Psychiatric symptoms related to the use of lamotrigine: a review of the literature

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Summary
Lamotrigine is an established anticonvulsant agent and also an effective maintenance therapy for bipolar disorder. In Italy it is approved for the treatment of epilepsy with partial seizures, partial seizures with secondary generalization and generalized seizures, both in monotherapy and as an add-on therapy in patients with refractory epilepsy; it is also approved, in the over-18s, for the prevention of depressive episodes in patients with bipolar disorder with a predominant depressive component.

Lamotrigine is generally well tolerated; however, some psychiatric problems have been reported in patients using the drug to treat mental disorders (mainly bipolar) or epilepsy. The clinical features of these psychiatric side effects are: affective switches, full acute psychotic episodes, and hallucinations.

In conclusion, lamotrigine is an effective drug, very useful in the therapy of epilepsy and mood disorders, but clinicians have to be aware of the risk that it can induce psychiatric symptoms or acute episodes.

KEY WORDS: acute psychosis, bipolar disorder, depression, epilepsy, lamotrigine.

Introduction
Lamotrigine, a phenyltriazine derivative, is an established anticonvulsant agent and also an effective maintenance therapy for bipolar disorder. Its mechanism of action may be related to inhibition of the high-frequency firing in depolarized neurons (through selective prolonging of the slow inactivation of sodium and calcium channels), and hence to stabilization of presynaptic neuronal membranes and suppression of the release of excitatory neurotransmitters, predominantly glutamate and aspartate (1).

Lamotrigine is an antiepileptic drug with efficacy in a wide variety of seizure types, both in adults and children (2). In Italy it is approved for the treatment, in the over-12s, of epilepsy with partial seizures, partial seizures with secondary generalization and generalized seizures, both in monotherapy and as an add-on therapy in patients with refractory epilepsy; it is also approved, in the over-18s, for the prevention of depressive episodes in patients with bipolar disorder with a predominant depressive component.

Lamotrigine is generally well tolerated: the most frequent adverse effects are nausea, headache, dizziness, ataxia, diplopia, somnolence, tremor, maculo-papular rash and blood dyscrasias (3); there are also rare reports of angio-oedema, Stevens-Johnson syndrome and Lyell syndrome. A serious rash occurs in a small number of patients and the incidence of this adverse effect can be reduced by starting treatment with a low dose, particularly if patients are receiving concomitant sodium valproate or another drug that inhibits lamotrigine metabolism. Nevertheless some psychiatric problems have been reported in patients using lamotrigine to treat mental disorders (mainly bipolar) or epilepsy. The main aim of this paper is to discuss this issue and the related clinical problems.

The efficacy of lamotrigine in psychiatric illness
The main psychiatric guidelines for the treatment of patients with bipolar disorder highlight lamotrigine’s considerable usefulness as mood stabilizer. There are strong data in support of this finding and we here mention the results of two significant large, randomized, double-blind, placebo-controlled studies (4,5).

The first, which considered patients who had recently suffered a depressive episode, showed that lamotrigine is statistically superior to placebo in preventing mood episodes in bipolar I patients and in prolonging the time to intervention for a depressive episode (4). In the second study, which investigated recent manic or hypomanic patients, similar results were found for the use of lamotrigine as a maintenance therapy; the drug was not superior to placebo as an intervention for mania (5). The data from both studies were pooled and showed that lamotrigine is an effective treatment for bipolar disorder, particularly for the prevention of depression (6).

On the basis of the data recorded in these studies (4-6), 200 mg/day was deemed a reasonable target dose in acute and maintenance treatment, also because there was no evidence of an increase in adverse events at this dose. Moreover, both the incidence of side effects and the rate of discontinuation were lower than those of the
other drug analyzed (lithium). With regard to the burden associated with the depressive phase of the illness and related morbidity and mortality, lamotrigine also appeared to provide a complementary benefit to other drugs used in the treatment of bipolar disorder.

