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Case Report

Multiple Adverse Side Effects with Low-Dose Lamotrigine: A Case Report.

Mark B. Detweiler[*1,2]

[1]Staff Psychiatrist, Veterans Affairs Medical Center, Salem, Virginia, USA.

[2]Professor of Psychiatry and Behavioral Health, Edward Via College of Osteopathic Medicine, Blacksburg, Virginia, USA.

[*]**Corresponding author:** Mark B. Detweiler (116A7), Veterans Affairs Medical Center, 1970 Roanoke Boulevard, Salem, Virginia, 24153, USA. Tel: 540-982-2463; Fax: 540-982-1080; E-mail: Mark.Detweiler1@va.gov

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Abstract

Lamotrigine (LTG) is an effective agent for mild bipolar depression and mood stabilization. A case report is presented in which a young woman with newly diagnosed bipolar I disorder with mixed features, that experienced an uncommon array of adverse effects with relatively low doses of LTG (50mg bid). The LTG destabilized the patient's executive function and forced her to seek a medical leave of absence and to briefly separate from her husband. These results add to the literature a unique adverse effect complex of LTG side effects. All six untoward symptoms (skin rash, episodes of irritability/aggressiveness, leg vermiculation, emotional lability (crying, seclusion), nightmares and flulike symptoms) resolved with LTG tapering to discontinuation.

Keywords: Adverse Effects; Flulike Symptoms; Irritability; Lamotrigine; Nightmares; Skin Rash; Vermiculation

Introduction

Lamotrigine (LTG) is a phenyltriazine derivative that was approved by the USDA in 1994 as an anticonvulsive, mood stabilizer and voltage sensitive sodium channel antagonist. It is effective in treating rapid cycling and mixed bipolar states in addition to refractory bipolar disorders [1-3]. Compared to other anticonvulsants and mood stabilizers, such as carbamazepine and valproate (VPA), LTG has more antidepressant effectiveness and reduces morbidity and mortality [4-6]. The behavioral side effects of antiepileptic drugs (AED) may differ between epilepsy and psychiatric populations [7]. It is thought that LTG's mechanism of action involves the inhibition of the high-frequency firing in depolarized neurons by selective prolonging of the slow inactivation of sodium and calcium channels. Subsequently, there is stabilization of presynaptic neuron membranes and suppression of excitatory neurotransmitters (e.g., glutamate and aspartate) [8]. LTG has multiple pharmacological actions: use-dependent blockage of voltage sensitive sodium channels; inhibited release of glutamate and aspartate; interaction with open channel conformation of voltage sensitive sodium channels; and, action at specific sites on voltage–sensitive sodium channel alpha pore forming subunits [9].

LTG has a relatively benign side effect profile and does not require routine blood monitoring as needed for VPA, carbamazepine and lithium. Notably, the incidence of LTG side effects and the rate of discontinuation are lower compared to lithium [10-13]. Generally, LTG side effects occur within a few days of the initial dose or after a dose increase. If LTG is titrated too rapidly, a small percentage of patients may experience a rash, particularly if they are receiving concomitant VPA or another drug that inhibits LTG metabolism [13]. Multiple studies suggest that 200mg/day is a target dose for acute bipolar disorder maintenance treatment and that this does not increase the risk of adverse events. Manufacturers' literature lists multiple possible side effects including: nausea; dizziness; drowsiness; headache; changes in menstrual periods; back pain; blurred or double vision; insomnia; ataxia; somnolence; tremor; maculopapular rash; blood dyscrasias; angioedema; Stevens-Johnson syndrome; and Lyell syndrome [13-15].

This case report presents an unusual array of six side effects, which do not appear to have been previously reported together in a single case report in the English literature. Moreover, the side effects occurred at relatively low LTG doses, significantly

impeding the progress of the patient's recovery from her bipolar I disorder with mixed features.

