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CASE REPORT

# Lacosamide-Induced Visual Hallucinations and Psychosis: a Case Report and Literature Review

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## Abstract

Lacosamide (LCM) has both frequent side effects, such as headache, diplopia, and nausea, and rare side effects such as depression, mood changes, and confusion. This article presents a case of possible LCM-induced psychosis and reviews the literature. A 22-year-old woman presented to the Emergency Department in Status Epilepticus. The seizure was treated with intravenous midazolam and valproic acid. However, she developed cardiopulmonary arrest and was resuscitated successfully. She was intubated and admitted to the intensive care unit. She had first been diagnosed with epilepsy 15 years earlier and had been seizure-free for 3 years. She had undergone a sleeve gastrectomy 1 year earlier. She was extubated the day after admission. LCM 200 mg/day was added to the treatment because of generalized seizures beginning in the right arm. Her seizures were controlled on the 4th hospital day. However, after starting LCM, she developed agitation, visual hallucinations with a sexual content, and intellectual delusions. Therefore, the LCM was discontinued and her psychosis resolved completely 4 days later. On the 12th hospital day, she was discharged. LCM blocks sodium channels and can act as a mood stabilizer and sedative. However, our patient developed psychosis with LCM treatment. This is the first reported case of LCM-induced psychosis in Turkey. Visual hallucinations and psychosis may develop immediately after starting LCM therapy. Clinical recovery can be achieved by discontinuing the drug.

Keywords: Lacosamide; psychosis; status epilepticus; visual hallucinations.

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## Introduction

Lacosamide (LCM) is an amino acid with an acetamido-N-benzyl-3-methoxypropionamide structure that selectively enhances the slow inactivation of voltage-gated sodium channels and stabilizes the hyperexcitability of neuronal membranes by modulating collapsin response mediator protein-2.[1,2] LCM was approved by the US Food and Drug Administration (FDA) in 2008 as adjunctive therapy for partial-onset epilepsy.[2] In addition to frequent side effects, such as imbalance, headache, diplopia, nausea, and vomiting, it may occasionally cause depression, mood changes, and confusion.[2]

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Drug-induced psychosis is usually reported with the use of antiepileptic medications, namely phenytoin, levetiracetam, topiramate, and zonisamide.[3–6] LCM-induced psychosis has been reported in a few cases.[7,8]

In this article, we report a 22-year-old woman who presented in status epilepticus and then developed LCM-induced psychosis, and review the literature. To the best of our knowledge, this is the first case of LCM-induced psychosis in Turkey.

## Case Report

A 22-year-old woman presented to the Emergency Department with seizures. She had had epilepsy for 15 years and, according to her family, regularly used levetiracetam 3000 mg/day and lamotrigine 200 mg/day. She had been seizure-free for 3 years, but in the past 2 days she had three seizures that began as oroalimentary automatisms with secondary generalization. Her mother reported that she had undergone a sleeve gastrectomy 1 year earlier and ate fewer calories than recommended for a few months. When the seizures recurred in the Emergency Department, she was given two 5 mg intravenous (IV) doses of midazolam (MDZ), 3 min apart. Valproic acid was administered at a loading dose of 30 mg/kg IV.