Lamotrigine is effective not only for the prevention of depression; according to the APA practice guideline (7) it is also one of the medications showing evidence of efficacy for the acute treatment of depression in bipolar patients.

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**Affective switches in depressive patients**

The occurrence of lamotrigine-related switches in depressive patients with unipolar and bipolar disorders has already been reported (8). Desarkar and Sinha (9) described the case of a 15-year-old boy who developed a moderate depressive episode about one year after a previous severe psychotic depressive episode treated effectively with lithium and olanzapine. For the new episode, the patient was again treated with lithium, but also with lamotrigine as an add-on therapy. Initially, the patient became overtalkative, hyperactive and offensive; he also displayed delusions of grandeur and sleep disturbance; these symptoms improved after lamotrigine withdrawal. Given the strong evidence of an association between lamotrigine and the severe manic switch in this adolescent, the authors suggested that caution may be warranted in the use of lamotrigine, especially in early-onset unipolar recurrent depressive disorder. The same year, in a Turkish paper on the treatment of bipolar affective disorders, Savas et al. (10) described two depressive patients treated with lamotrigine who switched to manic episodes. Commenting on these two studies, both published in 2006, Selekk and Savas (8) suggested that lamotrigine's probable propensity to cause manic switch should have been borne in mind in the treatment of these patients.

The current literature includes other case reports of lamotrigine-induced affective switches both in depressive unipolar and depressive bipolar patients, and both in adults and younger patients. In 2003 Margolese et al. (11) reported the case of a 23-year-old woman with major depression who showed a partial response to bupropion combined with cognitive therapy. The patient had a negative personal and family history of bipolar depression. After lamotrigine add on, the patient experienced an enhanced mood with decreased anxiety. However, when the dose was increased to 75 mg/day, her symptoms worsened: she presented mood lability, increased energy and disturbed sleep, but no grandiose or other delusions. These hypomanic symptoms subsided when the lamotrigine dose was reduced to 50 mg/day. The patient remained euthymic for many months. The authors concluded that lamotrigine has potentiating antidepressant properties, likely through its ability to decrease glutamate release, and that it is an effective adjunctive treatment in partially responsive unipolar depression.

In 2006 Raskin et al. (12) reported lamotrigine-related affective switches in two patients with bipolar I disorder. The first case was that of a 41-year-old woman who was treated with lamotrigine as an add-on therapy to valproic acid following the onset of depressive symptoms. Perceiving an improvement in her mood, the patient was prompted to ask for an increase of the dosage. A few days after lamotrigine was increased from 50 mg/day to 100 mg/day, the patient became hyperactive, agitated, and sleepless; she also began to spend money recklessly. These symptoms rapidly subsided after lamotrigine withdrawal. The second case was that of a 32-year-old man who experienced rapid mood changes with delusions of grandeur and suicidal ideation. On account of this serious condition, lamotrigine was added on to carbamazepine and quetiapine therapy. The dose was then increased, over a week, from 25 mg/day to 200 mg/day and 48 hours later he displayed a typical manic episode. After reduction of the lamotrigine dose to 50 mg/day his symptoms improved within the space of a few days. According to the authors, lamotrigine, added to other mood stabilizers, may have acted as a quick antidepressant in these cases; they also remarked that the onset of mania in these patients seemed to be related to the drug titration strategy (a high dose introduced too quickly).