Case Report

A 39-year-old, married female presented to the mental health clinic four days following a visit to the Emergency Department (ED) four days prior. In the ED she had complained of increasing anxiety, fatigue, irritability and insomnia. She reported smoking cannabis and drinking alcohol to try to control her anxiety. She endorsed smoking cannabis three to four times a day and drinking two to three drinks once or twice a week with occasional episodes of binge drinking of an unquantified amount of alcohol. The patient did not want to continue using cannabis as she was spending $40 to $150 a week and her cannabis and alcohol use was interfering with her executive control while she was working at a bank. The substances were also interfering with her interpersonal relationship with her partner. She had been followed in the woman's clinic for 16 years without any medical or substance problems (no positive urine drug screens) other than tobacco use of one to two packs of cigarettes a day. She had no prior psychiatric history. Two months prior to her ED appearance she had failed trials of sertraline and venlafaxine initiated by her woman's health clinician for depression. Successively, the patient went to a substance abuse clinic in an effort to stop her cannabis and alcohol use. The rehabilitation clinic did not think that the alcohol and cannabis were the patient's primary problem, rather that the substance use was a response to underlying psychiatric conditions.

The patient left the substance abuse clinic and returned to her primary care clinic where she was directed to the ED for a complete evaluation. In the ED, the patient's most significant presenting complaints were anxiety and panic attacks, depression, anhedonia, poor concentration, insomnia, fluctuating appetite and guilt about not being able to complete her work at the bank. She denied suicidal and homicidal ideations, intent and plan. There were no signs of psychosis, bizarre thought disorders or bizarre behavior. Provisional diagnoses were: anxiety disorder, unspecified; rule out mood disorder; rule out panic disorder; rule out borderline personality disorder; cannabis use disorder severity deferred; alcohol use disorder severity deferred; and, tobacco use disorder. The medical workup was noncontributory except for vitamin D deficiency (23.7 ng/mL). The urine drug screen was negative, Vitamin B12, gamma-glutamyl transferase, liver function panel, complete blood count, thyroid function test (1.600) and urinalysis were all within normal range.

The patient's social history included growing up in a military family so that she frequently moved from one location to another. Her father left the family when the patient was 2 years old. The patient had experienced verbal and sexual abuse from her mother until she was 12 years of age and she grew up separated from her sister due to family separation. She stated that she drank alcohol and used cannabis as a teenager. The family history included one aunt that made multiple suicide attempts without completion, the patient's mother threatened to commit suicide as she had terminal cancer, an older sister had been diagnosed with bipolar disorder and an uncle had been diagnosed with schizophrenia.

The patient had served in the military without disciplinary difficulties. She did not experience combat or disabilities related to her military duties. The patient's first marriage occurred when she was in uniform and it lasted approximately two years. Her second marriage was ongoing for approximately 18 years. The couple's 18-year-old son was serving in the United States armed forces. The patient denied any legal history. She had been employed as a bank investigator for over a decade. She enjoyed her work and was upset that she had to seek medical leave secondary to her psychiatric symptoms.

When the patient presented to the mental health clinic, she stated that for the past several months she was not able to remember anything that she read at work or when reading for pleasure. The patient's treatment goals were to have restful sleep and to return to her former baseline of being able to read, focus and concentrate at work. She expressed her desire to have minimum medications and to eventually be tapered off all medications prescribed. She did not accept her diagnosis of bipolar disorder despite knowing that her older sister had bipolar disorder. The medication plan was to rapidly stabilize the patient with quetiapine and then to begin a slow cross titration to LTG to minimize sedating side effects.

The patient was started on quetiapine 50mg in the morning and 50mg in the evening for immediate mood stabilization. She initially requested a medical leave of absence from employment for at least three weeks. At the one-week follow-up, the patient reported that her racing thoughts had slowed down and she was able to read for the first time since her manic symptoms began. However, she still could not remember what she had read after 30 to 40 minutes. She reported less catastrophizing and increased energy and coping skills. Moreover, she endorsed increased appetite and a decreased sense of hopelessness with futuristic ideations. On the negative side she remained unable to mentally compute complex mathematics in her head and she still became easily agitated by being out in public and by encounters with persons in social situations. The quetiapine was reduced to 25mg in the morning and 50mg at night.

