

After the ‘pink clouds,’ he sees red

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Mr. T receives lamotrigine for longstanding mood swings, hypomania, irritability, and anxiety. Two weeks later, a rash covers much of his body. Is the anticonvulsant to blame?

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HISTORY Depressed and sick

Mr. T, age 53, was diagnosed last year with hepatitis C and for 20 years has battled recurrent major depression with euthymia between episodes. His hepatologist asks us to evaluate his recent depressed mood and erratic behavior.

Less than 2 months ago, the hepatologist prescribed ribavirin, 1,000 mg bid, and peginterferon alfa-2B, 10 million IU/1.0 mL weekly, for hepatitis C. Soon afterward, Mr. T became irritable, especially toward his wife. He now refuses to leave his house most days because of overwhelming sadness and hopelessness. Once an avid motorcycle enthusiast, Mr. T has stopped riding and complains of fatigue, “fuzzy” thinking, and diminished concentration, but he denies suicidal thoughts or intent. He weighs 232 lb but has lost 15 lb in the last 6 weeks.

Five weeks ago, the hepatologist added bupropion XL, 150 mg/d, for Mr. T’s depressive symptoms, but the patient complained that the antidepressant “amped me up” and “made my mind race.” After 3 weeks, the hepatologist switched to escitalopram, 10 mg/d, but Mr. T’s agitation continued.

Several days after starting escitalopram, Mr. T experienced what he calls a “pink cloud” period—intensely pleasurable episodes that he says began in late childhood, usually last about 4 days, and occur 6 times annually. During these episodes, his thoughts race, his speech is mildly

pressured, and he sleeps 5 hours or less nightly. While euphoric, he drives his motorcycle at 100 mph, starts several projects at once, and is distractible.

Once the “pink clouds” clear, Mr. T feels fatigued and “let down” as he does now. He says he has never reported these euphoric periods because he usually enjoys them.

Mr. T also has longstanding anxiety. Most days he is “on edge” and restless, feels muscle tension in his neck, and has trouble falling and staying sleep. After changing jobs last year, he began having panic attacks triggered by excessive worry. He denies anticipatory fear or avoidance, so we rule out panic disorder.

Additionally, Mr. T has been engaging in weekly binge-eating episodes during which he consumes nearly 50 large-sized cookies and 2 to 3 2-ounce bags of potato chips in 2 hours. He is wracked with guilt after bingeing and often feels embarrassed about being overweight (body mass index, 31 kg/m²). He does not purge but moderately restricts his diet between binges. He says he started bingeing at age 20, and at one point was bingeing 3 times a week.

Mr. T also complains that ribavirin and

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Figure**Did lamotrigine cause Mr. T's rash?**

PHOTOS PROVIDED BY STEPHEN KLINGER, MD

Folliculocentric pustules around patient's left elbow and throughout his left side.

peginterferon are causing headaches, fatigue, and myalgias. He also takes hydrochlorothiazide, 25 mg/d, for hypertension, and is allergic to sulfonamides. He denies using alcohol and drugs but smokes 2 packs of cigarettes per day.

We diagnose bipolar II disorder based on Mr. T's extreme mood shifts, history of major depressive episodes, recent hypomania, lack of manic or mixed episodes, and significant distress. His hypomania episodes last <1 week; episodes that last ≥1 week or require hospitalization would signal bipolar I disorder.

We rule out interferon-induced depression and hypomania¹ because Mr. T showed signs of mood dysfunction long before he contracted hepatitis C. We also diagnose generalized anxiety disorder and eating disorder, not otherwise specified.

How would you treat Mr. T's bipolar II disorder?

