RECHALLENGE WITH LAMOTRIGINE AFTER A RASH: A Prospective Case Series and Review of the Literature

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ABSTRACT

Objective: To investigate the safety of rechallenge with lamotrigine after an initial rash in patients with refractory bipolar depression.

Design: 1) Prospective, open-label case series in a private practice setting. Patients who developed an initial rash on lamotrigine and were refractory to other treatments were offered rechallenge with the drug using very-low-dose titration (5mg every other day or daily for 14 days, then raised every 14 days by daily-dose increments of 5mg; after 25mg/day the titration proceeded according to the manufacturer's guidelines); and 2) A meta-analysis of prior reports of rechallenge with lamotrigine was conducted.

Measures: A rating scale for rash severity was developed for this study.

Results: Of 27 patients rechallenged with lamotrigine, five required discontinuation due to rash or inflammation. Two of these were potentially serious and all resolved with discontinuation of lamotrigine. Review of the literature identified 48 cases of lamotrigine rechallenge with a success rate of 87 percent; in pooled analysis with the current study the success rate was 85 percent. No

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TABLE 1. Rating scale for dermatological drug eruptions

Clinical Feature	Present	Absent
Exfoliation or erythroderma	3	0
Purpura, tenderness, or blistering	1	0
Facial or mucous membrane involvement	1	0
Lymphadenopathy	1	0
Hematological abnormalities (e.g., eosinophilia), or elevated transaminase enzymes	1	0
Constitutional symptoms (fever, malaise, arthralgia, meningism, pharyngitis, cough)	1	0

Scoring: add the scores for each item above (range = 0–8)

patients developed Stevens-Johnson syndrome or toxic epidermal necrolysis after rechallenge. The rate of rash was elevated when rechallenge began within four weeks of the initial rash (36% vs. 7%, p=0.002) and reduced when the initial rash had no signs of potential seriousness (0% vs. 23%, p=0.01).

Conclusions: Rechallenge is a viable option after a benign rash on lamotrigine and can be undertaken with more caution after rashes with 1 to 2 signs of potential seriousness. For rashes with three or more signs of seriousness, rechallenge is not well-studied and may carry significant risk. Rechallenge should be avoided within four weeks of the initial rash.

INTRODUCTION

Lamotrigine is an important advance in the treatment of bipolar disorder. Its use, however, has been limited by the risk of potentially life-threatening dermatological reactions, principally Stevens-Johnson syndrome and toxic epidermal necrolysis. Risk factors for these reactions include rapid titration, concurrent valproic acid administration, prior history of an anticonvulsant-associated rash, female gender, and age less than 13 years.[1–5]

Since the introduction of a gradual titration schedule in 1994, the rate of severe rashes with lamotrigine has declined from 1 to 0.1–0.01 percent.[6–8] However, there was not a substantial reduction in the rate of benign rashes, which has remained between 8 and 11 percent.[2,5,6,9] Since it is unknown which dermatological changes herald the onset of severe eruptions, it is recommended to discontinue lamotrigine at the appearance of any rash.[5]

These benign rashes pose a dilemma for clinicians who have few effective alternatives for bipolar depression. Patients with bipolar disorder spend 30 to 40 percent of their lives in the depressed phase,[10–12] and lamotrigine's most robust effects are in the prevention of these depressions. Further advantages of lamotrigine include its tolerability,[13] cognitive profile,[14–16] and high rates of patient adherence.[13] This profile is particularly relevant in bipolar disorder, where rates of adherence approach only 50 percent[31] and rates of mortality approach those associated with nicotine use in the general population.[32]

To address the problem of benign rashes, dermatological precautions have been developed for patients starting lamotrigine,[17] but these did not significantly reduce their rate in a randomized, controlled trial.[18] A separate strategy, developed in neurological clinics, is to rechallenge patients with a very slow retitration of lamotrigine, usually starting at 5mg/day, when its use is clinically indicated after a benign rash. These studies were not large enough to identify predictors of failure with rechallenge. This paper extends those results to a psychiatric setting and, through pooled-analysis, investigates predictors of adverse events during lamotrigine rechallenge.