At the two-week follow-up, the patient reported improved sleep (6-7 hours + 2-3 hour naps) and reduced anxiety. However, she complained of feeling chronically fatigued. The morning dose of quetiapine was stopped and the evening dose was reduced to 25mg. The LTG titration was initiated at 25mg twice a day. The planned titration was: 25mg twice a day for 14 days; then 50mg twice a day for 14 days; then 75mg twice a day for 14 days with titration to effect. The objective was to replace quetiapine with the

lowest therapeutic LTG dose as the single mood stabilizer.

At week three, the patient reported that when she was taking quetiapine 25mg in the evening and 25mg of LTG twice a day, her insomnia worsened significantly. Therefore, she self-stopped the quetiapine 25mg daily at bedtime. This allowed her to sleep for several hours, however, she woke up every hour. She continued to complain of irritability with her husband. The evening dose of quetiapine 25mg was restarted and then titrated to 75mg over the next several days. This improved her sleep to six to seven hours at night with two to three, one-hour naps during the day. The patient continued to report poor mathematical skills, left and right confusion and agoraphobia.

At the week four clinic visit, the patient denied feelings of grandiosity, euphoria, depressive symptoms, and excessive spending. The LTG was increased to 50mg twice a day and the quetiapine was tapered to discontinuation. Several days later the patient called reporting that since the dose of LTG had been increased and the quetiapine stopped, she experienced increased irritability, marked mood swings with periods of crying for several hours. She reported a skin rash on her arms and legs with an overwhelming sensation of vermiculation of "ants crawling everywhere on my legs". Moreover, she described the onset of nightmares that she had not experienced since her primary care was initiated in 2004. Consequently, the LTG was tapered to discontinuation. The patient was followed every two days. All the symptoms gradually receded after seven to eight days including the leg vermiculations, extreme irritability, severe mood changes and the skin rash. She also reported the cessation of previously unreported concurrent flu-like symptoms (bilateral ear aches, chest pain without cough) that she had been suffering from for at least two weeks while on the LTG. The patient did not return to clinic and she was lost to follow-up as she did not return to either her primary care clinic or the mental health clinic. Her diagnoses at her final clinic visit were bipolar disorder I with mixed features, alcohol use disorder, episodic in early remission, cannabis use disorder, in early remission, tobacco use disorder and rule out borderline personality disorder.

Discussion

Lamotrigine and Skin Rash

LTG is effective in treating rapid cycling and mixed bipolar states in addition to refractory bipolar disorder [1-3]. The most significant adverse side effect for LTG that results in medication discontinuation is a rash secondary to development of the Stevens-Johnson syndrome and/or the Lyell syndrome [13,16]. In the present case, the 39-year-old female, reported having a skin rash on her arms and legs with an overwhelming sensation of vermiculation at an LTG dose titrated to 50mg twice a day. LTG was not augmented with another AED, but low dose quetiapine was being administered contemporaneously. The rash and vermiculation both resolved seven to eight days after LTG discontinuation. There is limited information about LTG as a monotherapy for mania in women during their fertile years. Research indicates that a rash can begin at any point during the titration [13]. Fertile females have been reported to have a higher risk of skin reactions compared to males in the same age range. Patients with learning disabilities have a lower rash risk than other patients without learning disabilities [17].