## Lakozamid ile Tetiklenen Görsel Halüsinasyonlar ve Psikoz, Sunumu ve Literatürün Gözden Geçirilmesi


### Öz

Lakozamid, voltaj-kapılı sodyum kanallarının yavaş inaktivasyonunu selektif olarak artırarak etki eden, parsiyel başlangıçlı epilepsi hastalarında ekleme tedavisi olarak onaylanan yeni bir antiepileptik ilaçtır. Baş ağrısı, diplopi, bulantı gibi sık yan etkilerinin yanında depresyon, mod düşüklüğü ve konfüzyon gibi nadir yan etkileri de görülebilir. Bu metinde olası lokazamid ile tetiklenmiş psikoz tablosu sunulacak ve literatür gözden geçirilecektir. Yirmi iki yaşında kadın hasta acil servise status epileptikus tablosunda getirildi. Midozalam uygulaması ve valproik asit yüklemesinden sonra arrest oldu. Kardiyoplumoner resusitasyon yapılırdı. Midozalam infzuyonu başlandı. Entübe halde yoğun bakım ünitesine alındı. Özgeçmişinden 15 yıldır epilepsi tanısı olduğu, üç yıldır nöbetsiz olduğu ve bir yıl önce sleeve gastrektomi operasyonu geçirdiği öğrenildi. Yatışının ertesi günü ekstube edildi. Sağ kolundan başlayıp jeneralize olan nöbetleri olması üzerine tedaviye lakozamid 200 mg/gün eklendi. Yatışının dördüncü gününde nöbet kontrolü sağlandı. Ancak ajitasyon ve görsel halüsinasyonlar gelişti. Cinsel içerikli halüsinasyonları, uygulanılan ilaçlarla ilgili delüzyonları ve yoğun bakım kapısında yakınlarının alıkonulduğu gibi varsanıları vardı. Bu yan etkilerin yeni başlanan lakozamide bağlı olduğu düşünülerek lakozamid dozu azaltıldı. Sonraki takiplerinde ajitasyonları ve görsel halüsinasyonları azalmakla beraber devam ediyordu. Lakozamid kesildikten dört gün sonra hastanın ajitasyonları ve psikoz tablosu tamamen düzeldi. Hasta yatışının 12. gününde taburcu edildi. Sodyum kanal blokajı yapması sebebi ile lakozamidin duygu durum stabilizatörü gibi davranması ve sedatif etkiye sahip olması beklenirdi. Ancak aksine bizim hastamızda lakozamid ile psikoz gelişmiştir. Bizim olgumuz Türkiye'de görülen ilk lakozamid ilişkili psikoz tablosudur. Lakozamid başlangıcının hemen ardından visuel halüsinasyonlar ve psikoz tablosu gelişebilir. İlacın kesilmesi ile klinik iyileşme sağlanabilir.


Anahtar sözcükler: Antiepileptik ilaç; klobazam; ilaca dirençli epilepsi; medikal tedaviye dirençli epilepsi.

However, the seizures did not stop and she developed cardiopulmonary arrest. Spontaneous circulation was achieved with 5 min of cardiopulmonary resuscitation. She was intubated, an MDZ infusion was started at 0.1 mg/kg/h, and she was admitted to the intensive care unit (ICU). The MDZ dose was subsequently increased to 1 mg/kg/h. The day after ICU admission, she was extubated. LCM 200 mg/day was added to the treatment because a new seizure developed, beginning in the right arm and becoming generalized. On the 3rd ICU day, MDZ infusion was tapered and discontinued. Electroencephalography (EEG) revealed three 11~15 s episodes of epileptiform activity during a 20 min period. The activity had a frequency of 2.5 Hz and was characterized by generalized spikes and slow waves. The seizures were controlled on the 4th hospital day. However, the patient became agitated and developed visual hallucinations with a sexual content, as well as delusions regarding the drugs administered. Her EEG showed no epileptiform activity. Her memory, orientation, and consciousness were normal. The LCM dose was decreased because it was thought that the delusions were side effects thereof. Her agitation and visual hallucinations subsequently decreased. Occasionally, she shouted her boyfriend's name for minutes at a time. Four days after discontinuing the LCM, her agitation and psychosis had resolved. Brain magnetic resonance imaging was normal. The patient was discharged on levetiracetam 3000 mg/day and lamotrigine 400 mg/day on the 12$^{th}$ hospital day. According to the Naranjo drug interaction probability scale, LCM-induced psychosis is a "probable" drug-induced side effect.[9] The Naranjo drug interaction score was 7.

We obtained consent from the patient to publish the case information and images.

