

# Journal of Psychiatry and Psychiatric Disorders

Volume 1, Issue 4

Case Report

## Dose Related Psychiatric Adverse Effect of Lamotrigine in Management of Bipolar Disorder

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**Received:** 14 June 2017; **Accepted:** 19 June 2017; **Published:** 10 July 2017

### 1. Abstract

Lamotrigine is increasingly being used as an effective maintenance treatment in bipolar disorders to control mood swings. This medication is generally well tolerated with most of its adverse reactions being well documented. However there are some reports of certain psychiatric symptoms associated with the use of Lamotrigine for treatment of mental disorders, but there is a paucity of data to support such findings. Here we discuss the case of a Caucasian female who presented to us with a history of bipolar disorder which was well controlled with Lithium. However the patient was advised to taper the use of Li due to long term Li induced damage to kidneys. She was started on Lamotrigine as an add-on, on a cross taper model. Initially she tolerated Lamotrigine well with mild-moderate physical side effects of nausea, warm flashes and constipation. After the dose was titrated to 100 mg/day

of Lamotrigine, the patient demonstrated some psychiatric side effects such as vivid dreams and nightmares, which was resolved on reducing the dose of Lamotrigine to 50 mg/daily. However over the long term, she had a relapse of bipolar symptoms as Lamotrigine seemed not to be tolerated at high enough dose to prevent such a relapse. This case is consistent with some previous reports of occurrence of dose related psychiatric adverse side effect of Lamotrigine.

**Keywords:** Lamotrigine; Psychiatric; Bipolar disorders; Hypothyroidism

## 1. Introduction

Lamotrigine, a phenyltriazine derivative, is an established anticonvulsant with effective mood stabilizing properties. Lamotrigine has been indicated for the maintenance therapy of Bipolar Disorder by the U.S. Food and Drug Administration (FDA). It also has got a predominant antidepressant effect and hence is regularly approved for the prevention of depressive episodes in patients with bipolar disorders [1]. The data derived from the study conducted by the National Health Collaborative Program suggest that the probability for patients remaining ill for at least one year was only 7% for those who presented in acute mania episodes than compared to the 22% who presented with depressive episode [2]. Commonly used mood stabilizers such as Lithium, Carbamazepine, and Valproate/Divalproex Sodium have shown to possess moderate-to-marked antimanic properties, but only poor-to-moderate antidepressant effects [3]. Lamotrigine with its antidepressant action thus stands out as an effective adjunct therapy for bipolar disorders. Several studies have underlined the use of Lamotrigine as an effective maintenance therapy for bipolar disorder, particularly for use during the depressive phases of the illness [4, 5, 6].

## 2. Case Presentation

Since March 2006, the patient, a 55 yr old Caucasian woman has been followed up in our psychiatric clinic as an outpatient for management of her bipolar disorder. She was a retired speech therapist and special education teacher who had recently moved to North Carolina to be close to her family. She lived alone and wanted to work as a substitute teacher.

According to her medical records, the patient first presented with bipolar symptoms in 1984. Her symptoms included loss of interest, depressed mood, fatigue, sense of failure, poor concentration, psychomotor retardation, hypersomnia, irritability, racing thoughts, periods of excessive energy and euphoria, social and employment

difficulties. She had a relapse of symptoms in 1987 with a history of attempted suicide by over dose. Patient's symptoms were managed by electroconvulsive therapy (ECT) in 1988. Following the ECT, she was started on Lithium to which she responded well and was hence was maintained on this medication since then. She had regular checkups with her primary care physician who also managed her psychiatric medications. Following relocation, she came to our clinic for maintenance of medication and was found to be stable on 900 mg/day of Lithium. The patient also had history of Hypertension since 1987 which was well controlled on Hyzaar and also Hypothyroidism which was managed on Synthroid.

In 2010, the patient's routine bloodwork showed abnormal renal function test results. Her Serum Creatinine was found to be elevated at 1.24 mg/dl with Estimated Glomerular Filtration Rate (eGFR) of 46 L. Her bloodwork also showed hypercalcemia. The patient was advised to discontinue Hydrochlorothiazide and also to lower her Lithium dose as the increase in her Calcium level was suspected to be due to interaction of Hydrochlorothiazide with Li. Her follow up blood work which was done in 2011 showed further reduction in her eGFR and increase in Ca levels in spite of discontinuing Hydrochlorothiazide. She was advised to discontinue Li as it was suspected she had chronic renal disease with secondary hyper parathyroidism due to more than 20 yrs of use of Li. The patient however was highly reluctant to discontinue Li as she was stable on the medication for 20+ years and was worried about possible relapse of symptoms. However her follow up lab reports showed progressive elevation in serum creatinine levels, serum calcium levels and progressive decline in her kidney functions since 2010. In 2013, the patient was referred to a nephrologist and an endocrinologist for complete workup and she was diagnosed with Stage 3 chronic kidney disease from chronic Tubulointerstitial Nephritis from Li related hypercalcemia and that her kidney function was at 50%.

