	0	0[b]
	LI	5	0	0
	PBO	3	0	0
606	LTG, 100–400 mg/d	2	0[c]	0
	LI	4	0	0
	PBO	6	0	0
609	LTG, 50 mg/d	7	0	0
	LI	3	0	0
	PBO	11	0	0
610	LTG, 200 mg/d	3	0	0
	LI	0	0	0
	PBO	3	0	0
611	LTG, 100–500 mg/d	8	0	0
	PBO	8	1	0
614	LTG, 100–300 mg/d	5	0	0
	PBO	3	0	0
613	LTG, 200 mg/d	11	0	0
	Desipramine	14	0	0
	PBO	8	0	0
20022	LTG, 200 mg/d	7	0	0
	PBO	1	0	0
20025	LTG, 200 mg/d	9	0	0
	PBO	6	0	0
Total	LTG (N = 1198)	100 (8.3%)	0 (0%)	0 (0%)
	LI (N = 280)	12 (4.3%)	0 (0%)	0 (0%)
	Desipramine (N = 147)	14 (9.5%)	0 (0%)	0 (0%)
	PBO (N = 1056)	68 (6.4%)	1 (0.1%)	0 (0%)

[a]Abbreviations: LI = lithium, LTG = lamotrigine, PBO = placebo, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis.
[b]1 case of mild SJS occurred in the preliminary phase of Study 605. The patient was not hospitalized and recovered uneventfully.
[c]1 case of serious rash occurring in the open-label stabilization phase of Study 606 is reflected in "All open-label phases" (N = 1955) in Table 3.

Table 3. Summary of Rash Data in Controlled and Open-Label Trials of Lamotrigine in Mood Disorders[a]

Studies/Phases	Treatment	N	Rash: No. of Cases	Rash: %	No. of Cases of Serious Rash
All controlled studies	LTG	1198	100	8.3	0
	PBO	1056	68	6.4	1
	Comparators	427	26	6.1	0
Monotherapy studies	LTG	686	66	9.6	0
	PBO	631	45	7.1	0
	Comparators	183	17	9.3	0
Add-on studies	LTG	142	11	7.7	0
	PBO	146	11	7.5	1
	Li	78	0	0	0
Monotherapy continuation phases	LTG	370	23	6.2	0
	PBO	279	12	4.3	0
	Li	166	9	5.4	0
All open-label phases	LTG	1955	257	13.1	2[b]

[a]Abbreviations: Li = lithium, LTG = lamotrigine, PBO = placebo.
[b]1 case was from a stand-alone open-label study (Study 601); 1 case was from the open-label phase preceding the randomized continuation phase of a controlled maintenance study (Study 606).

stabilization phase of a maintenance study conducted in bipolar I patients (Study 606[4]). A 54-year-old female patient who had received lamotrigine titrated from 25 mg/day to 100 mg/day over 2 months developed a moderately severe maculopapular nonpruritic facial rash associated with facial erythema. No dermatologic treatment was initiated, but 10 days later she showed signs of moderately severe mania and was hospitalized for treatment of her mania and observation of the rash. The dose of lamotrigine was increased to 200 mg/day, resulting in slight improvement in her mania but subsequent spread of rash to 80% of her body area, without desquamation or mucosal involvement. The rash subsequently resolved uneventfully over a 6-week period following discontinuation of lamotrigine.

The second case of serious rash was observed in a 12-month open-label study (Study 601). A 50-year-old female patient who had received lamotrigine titrated to 100 mg/day over a 5-week period was hospitalized for a pruritic rash. Symptoms included fever, chills, tachypnea, and dyspnea, and a skin biopsy was consistent with purpuric (hemorrhagic) drug eruption. The rash resolved after discontinuation of lamotrigine and treatment with oral steroids, and the patient was discharged 9 days later. Subsequently, this patient was readmitted for evaluation of another rash, which appeared to be secondary to erythromycin treatment.