Risk factors for skin reactions include rapid titration, administration of other concurrent AED, prior history of an anticonvulsant-associated rash, female gender, learning disabilities and an age less than 13 years [18-21]. In this case report, the patient had only one risk factor, female gender. Arif et al. studied the predictors of rash associated with 15 different AEDs among a population of 1,890 outpatients [21]. Rash incidence was approximately five times greater in patients administered more than one AED (8.8%) when compared to those taking a single AED (1.7%). Rash rates were highest with phenytoin (5.9% overall, 25.0% with 2 or more AEDs), LTG (4.8%, 14.4%, $p = 0.025$) and carbamazepine (3.7%, 16.5% with 2 or more AEDs, $p=0.01$). Rash rates were lower (<1%) with levetiracetam (0.6%), gabapentin (0.3%) and VPA (0.7%, $p=0.01$) [21]. A retrospective study of 15 AEDs in a population of 663 patients, evaluated the influence of gender, age, and learning disability. Skin reactions occurred in 14% of the patients and in 5% of the AED exposures. Carbamazepine had the highest reaction rate (CBZ, 11%) with lower, but similar rates (8.0%) for phenytoin, LTG, and oxcarbazepine [17]. Skin rash risk increased using LTG with concurrent VPA [5]. In a large study of 688 patients (350 monotherapy LTG, 338 with LTG add-on) diagnosed with generalized epilepsy or focal epilepsy, 7.6% experienced a rash at LTG initiation or with titration [22].

LTG and Irritability/ Aggressive Behavior

The side effects of irritability and aggressive behavior with LTG use are reported less often than for skin rash. Irritability is mentioned on the Mayo Clinic web site and by several other authors [23-27]. Serum LTG levels do not predict the risk of a irritability, aggression or psychotropic behavior. Much of the research regarding LTG precipitated aggression and irritability has come from the research about patients with epilepsy and developmental disabilities. LTG is reported to cause both increased and decreased irritability in this population [25-27]. Generally, positive LTG effects include diminished irritability, hyperactivity and perseveration, as well as improved energy and social function. Negative LTG side effects may include irritability, hyperactivity and stereotypic or aggressive behavior. In a study of 19 patients with intellectually disabilities and concurrent epilepsy, five patients had their LTG discontinued secondary to unprovoked aggressive behavior [26]. At the 27-month follow-up of 108 seizure patients receiving VPA augmented with LTG, irritability was reported in

1.0 percent of the patients using the VPA-LTG combination [27].

In the present case, the female patient had neither epilepsy nor developmental disabilities. Rather, she was above average in intellectual capabilities as illustrated by her bank position and capability of doing less than mundane mathematics in her head. She had some irritability at clinic admission, but less with quetiapine. The irritability returned increased in severity with the LTG titration to the point of the patient seeking refuge from her partner, business associates and persons she encountered in public. As with her other LTG side effects, her irritability receded to marginable levels when the LTG was stopped.

LTG and Skin Vermiculation's/Tactile Hallucinations

The sensation of "bugs crawling on my skin", or vermiculations, is classified under the broad diagnostic category of Schizophrenia Spectrum and Other Psychotic Disorders in DSM-5 [28]. This diagnostic category has three subtypes: primary, insect/ parasite-related delusions without signs of other mental illness; secondary, insect/ parasite-related delusions secondary to mental illness such as depression or schizophrenia; and tertiary, organic delusional parasitosis, related to medical problems such as medication side effects (e.g., LTG), drug abuse (e.g., methamphetamine) and/or medical conditions (e.g., diabetes mellitus, hypothyroidism, some types of cancer) [29]. The present case report would be classified under the second category, insect/ parasite-related delusions secondary to bipolar disorder.

Oh et al. described the case of a 44-year-old male taking VPA 400mg twice daily and escitalopram 20mg daily who was titrated to LTG 100mg twice a day. After four weeks of taking these three medications, the patient began experiencing sensations of vermiculation described as "tiny insects crawling over the skin" without visual evidence or rash. The vermiculations changed sites often affecting multiple sites simultaneously. The LTG was tapered and stopped resulting in the vermiculations ceasing two days following LTG discontinuation. Due to returning depression, the patient was rechallenged with LTG 25mg once daily on alternate days as monotherapy. The vermiculations returned immediately with the first 25mg dose. Despite the unpleasant vermiculations, the patient endured the side effect until the LTG dose was titrated to 50mg twice daily. At this point, the patient could no longer tolerate the tactile sensations and the LTG was tapered to discontinuation with the vermiculations stopping two days following LTG cessation [30]. Similarly, In the present case report, the patient began experiencing a severe sensation of vermiculations described as ants crawling everywhere on her arms and legs when the monotherapy of LTG was titrated to 50 mg twice a day. When the LTG was then tapered to discontinuation, the vermiculations resolved in seven to eight days. The patient was not re-challenged.

