

# Rash and Liver Dysfunction Related to Lamotrigine Therapy

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**Objective:** To report a case of rash and liver dysfunction associated with lamotrigine treatment.

**Case Summary:** An 81-year-old woman with a history of bipolar disorder presented to the emergency department with complaints of fever, chills, nausea, and headache. Two weeks prior to presentation, liver enzymes were normal. Lamotrigine 50 mg/day and sustained-release bupropion 200 mg/day were started after discontinuation of citalopram. The patient had previous exposure to bupropion and documented rash with exposure to penicillin and sulfa. On admission, laboratory tests revealed slightly elevated liver enzymes and slightly low serum albumin. All medications were continued. On hospital day 3, a diffuse maculopapular rash developed on the patient's chest, abdomen, neck, and upper extremities, which was pruritic and warm to the touch. Both lamotrigine and bupropion were discontinued. Liver enzymes increased to more than 3 times the upper limit of normal, and serum albumin decreased. Liver function tests improved on day 6, and the rash resolved.

**Discussion:** Predictive risk factors associated with lamotrigine-induced rash and liver dysfunction include rapid dose titration, previously reported rash with other medications, age, and concurrent interacting medications. More serious adverse effects, such as Stevens–Johnson syndrome and fulminant hepatic failure, have also been associated with lamotrigine treatment. If rash appears at any time during treatment, lamotrigine must be discontinued. According to the Naranjo probability scale, an association between lamotrigine and rash and liver dysfunction could be considered probable in this case.

**Conclusions:** A faster than recommended dose titration may lead to lamotrigine-induced adverse effects such as rash and liver dysfunction in patients with risk factors.

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Lamotrigine is an antiepileptic drug that inhibits the release of excitatory neurotransmitters such as glutamine and aspartate by antagonizing voltage-dependent sodium channels.<sup>1</sup> Current FDA-approved indications include bipolar I disorder, partial seizures, tonic-clonic seizures, and Lennox–Gastaut syndrome. Lamotrigine is generally well tolerated, with the most common adverse effects being nausea, dizziness, headache, somnolence, rhinitis, diplopia, blurred vision, ataxia, dry mouth, constipation, and nonserious rash.<sup>1,2</sup> More serious adverse reactions have been reported, including life-threatening Stevens–Johnson syndrome, toxic epidermal necrolysis, and anticonvulsant hypersensitivity syndrome.<sup>2,4</sup> These more serious adverse effects most commonly occur early in treatment and are related to dose titration.<sup>1,5</sup> Concurrent medications such as valproic acid can also increase the likelihood of serious reactions by inhibiting the metabolism of lamotrigine.<sup>5</sup> A number of cases describ-

ing asymptomatic elevation in liver enzymes associated with maculopapular rash and fever have been reported.<sup>2,4,6-12</sup> However, lamotrigine-induced hepatic dysfunction or injury is not a commonly reported adverse effect. In addition to a review of existing cases involving lamotrigine-associated hepatic dysfunction and injury, we report a case of liver dysfunction associated with maculopapular rash and fever in an elderly patient with bipolar disorder. These events occurred 2 weeks after initiation of lamotrigine therapy. Upon discontinuation of lamotrigine, the adverse effects resolved and more serious adverse effects may have been avoided.

## Case Report

An 81-year-old female with a 50 year history of bipolar disorder and no known history of liver dysfunction

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presented with a 4–5 day history of fever (maximum temperature 39.4 °C), chills, nausea, and headache. Her past medical history was also significant for suicide attempts and hypothyroidism. The patient denied alcohol or illicit drug use. She was undergoing treatment for acute depression and suicidal ideation at an inpatient psychiatric institution. She had been diagnosed with gastroenteritis at a local emergency department 2 weeks before presentation and was prescribed loperamide. During that hospital visit, normal liver enzymes, white blood cell count, and metabolic panel, and abnormal lipase and amylase were reported. She had a documented history of hypersensitivity reactions that manifested as rash when she was exposed to penicillin and sulfa. Two weeks earlier, while at the inpatient psychiatric institution and after citalopram was discontinued, she was also started on oral lamotrigine 50 mg once daily at bedtime and sustained release bupropion 200 mg every morning. It was noted that the patient had previously taken bupropion but had no prior exposure to lamotrigine.

