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Lamotrigine-induced obsessional symptoms in a patient with bipolar II disorder: a case report

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Abstract

Lamotrigine is an anticonvulsant that appears to have a mainly antidepressant effect and is indicated for the maintenance treatment of bipolar depression. Literature associated with obsessional symptoms related to lamotrigine treatment is limited. We report the emergence of obsessive symptoms during treatment with lamotrigine in a patient who subsequently experienced significant improvement after dose reduction and stopping of this medication. The obsessive symptoms associated with lamotrigine treatment were observed after the lamotrigine dose was increased to 100 mg/day. The possible mechanisms, including inhibition on the presynaptic release of glutamate and alteration of striatal dopamine uptake, are discussed. It is unclear why lamotrigine induces obsessions in some patients. Controlled studies are necessary to identify the population at risk for obsessionality in bipolar illness following treatment with lamotrigine and to investigate a possible dose–response relationship between obsessive symptoms and lamotrigine.

Key words
dopamine; glutamate; lamotrigine; obsession

Introduction

Lamotrigine is a phenyltriazine-derived anticonvulsant that stabilizes neuronal membranes and attenuates cortical glutamate release. However, lamotrigine appears to have a mainly antidepressant effect and is indicated for the maintenance treatment of bipolar depression to delay the time to occurrence of mood episodes (Calabrese, *et al*., 2003; Goodwin, *et al*., 2004).

Some articles have previously described obsessionality associated with lamotrigine in other neurologic and psychiatric diseases (Alkin, *et al*., 2007; Lombroso, 1999). There are also case series involving bipolar disorder associated with new-onset intrusive and repetitive phrases possibly related to lamotrigine treatment (Kemp, *et al*., 2007). We report a female patient who developed obsessional symptoms associated with lamotrigine treatment and who subsequently experienced significant improvement after dose reduction and stopping of this medication.

Case report

Mrs N was a 38-year-old married woman with a high school education admitted to our hospital. She had suffered from bipolar II disorder for the previous 3 years and had experienced two depressive episodes and one hypomanic episode within that time. The first episode of her illness was a hypomanic episode at age 35. She had no personal history of substance abuse or previous psychiatric disorders, and no family history of mental illness.

Upon examination, she was found to suffer from severe pervasive sadness, anhedonia, hypersomnia, moderate psychomotor retardation, feelings of worthlessness, distractibility, occasional passive suicidal ideation and decreased energy, concentration and self-esteem. She experienced these symptoms on most days and nearly every day during the month before admission. She stayed in bed most of the time, rarely cared for her, and could not work at all. Initially, her 17-item

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Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) total score was 30.

At admission, the patient's physical, neurological and laboratory examinations, including electroencephalograph (EEG) and brain magnetic resonance imaging (MRI), showed normal findings. She had been regularly maintained on a treatment regimen (included olanzapine p.o. at a dose 5 mg/day and citalopram 20 mg/day) for 3 months. Lamotrigine p.o. at a dose of 25 mg/day was added to the treatment for the depressive episode, and the dose was gradually increased to 100 mg/day within 2 weeks.

Approximately 3 days after the lamotrigine was increased to 100 mg/day (3 weeks after initiation of lamotrigine), the patient experienced a new onset of aggressive obsessions and intrusive phrases without compulsion. She had not experienced any obsessive symptoms until that time. She had a fear that she would harm her children because of not being careful enough and that she would be responsible for the death of her children. In addition, some phrases began to intrusively repeat in her mind, such as 'I wish I had not recommended my carpenter to my neighbour' and 'I wish I had not moved to another village'. Her obsessive symptoms were time consuming (taking more than 4 h/day) and were subjectively described as impairing her social interactions. Although she acknowledged that the thoughts and phrases were irrational and unmeaning, she was not able to ignore them. We decided to assess her obsessive symptoms by using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman, *et al*., 1989). She scored 15 of 20 on the Y-BOCS obsession subscale.

Because we believed that her obsessive symptoms were associated with the increase in the dose of lamotrigine to 100 mg/day, the dose was reduced to 50 mg/day and stopped within a week. With only the reduction of the lamotrigine dose, the intensity and frequency of the obsessive symptoms dramatically diminished in 1 week. Her Y-BOCS obsession subscore decreased from 15 to 7. Two days after stopping the lamotrigine, the patient reported that the intrusive phrases and obsessions had completely resolved. Her Y-BOCS obsession subscore was 2.

