Rechallenge of Lamotrigine After Rash:

A Systematic Review

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Abstract

Objective: This study aims to characterize the rate of successful rechallenge considering the risk of recurrence of cutaneous adverse reactions with reintroduction of lamotrigine, as well as how to characterize cutaneous reactions appropriately, and important considerations in deciding whether to attempt reintroduction of lamotrigine.

Data Sources: A systematic review was conducted of PubMed, SCOPUS, and Web of Science databases. Search terms included lamotrigine, rash, and rechallenge or reintroduction.

Study Selection: The resulting articles (59) were imported into Covidence. After screening and application of inclusion/exclusion criteria, 11 articles were included.

Data Extraction and Synthesis: Variables extracted included study design, age of patient, lamotrigine dosing regimen, concomitant valproate use, use of other concomitant enzyme-inducing antiepileptic drugs, rash timing after starting lamotrigine, rash description, rash diagnosis, dermatologist evaluation, skin biopsy, hospitalization, time from initial rash onset until rechallenge, rechallenge lamotrigine dosing regimen, and response.

Results: There were 106 cases of rechallenge of lamotrigine. Over half (57%) of patients were female, and the average age was 35 years. Time from discontinuation of lamotrigine until rechallenge ranged from 1 week to 26 months, and there were 12 cases that continued lamotrigine without interruption or by reducing the dose. Patients who were rechallenged with lamotrigine successfully typically started the rechallenge with either 5 mg or 12.5 mg daily with a gradual upward titration until reaching desired dose. Successful rechallenge occurred in 84% of cases; reasons for unsuccessful rechallenge included severe or intolerable rash or other symptoms. Only 3 out of 106 cases had a dermatologist confirm the initial rash diagnosis.

Conclusions: Lamotrigine has been rechallenged safely in select cases; however, it is critical to confirm that the initial rash did not have specific features of a severe rash in order to proceed with safe reintroduction of lamotrigine. This article analyzes the cases in the literature to date and gives recommendations for how to assess whether to rechallenge lamotrigine.

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Lamotrigine is an antiepileptic drug (AED) primarily used in epilepsy and as a mood stabilizer in bipolar disorder. It works by inhibiting voltage-sensitive sodium channels, suppressing the presynaptic release of the excitatory amino acid, glutamate.[1] Lamotrigine has been associated with a risk of cutaneous adverse reactions including mild described forms of reactions such as simple morbilliform rash, urticaria, and erythema multiforme, as well as severe cutaneous adverse reaction (SCAR) such as Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug-induced hypersensitivity syndrome (DiHS).[2] DiHS was formerly known as drug reaction with eosinophilia and systemic symptoms (DRESS) and, when associated with lamotrigine and other antiepileptics, also as anticonvulsant hypersensitivity syndrome. There are also several case reports in the literature of lamotrigine associated with hemophagocytic lymphohistiocytosis (HLH),[3] with or without a rash, and 1 of these cases with HLH and DRESS co-occurring.[4] In addition, a case of acute localized exanthematous pustulosis (ALEP) resulting from lamotrigine has been reported.[5]

The safety and tolerability of lamotrigine monotherapy in bipolar disorder and in epilepsy have been established in randomized controlled trials.[6–9] Lamotrigine has been described as comparable to placebo in risk of adverse events in controlled trials; comparison of incidence of rash specifically among placebo vs lamotrigine groups across 12 controlled clinical trials found an incidence of 6.7% in placebo groups compared with 8.2% in lamotrigine groups.[10] Of patients on lamotrigine in the 12 controlled trials, 0.3% of patients were hospitalized with a serious rash, and 0.1% of patients were reported as having possible SJS.[10]

Clinical Points

- Due to the risk of severe cutaneous adverse reaction, lamotrigine is often discontinued at the first report of a rash. However, rechallenge has been reported successfully in some patients. Synthesis and analysis of the evidence are needed to understand if and when to attempt rechallenge.
- Lamotrigine has been rechallenged safely in select cases; it is critical to confirm that the initial rash did not have the described features of a severe rash in order to proceed with safe reintroduction of lamotrigine.