The patient was also taking the following: levothyroxine 75 µg once daily, quetiapine fumarate 100 mg each evening, lorazepam 0.5 mg each evening, 1 multivitamin tablet daily, psyllium mucilloid 1 packet daily, docusate 200 mg daily, zinc sulfate 220 mg daily, calcium carbonate 1250 mg twice daily, and vitamin E 400 IU daily. Upon presentation to our hospital's emergency department, she denied any diarrhea, dysuria, rash, or joint pain. Laboratory tests on hospital day 1 showed levels of aspartate aminotransferase (AST) 68 U/L (reference range 15–46), alanine aminotransferase (ALT) 67 U/L (13–69), alkaline phosphatase (ALP) 132 U/L (38–126), lactic dehydrogenase (LDH) 633 U/L (313–618), erythrocyte sedimentation rate (ESR) 58 mm/h (0–20), and albumin 3.3 g/dL (3.5–5.0). Hepatitis B surface antigen and hepatitis C titers were negative.

All of the medications that the patient was taking prior to this hospital admission, including lamotrigine and bupropion, were continued. No new medications were initiated. On hospital day 3, she developed a diffuse maculopapular rash on her chest, abdomen, neck, and upper extremities, which was pruritic and warm to the touch; both lamotrigine and bupropion were discontinued at that time. The patient received diphenhydramine 25 mg every 6 hours as needed; hydrocortisone 2.5% topical cream 4 times daily, applied to affected areas to manage pruritus; and acetaminophen 650 mg every 6 hours as needed for fever. Liver function test results were significantly elevated: AST, ALT, and ALP were 124, 141, and 311 U/L, respectively. Her total bilirubin remained within normal range at 0.4 mg/dL (0.2–1.3). Albumin had decreased to 2.5 g/dL. Elevations in ESR (67 mm/h) and C-reactive protein (48.3 mg/L, normal <10 mg/L) were reported. On hospital day 4, the patient was afebrile and the rash was greatly improved in appearance, with some residual itch. Two days after discontinuation of lamotrigine and bupropion (hospital day 5), her AST, ALT, and ALP levels continued to increase (197, 278, 388 U/L, re-

spectively). Then, on hospital day 6, her liver function began to improve: AST 111 U/L; ALT 241 U/L; ALP 397 U/L; albumin 3.6 g/dL; and C-reactive protein 14.8 mg/L. The lamotrigine reaction was documented in the allergy section of the patient's permanent medical record. She was discharged with liver enzymes trending downward and the rash resolving. A follow-up appointment with her psychiatrist was confirmed.

## Discussion

In this patient, concurrent medications, namely acetaminophen, bupropion, and quetiapine, cannot be ruled out as the possible causes of her symptoms and laboratory abnormalities; however, the similarity of this case to previously reported cases describing lamotrigine-induced rash and laboratory abnormalities and time to onset of symptoms suggest a causal relationship. The Naranjo probability scale indicated a probable relationship between lamotrigine and the described events in this case.<sup>13</sup>

Although rare, adverse reactions to lamotrigine, such as elevated liver enzymes, rash, and fever, have been documented.<sup>2,4,6–12</sup> Mansouri et al.<sup>7</sup> reported the case of a 25-year-old woman with a seizure disorder who had been treated with carbamazepine for 3 years. Due to poor control of symptoms, lamotrigine was added to her regimen. After 7 weeks, the woman presented with fever, chills, and a pruritic maculopapular rash on her face, neck, and trunk, with mucous membrane involvement. Laboratory tests performed 3 days later revealed elevated ALT, AST, ALP, LDH, C-reactive protein, and ESR. Lamotrigine was discontinued and she was discharged from the hospital, followed by a complete recovery 23 days later.

A report by Mecarelli et al.<sup>6</sup> involved a 30-year-old woman with a history of frequent complex partial seizures treated with carbamazepine. One month after treatment with carbamazepine 800 mg/day, the woman developed severe liver dysfunction with disseminated intravascular coagulation, which normalized within 4 weeks of discontinuation of carbamazepine. Valproate, topiramate, and levetiracetam were initiated in succession, but seizure control was inadequate. Levetiracetam was tapered over 2 weeks, and lamotrigine was started at 25 mg/day and increased by 25 mg each week. After 21 days of lamotrigine treatment (75 mg/day), the patient presented with a fever of 39.4 °C, diffuse maculopapular rash, and a 2 day history of jaundice. She complained of headache, vomiting, and diarrhea. Laboratory tests showed gross elevations in AST (4,960 U/L), ALT (7,268 U/L), total bilirubin (14 mg/dL), and international normalized ratio (INR; 2.44). Her serum creatinine was 2.0 mg/dL, blood urea nitrogen (BUN) was 35 mg/dL, and albumin was 3.2 g/dL. Results of an electroencephalogram were consistent with hepatic encephalopathy. Lamotrigine was discontinued at that time. After treatment

with molecular adsorbents, a type of albumin dialysis, she began to improve, and 24 days after admission, she was discharged with the following laboratory values: AST 181 U/L, ALT 60 U/L, total bilirubin 3 mg/dL, INR 1.11, serum creatinine 0.73 mg/dL, BUN 19.1 mg/dL, and albumin 3 g/dL.