- add olanzapine
- add lamotrigine
- add valproic acid
- add lithium

The authors' observations

Diagnosing and managing bipolar disorder is challenging, especially when hypomania is not readily apparent.²

After we discuss treatment options with

Mr. T, he chooses lamotrigine because it causes relatively few side effects and is less likely than valproic acid and other mood-stabilizing anticonvulsants to cause hepatotoxicity or pancreatitis.³ Lamotrigine also might reduce Mr. T's anxiety.⁴

We do not try lithium because Mr. T is taking a diuretic (hydrochlorothiazide), which can cause lithium toxicity when used concomitantly. Also, lithium requires close laboratory monitoring, interacts with many medications, and can cause drowsiness, dry mouth, blurry vision, and fatigue.⁵ These factors contraindicate lithium for Mr. T, who is taking several medications and suffers side effects from ribavirin and interferon.

Olanzapine might control Mr. T's mood swings, but the neuroleptic can cause weight gain and metabolic syndrome⁶ and might complicate his eating disorder.

TREATMENT A 'rash' reaction

We add lamotrigine, 25 mg/d, for 2 weeks and then increase to 50 mg/d.

Two days after the lamotrigine increase, Mr. T reports a rash on the left side of his trunk and left hip, buttock, and elbow (*Figure*). He also complains of mild chills and night sweats, although these symptoms emerged

Clinical Point

Compared with other anticonvulsants, lamotrigine has relatively few side effects and carries a lower risk of hepatotoxicity or pancreatitis

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several weeks ago. He denies blistering, fevers, dysuria, nausea, or vomiting. We see no signs of lymphadenopathy, and mucosae are unaffected. Since he started lamotrigine, he says, he has not tried unfamiliar brands of shampoos, laundry detergents, or shower gels that might irritate his skin.

We have Mr. T come in that day for an emergency physical examination. At presentation, the rash appears infectious with isolated pustules throughout. We refer him to a dermatologist for same-day evaluation.

When Mr. T reported the rash, I would have:

- discontinued lamotrigine
- reduced lamotrigine dosage
- maintained lamotrigine dosage

The authors' observations

A rash is an immunologic reaction to an offending agent. If lamotrigine were causing the rash, lowering the dosage would not mitigate it.

We continued lamotrigine because the dermatologist could examine the rash within 24 hours of Mr. T's complaint. Also, the agent was decreasing the patient's mood, irritability, and anger. If we believed lamotrigine was causing the rash and could not obtain an immediate dermatology consult, we would have stopped the medication.

FOLLOW-UP 'Hot' findings

During the patient history interview, the dermatologist discovers that Mr. T recently installed a whirlpool bath, and that the eruption occurred 3 to 5 days after the patient first used it. Physical examination shows groups of discrete folliculocentric pustules with surrounding erythema mainly on his extensor surfaces and left buttock. These findings and Mr. T's history suggest a skin infection.

The dermatologist diagnoses hot tub folliculitis, an infection caused by exposure to contaminated whirlpools, hot tubs, or water slides. Cultures obtained that day grow *Pseudomonas aeruginosa*, confirming the

diagnosis. The dermatologist tells Mr. T to stop using his whirlpool bath and prescribes topical gentamicin and ciprofloxacin, 500 mg bid for 10 days. We continue lamotrigine based on the dermatologist's recommendation.

Two weeks later, Mr. T's eruption resolves, and we increase lamotrigine to 100 mg/d, which improves his mood and achieves steady-state effectiveness.⁷ We continue escitalopram, 10 mg/d, then increase to 20 mg/d to treat his generalized anxiety. Mr. T begins experiencing anorgasmia 1 week after the escitalopram increase, so we switch to buspirone, 15 mg bid. After another 4 weeks, his anger, irritability, panic attacks, anxiety, and depression have diminished.

After 3 months, Mr. T's hepatologist stops ribavirin and peginterferon because they are not helping his hepatitis C infection. Days later, Mr. T's chills, sweats, and fatigue remit. The hepatologist considers an experimental hepatitis C medication.

We see Mr. T once monthly for supportive psychotherapy and medication management. Despite divorce proceedings and persistent mild depression he is optimistic, enjoys work, and rides his motorcycle safely twice a week.

Cutaneous eruption affects:

- <1% of patients taking lamotrigine
- 3%
- 7%
- 10%

The authors' observations

Although Mr. T's presentation and patient history clearly suggested an independent skin infection, distinguishing between an infection and anticonvulsant-induced rash can be difficult.