METHODS

Case series. Patients who developed a rash within three months of starting lamotrigine were identified prospectively between 10/1/2005 and 12/15/2009 in a private outpatient psychiatric practice specializing in bipolar disorder. To rate the rash, an 8-point scale was developed based on known risk factors for severe drug-related dermatological eruptions (Table 1).[19] For each patient, the severity of the rash was weighed against the potential for therapeutic benefit with lamotrigine, and informed consent was obtained for those considered appropriate for rechallenge. Rechallenge was not considered for patients with exfoliation or erythroderma because of the close resemblance these eruptions bear to Stevens-Johnson syndrome.

For benign rashes (rated 0 in Table 2), attempts were first made to relieve the rash by dose reduction. If this did not resolve the rash, lamotrigine was discontinued and the patient was considered for the rechallenge study.

At least one week was required after clearance of the rash before attempting rechallenge. Rechallenge was initiated at 5mg daily (or 5mg every other day for patients on concurrent valproic acid therapy). The daily dose was then increased by 5mg every two weeks until a dose of

TABLE 2. Case series of lamotrigine rechallenge

Subject	Diagnosis	Age	Sex	Onset of Rash (wks)	Description of Rash	Severity Rating	Interval Between Discontinuation and Rechallenge (wks)	Follow-up Since Rechallenge (wks)	Outcome	CGI Improvement
1	Bipolar NOS	27	F	3	Symmetric morbilliform rash of chest, pruritic and blanching	0	11	230	Successful	0
2	Bipolar II depression	42	F	1	Macules and wheals on face and back	1	11	230	Successful	1
3	Bipolar I depression	31	F	22	Macular facial rash	1	79	228	Successful	1
4	Bipolar I, mixed state, rapid cycling	25	F	1	Macular facial rash	1	76	226	Successful	2
5	Bipolar NOS	34	F	2	Vesicles on tongue	1	97	224	Successful	3
6	Bipolar II depression	41	F	1	Erythematous pruritic wheals on arms and tongue	2	6	223	Successful	1
7	Bipolar II depression	32	F	2	Blanching pruritic macules on face and neck	1	19	219	Successful	1
8	Bipolar II depression	42	F	2	Tender vesicles on lip	2	10	214	Successful	1
9	Bipolar I depression, rapid cycling	20	F	3	Morbilliform rash, generalized	1	11	213	Successful	1
10	Bipolar due to a general medical condition (frontal lobe infarct)	19	M	-	Unknown (lamotrigine had been stopped 11 years prior to the study due to a rash)	-	520 (approximately)	177	Successful	4
11	Cyclothymia	44	F	4	Wheals on legs, 3 blistering papules on knuckles	1	7	177	Successful	2
12	Bipolar II depression	44	M	6	Macular rash on chest and extremities with fever	1	5	171	Successful	3
13	Schizoaffective, bipolar type, rapid cycling	26	F	7	Wheals and macules on lips, tongue and arm; edema on legs	2	4	165	Successful	2
14	Bipolar I depression	22	F	1	Pruritic erythema on extremities	0	10	150	Successful	3
15*	Bipolar II depression	47	F	4	Patch and papules on abdomen, pruritic	0	3	136	Successful	1
16	Bipolar II depression	55	F	12	White vesicles on mouth	1	1	124	Successful	2
17	Bipolar NOS	45	M	2	Pruritic vesicles on arms and chest	0	19	110	Successful	3
18	Bipolar II depression	22	F	5	Urticaria on neck	1	49	80	Successful	2
19	Bipolar II depression	20	F	5	Perioral papules and dry patches on face, pruritic	1	6	47	Successful	2
20	Bipolar II depression	40	M	12	Blistering vesicles on mouth	2	7	13	Successful	2
21	Bipolar II depression	20	M	3	Diffuse petichial rash on abdomen, chest, back, legs and face; lymphadenopathy	2	4	16	Successful	1
22	Bipolar I depression	46	M	9	Tender, raised papules on legs	1	41	14	Successful	2
23	Bipolar NOS	19	M	5	Pruritis on face, sore throat, malaise	2	13	13	Fever, malaise, headache (no rash)	0
24	Bipolar II depression	37	F	4	Vesicles in mouth	1	4	300	Mild erythema of bilateral arms	2
25*	Bipolar I depression	53	M	1	2 raised erythematous patches on face and neck	1	1	160	Benign fixed drug eruption	3
26	Bipolar I depression	17	F	3	Pruritic, tender erythema on back	1	2	50	Painful erythema with dyspnea, neuralgia	3
27	Bipolar II depression	23	M	5	Throat blisters, malaise, fever, shoulder erythema, eosinophilia (5.6%)	4	4	11	Nonblistering erythematous vesicles on shoulder and face	1