Several additional factors affect risk of cutaneous adverse reaction. Risk of any form of rash is higher in the first weeks of lamotrigine initiation,[11,12] and risk of serious rash is up to 3 times higher in children than in adults.[13] The rate of lamotrigine dose escalation is directly associated with risk of adverse cutaneous reaction.[10] Concomitant therapy with valproate may cause increased risk of rash due to valproate's inhibition of hepatic metabolism of lamotrigine,[14] though some studies did not find an association.[15]

The mechanism of skin hypersensitivity to lamotrigine has not been well elucidated. It has been hypothesized that metabolites of lamotrigine deposit in the skin, prompting an immunogenic reaction.[16,17] T cells have been found to play an important role in some cutaneous hypersensitivity reactions to lamotrigine and other antiepileptics.[18] Certain human leukocyte antigen (HLA) genotypes, particularly HLA-B*1502 with lamotrigine, have been found to be associated with SJS/TEN with a 2.4- to 7.9-fold increased risk of SJS/TEN with exposure to lamotrigine in patients with positive HLA-B*1502.[19] Testing patients for HLA genotypes prior to initiating lamotrigine therapy has been studied and has not yet been widely implemented.

Due to the risk of SCAR, lamotrigine is often discontinued at the first report of potential adverse cutaneous reaction, even when the rash has not been confirmed to likely constitute a related severe cutaneous reaction. However, there are patients that have been successfully restarted on lamotrigine for effective control of seizures or mood disorders. Synthesis and analysis of the evidence are needed to understand if and when to attempt rechallenge.

This study aims to characterize the rate of successful rechallenge considering the risk of recurrence of SCARs with reintroduction of lamotrigine.

METHODS

A systematic review was conducted in November 2024 of PubMed, SCOPUS, and Web of Science databases for adverse cutaneous reactions associated with lamotrigine use and rechallenge/reintroduction of lamotrigine. The search terms included [lamotrigine AND rash AND (rechallenge OR reintroduction)]. From the 3 databases, 59 articles resulted and were imported into Covidence; after removal of duplicate articles, 29 articles were screened by 2 independent reviewers; any conflicts were resolved with mutual discussion of reasons for exclusion or inclusion and consultation with a tiebreaker reviewer. Review articles, articles pertaining to other medications or irrelevant topics, and non-English articles were excluded. After application of inclusion and exclusion criteria, 11 articles were included and can be referenced in Supplementary Material. A PRISMA diagram of the search query process is shown in Figure 1.

Variables extracted included study design, age of patient, lamotrigine dosing regimen, concomitant valproate use, use of other concomitant enzyme-inducing AEDs, rash timing after starting lamotrigine, rash description, rash diagnosis, dermatologist evaluation, skin biopsy, hospitalization, time from initial rash onset until rechallenge, rechallenge lamotrigine dosing regimen, response, and any HLA subtype genetic testing performed.