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November 2006

Clinical Point

Immediately consult a dermatologist before stopping lamotrigine in patients with rash; also consider whether the drug is improving the patient's mood

continued

Table 1

Estimated risk of severe rash among first-time antiepileptic users*

Drug	Total new users [†]	Total SJS/TEN cases	Risk per 10,000 new users
Carbamazepine	286,360	39	1.4
Lamotrigine	55,154	14	2.5
Phenobarbital	8,659	7	8.1
Phenytoin	36,171	30	8.3
Valproic acid	103,150	4	0.4

* Researchers reviewed records of patients hospitalized between 1998 and 2001 with SJS or TEN after using an anticonvulsant.

[†] Estimates based on number of dispensed prescriptions, average prescribed dosages, and duration of anticonvulsant use as recorded in Germany's Mediplus database.

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis

Source: Adapted from reference 8

Clinical Point

Because a severe cutaneous eruption can develop quickly, see the patient within 12 hours after he reports a rash

Lamotrigine and other antiepileptics (*Table 1*)⁸ have been associated with morbilliform eruptions, anticonvulsant hypersensitivity syndrome, erythema multiforme, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), a severe form of SJS with a 20% to 30% mortality rate.^{9,10}

Although most lamotrigine-induced cutaneous eruptions are mild or self-limited, some are severe and potentially fatal. In clinical trials, approximately 10% of patients receiving lamotrigine for epilepsy developed cutaneous reactions.¹¹ Among 3,348 patients with epilepsy who received lamotrigine, 11 (0.3%) required hospitalization for SJS or TEN.¹¹

Anticonvulsant hypersensitivity syndrome, estimated to occur once per 1,000 to 10,000 exposures to anticonvulsants,¹² can lead to fever, lymphadenopathy, hepatomegaly, and arthralgias. Although hypersensitivity to aromatic anticonvulsants such as phenytoin, carbamazepine, or phenobarbital is most common, hypersensitivity to lamotrigine also has been reported.^{13,14}

Roughly 90% of patients with anticonvulsant hypersensitivity syndrome develop leukocytosis with eosinophilia, and some develop leukocytosis with agranulocytosis.¹⁵⁻¹⁷ Fulminant hepatitis can occur, which leads to most deaths associated with this syndrome.

4 steps to gauging rash

Taking a thorough history, examining the eruption, ordering liver function tests (LFTs) and a complete blood count (CBC), and referring the patient to a dermatologist are key to determining the seriousness of an eruption and planning treatment in patients taking anticonvulsants (*Table 2*). See the patient within 12 hours after he reports the rash, as SJS and TEN often progress rapidly.

STEP 1 Take a thorough history

Ask the patient:

What medications are you taking? Because more than 100 medications could cause SJS or TEN, a detailed drug history is critical to determining whether a medication has induced the eruption.

When did you start taking the potentially offending medication? True lamotrigine-induced eruptions usually occur 5 days to 8 weeks after the first dose.¹⁰ SJS and TEN generally take 1 to 2 weeks to develop.

What is your current dosage? Has it increased or decreased recently? Rapid lamotrigine dosage escalations or use of lamotrigine with valproic acid can cause severe rash.^{9,10,18} Valproic acid increases serum lamotrigine by inhibiting its hepatic metabolism, thereby raising side-effect risk. In clinical trials, 30% of patients who received both anticonvulsants developed a rash.¹⁰

Have any family members had rashes after taking an anticonvulsant? Compared with the general population, siblings and first-degree relatives of patients with anticonvulsant-related eruptions are at higher risk for this complication.¹⁹ Decreased epoxide hydrolase activity might negate these patients' ability to detoxify the arene oxide metabolite, which can cause adverse effects if it accumulates.