DISCUSSION

Of 1198 patients with either bipolar disorder or recurrent major depression treated with lamotrigine in placebo-controlled trials, 8.3% of patients developed a benign rash and none developed a serious rash, compared with a benign rash rate of 6.4% and 1 case of serious rash (0.1%) in patients treated with placebo. There were no cases of Stevens-Johnson syndrome reported in any of the lamotrigine-treated patients in placebo-controlled trials. One case of nonserious Stevens-Johnson syndrome, which did not require hospitalization, occurred in a patient with several risk factors and was reported in the open stabilization phase of Study 606. Of the 129 patients with bipolar I depression treated with lamotrigine in Study 602, 11.6% developed a benign rash and none a serious rash, compared with a benign rash rate of 10.8% and no cases of serious rash in 65 patients treated with placebo. These data suggest that the rate of benign rash with lamotrigine is similar to that observed with placebo in patients with bipolar I disorder.[1]

The greatest risk of rash appeared to be during the first 8 weeks of treatment. The rate of serious rash has previously been reported to be 0.3%[12]; the sample sizes evaluated in the current series are not sufficient to provide additional information regarding the prevalence of serious rash. Since serious rash has previously been reported to be

rare and benign rash is present in about 10% of patients, the ability of the treating physician or dermatologist to separate benign rash from serious rash has become an important clinical management issue. In addition, predictors of serious rash have been identified and can be used to minimize its likelihood.

The starting dose and the rate of titration of lamotrigine have been shown to influence the incidence of serious rash, but not benign rash. In 1999, Wong and colleagues[17] published the results of a retrospective case record survey identifying the incidence of serious and nonserious lamotrigine-related rash from 1993 to 1995 in 5 tertiary epilepsy referral centers in the United Kingdom. Serious rash was defined as any rash with an associated systemic disorder, including abnormal hematologic or hepatic laboratory results, angioedema, erythema multiforme (papular or vesicular lesions and reddening or discoloration of the skin, frequently in concentric zones around the lesions), or Stevens-Johnson syndrome. Of the 1050 cases included in statistical analysis, 1.1% (N = 12) had a serious rash and 7% (N = 74) had a nonserious rash. Except for 1 patient whose starting dose was unknown, all of the patients experiencing a serious rash were started at a dose higher than recommended by the manufacturer, and almost all (11 of 12) were receiving concurrent valproate, which is known to increase blood levels of lamotrigine due to a metabolic interaction that increases the half-life of lamotrigine.[12] Higher rates of rash have also been associated with patients younger than 12 years.[13]

Another evaluation of the risk for Stevens-Johnson syndrome and toxic epidermal necrolysis was undertaken in Germany using a population-based registry.[18] The registry provided a comprehensive population assessment for the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with medications by regularly contacting burn units, departments of pediatrics and dermatology, and departments of internal medicine in larger hospitals with intensive care units. In this study, all hospitalized patients admitted for a serious cutaneous reaction from 1990 to 1998 were entered into the database. Cumulative drug-based incidences for Stevens-Johnson syndrome or toxic epidermal necrolysis were stable for carbamazepine (12%), phenytoin (45%), and phenobarbital (86%) during this period. The annual drug-based incidence of serious cutaneous drug reactions associated with lamotrigine was highest in 1993 (4.2%) but steadily declined and stabilized by 1998 (0.02%) after the manufacturer's dosage revision in 1994. During this period, the number of prescriptions of lamotrigine increased.[9] These data suggest that proper titration of lamotrigine has an impact on rash risk reduction.

Pathophysiology of Lamotrigine Rash

The pathophysiology of lamotrigine-induced rash is unclear, but allergic mechanisms are hypothesized on the basis of time of onset and the more rapid recurrence of rash after rechallenge.[19] Rash associated with the administration of lamotrigine typically occurs between day 5 and week 8 after the start of lamotrigine therapy.[16] It is most commonly a simple benign morbilliform rash, but serious cutaneous reactions to lamotrigine can occur. These include Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug hypersensitivity syndrome.