LTG and Emotional Lability

Emotional lability is a side effect for some medications such as Zonisamide [13]. LTG has also been reported to induce emotional lability in persons suffering from epilepsy and mental retardation [24]. If "emotional lability" secondary to LTG is broadened to include agitation, irritability and other abnormal behaviors including suicidal thoughts and tendencies or increased depression, the number of internet sites reporting emotional lability is increased [23]. In the present case, the patient experienced increased irritability, drastic changes in mood with periods of crying for several hours accompanied by difficulty returning to a less depressive status when the LTG was increased to 50mg bid at week four of treatment. The emotional volatility was so intense that the patient had to briefly live in a separate apartment from her husband as the rapid mood fluctuations were causing significant marital distress as verified by the patient's husband who accompanied the patient on one visit when her symptoms were at their most severe.

Nightmares

Nightmares are an uncommon negative side effect in persons taking LTG. The most common profile for nightmares includes females 30-39 years old that: have been taking the LTG for one to six months; are concurrently taking quetiapine; and, have bipolar disorder. This profile is congruent with the factors in this case report as the patient was 38-year-old at the onset of her symptoms and 39 years of age when she first came to the mental health clinic, who was diagnosed with bipolar disorder I with mixed features and she was started on quetiapine for rapid mood stabilization and a cross titration to LTG was attempted. Nightmares related to LTG have been reported in large epidemiologic studies. One investigation including 48,953 cases taken from FDA and social media data of people who experienced side effects while taking LTG found that 215 persons (0.004%) had reported nightmares [31].

The Netherlands manufacturer of LTG [32] internet mentions three cases of nightmares in women with an age range of 31 to 60 years (2 bipolar, 1 epilepsy) that experienced nightmares on LTG does of 50 -200mg/day. In two cases the nightmares stopped following dose reduction from 200mg to 50mg/day. In the third case, when the LTG 50mg dose was stopped, the nightmares ceased. Rechallenge with 50mg/day rekindled the nightmares. Moreover, the Netherlands site mentions that the World Health Organization database of the Uppsala Monitoring program includes 107 nightmare cases. Other data bases including the Dutch SmPC and USA SMPC for LTG mention confusion, hallucinations, somnolence, insomnia and agitation as adverse LTG reactions, but do not mention nightmares per se [33,34].

Lamotrigine and "Flu Like Symptoms" for Two Weeks with Bilateral Ear Aches, Chest Pain and Cough

Case reports including "flu-like symptoms" secondary to LTG use as experienced by the patient in this case report are uncommonly reported in the English literature. An internet search revealed no case studies of flu-like symptoms including bilateral ear aches and chest pain with cough as reported in the present case study. Several web sites mention LTG side effects of "flu-like symptoms such as body aches or swollen glands" classified as "serious side effects of Lamictal [that] you should report to your doctor" [35]. The Mayo clinic sites mentions "less common" LTG side effects including chest pain, confusion, irritability, chills, fever, flu-like symptoms, memory loss and sore throat among others [36].

Conclusion

Generally, LTG is an effective agent for treating mild bipolar depression and mood stabilization. The present case illustrates an uncommon array of side effects with relatively low LTG doses (50mg twice a day) in a relatively young woman with new onset bipolar I disorder with mixed features. The LTG titration destabilized her executive control faculties, rendering her housebound and temporarily interfering with her return to work and to her former quality of life. All six untoward symptoms (skin rash, episodes of irritability/aggressiveness, leg vermiculation, emotional lability (crying, seclusion), nightmares and flulike symptoms) receded to resolution with LTG tapering and discontinuation. The most common education of patients about LTG includes the possibility of a skin rash. However, this case demonstrates that the complex side effect profile experienced by the 39-year-old woman may be a rare clinical presentation precipitated with low to intermediate LTG doses.

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