The literature also contains two case reports of lamotrigine-induced mania in adolescents. In 2007 Moor et al. (13) described the case of a 17-year-old girl with a two-year history of bipolar disorder and comorbid substance abuse disorder, under treatment with lithium and quetiapine. For many months the patient had experienced low mood with significant impairment of functioning, therefore she started lamotrigine, at a dose of 25 mg/day. The authors described the onset of elevated mood, racing thoughts and grandiose ideation with agitated behaviour and increased sexual interest. These symptoms resolved spontaneously within 10 days of lamotrigine withdrawal. The authors also reported the case of a girl with similar characteristics: age 17 years, a three-year history of bipolar disorder (with at least one previous episode of mania), under treatment with lithium and quetiapine. The patient had previously experienced a mixed mood state induced by a selective serotonin reuptake inhibitor. As in the first case, the patient started lamotrigine after many months of a worsening low mood with suicidality and impaired functioning. The drug was titrated slowly over 8 weeks to 100 mg/day. At the dosage of 50 mg/day, she began to notice an effect on her mood: she felt more energetic and had a renewed interest in previously neglected activities; at the target dose these symptoms increased, culminating in a manic episode for which she required hospitalization. The authors alerted colleagues to this serious effect of lamotrigine therapy, which might be a feature of its use in younger patients with bipolar disorder.

These data suggest that some prudence is warranted in the use of lamotrigine in concomitance with antidepressants in bipolar depression. The therapy of this disorder is one of the most critical issues in psychiatry because of the instability of these patients and the risk of inducing a switch. The literature on the role of antidepressants in the treatment of bipolar disorder is, indeed, controversial: different guidelines take different positions and data are ambiguous. Some authors do not consider antidepressants useful in these patients, whereas others are more flexible and feel that there is a place for an-
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Hallucinations in a depressive patient

In 2006 Uher and Jones (16) reported the clinical case of a 42-year-old woman who experienced episodes of depression and hypomania fulfilling the DSM-IV criteria for a diagnosis of bipolar II disorder, with comorbid alcohol abuse and without neurological illness. The patient was treated with lamotrigine initially at 50 mg/day on which she experienced an improved mood without side effects. After a dose increase to 100 mg/day, her sleep became disturbed by vivid dream-like experiences and subsequently she reported visual hallucinations; these symptoms subsided over a few days when the dose was decreased to 50 mg/day. After this, two more titrations were performed (first up to 75 mg/day and then up to 100 mg/day) with the aim of improving her mood. She experienced sleep disturbance, nightmares and threatening visual hallucinations; these symptoms regressed when the dose was again reduced. The authors remarked that psychotic symptoms arising during initiation of pharmacotherapy should not automatically be attributed to the underlying bipolar disorder, that the patient experienced these symptoms in the absence of a manic/depressive episode, and that the repeated dose-related occurrence of hallucinations suggests a causal association. They also underlined that, in this case, alcohol abuse may have been a contributing factor.

Psychotic episodes in patients with epilepsy

Brandt et al. (17) reported six cases of patients who had both a history of epilepsy (five with symptomatic focal epilepsy and one with both focal and generalized seizures) and a psychiatric history. It was underlined that only one of these patients had previously experienced psychotic episodes. According to the case reports, all the patients experienced paranoid thoughts, visual and auditory hallucinations, agitation and sleep disturbances. For the following reasons, the authors felt that these psychotic episodes were caused by lamotrigine: the onset of psychotic symptoms was generally rapid and closely related to an increase in the dose of lamotrigine, or to a change in a concomitant medication leading to an increase in lamotrigine serum levels; symptoms rapidly improved after decreasing the dose or withdrawing the drug; one patient who was re-exposed to lamotrigine again presented these symptoms. They concluded that further studies of the possible toxic or intrinsic psychotogenic effects of lamotrigine are needed. Two other contributions (18,19) drew further attention to these clinical cases (17) in order to underline the importance of a differential diagnosis versus delirium and manic switch related to lamotrigine treatment. Delirium was excluded because none of the patients described had psychotic symptoms typical of this disorder (i.e., fragmented, unsystematic and fluctuating significantly in the course of the day); furthermore, in delirium there is also impairment of consciousness, cognition, and attention. With regard to manic switch, the authors affirmed that there were no affective changes sufficient to attribute the symptoms to an episode of an affective disorder. With regard to psychotic episodes in patients with epilepsy, Matsuo et al. (20), in an early randomized and placebo-controlled study on the efficacy and safety of lamotrigine in 216 patients with partial seizures, described four patients who had to discontinue the drug because of psychiatric side effects rated by the investigator as serious. They expressly mentioned a psychotic episode (in one patient in the 300 mg lamotrigine group) and the onset of delusions (in one of the three patients who received a dose of 500 mg). In 1995 Martin et al. (21) reported psychotic symptoms in a 44-year-old woman with severe intractable epilepsy due to left mesial temporal sclerosis and complex partial seizures; she did not have a psychiatric history. The patient developed a sub-acute psychosis with visual and auditory hallucinations, confusion, behaviour disturbance and agitation, while her EEG was normal. The symptoms arose after starting lamotrigine treatment and stopped several weeks after its withdrawal and the introduction of neuroleptic drugs as an on-off therapy. In 1998, Poliselli et al. (22) reported the case of a 34-year-old man with therapy-resistant temporal lobe epilepsy characterized by pseudo-absence. Nine days after lamotrigine add-on, he had an epileptic attack with loss of consciousness and the following day exhibited delusional thinking with mystical ideas, auditory hallucinations and agitations. The patient was admitted to hospital and treated with haloperidol and chlorpromazine. After lamotrigine withdrawal the psychotic symptoms improved dramatically within the space of a day and the neuroleptic drug was suspended. The patient had a negative psychiatric history but a positive family history for bipolar disorder (father). The authors concluded that it is possible that lamotrigine, by reducing glutamate release, triggered the acute psychosis. This risk is higher mainly in patients prone to psychiatric disorders.