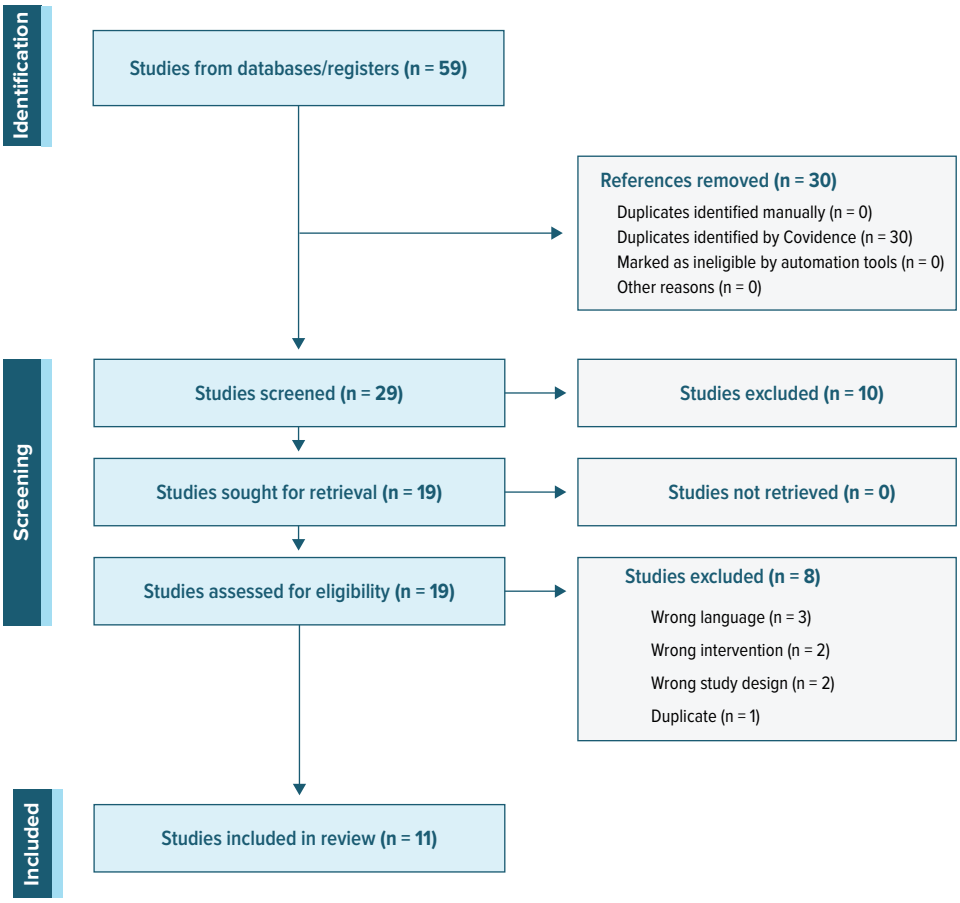
RESULTS

After application of inclusion and exclusion criteria, 11 articles were included: 5 retrospective case series, 3 case reports, 2 prospective case series, and 1 retrospective cohort study. Table 1 provides a summary of the findings of the 11 studies.

There were 106 cases of rechallenge of lamotrigine. Fifty-seven percent of patients were female, and the average age was 35 years. Time from discontinuation of lamotrigine until rechallenge ranged from 1 week to 26 months, and there were 12 of the total cases that continued lamotrigine without interruption or by reducing the dose. Patients who were rechallenged with lamotrigine successfully typically started the rechallenge with either 5 mg or 12.5 mg daily. This dose was then gradually increased by 5 mg every 1–2 weeks (2 weeks being more common) until reaching 25 mg, after which the titration continued in 25 mg increments every 2 weeks or in accordance with the manufacturer's standard titration schedule.

Successful rechallenge occurred in 84% of cases; reasons for unsuccessful rechallenge included severe or intolerable rash or other symptoms. No successful rechallenge cases were attempted after an initially diagnosed severe cutaneous reaction. However, only 3 out of 106 cases had a dermatologist confirm the initial rash diagnosis, and 1 study had a dermatologist retrospectively review the charts of the 15 cases that were rechallenged or continued on lamotrigine to assess whether cutaneous adverse drug reaction might have

Figure 1.
PRISMA Flow Diagram of Systematic Review



Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

been possible or probable. Further, of all the rechallenge cases, only 1 skin biopsy was performed in 1 case to evaluate initial rash diagnosis. None of the cases underwent testing for HLA genotypes in assessing risk of lamotrigine rechallenge.

