

Lamotrigine Drug Interactions: Ignorance is not Bliss

Austin G. Armstrong, M.D.¹, Rachna Kalia, M.D.¹, Megan Troutman, Pharm.D.²

¹University of Kansas School of Medicine-Wichita, Wichita, KS
Department of Psychiatry and Behavioral Sciences

²Ascension Via Christi Hospital, Wichita, KS

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INTRODUCTION

Lamotrigine (LMG) and valproic acid and derivatives (VPA) are antiepileptics commonly used for primary generalized or unclear type seizures.^{1,2} The U.S. Food and Drug Administration (FDA) approved LMG as monotherapy for bipolar disorder and adjunctive treatment in generalized seizures (primary and Lennox-Gastaut syndrome) and focal onset seizures, while VPA is FDA-approved for monotherapy in bipolar disorder acute mania and adjunctive therapy for simple and complex partial seizures (including absence), as well as migraine prophylaxis.^{3,4} Drug interactions with antiepileptics arise from a variety of mechanisms, especially alterations in drug metabolism through the cytochrome p450 (P450) and uridine glucuronyl transferase (UGT) enzymes.⁵ VPA is metabolized through a variety of pathways (P450 and UGT) and inhibits P450 enzymes 2C9 and UGT 1A4, 1A9, 2B7, and 2B15.⁶ LMG is metabolized principally by UGT 1A4, which is inhibited by VPA. This interaction increases total LMG level by decreasing clearance and increasing half-life.⁷ Inhibition of UGT and shunting LMG metabolism towards the P450 system results in production of toxic metabolites that may be related to cutaneous reactions as an adverse effect of LMG.⁸

Antiepileptic drug-induced hypersensitivity syndrome consists of Steven-Johnson syndrome, toxic epidermal necrolysis, and anticonvulsant hypersensitivity syndrome,⁹ for which LMG received a black box warning from the FDA.⁴ These reactions are dose dependent,^{9,10} and highest incidence occurs within the first two months with a rate of 0.08% in adults when titrated appropriately.^{9,11} Factors that are known to increase the risk of rash are use in pediatric patients, simultaneous use with VPA, and rapid escalation of dose.⁴ The mechanism behind these reactions is poorly understood, though formation of reactive arene oxide metabolites from the P450 system, susceptibility due to human leukocyte antigen allele associations, and proliferation of T cells have been implicated.^{9,12} In addition to severe cutaneous reactions, LMG can precipitate delirium, especially when used concomitantly with VPA.¹³⁻¹⁶

CASE REPORT

The patient was an 82-year-old female with history of major neurocognitive disorder (MNCD), type II diabetes mellitus, atrial fibrillation, hypertension, coronary artery disease, history of COVID-19 infection, and an unknown type of seizure disorder who was admitted to inpatient geriatric psychiatry after being transferred from the medical floor. She

had a substance use history of smoking one pack of cigarettes per day for nearly 40 years until she was diagnosed, and she was treated successfully for lung cancer 20 years prior. The patient was admitted for a change of baseline with agitated behaviors towards family caretakers, scoring 2/30 on St. Louis University mental status examination (SLUMS) at the time of admission.

Home medications of amiodarone 100 mg daily, amlodipine 10 mg daily, diltiazem extended release 120 mg daily, lamotrigine 200 mg twice daily, and levetiracetam 500 mg twice daily were continued on the medical floor. In addition, she was given intravenous fluids for management of acute on chronic renal failure, and intravenous potassium for hypokalemia. Vital signs, complete blood count and complete metabolic panel, and serial troponins otherwise were found to be unremarkable. Immediately prior to transfer to geriatric psychiatry, the patient sustained a fall that resulted in a subdural hematoma. Of note, a close family member later reported the patient had not been compliant with home medications for at least two weeks prior to admission.

On arrival to geriatric psychiatry, the patient was oriented to self and location, was conversational though disorganized, and no psychomotor agitation was noted. Geriatric psychiatric admission workup was within normal limits (complete blood count, comprehensive metabolic panel, thyroid-stimulating hormone, urinalysis, drug screen, vitamin B12 and folate, syphilis antibody, human immunodeficiency virus antibody, and hepatitis panel). Serial computed tomography head imaging without contrast showed stable right frontal subdural hematoma, global volume loss, and chronic microvascular changes in areas of the subcortical and periventricular white matter.

Due to possible neuropsychiatric side effects of levetiracetam,¹⁷ the decision was made to change antiepileptic medication by titrating off levetiracetam and starting divalproex. Divalproex extended release was started and titrated (up to 1000 mg daily over five days) to target serum level of about 80 mcg/mL before titrating off levetiracetam, while LMG was continued at 200 mg twice daily. On day nine, the patient began to be titrated off levetiracetam over seven days. Bedside electroencephalogram revealed no epileptogenic activity. In this period, patient behavior worsened resulting in psychomotor agitation, aggression, and three falls. She also exhibited delusions, auditory and visual hallucinations, and a declining oral intake. Due to refusal to take oral medications, VPA briefly was trialed via intravenously before switching to divalproex sprinkles.