Hallucinations in a patient with epilepsy

In 2008 Roberts et al. (23) described the case of a 14-year-old girl submitted to clinical tests for the onset of daily episodes of dizziness, backwards eye rolling, confusion and tiredness. Epilepsy with partial complex seizures with secondary generalization was diagnosed. The patient was initially treated with carbamazepine, but later she was switched to valproic acid in association with amitriptyline to treat resistant headaches. After some time, the onset episodes recurred and so lamotrigine was added on, decreasing the valproic acid dose. After a few days on lamotrigine 25 mg/day, the patient claimed to hear heavy breathing and experienced a visual hallucination (accompanied by backwards eye rolling and rocking forwards). She also developed a low-grade temperature, an ankle pain and a fine rash over her arms and legs. The paediatrician diagnosed this rash as viral, and indeed it resolved spontaneously. The lamotrigine therapy was discontinued and there have been no more visual or auditory hallucinations. The authors discussed in detail the diagnosis of lamotrigine-induced psychiatric symptoms, although never in monotherapy (14,15). In fact the concomitant use of mood stabilizers is strongly suggested to minimize the risk of a manic switch. Of all the available mood stabilizers, lamotrigine is not the first choice for this purpose, because of its low antimanic efficacy (6).
hallucinations and its differential diagnosis versus migraine aura, migrainous manifestations, ictal phenomena, encephalopathy, head injury and also psychiatric disorders. They favoured the drug side effect hypothesis because the hallucinations stopped shortly after lamotrigine discontinuation and have not recurred; they also underlined that the concurrent use of valproic acid might have made the patient more susceptible to this unusual side effect.

Concluding remarks

Lamotrigine has been shown to be an established anticonvulsant agent and also an effective maintenance therapy for bipolar disorder, particularly for the prevention of depressive episodes. However, some psychiatric problems have been reported in association with the use of lamotrigine, both to treat mental disorders (mainly bipolar disorders) and epilepsy. These psychiatric side effects took the form of affective switches, full acute psychotic episodes and hallucinations. The authors of the majority of the case reports discussed the possible causes of the symptoms and the differential diagnosis and generally concluded that these were lamotrigine-induced psychiatric symptoms. Often this hypothesis was chosen because of the favourable course shown by the patient following withdrawal of the compound or the reduction of the dose. In conclusion, lamotrigine is an effective drug, very useful in the treatment of epilepsy and mood disorders, but it appears to be capable of inducing psychiatric symptoms or acute episodes.

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