DISCUSSION

This review demonstrated that rechallenge of lamotrigine can be successful when utilized selectively in the appropriate patient. Rechallenge after severe rash, however, including SJS/TEN, DiHS, or acute generalized exanthematous pustulosis (AGEP)/ALEP, should *not* be performed.[30,31] Multiple studies have demonstrated higher incidence of successful rechallenge in cases that did not show severe initial rash.[20,23,24] One study specifically found that the rate of rash in rechallenge cases was decreased when the initial rash showed no potentially serious signs vs when the initial rash did show potentially serious signs (0% vs 19%, $P = .01$).[23] Thus, it is absolutely imperative to determine that severe features of the initial rash were appropriately ruled out if rechallenge is to be considered in the future. We developed Table 2 to use as a reference in evaluating a rash to list features that would be more concerning for a complicated or severe rash. Some of these features include a patient that appears ill or has systemic signs/symptoms including fever, lymphadenopathy, malaise, or sore throat.[32] Any facial/hand swelling or involvement of the mucosa or palms/soles is concerning for a complicated/severe rash. The morphology of the lesion is critical to evaluate, and any petechiae, vesicles/bullae, or pustules are indicative of a complicated/severe rash.[30] Two-toned erythema, threatened/dusky skin, or a positive Nikolsky sign are also quite concerning. Lastly, certain laboratory abnormalities should be considered.

The studies reviewed in this systematic review used inconsistent rash descriptions and inconsistent classifications of rash severity. Several unsuccessful rechallenge cases had initial rashes with no description, insufficient description, or severe features. For example,

Table 1.

Summary of Included Studies

Study	Diagnosis	Specialty	n Rechallenged	Age, mean	Sex	Mean time from discontinuation to rechallenge	Rechallenge success (%)	Dermatology consult
Shirzadi et al[20]	Epilepsy	Neurology	15	35	7 F 8 M	Continued LTG or from 1 to 4 weeks	80	No
Houser et al[21]	Bipolar disorder	Psychiatry	1	53	M	5 wk	100	No
Inaba et al[22]	Bipolar disorder	Psychiatry	12	49	10 F 2 M	74 wk	75	No
Serrani[23]	Bipolar disorder	Psychiatry	10	43	5 F 5 M	2–3 wk	80	No
Aiken[24]	Bipolar disorder	Psychiatry	27	34	18 F 9 M	19 wk	81	No
Lukic et al[25]	Epilepsy	Neurology	9	26	not specified	Not specified	100	No
Codrea et al[15]	Epilepsy	Neurology	19	32	15 F 4 M	113 wk	84	No
Manfredi et al[26]	Bipolar disorder, depression	Psychiatry	1	61	F	13 wk	100	No
Huang et al[27]	Epilepsy	Neurology	3	31	1 F 2 M	2 mo, 10 d, and 1 year later, respectively	100	Yes
Buzan et al[28]	OCD, bipolar disorder	Psychiatry	1	25	M	Not specified	0	No
Tavernor et al[29]	Epilepsy	Neurology	8	18.5	4 F 4 M	78 wk	100	No

Abbreviations: F = female, LTG = lamotrigine, M = male, OCD = obsessive-compulsive disorder.

Table 2.

Features That Would Be Concerning for a Complicated/Severe Rash

Systemic symptoms (malaise, fever, or sore throat) or appears ill
Facial or hand swelling
Palm/sole involvement
Lymphadenopathy
Petechiae, vesicular/bullous (blistering) lesions, or pustular lesions
Two-toned erythema, threatened/dusky skin, or a positive Nikolsky sign[a]
Mucosal involvement
Laboratory abnormalities, including but not limited to peripheral eosinophilia, circulating atypical lymphocytes, elevated liver function tests, elevated creatinine

[a]Slight rubbing of skin causes peeling away of the outer skin layer.

in one case of rechallenge, the patient's initial rash had facial involvement and thus should have been recognized as a severe feature and not rechallenged. Another study emphasized that none of the patients developed SJS/TEN despite initial rash descriptions including localized skin peeling and insufficient description to assess for severe features. Importantly, there are severe, life-threatening rashes other than SJS/TEN, and clinicians need to be aware of the features of these severe rashes included in Table 2 in addition to the features of SJS/TEN.