On hospital day 17, the patient was concurrently on VPA 1000 mg daily and LMG 200 mg twice daily. Due to interaction between these medications, LMG was held until the next day and dose was quartered and continued thereafter (100 mg daily). By day 22, the patient began to improve and was no longer displaying agitated behaviors, and low dose mirtazapine was started for appetite stimulation. Though she was not reassessed with a SLUMS exam, clinically she continued to have dramatic behavioral improvement and resumed oral intake. Over the next several days, she was noted to be oriented (i.e., self, location, time), ambulating with steady gait, talking pleasantly, and listening to music (Figure 1).

Day Number	Significant Event
0	Emergency department visit for agitation and admission to hospital
1	Psychiatry consult determined lack of capacity
2	Patient exhibits aggressive behaviors inpatient, sustained a fall
3	Stable right sided SDH on repeat CT. Family desired hospice upon discharge
5	Transferred to geriatric psychiatry for stabilization
6	Valproic acid started at 125 mg at bedtime
7-10	Valproic acid increased to 250 mg at bedtime, increased by 250 mg daily until 1000 mg at bedtime
14	Valproic acid level 0.78 mcg/mL; levetiracetam halved to 250 mg twice daily
17	Levetiracetam halved to 250 mg at bedtime; no epileptogenic activity on EEG
20	Levetiracetam halved to 125 mg at bedtime
21	Lamotrigine stopped
22	Lamotrigine continued at 100 mg at bedtime; Mirtazapine 7.5 mg at bedtime started; no further agitated behaviors
25	Levetiracetam discontinued
25-28	Dramatic behavioral improvement
34	Discharge to nursing home

Figure 1. Timeline of case events.

DISCUSSION

This case illustrated a common, but often missed, pharmacologic interaction that has the possibility for adverse outcomes and medicolegal implications. This patient was admitted for MNCD with behavioral disturbance of unknown etiology and developed a delirium after sustaining many deliriogenic insults (inaccurate medication reconciliation on admission, multiple falls with subdural hematoma, hypokalemia, acute kidney injury, and starting VPA in setting of LMG). Though development of this patient's delirium may have been multifactorial, the most glaring, and preventable, risk factor was the well-documented, but often overlooked, pharmacologic interaction between VPA and LMG. Discontinuation of levetiracetam may have led to this patient's improvement, though she had been stable on this medication as an outpatient and her rapid decline as an inpatient and subsequent improvement was not related temporally to levetiracetam.

Lamotrigine and VPA are common antiepileptics^{1,2} and mood stabilizers indicated for use in bipolar affective disorder.^{18,19} Side effects of LMG appear to be dose-dependent, prompting a recommended titration schedule in the package insert to minimize adverse effects. Titration schedules and dosing for LMG monotherapy and adjustments for multidrug therapy with known pharmacokinetic interactions (i.e., VPA, carbamazepine, phenytoin, phenobarbital, primidone, rifampin) for each FDA-approved indication are delineated in the package insert to lower risk of adverse events (Table 1).⁴

If a patient misses five half-lives of LMG during titration or maintenance, it is recommended to restart initial titration ($t_{1/2}$ 25.4 hours = approximately five days).⁴ Valproic acid's inhibition of LMG metabolism is rapid and profound, leading to increased levels of lamotrigine that can precipitate adverse events. Over half of cases (60%) of LMG hypersensitivity occur in patients concurrently taking VPA.²⁰ Therapeutic drug monitoring can be useful to determine if serum drug concentrations are at an effective level, which is used commonly for VPA. Serum drug levels should be measured at trough levels after drug has reached steady state, with reference ranges of 50-100 mcg/mL and 50-125 mcg/mL, for use as AED and mood stabilizer, respectively. VPA is highly protein-bound (> 90%), which should be taken into consideration when levels are checked. In addition to the VPA level, complete blood count and complete metabolic panel should be monitored, particularly to monitor

liver enzymes, leukocyte, and thrombocyte levels.^{3,21-23}

Table 1. Escalation regimen for lamotrigine in patients with bipolar affective disorder.

Escalation timeline	For patients taking Valproate	In patients not taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate	In patients taking Carbamazepine, Phenytoin, Phenobarbital, or Primidone, and not taking Valproate
Weeks 1 and 2	25 mg every other day	25 mg daily	50 mg daily
Weeks 3 and 4	25 mg daily	50 mg daily	100 mg daily, in divided doses
Weeks 5	50 mg daily	100 mg daily	200 mg daily, in divided doses
Week 6	100 mg daily	200 mg daily	300 mg daily, in divided doses
Week 7	100 mg daily	200 mg daily	Up to 400 mg daily, in divided doses

The above case illustrated that delirium and an increased risk for other adverse effects likely were caused by restarting LMG at home dose after extended noncompliance and adding VPA to LMG without adjusting LMG dose. This case underscored the importance of performing a careful and diligent medication reconciliation and consideration of black box warnings. These processes are critical for both patient safety (nonmaleficence) and obtaining full informed consent with knowledge of black box warnings (autonomy), in accordance with ethical and legal obligations in the patient-physician relationship.

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