

## Lamotrigine-induced hallucination in patient with bipolar disorder and no history of epilepsy or psychosis: a case report and literature review

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### Abstract

We report a rare case of hallucinations in a patient with bipolar affective disorder BAD without any history of psychosis or epilepsy following the introduction of lamotrigine as an add-on medication to her current treatment with lithium carbonate. The patient has been on two previous medications (quetiapine and sodium valproate) without significant improvement and only showed partial response to lithium. Lamotrigine was introduced as an adjunctive medication with her lithium carbonate. Her dose of lithium was 800 mg once daily with satisfactory lithium levels.

She started to report complex auditory and visual hallucinations which started two days after starting lamotrigine (25 mg once daily) and increased with its dose increase to 50 mg once daily two weeks later and resolved completely with stopping it. Hallucinations following lamotrigine treatment in non-epileptic patients are an extremely rare reaction and only few similar case reports are reported in literature.

Awareness of this rare but serious side effect is important to avoid confusion with other psychotic symptoms related to mental illness and avoid unnecessary treatment.

**Keywords:** Anticonvulsants; Bipolar Affective Disorders; Drug interactions and side effects; Education and training; Mood stabilisers  
**Abbreviations:** BAD: Bipolar affective disorder. ICD 10: International Classification of Diseases, Tenth Edition. DSM 5: Diagnostic and Statistical Manual, Fifth Edition.

### Case Presentation:

We report the case of 36 year old white Caucasian female who used to work as a driving instructor and living with her parents.

She has a diagnosis of congenital adrenal hyperplasia (21 hydroxylase deficiency) and is on long term corticosteroid replacement (prednisolone 4 mg once daily and fludrocortisone

100 mcg once daily) and she is under the care of an endocrinologist.

She was referred for psychiatric evaluation with “anxiety and depressive symptoms” and failure to respond to antidepressant treatment which was prescribed by her General Practitioner.

During the psychiatric assessment, she reported long history of recurrent episodes of elevated mood and depression dating back to her late teens with clear description of distinct periods of mood elevations lasting for few weeks and longer periods of persistent low mood. There was no history of psychotic symptoms and no family history of mental illness.

She was diagnosed with bipolar affective disorder and failed to achieve remission of symptoms on two different antipsychotic medications (quetiapine and olanzapine) and anticonvulsant medication (sodium valproate) before starting lithium carbonate.

The introduction of lithium and gradual titration resulted in significant improvement in her symptoms and mood stability. However, few months later, she reported relapse in her symptoms (mainly reporting features of bipolar depression) despite adequate lithium levels.

She agreed on the introduction of lamotrigine as an adjunctive medication to lithium. The initial dose of lamotrigine was 25 mg daily for two weeks in line with dose recommendation from manufacturer and drug guides.

On the same day of lamotrigine introduction, the patient started to experience visual hallucinations that she never had before (please see patient’s perspective for detailed description of her hallucinations).

With the dose of lamotrigine increased to 50 mg daily after the initial two weeks, she started to report worsening of these abnormal perceptions which developed into more complex visual and auditory hallucinations.

More importantly, there was no evidence of accompanying manic symptoms or severe depressive symptoms to explain these symptoms and also no alcohol or drug use.

Following a psychiatric review, the dose of lamotrigine was reduced to 25 mg which resulted in immediate reduction in the intensity of the abnormal perceptions. When the lamotrigine

was eventually stopped after one week, there was complete cessation of abnormal perceptions.

Lamotrigine was never re-started again and she was maintained on a combination of lithium and quetiapine with good effect.

#### Investigation:

We used the Naranjo Adverse Drug Reaction Probability Scale (1) to determine the likelihood of whether an adverse drug reaction is related to this specific drug or may be related to other factors. This tool examines factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose – response relationships and previous patient experience with the medication.

The probability of the adverse drug reaction is concluded from the total score (Definite if the overall score is 9 or greater, Probable for a score of 5-8, Possible for 1-4 and Doubtful if the score is 0).

#### Questionnaire

1. Are there previous conclusive reports on this reaction? Yes (+1)
  2. Did the adverse events appear after the suspected drug was given? Yes (+2)
  3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? Yes (+1)
  4. Did the adverse reaction appear when the drug was re-administered? Do not know or not done (0)
  5. Are there alternative causes that could have caused the reaction? No (+2)
  6. Did the reaction reappear when a placebo was given? Do not know or not done (0)
  7. Was the drug detected in any body fluid in toxic concentrations? No (0)
  8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? Yes (+1)
  9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? No (0)
  10. Was the adverse event confirmed by any objective evidence? Do not know or not done (0)
- Scoring 7 (Probable Adverse drug reaction)

#### Discussion:

Lamotrigine is a phenyltriazine derivative used as an anticonvulsant drug with established mood stabilising properties. In the United Kingdom, it is recommended for use in bipolar affective disorder according to the guidelines from

the National Institute of Health and Care Excellence (2) and the British Association for Psychopharmacology (3).

We performed a literature search to find similar case reports. We searched the following databases using the keywords (lamotrigine AND hallucinations): Complementary Medicine (AMED), British Nursing Index (BNI), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), Health Business Elite (HMIC), Medline, PsycINFO and Health Management Information Consortium (HMIC).