The insufficient rash description and inadequate workup to rule out severe rash features are concerning areas that deserve further attention and underscore the importance of dermatologic consultation to rule out severe adverse cutaneous reaction for the initial rash as well as the importance of obtaining an accurate rash description and diagnosis including consideration of skin biopsy. This is especially critical because rashes with severe features can be life-threatening and should never be rechallenged with the offending medication.

In evaluating the initial rash, consider ordering laboratory studies if the patient has any of the high-risk features above and in Table 2. A complete blood count with differential and a comprehensive metabolic panel should be ordered if high-risk features are present. If there is high suspicion for a viral exanthem (consider when there are atypical features of morbilliform rash such as lack of pruritus), specific viral serologies and polymerase chain reaction (PCR) testing can be obtained. Of note, preceding systemic symptoms can be seen with viral etiologies and with SJS or DiHS. Inflammatory markers (erythrocyte sedimentation rate/C-reactive protein) are nonspecific and usually of limited value. After obtaining laboratory results, look for peripheral eosinophilia that may point to DiHS, elevated creatinine that may point to DiHS, liver function test abnormalities that may point to DiHS or viral exanthems, and any positive viral serologies/PCR.

When evaluating patients with skin of color, other factors are important to take into account. Erythema in skin of color can have a hyperpigmented or violaceous appearance and can be more difficult to appreciate than

in lighter skin tones.[33] Ask patients with skin of color or their family members if their skin looks more red or a different color than usual.[30] Of note, duskiness may actually be easier to detect in skin of color.

Biopsy should be performed when there are high-risk features to confirm the diagnosis, for example, of SJS, DiHS, or AGEP. A skin biopsy is also necessary in challenging cases to differentiate between conditions such as SJS and AGEP. SJS can also be confused clinically with another blistering disorder. In our study, no cases of rechallenge of lamotrigine mentioned that a biopsy was performed. Again, it is critical to rule out a severe rash as the initial rash if rechallenge of lamotrigine is to be considered in the future; a skin biopsy can be helpful in ascertaining the diagnosis. When uncertainty arises, monitor morphological progression over subsequent days to determine if a severe rash is developing.

If a severe rash has been ruled out, it may be possible to "treat through" low-risk drug eruptions.[24,31] This involves a discussion with the patient to see if they are willing or able to tolerate their current symptoms such as rash or pruritus. It is imperative to educate the patient about high-risk features to look for if they arise.

Additional Testing Considerations

Additional testing that may be considered in evaluating etiology of rash associated with lamotrigine are skin patch testing, lymphocyte stimulation testing, and HLA genotyping.

One case report demonstrated the utility of lymphocyte stimulation testing in determining the etiologic drug of the patient's hypersensitivity syndrome. A patient developed severe hypersensitivity syndrome affecting the skin, liver, and lymph nodes 1 month after starting on high-dose valproate and lamotrigine for seizure control. Skin patch testing for both antiepileptics was negative. However, lymphocyte stimulation testing was twice positive for lamotrigine and was negative for valproate; the patient was thus subsequently successfully restarted on valproate with no resulting adverse reaction.[34] This case also illustrates the limited value of patch testing considering the low negative predictive value of patch testing for AEDs in hypersensitivity reactions.[35]

Though none of the included studies in this systematic review tested patients for HLA genotypes, this is an important emerging area in assessing individual risks in the use of AEDs and other medications. The Dutch Pharmacogenetics Working Group recommends HLA-B*15:02 genotyping prior to initiation of lamotrigine in patients with ancestries with a prevalence of this genotype.[19] This HLA genotype has been studied in various populations; one study in the Han Chinese population found that positive HLA-B*15:02 is a positive predictor of risk of SJS/TEN; however, a negative HLA-B*15:02 did not negatively predict the risk of SJS/TEN.[36] A positive result can be helpful in anticipating increased risk of serious rash and in considering alternative medication therapy. A recent study found that broad screening of a US population cohort for HLA-B*15:02 identified more than twice the number of carriers than only screening patients of Asian populations.[37] Retrospective analysis of the positive individuals notably included 28 Asians (42%), 15 African Americans (22%), 11 Caucasians (17%), 2 Hispanics (3%), and 10 "Other" (15%), and the authors point out that screening based on assumptions of ethnicity screening may not be adequate in a US population.[37]