The patient's depressive symptoms, however, continued. Her HAM-D total score was 28. Therefore, 2 days after stopping lamotrigine, lithium was added to her treatment, and the dose was gradually increased to 1200 mg/day. Her depressive symptoms improved gradually. The patient's total score on the HAM-D on the last week of admission was 2. The patient was discharged after an 8-week period of hospitalization. At outpatient follow-up 4 months after discharge, the patient did not report any obsessive symptoms.

Discussion

This case report discusses the possibility of a causal relationship between lamotrigine treatment and a patient's obsessive symptoms.

There is limited literature available that addresses obsessional symptoms related to lamotrigine treatment. Kemp, *et al*. (2007) described a series of five patients with bipolar II disorder who developed intrusive, repetitive phrases and other forms of obsessionality while undergoing treatment with lamotrigine, similar to the present case. Also, tic disorders and Tourette's syndrome (suggested as an obsessive-compulsive spectrum disorder) have been reported with lamotrigine treatment (Lombroso, 1999; Sotero de Menezes, *et al*., 2000; Alkin, *et al*., 2007). Most of the patients described in the literature experienced significant improvement when the drug was reduced in dosage or stopped.

Functional neuroimaging studies have repeatedly reported metabolic hyperactivity in the cortico-striato-thalamo-cortical (CSTC) circuitry in patients with obsessive-compulsive disorder (OCD) (Saxena and Rauch, 2000). Although a large amount of evidence points to the role of the serotonin system in mediating OCD, recent studies have indicated alterations in the glutamatergic system in CSTC circuitry in OCD (Rosenberg, *et al*., 2004; Grant, *et al*., 2007). Lamotrigine has a potent inhibitory effect on the presynaptic release of the excitatory neurotransmitter glutamate. This may be a possible explanation for lamotrigine-induced obsessional symptoms. Another CSTC neurotransmitter system that may be particularly important in mediating OCD in some patients is dopamine. It has been suggested that obsessive-compulsive symptoms are associated with increased dopaminergic transmission (Denys, *et al*., 2004). Also, dopamine may play a more significant role in subtypes of OCD because OCD spectrum disorders such as Tourette's syndrome and tic disorders have also responded well to D2-blocking agents (Potenza, *et al*., 1998).

It is known that glutamate inhibits dopamine release in the substantia nigra and striatum (Morari, *et al*., 1998; David, *et al*., 2005). The inhibition of the excitatory neurotransmitter glutamate by lamotrigine may alter striatal dopamine uptake (Goa, *et al*., 1993). Therefore, the alteration of dopaminergic activity may be a contributing factor in the genesis of lamotrigine-induced obsessional symptoms.

In our patient, the emergence of obsessive symptoms occurred after the dose of lamotrigine was increased to 100 mg/day. In a case report series (Kemp, *et al*., 2007), intrusive and repetitive phrases associated with lamotrigine treatment have been observed only at doses of 200 mg/day or above, and the authors suggested a possible dose–response relationship. Concomitant medications taken by our patient may have contributed to the genesis of obsessional symptoms. Although some studies have confirmed the effectiveness of olanzapine in OCD (Bystritsky, *et al*., 2004), this agent may induce obsessionality (Lykouras, *et al*., 2000). The co-administration of olanzapine and lamotrigine also could induce obsessional symptoms. It is possible that there is a pharmacodinamic interaction despite of the minimal pharmacokinetic interaction between both drugs (Sidhu, *et al*., 2006). This may be a possible explanation for the genesis of obsessional symptoms in the lower doses of these agents.

The most important question to be answered is whether these obsessive symptoms should be considered side effects of lamotrigine. Otherwise, they may be coincidental or the result of a comorbid psychiatric disease. There is, however, a strong indication that the obsessions were caused by lamotrigine. The rapid remission of the obsessive symptoms after dose reduction or withdrawal leads to the conclusion that the obsessive symptoms were caused by lamotrigine.

Conclusion

This case highlights the potential role of lamotrigine on obsessionality in the treatment of bipolar II disorder. As our data are purely observational, further studies are necessary concerning possible intrinsic obsessiogenic properties of lamotrigine.

It is unclear why lamotrigine induces obsessions in a small number of patients. Controlled studies are necessary to identify the population at risk for obsessionality in bipolar illness following treatment with lamotrigine. Additionally, prospective studies assessing the possible dose–response or dose-severity relationships between obsessive symptoms and lamotrigine are warranted.

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