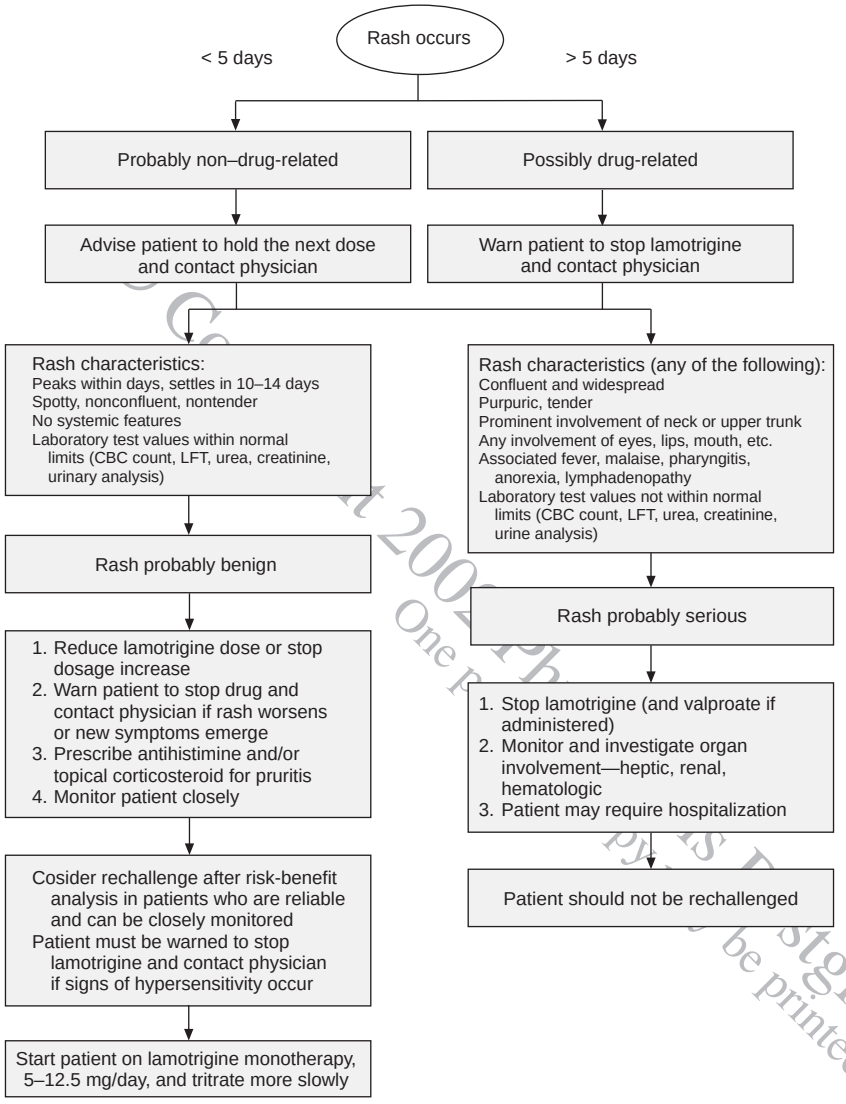
Stevens-Johnson syndrome has been associated with more than 100 different medications, including sulfonamide antimicrobials and anticonvulsants.[20] It is characterized by a high fever, malaise, skin blistering or crusting, and ulceration of mucous membranes.[21] The mortality rate associated with Stevens-Johnson syndrome is 5% or less.[22] Toxic epidermal necrolysis is associated with the same drugs that cause Stevens-Johnson syndrome[20] and presents in a similar manner (high fever and malaise with mucosal changes). It is a more serious mucocutaneous disorder, resulting in death in 25% to 30% of cases.[20] Skin involvement in toxic epidermal necrolysis can progress rapidly over 1 to 5 days and results in widespread erythema and skin detachment, involving greater than 30% of the body surface area.[23]