Further Considerations for Rechallenge

Strategies to reduce the risk of cutaneous adverse reaction with rechallenge include slow increase in titration of lamotrigine dosing, considering low to moderate target dosing, waiting at least 4–6 weeks for reintroduction, and avoidance of coadministration of lamotrigine with valproate or other drugs that induce glucuronidation of lamotrigine such as phenytoin, phenobarbital, or rifampin.[1] In the studies reviewed, patients who were rechallenged with lamotrigine successfully typically started the rechallenge with either 5 mg or 12.5 mg daily. This dose was then gradually increased by 5 mg every 1 or, more commonly, every 2 weeks until reaching 25 mg, after which the titration continued in 25 mg increments every 2 weeks or in accordance with the manufacturer's standard titration schedule. Regarding waiting for reintroduction after initial rash, one study found specifically that the rate of rash was higher when rechallenge was begun within 4 weeks from discontinuing lamotrigine due to rash vs greater than 4 weeks (19% vs. 7%, $P = .001$).[23]

Most importantly, severe features of the initial rash must be ruled out before considering rechallenge, as the risk of recurrence of a severe rash is serious. We found it quite concerning that so many of the reported rechallenge cases appeared to have insufficient assessment of the initial rash. Thorough and systematic assessment of cutaneous signs and symptoms of patients taking lamotrigine not only minimizes the risk of severe reactions by rechallenging when inappropriate but also ensures that patients without severe rash features are identified as possible candidates for rechallenge. As a result, more patients who may actually benefit from lamotrigine therapy can be continued on the medication.

Limitations of this systematic review include a small sample size in the case reports and the inherent risk of positive publication bias with case reports. However, only 3 case reports were included of the 106 cases, and most of the cases were from prospective and retrospective case series. Another limitation is the exclusion of non-English language articles due to resource constraints, which may have limited the scope of our dataset. Additionally, given the heterogeneity of study designs (case reports, case series, cohort studies) and the

relatively small sample size, a formal sensitivity analysis was not methodologically feasible or statistically robust. Instead, we emphasized descriptive synthesis and highlighted consistent patterns across the studies.

The inclusion of patients with either epilepsy or a mood disorder strengthens the generalizability of our findings, as cutaneous adverse reactions to lamotrigine are not indication-specific. However, indication may influence clinical decision-making (eg, availability of alternative therapies). A strength of this study is that it is an up-to-date systematic review and the largest systematic review on rechallenge of lamotrigine including insights importantly from both psychiatry and dermatology on this challenging topic.

In conclusion, lamotrigine has been rechallenged safely in select cases. It is critical to confirm that the initial rash did not have features of a severe rash in order to consider proceeding with safe reintroduction of lamotrigine. This is especially critical because rashes with severe features can be life-threatening and should never be rechallenged with the offending medication in those cases. Our table of features concerning for a severe rash can serve as a valuable reference, particularly in the context of evaluating a patient who develops a rash while taking lamotrigine. Dermatologic consultation is advised to rule out severe adverse cutaneous reaction for the initial rash considering the importance of obtaining an accurate rash description and diagnosis including consideration of skin biopsy to confirm the correct rash diagnosis. Considering that this medication can be a quite effective therapy for many patients including in psychiatry and in neurology, following this guidance can help guide consideration of determining appropriate scenarios to attempt rechallenge and when to avoid rechallenge.

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Supplementary Material: Available at Psychiatrist.com.

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Supplementary Material

Article Title: Rechallenge of Lamotrigine After Rash: A Systematic Review

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **References of Included Studies**

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This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Material

References of Included Studies:

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