The search returned 57 results. Only 8 articles discussed hallucinations and other psychiatric symptoms as side effects associated with lamotrigine and therefore were included in this review.

Psychotic symptoms have been reported with the use of lamotrigine (both as an anticonvulsant or mood stabiliser) but this reaction is mainly seen in patients with history of epilepsy. One study reported 4.8% incidence of psychiatric and behavioural side effects with lamotrigine in 546 patients with epilepsy. (4)

Another study on paediatric patients showed that reversible visual and auditory hallucinations were reported in one patient among 9 patients with epilepsy who received lamotrigine treatment (mean age 5 years). (5)

Villari et al published a literature review on psychiatric symptoms related to lamotrigine and included case reports documenting full acute psychotic episodes, hallucinations and affective switching in patients with and without history of epilepsy. (6)

They found one case report on hallucination with lamotrigine in a bipolar patient without epilepsy. In patients with epilepsy, they reported two case reports and one case series (total number of patients 9) developing psychotic symptoms following lamotrigine and one randomised controlled trial in which four out of 216 patients stopped lamotrigine due to psychotic symptoms (including hallucinations and delusions).

The authors concluded that the majority of the case reports concluded that these symptoms were lamotrigine-induced due to the temporal association with lamotrigine treatment and favourable outcome following drug withdrawal. It also appeared that more case reports were from patients with epilepsy, suggesting lower incidence in patients without this condition.

Chistyakova and Amos (7) reported a case of delirium associated with lamotrigine use. The dose of lamotrigine was increased from 200 to 400 mg over two weeks prior to her admission. The patient reported visual and auditory hallucination with confusion. She took an accidental overdose of her medication (200 mg of fluoxetine and 2800 mg of

lamotrigine) due to her confusion and medications were stopped.

The authors concluded that delirium may result from lamotrigine toxicity or drug interaction with fluoxetine.

Uher and Jones in 2006 (8) reported a case of a 42-year-old woman with bipolar affective disorder with comorbid alcohol abuse and no history of neurological illness.

The patient tolerated an initial dose of lamotrigine 50 mg/day but following a dose increase to 100 mg/day, she reported 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.

The authors suggested a causal association through this dose dependent effect but also pointed out that the concurrent alcohol abuse may have been a contributing factor.

They also highlighted the paucity of case reports documenting this rare adverse reaction and identified two similar case reports in their references (which we were unable to get their full text) and a third paper reporting hallucination in 2 out of 108 patients with epilepsy on a combination of lamotrigine and sodium valproate (9)

Hallucination with lamotrigine when combined with valproic acid was also reported in a case report by Roberts et al (10) in 14 year old girl with epilepsy when it was added to valproic acid and it was suggested that this adverse effect may be due to an interaction between the two medications causing lamotrigine half-life to triple with valproic acid.

#### Learning points:

- Lamotrigine is an anticonvulsant with an established role in management of bipolar affective disorder, particularly for the treatment and prevention of depressive episodes.
- However, it appears to be associated with variable incidence of psychiatric symptoms which should be known to the prescriber and patient.
- These adverse effects are mainly seen in patients with history of epilepsy but can occur in patients with mental health problem without epilepsy.
- Different mechanisms for inducing these psychiatric symptoms have been suggested, including idiosyncratic reaction, lamotrigine toxicity as a result of concomitant use of another drug that affect lamotrigine metabolism (e.g., valproic acid) and delirium.
- Examples of these psychiatric symptoms including affective switches in depressed patients with bipolar disorder, hallucinations in depressed patients, delirium and psychotic symptoms (mainly hallucinations and delusions) in patients with or without epilepsy.

- Reversible and severe psychiatric disturbances associated with lamotrigine therapy are rarely reported in literature and more research is needed to identify population at risk.
- Patient education about these rare but frightening side effects is essential to improve medication adherence and better outcome of the management of the mental disorder.

#### Patient perspective:

“The first hallucination I had was one hour roughly after taking lithium and lamotrigine. It was the Pope which appeared as bright light on my wall. He was wearing a white gown and he had gold jewellery. The picture was so clear and very detailed. I’m not religious and this image would not be something I would think of.

Every day on lamotrigine I had black spots moving quickly around the walls. They were in size of about an inch, 20-30 moving around at one time. Like spiders but without legs. I was really scared at first because I hate spiders. It was very unsettling and I changed my whole bed, away from my wall, and had trouble sleeping.

There was another night when I had similar to the black dots, where instead I had smaller black dots like bees moving into the corner of my room. They were all slightly moving as if they were getting their places. There were hundreds of them.

The scariest incident that happened was hearing voices downstairs. I was so sure that people had broken into the house; I went downstairs armed with razors. I was going to cut DNA from the burglars to give to the police as evidence. When I checked the house, there was no one there.

When I was taking lamotrigine with the lithium, it made me very unsettled, more anxious and mentally unstable. I was so tired for not sleeping and my decisions irrational. It wasn’t a pleasant place to be for me personally.”

#### Competing Interests

None declared.

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