*In these cases the patient mistakenly raised lamotrigine every week instead of every 2 weeks; CGI = Clinical Global Impression

TABLE 3. Meta-analysis of current and prior studies of lamotrigine rechallenge

Available Literature	Cases	Bipolar Disorder (%)	Age (mean)	Female (%)	Onset of Rash (mean, wks)	Severity Rating (mean, 0–8)	Interval Between Discontinuation and Rechallenge (mean, wks)	Rate of Successful Retitration (%)
Prior studies	48	6%	25	54%	3.3	0.6	55	87%
Current study	27	100%	34	67%	4.9	1.1	19	81%
Combined analysis	75	40%	28	59%	3.9	0.9	35	85%

TABLE 4. Rate of rash by initial severity (pooled meta-analysis)

Severity	Number of Subjects	Rate of Rash
0	19	0% (n=0)*
1	20	20% (n=4)
2	9	22% (n=2)
4	2	50% (n=1)

* p=0.01

25mg/day was reached, at which point titration was continued according to the manufacturer's guidelines.[5] Two patients did not follow the rechallenge schedule correctly (titrating it approximately twice as fast as directed); they were included in the analysis and identified as such.

Improvement with lamotrigine was rated at the end of the study using the clinical global impression (CGI) scale;[20] response to both the initiation and rechallenge phase was considered in judging the CGI.

Meta-analysis of prior studies. A Medline search was conducted using the key words "lamotrigine" and "rash" (number=168). These abstracts were reviewed to identify reports where lamotrigine was reintroduced after a rash by titrating more slowly than the initial titration schedule (number=9); this search was supplemented by a review of references (number=1 additional paper). The search strategy was repeated on 3/5/2010 with no new reports identified.

Data from these 10 papers was extracted and, where possible, rashes were rated with the scale in Table 1. These cases were combined with the current case-series to conduct the meta-analysis. A *post-hoc* analysis was performed to evaluate whether the risk of rash during rechallenge varied with the severity of the initial rash or with the time between the first rash and rechallenge.

RESULTS

Case series. Of 1,022 patients who began lamotrigine, 122 (12%) developed a rash within three months and 27 were rechallenged. Rechallenge was unsuccessful in five (18%) patients: two who developed serious rashes, two with benign rashes, and one who developed signs of inflammation without rash. No patients developed Stevens-Johnson syndrome or toxic epidermal necrolysis during initiation or retitration with lamotrigine. The full results of rechallenge are described in Table 2.

Reasons for not attempting rechallenge were as follows: 1) episode resolved with a different treatment (n=41), 2) the rash was benign (severity rating = 0) and resolved with dose-reduction (n=36), 3) the rash was too severe (n=13), and 4) the patient declined further treatment (n=4) or was lost to follow-up (n=2).

For patients who underwent rechallenge, the average rash-severity was 1.2. Only one patient with a severity rating greater than 2 was rechallenged, and this resulted in a second potentially serious rash. Initially, we decided not to rechallenge this patient because the rash was severe (rated 4) and involved eosinophilia, fever, malaise, and sore throat. However, a consulting physician diagnosed streptococcal infection, so we proceeded to rechallenge after resolution of the inflammatory symptoms, wherein the patient developed nonblistering erythematous vesicles on his shoulder and face, which resolved after discontinuation of lamotrigine.

Sixty-seven percent of the patients were rated "much improved" or "very much improved" on the CGI after lamotrigine rechallenge.

Meta-analysis. Forty-eight published cases were identified from 10 papers in which lamotrigine was rechallenged after a rash (Table 3).[21–30] In 13 percent of the cases, a rash reappeared during rechallenge, and in each case it resolved with discontinuation of the drug. No cases of Stevens-Johnson Syndrome or toxic epidermal necrolysis were reported after rechallenge.