Despite these reports of her declining renal function, the patient was highly reluctant to discontinue Lithium and wanted to continue the medication. However we were able to convince her that at this point the risks of Li far outweighed the benefits and it was better for her health to consider alternatives to Li. We discussed in detail about the patient considering Lamotrigine as an alternative to Li and she agreed to cross taper Li with Lamotrigine. She was started on starter kit of Lamictal 25 mg – 100 mg/day and her Li dose was reduced to 600 mg/day. She initially had a smooth transition to Lamotrigine 100 mg/day and was able to reduce her dose of Lithium. The patient did not report any signs or symptoms of depression and her mood was found to be stable. She however complained of some

non-specific physical side effects of Lamotrigine which consisted of warm flashes, constipation, nausea and soreness in the mouth. After being medicated on Lamotrigine 100 mg/day for over 2 weeks, the patient started complaining of severe nausea, aching joints and hot flashes. She also reported of having vivid dreams and nightmares, forcing her to wake up regularly and having difficulty in falling back to sleep. She was advised to lower her Lamotrigine dose to 75 mg/day which resolved her physical side effects but the patient continued to have interrupted sleep with frequent waking and had vivid dreams. Her Lamotrigine dose was further reduced to 50 mg/day and in her follow up visit; the patient reported tolerating Lamotrigine well with complete resolution of the side effects.

In the following 3 years, the patient was well managed with Lamotrigine 50 mg with no relapse of bipolar symptoms. She was also able to cope with several major stressors during difficult times, such as the passing of her father. Her mood was stable and she denied having bipolar symptoms such as sadness, loss of motivation, mind racing, feeling good for no reason, fatigue, interrupted sleep, loss of interest or mood swings. However the patient still complained of on and off nausea which was resolved on taking Zofran. However in 2015 she again started experiencing severe nausea, insomnia, vivid dreams and nightmares. Despite this, she was willing to continue the current dose of Lamotrigine as she was very apprehensive of changing her medications again and having a full blown relapse of bipolar symptoms. The patient however did have a relapse of depressive episode late in 2015 following a major stressor, a dispute with her neighbor. She was advised to consider ECT again as it was suspected that she did not tolerate Lamotrigine at sufficient levels enough to prevent relapse of her original symptoms.

### **3. Discussion**

Lamotrigine is clinically a well-tolerated option for maintenance therapy and as an add-on drug for bipolar depression [1, 3, 4]. With this patient, our original treatment plan was to add on lamotrigine on a cross taper model along with Li in order to reduce the toxic effects of Li, a plan which is well supported by the literature. Adjunctive use of Lamotrigine in patients already using mood stabilizers had been shown to be more effective in terms of tolerability and safety [7]. Literature also supports the effectiveness of Lamotrigine as add-on therapy along with mood stabilizers due to its additive effects [8, 9].

The side effects of Lamotrigine is well documented with the most frequent adverse effects being nausea, dizziness, headache, tremors, ataxia, maculopapular rashes and blood dyscrasia [3, 5, 10]. There are few reports of variable incidence of psychiatric side effects of lamotrigine [5]. These psychiatric adverse effects seems to be seen more in patients with history of epilepsy [11, 12], however there are also a few reports of similar effects in patients with bipolar disorders with no history of epilepsy [5, 13]. In 2006, Uher and Jones [14] reported a case of a 42 year old woman with bipolar affective disorder and no history of neurological illness who presented dose related psychotic side effects of vivid dreams followed by hallucinations, when she was started on Lamotrigine. However the authors underlined the comorbid condition of alcohol abuse in the patient that could have been another causal association for the psychiatric symptoms. In addition, there are few other case reports reporting similar psychiatric symptoms such as auditory and visual hallucinations, vivid dreams, delirium and delusions [13, 14, 15].

There is however paucity in case reports on the psychiatric side effects of lamotrigine in patients of Bipolar disorder with no history of neurological illness. It is very important to document these side effects as it could help the prescribers as well as the patients recognize these symptoms as adverse effects of the medication, rather than as a relapse of the disorder or as an acute episode. Based on our research, this is the third documented case which reports the psychiatric adverse effect of Lamotrigine in patients with Bipolar disorder with no history of neurological disorder. This case report also serves to highlight the dose related occurrence of the symptom with complete resolution of symptoms on lowering the dosage. With the growing use of Lamotrigine in Bipolar disorders, it is important to note that Lamotrigine is capable of inducing psychiatric symptoms and educate the prescribers about the rare side effects of this medication.

#### **4. Disclosures**

The authors declare that there is no conflict of interest regarding the publication of this paper.

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