Cases involving hepatotoxicity without rash have also been documented.<sup>2,10</sup> Arnon et al.<sup>10</sup> reported on an 8-year-old boy with a history of seizure disorder being treated with valproic acid 250 mg 3 times per day. He was hospitalized for aggressive behavior, ataxia, and tremor, during which time his renal and hepatic function were within normal limits. During hospitalization, his valproic acid dose was tapered over 5 days and he was started on lamotrigine 50 mg twice per day. There were 3 days in which he was taking both drugs. He was discharged after 1 week on lamotrigine 50 mg 3 times daily and thioridazine 10 mg/day. After 2 weeks, he developed fever (up to 40.6 °C), vomiting, headache, and diplopia; thioridazine was discontinued and he was given acetaminophen 325 mg 3 times per day and ibuprofen 200 mg 4 times per day for 3 days for fever. After 3 days he presented to the emergency department with jaundice. Results of liver function tests were grossly elevated:

AST 5,585 U/L, ALT 5,218 U/L, ALP 234 U/L, total bilirubin 14.3 mg/dL (direct bilirubin 8.0 mg/dL), and prothrombin time 21.4 seconds (reference range 11.1–12.9). His BUN was 63 mg/dL and serum creatinine was 1.5 mg/dL. On hospital admission, lamotrigine was discontinued. The boy was discharged 3 weeks later with normal renal function and mildly elevated liver enzymes (AST and ALT, 121 and 932 U/L, respectively).

Similar to the patients in the cases summarized in Table 1,<sup>2,4,6-12</sup> our patient developed a fever, rash, and elevated liver enzymes that continued to rise after discontinuation of the drug and then gradually improved. The existing reports of lamotrigine-associated liver toxicity are consistent with known risk factors for lamotrigine-associated adverse reactions. Some of the factors that influence the incidence of lamotrigine-associated serious adverse reactions include age, concurrent interacting drugs, previous hypersensitivity reactions to anticonvulsants, and the rate of dose titration.<sup>5,14-17</sup> A faster than recommended dose titration may lead to lamotrigine-induced adverse effects such as serious rash and hepatotoxicity in patients with risk factors. Slow titration results in a lower frequency of adverse reactions.<sup>15</sup> Serious skin reactions, including Stevens–Johnson syndrome and toxic epider-

**Table 1. Summary of Case Reports Describing Lamotrigine-Associated Liver Dysfunction**

REFERENCE	AGE (Y)/SEX	CLINICAL MANIFESTATIONS	TIME TO ONSET	CONCURRENT DRUGS	TIME TO RESOLUTION	CAUSALITY ASSESSMENT
Arnon (1998) <sup>10</sup>	8/M	fever, vomiting, headache, diplopia, elevated LFT, jaundice	14 days	valproic acid, thioridazine, acetaminophen, ibuprofen	1 wk	probable
Fayad (2000) <sup>11</sup>	10/M	fever, oliguria, hepatomegaly, ascites, elevated LFT	6 days	phenytoin, phenobarbital, thiopental, vancomycin, ceftazidime, acyclovir	unclear	probable
	3/M	maculopapular rash, elevated LFT	14 days	valproic acid, clonazepam	unclear (2–3 days)	probable
	4/F	elevated LFT	6 wk	carbamazepine, phenytoin, phenobarbital, vigabatrin, ganciclovir	5 days	probable
Makin (1995) <sup>9</sup>	22/F	fever, maculopapular rash, elevated LFT, fulminant hepatic failure	23 days	carbamazepine, vigabatrin, valproate	LFTs improved; however, pt. died of pulmonary embolism after 58 days	possible
Overstreet (2002) <sup>12</sup>	35/F	fever, maculopapular rash, elevated LFT, nausea, vomiting	39 days	acetaminophen #3, chloral hydrate, olanzapine, topiramate, trazodone, risperidone	died from liver failure	probable
Schaub (1994) <sup>8</sup>	45/F	fever, maculopapular rash, ataxia, drowsiness, elevated LFT	14 days	carbamazepine, clonazepam	2 wk	probable
Selek (2005) <sup>2</sup>	19/F	elevated LFT, jaundice	6 wk	lithium	2 mo	probable
Mylonakis (1999) <sup>4</sup>	49/M	fever, erythema, periorbital edema, maculopapular rash, elevated LFT	5 days (inadvertently took 4 doses)	methylphenidate, allopurinol, gabapentin, levothyroxine, buspirone, lithium	4 days	probable
Mansouri (2005) <sup>7</sup>	25/F	fever, maculopapular rash, elevated LFT	7 wk	carbamazepine	23 days	probable
Mecarelli (2005) <sup>6</sup>	30/F	fever, maculopapular rash, elevated LFT, jaundice	20 days	levetiracetam	unclear (discharged at day 24)	probable
Current case	81/F	fever, maculopapular rash, elevated LFT	2 wk	bupropion, levothyroxine, quetiapine, trazodone	unclear (discharged at day 7 with improving LFTs)	probable