A drug hypersensitivity syndrome is characterized by fever, internal organ involvement, and rash. Mucous membrane involvement is not as prominent or severe as in Stevens-Johnson syndrome and toxic epidermal necrolysis. Fever and systemic symptoms typically precede or coincide with cutaneous eruption. Occasionally, patients develop rash first and then rapidly develop fever with other systemic symptoms. The rash usually begins with patchy macular erythema that may become pruritic and papular.[24] The cutaneous eruption can evolve to erythroderma, an abnormal redness of the skin over extensive areas of the body, with prominent desquamation and occasionally pustules. The upper trunk, upper extremities, and face are usually affected early in the course of eruption. A wide range of internal organs can be involved in a drug hypersensitivity syndrome, and the severity of internal organ changes varies greatly between cases. Internal organ changes associated with the traditional aromatic anticonvulsants include hepatitis, nephritis, pneumonitis, colitis, meningitis, myocarditis, and even orchitis or thyroiditis.[25] Lymphadenopathy, hepatitis, nephritis, pneumonitis, colitis, and meningitis/encephalitis have been seen in the drug hypersensitivity syndrome associated with lamotrigine.[26,27] Hematologic abnormalities include eosinophilia, atypical lymphocytes, thrombocytopenia, neutropenia, agranulocytosis, and hemolytic anemia.[26]

Predictors of Rash

Identified risk factors for rash include lamotrigine dosing (i.e., starting dose and rate of titration above current recommendations) and coadministration with valproate.[9,13] When lamotrigine is used as monotherapy or in the ab-

Figure 1. Decision-Making Flow Chart for Rash Related to Lamotrigine Treatment[a]



[a]Abbreviations: CBC = complete blood cell, LFT = liver function test.

sence of enzyme inhibitors or enhancers, the following schedule is recommended: 25 mg/day during weeks 1 and 2, 50 mg/day during weeks 3 and 4, and then weekly increases of 50 to 100 mg as clinically indicated thereafter.[12] Additionally, children under the age of 12 years may be more likely to experience rash than adults,[13] although pediatric data are not within the scope of this review. Lamotrigine should be initiated at a low dose and increased slowly to an effective maintenance dose. The starting dose of lamotrigine will also vary depending on coadministration with another anticonvulsant having either enzyme-inducing (e.g., carbamazepine) or enzyme-inhibiting (e.g., valproate) activity. Although adherence to the manufacturer's dosing recommendations will not obviate the occurrence of rash, the risk of serious rash appears to be greatly diminished.

Valproate inhibits the hepatic metabolism of lamotrigine, increasing its half-life and steady-state concentrations. In earlier clinical trials, up to 30% of patients who received concomitant valproate and lamotrigine developed a rash.[28] However, 1 study demonstrated that both agents can be concurrently administered with an acceptable level of adverse effects when lamotrigine is added very slowly and at lower initial doses.[26] The starting dose of lamotrigine should be decreased by half when lamotrigine is added to valproate, i.e., 12.5 mg/day during weeks 1 and 2, 25 mg/day during weeks 3 and 4, etc. The frequency of rash was 13% in 108 patients receiving concurrent lamotrigine and valproate, similar to a 14.2% incidence of rash in 310 patients receiving lamotrigine without concurrent valproate.[29]

Other minor risk factors that increase liability of serious rash with anticonvulsants include patients with human immunodeficiency virus or systemic lupus erythematosus, patients receiving corticosteroids when an anticonvulsant is initiated, and patients with a family history of serious rash to the same or cross-reacting medications.[20,30,31]

Clinical Management of Rash

The prescribing physician can minimize the risk of a serious reaction to lamotrigine by warning the patient not to exceed the recommended dosing schedule; should rash occur, the patient should defer taking the next dose and contact medical staff. Current dosing guidelines have been designed to reduce the risk of a serious reaction. Rashes are common, and many non–drug-related eruptions can occur in patients taking therapeutic agents. Common causes of rash include eczema, irritant and allergic contact dermatitis such as poison ivy, and insect bite reactions. A rash during the first 5 days of therapy (in the first exposure) is usually due to a nondrug cause (Figure 1).

Patients who develop a rash in the first few months of lamotrigine therapy need to be carefully evaluated.[9] The most common lamotrigine-associated eruption is an isolated, viral, eruptive rash usually described as morbilli-

form or maculopapular in appearance. This rash is self-limiting; however, a clinically similar eruption may accompany rare but more serious systemic hypersensitivity reactions.[22] Thus, all patients who develop rash during the first few months of lamotrigine therapy should be instructed to hold the next dose and immediately contact their physician for consultation.