## Discussion

Compared with the healthy population, patients with epilepsy are more susceptible to developing psychosis.[10] In a recent meta-analysis, the prevalence of psychosis in patients with epilepsy was 5.6%.[11] The confinement of epileptic activity to active and subcortical areas of the brain may be an underlying mechanism of psychosis development, in which amygdaloidal and limbic injury may also play a role.[12,13] Complex partial seizures, polytherapy, and past psychiatric disorders increase the risk of developing psychosis.[14]

Antiepileptics can also cause psychosis.[15] Patients administered phenytoin have a high risk of developing psychosis.[16] Although new drugs have better safety profiles, there may be a link between these agents and psychosis. Psychosis is also observed with the use of levetiracetam, topiramate, zonisamide, and felbamate.[4–6,17]

Postictal psychosis can trigger psychosis between 12 h and 1 week after the end of the seizure activity. Audio-visual hallucinations, delusions, paranoia, aggression, mania, depression, and psychotic episodes may develop.[18] Our patient had visual hallucinations and delusions that developed 2 days after her last seizure, suggesting postictal psychosis. However, she had no risk factors for psychosis, such as psychiatric disorder or substance use. Moreover, she had not had any psychotic episodes during combined antiepileptic therapy for many years. Because the visual hallucinations and agitation disappeared 4 days after discontinuing the LCM, drug-induced psychosis was considered the most like etiology in our patient.

Intensive care-related delirium (ICRD) must be differentiated from psychotic conditions. Patients with ICRD typically have no history of major psychiatric illnesses and the onset of the delirium is acute or subacute, as in our patient. However, our patient's hallucinations did not fluctuate, her memory and orientation were not impaired, and her consciousness was normal. Therefore, we considered LCM-induced psychosis the most likely diagnosis. Non-convulsive status epilepticus (NCSE) also has similar clinical features and should be considered in the differential diagnosis. However, our patient's EEG was normal after the psychotic episode, so the diagnosis of NCSE was eliminated.

LCM has absolute bioavailability, binds to plasma proteins at a low rate, and is excreted renally. It has fewer drug interactions than older antiepileptics and a relatively long half-life.[19] The most common side effects of LCM are dizziness, nausea, vomiting, headache, nystagmus, diplopia, and ataxia.[2] Depression and a confused state may also be seen, while psychosis and hallucinations have been seen only in a few cases since FDA approval of the drug.[7,8] Our case is the first report of LCM-induced psychosis in Turkey.

Because it blocks sodium channels, LCM can act as a mood stabilizer and has sedative effects. However, compared with other antiepileptics, it has a lower sedative effect and causes less cognitive impairment and depression.[20,21] In animal experiments, at doses of 800 mg, potential effects of LCM on schizophrenia and anxiety were demonstrated.[22] By contrast, our patient developed psychosis with LCM treatment. The mechanism of the LCM-induced psychosis is not known. Slow inactivation of sodium channels or poor drug metabolism (given her history of sleeve gastrectomy) may have been the cause.

In literature cases of LCM-induced psychosis, when the symptoms developed, the drug was discontinued and antipsychotics were started.[7,8] It is not clear whether the clinical improvement in these patients was due to discontinuing the LCM or starting antipsychotics. In our patient, only LCM was discontinued; no additional antipsychotics were added. After discontinuing the LCM, our patient recovered completely. Therefore, clinicians should be aware that psychotic episodes may be associated with the use of LCM. Further research is needed to explain the mechanism and underlying pathophysiology of this phenomenon.

**Informed Consent–** Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

**Peer-review–** Externally peer-reviewed.

**Authorship Contributions–** Concept: S.K.G., S.D., E.T.İ., T.Y.; Design: S.K.G.; Supervision: T.Y.; Data collection &/or processing: S.K.G., S.D., E.T.İ., T.Y.; Analysis and/or interpretation: S.K.G.; Literature search: S.D., E.T.İ.; Writing: S.K.G.; Critical review: T.Y.

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