LFT = liver function test.



mal necrolysis, may arise as often as 1:100 in patients under 13 years of age.<sup>14,17</sup> Concomitant medications may interfere with the metabolism of lamotrigine. For example, valproic acid nearly doubles the elimination half-life of lamotrigine by inhibiting glucuronidation, which is also the elimination pathway of valproic acid. Usually, the dose titration of lamotrigine should begin with 25 mg/day in weeks 1 and 2, then 50 mg/day in weeks 3 and 4, 100 mg/day for week 5, and 200 mg/day for bipolar disorder when no known interacting drugs are concurrently administered. However, dose titration of lamotrigine should be slower, starting at 12.5 mg/day for 2 weeks and doubling every 2 weeks until reaching 200 mg/day, when the patient is concomitantly taking valproic acid. In the case described by Arnon et al.,<sup>10</sup> the boy was started on lamotrigine 50 mg twice daily while valproic acid was being tapered. The lamotrigine dose was also increased to 50 mg 3 times per day after 5 days, demonstrating a quick titration that increased the likelihood of serious rash and liver injury. Conversely, in patients taking enzyme inducers, such as carbamazepine, phenobarbital, or rifampin, the dose of lamotrigine can be titrated more quickly (eg, starting at 50 mg/day for 1–2 weeks, then doubling every 1–2 weeks to a maximum dose of 400 mg/day).<sup>5</sup> Most serious adverse reactions occur during dose titration within the first 2–6 weeks.



Some of the factors that influence the incidence of lamotrigine-associated serious adverse reactions include age, concurrent interacting drugs, previous hypersensitivity reactions to anticonvulsants, and the rate of dose titration.



Previous serious adverse reactions to other anticonvulsants can also increase the risk of lamotrigine-associated serious adverse reactions. A chart review found that patients with a history of rash with exposure to another anticonvulsant were more likely to experience a rash with lamotrigine (OR = 3.37;  $p < 0.001$ ).<sup>14</sup> Of patients who had a rash with carbamazepine, 18.8% also had a rash with lamotrigine compared with 9.1% with phenytoin and 8.1% with penicillin. Although this does not necessarily apply to

the cases of liver toxicity, it suggests a cross-reactivity of some kind. The report by Mecarelli et al.<sup>6</sup> described a 30-year-old female who had a previous liver dysfunction episode one month after starting carbamazepine before having a similar situation with lamotrigine.



Patients with a history of rash with exposure to another anticonvulsant were more likely to experience a rash with lamotrigine.



Our patient was at risk for lamotrigine-induced adverse reactions. First, the starting dose of lamotrigine was 50 mg/day, higher than the recommended starting dose of 25 mg/day for bipolar disorder. The patient also stated that she had had a number of drug-induced rashes related to medications that she had taken in the past, although her only documented allergies were to penicillin and sulfa.

## Conclusions

Based on existing cases, including ours, that implicate lamotrigine as the cause of hepatic dysfunction and injury, it is clear that predictive risk factors need to be taken into account when determining treatment plans. In particular, a patient's age, concurrent medications, and previous hypersensitivity reactions to drugs should be considered in determining the dose titration schedule. A faster than recommended dose titration may lead to lamotrigine-induced rash and hepatotoxicity. Slow titration is associated with a lower frequency of adverse reactions. More time and research are needed to determine the exact mechanism by which lamotrigine causes serious hepatic dysfunction; in the meantime, we must do everything possible to diminish the risk of serious complications in our patients. ≡

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