Benign drug-associated eruptions typically peak within days and progressively settle over 10 to 14 days. A benign, isolated, drug-related rash is spotty, nonconfluent, and nontender. There should be only minor facial involvement and no periorbital puffiness; no facial or neck edema; and no involvement of the eye, lip, or mouth. The diagnosis of a benign rash is consistent with the absence of systemic symptoms such as fever, malaise, pharyngitis, anorexia, or headache. There should be no lymphadenopathy, hepatomegaly, or splenomegaly, and results of laboratory tests should be within normal limits (i.e., complete blood count with differential, liver function tests, urea, creatinine, and urinary analysis). If a benign, isolated rash occurs, the lamotrigine dose should not be increased until the rash has entirely resolved; ideally, the dose should be reduced. Patients who develop a rash should be closely monitored and warned to withhold the drug and contact medical staff should the rash worsen or new symptoms emerge. Pruritis associated with a benign rash can be treated with an antihistamine and/or topical corticosteroid. These drugs will not mask the development of a serious reaction. The characteristics of benign rashes are also relevant to the assessment of rash in the context of medications other than lamotrigine.

Serious drug rashes are usually confluent and widespread or show prominent facial, neck, and upper trunk involvement. Serious rashes may be tender or have a purple "purpuric," or hemorrhagic, appearance that does not blanch with pressure. They are accompanied or preceded by symptoms and signs of internal toxicity such as fever, malaise, pharyngitis, anorexia, or lymphadenopathy.[22] Rashes with any feature(s) suggestive of a serious reaction necessitate immediate drug cessation and investigation and monitoring for internal organ involvement, particularly in the hepatic, renal, and hematologic systems. New organ involvement can occasionally occur, and the severity of internal organ toxicities may increase despite drug cessation and may necessitate hospitalization.[24] Serious reactions associated with lamotrigine should lead to prompt discontinuation of both lamotrigine and valproate if the latter is being given concomitantly. Early discontinuation of associated drug(s) after onset of a serious reaction improves patient outcome; however, drug discontinuation may not always prevent a more serious, life-threatening reaction from developing.[32]

Patients should not be rechallenged if they have had a serious rash such as a reaction associated with systemic symptoms or internal toxicity.[33] Reports of successfully restarting patients on lamotrigine treatment after a mild isolated rash are documented in the literature.[32,34] However, anticonvulsant rechallenge should be considered only after a careful risk-benefit assessment (e.g., treatment options, severity of mood disorder, nature of rash) and only if the patient is reliable and can be closely supervised. Patients should always be counseled to hold the next dose and notify their physician immediately if signs of hypersensitivity including rash recur. This is particularly important should symptoms recur within hours to days of restarting therapy. At rechallenge, the patient should be started on a lower dose, such as 5 to 12.5 mg daily (monotherapy), and the titration rate should be slower.

CONCLUSION

Serious drug eruptions associated with lamotrigine appear to be rare when the drug is started at 25 mg/day during weeks 1 and 2, increased to 50 mg/day during weeks 3 and 4, and then increased weekly by 50 to 100 mg/day as clinically indicated. The starting dose of lamotrigine and its titration should be adjusted when the drug is added to enzyme-inducing (carbamazepine) or enzyme-inhibiting (valproate) anticonvulsants. A rash, particularly during the first 8 weeks of therapy, warrants holding of the next dose pending evaluation by the treating physician and/or dermatologist. If a rash shows cutaneous features of a severe reaction or is associated with systemic symptoms, lamotrigine, as well as any concomitant valproate, should be promptly discontinued to reduce the consequences of a potentially life-threatening reaction.

Thus, the clinician needs to be aware of risks, clinical features, and management of lamotrigine-associated rashes. The decision to use lamotrigine should be based on a risk-benefit analysis, with the rare risk of serious rash weighed against the more common risks associated with untreated or undertreated bipolar depression.

Drug names: carbamazepine (Tegretol and others), desipramine (Norpramin and others), erythromycin (Ery-Tab, E-Base, and others), lamotrigine (Lamictal), phenobarbital (Donnatal and others), phenytoin (Dilantin and others), topiramate (Topamax), valproic acid (Depakene and others).

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