Three of the 48 cases were from single-case reports,[23,25,29] and the rest

Table 5. Rate of rash by time to rechallenge (pooled meta-analysis)

Time to Rechallenge	Number of Subjects	Rate of Rash
Rechallenged >4 weeks after initial rash	38	7% (n=4)
Rechallenged 1–4 weeks after initial rash	14	36% (n=5)*

*p=0.002

were from prospective or retrospective case series. To address the possibility that case reports represented a biased sample favoring publication of severe reactions, we reanalyzed the data without the case reports, which lowered the rate of recurrent rashes from 13 to 9 percent.

In 40 percent of the cases, lamotrigine was rechallenged at doses higher than 5mg/d, usually because the original dosing was begun at high doses typical of older titration strategies (e.g., reaching 200mg/d within one week). The success rate of these cases (84%) did not differ significantly from that of cases rechallenged at 5mg/d (90%).

Predictors of rash. In a *post-hoc* analysis, we tested the relationship between the risk of rash during rechallenge and 1) the timing of rechallenge and 2) the severity of the initial rash. We included previously published cases in this analysis where data were adequate (24 in the analysis of severity, 44 in analysis of timing).

As shown in Table 4, the success rate for retitration after a benign rash (rated 0) was 100 percent, which is significantly greater than the rate after more severe rashes (p=0.01). Rashes with initial severities of 1 and 2 had similar rates of adverse events during rechallenge (20% and 22%). Only two patients with an initial severity greater than 2 were rechallenged. One of these developed a second rash and is described in the case series (subject 28). The other was previously published and involved an initial generalized papular rash, fever, nausea, malaise, and reduction of platelets (from 217 to 160 x 10s/1) and white cell count (from 8 to 3.6 x 109/1); severity was rated as 3 and retitration was successful.[26]

As shown in Table 5, the success of rechallenge was significantly greater when initiated more than four weeks after the initial rash (7% vs. 36%, p=0.002).

DISCUSSION

The results of this study support the following algorithm for managing a rash during lamotrigine titration. For benign rashes (rated 0), titration can be reduced a step (e.g., lowering the dose by 25–50mg) with close clinical monitoring until the rash resolves. After resolution of the rash, the titration can be continued if a higher dose is still clinically necessary. If dose-reduction does not resolve the rash, lamotrigine should be discontinued and very-slow retitration can be considered after at least four weeks have passed without a rash.

For moderate rashes (rated 1–2), rechallenge is still a viable option, but one whose risks warrant more careful consideration. Rechallenge after a severe rash, rated greater than 2 on the scale, has not been adequately tested and the 50-percent failure rate of the two cases here do not support its safety.

The guidelines for this study were based on previously published reports from neurological clinics, and the results are consistent with those reports. *Post-hoc* analysis of the results suggests that one guideline—to wait at least one week after resolution of a rash before rechallenge—warrants revision, and that waiting four weeks provides a greater margin of safety. This is also more conservative than the dermatological precautions for initiating lamotrigine, which recommend waiting at least two weeks after resolution of a pre-existing rash.[17]

Despite the strategies presented in this paper, we are still faced with patients who experience unique benefit from lamotrigine but are unable to tolerate even slow retitration of the drug without a rash. Preliminary research suggests that riluzole is a promising option in these cases and one worthy of future study. Riluzole and lamotrigine both inhibit glutamate by blocking sodium channels. It has been studied in treatment-resistant depression and, in a case report, as a substitute for lamotrigine after a severe rash.[29]

Classification of drug eruptions presents a challenge to psychiatrists who may have limited training in dermatology. Clinicians should consider consultation with a dermatologist or primary care physician before rechallenge. Photographs of Stevens-Johnson syndrome and other severe reactions are available through online collections, such as http://www.lib.uiowa.edu/hardin/md/stevensjohnson.html. It is often helpful to have patients photograph their own rashes in case the eruption resolves before it can be examined.

The scale presented in this paper was developed by the authors as a guide for clinical judgment and has not been validated as a measure of rash severity. Future research is needed to refine and validate a measure of drug-induced rashes so that individual items are weighed to more closely reflect their clinical relevance.

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