Do you have other medical problems? Hepatitis C, for example, can theoretically increase lamotrigine's half-life, thereby elevating side-effect risk.¹¹

Watch for anticonvulsant-related adverse events in patients with hepatic insufficiency because hepatitis might hinder anticonvulsant metabolism.²⁰ Other medical comorbidities—such as HIV infection and systemic lupus erythematosus—also could increase the risk of antiepileptic-induced rash.¹⁰

Have you had fever, chills, or other symptoms? Patients with SJS and TEN usually present with systemic symptoms such as malaise, rash, lymphadenopathy, mucosal lesions, and/or symptoms such as photophobia, difficulty swallowing, rectal erosions, or dysuria. Patients with anticonvulsant hypersensitivity syndrome typically have fever and associated arthralgias, skin pain, lymphadenopathy, or a burning sensation on their skin. These symptoms generally are absent in localized cutaneous infections.

STEP 2 Examine the eruption

Cutaneous SJS and TEN findings usually include abrupt onset of erythematous macules—which progress to targetoid lesions containing central bullae—followed by extensive epidermal necrosis. Superficial lip and mouth necrosis occur early, leading to severe stomatitis.

TEN and SJS can appear similar clinically, but TEN covers >30% of body surface area, whereas SJS covers <10%. Rashes that

Table 2

4 steps to determining rash severity and cause

Take a thorough history	<p>Find out when eruption occurred and when patient started the anticonvulsant</p> <p>Ask about past rashes, other medicines, and family history of reactions to medications</p> <p>Find out if patient has had fever/chills, malaise, lymphadenopathy, or mucosal symptoms such as photophobia or dysuria</p>
Examine the eruption	<p>Examine for mucosal involvement, facial edema, and blistering; describe the symmetry and extent of involvement</p> <p>Look for systemic findings such as fever, chills, lymphadenopathy, and organomegaly</p> <p>Photograph the eruption for the dermatologist if possible</p>
Order laboratory tests	Order liver function tests and complete blood count with differentials; assess for eosinophilia
Closely monitor patient	<p>Stop anticonvulsant if history, physical findings suggest a drug-induced eruption</p> <p>Refer patient to a dermatologist</p>

cover 10% to 30% of body surface suggest SJS-TEN overlap syndrome.

Anticonvulsant hypersensitivity syndrome usually manifests as a morbilliform eruption on the face, arms, and/or torso. The lesions might become edematous and progress to exfoliation or vesiculobullae. Facial edema is a hallmark of anticonvulsant hypersensitivity,^{15,16} and pustules and/or erythroderma might also appear. Other warning signs include symmetrical widespread eruption and organomegaly.

STEP 3 Order laboratory tests

Check liver function and order a CBC with differential to measure eosinophils. Eosinophilia and abnormal LFT results can signal anticonvulsant hypersensitivity.

Clinical Point

2 crucial questions:

- When did the patient start the anticonvulsant?
- When do cutaneous reactions typically develop after the first dose?

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Eosinophils. A normal eosinophil count ranges between 0% and 5% of peripheral blood leukocytes in adults, at a count of 350 to 650/cm. Although upper limits of normal vary, values >500/cm suggest hypereosinophilia.²¹

LFTs. Normal aspartate aminotransferase and alanine aminotransferase levels are 0 to 42 U/L and 0 to 48 U/L, respectively. Any LFT elevation could signal anticonvulsant hypersensitivity syndrome.

STEP 4 Closely monitor the patient

Discontinue the anticonvulsant if findings suggest a cutaneous drug reaction, and contact the patient's primary care physician or dermatologist immediately. Early consultation with a dermatologist can help determine the eruption's cause and reveal therapeutic options.

References

- Crone CC, Gabriel GM, Wise TN. Managing the neuropsychiatric side effects of interferon-based therapy for hepatitis C. *Cleve Clin J Med* 2004;71(suppl 3):S27-S32.
- Phelps JR, Ghaemi SN. Improving the diagnosis of bipolar disorder: predictive value of screening tests. *J Affect Disord* 2006;92:141-8.
- Lacerda G, Krummel T, Sabourdy C, et al. Optimizing therapy of seizures in patients with renal or hepatic dysfunction. *Neurology* 2006;67(suppl 4):S28-S33.
- Yumru M, Savas HA, Kurt E, et al. Atypical antipsychotics related metabolic syndrome in bipolar patients. *J Affect Disord* 2007;98:247-52.
- Finley PR, Warner MD, Peabody CA. Clinical relevance of drug interactions with lithium. *Clin Pharmacokinet* 1995;3:172-91.
- Keck PE Jr, Strawn JR, McElroy SL. Pharmacologic treatment considerations in co-occurring bipolar and anxiety disorders. *J Clin Psychiatry* 2006;67(suppl 1):S8-S15.
- Sachs GS, Printz DJ, Kahn DA, et al. *The expert consensus guidelines: medication treatment of bipolar disorder 2000. A postgraduate medicine special report.* New York: McGraw-Hill; 2000:24.
- Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology* 2005;64:1134-8.

Related Resource

• High WA. Stevens-Johnson syndrome and toxic epidermal necrolysis in adults. UpToDate Online (version 15.1); June 9, 2007. www.uptodate.com.

Drug Brand Names

Bupropion • Wellbutrin	Lithium • Eskalith, others
Bupirone • BuSpar	Olanzapine • Zyprexa
Carbamazepine • Tegretol,	Peginterferon alfa-2B •
Equetro, others	PEG-Intron
Ciprofloxacin • Cipro, Proquin	Phenytoin • Dilantin
Escitalopram • Lexapro	Ribavirin • Copegus,
Hydrochlorothiazide • various	Rebetol, others
Lamotrigine • Lamictal	Valproic acid • Depakote

Disclosures

Dr. Conrad receives research/grant support from AstraZeneca, Bristol-Myers Squibb, Forest Pharmaceuticals, GlaxoSmithKline, and Wyeth.

Drs. Pejic, Nesbitt, and Klinger report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

- Schlienger RG, Shapiro LE, Shear NH. Lamotrigine-induced severe cutaneous adverse reactions. *Epilepsia* 1998;29(suppl 7):S22-S26.
- Calabrese JR, Sullivan JR, Bowden CL, et al. Rash in multicenter trials of lamotrigine in mood disorders: clinical relevance and management. *J Clin Psychiatry* 2002;63:1012-19.
- Physicians' desk reference, 61st ed.* Montvale, NJ: Thomson PDR; 2007:1483-4, 1488.
- Knowles SR, Shapiro LE, Shear NH. Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Saf* 1999;21:489-501.
- Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. *Neurology* 1997;49:542-6.
- Knowles SR, Shapiro LE, Shear NH. Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Saf* 1999;21:489-501.
- Chang DK, Shear NH. Cutaneous reactions to anticonvulsants. *Semin Neurol* 1992;12:329-7.
- Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. *Arch Intern Med* 1995;155:2285-90.
- Callot V, Roujeau JC, Bagot M, et al. Drug induced pseudo-lymphoma and hypersensitivity syndrome. Two different clinical entities. *Arch Dermatol* 1996;132:1315-21.
- Yalcin B, Karaduman A. Stevens-Johnson syndrome associated with concomitant use of lamotrigine and valproic acid. *J Am Acad Dermatol* 2000;43:898-9.
- Gennis MA, Vemuri R, Burns EA, et al. Familial occurrence of hypersensitivity to phenytoin. *Am J Med* 1991;91:631-4.
- McLaren KD, Marangell LB. Special considerations in the treatment of patients with bipolar disorder and medical comorbidities. *Ann Gen Hosp Psychiatry* 2004;3:7.
- Valencak J, Ortiz-Urda S, Heere-Ress E, et al. Carbamazepine-induced DRESS syndrome with recurrent fever and exanthema. *Int J Dermatol* 2004;43:51-4.

Clinical Point

Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) look similar, but TEN covers more than 3 times the body surface

Bottom Line

A thorough patient history, prompt examination, liver function tests, complete blood counts, and close monitoring are critical to determining if a rash is benign or potentially fatal—and whether an anticonvulsant is causing it. Stop the medication if you suspect it is causing the rash or if you or a dermatologist cannot see the patient.