

Levetiracetam induced hypomania: a case report

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Abstract: Levetiracetam (LEV) is a newer second-generation antiepileptic drug that is found to be effective in tonic-clonic seizures, partial onset seizures, and myoclonic seizures. Among antiepileptic drugs, LEV is usually known for fewer adverse drug reactions. Psychiatric disorders after the administration of LEV have been reported in the literature. There are many case reports on LEV-induced psychosis, but there are only three case reports of mania induced by LEV use. In this report, we present a case with no history of psychiatric disorder who had a hypomania episode after receiving LEV for epilepsy treatment. The development of manic symptoms with LEV therapy is unusual. Clinicians should consider monitoring patients closely for treatment-related psychological symptoms and psychotic symptoms, including the possibility of mania.

Keywords: drug-induced bipolar disorder, hypomania, levetiracetam, mania

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Introduction

Levetiracetam (LEV) is a newer second-generation antiepileptic drug that is found to be effective in tonic-clonic seizures, partial onset seizures, and myoclonic seizures. Among antiepileptic drugs, LEV is usually known for fewer adverse drug reactions.¹ Unlike other antiepileptic drugs, 'the mechanisms of action of LEV appear to involve neuronal binding to synaptic vesicle protein 2A, inhibiting calcium release from intraneuronal stores, opposing the activity of negative modulators of GABA and glycine-gated currents and inhibiting excessive synchronized activity between neurons, in addition, LEV inhibits N-type calcium channels'.² Although some case reports and open-label trials have claimed anti-manic effectivity of LEV,^{3–5} the literature on the antimanic efficacy of LEV is lacking and controversial,⁶ unlike other antiepileptics. Among patients using LEV, 12.7% are reported to have adverse psychological effects such as affective disorder, aggressive behavior, emotion lability agitation, anger, and hostile behavior.⁷ There are many case reports on LEV-induced psychosis, but there are only three case reports of mania induced by LEV use.^{8–13}

In this report, we present a case with no history of psychiatric disorder who had a hypomania episode after receiving LEV for epilepsy treatment. Ethical approval is not required at our Institution for case reports. In addition, written consent was obtained from the patient.

Case report

A 52-year-old male, married, graduated from primary school, with two children, working as a construction worker, had been diagnosed with generalized tonic-clonic epilepsy at 4 years old. The patient was diagnosed with status epilepticus due to a long-lasting seizure, and was referred to our hospital intensive care unit from the emergency department of another hospital. The patient was referred to the neurology outpatient clinic from the intensive care unit. Before discharge, the patient was referred to psychiatry with the symptoms of loud and abusive speech, agitation, and refusal of treatment.

The patient stated that he had no psychiatric complaints. According to the information received from the patient, he had been speaking loudly

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recently, and his family had often warned him about this.

According to the information received from his daughter, he had been receiving 300 mg phenytoin per day for epilepsy. Due to the increase in seizure frequency, LEV was initiated at 500 mg twice daily, and had been titrated to 1500 mg per day 2 months previously. Despite having no psychiatric complaints and psychiatric admissions before, complaints such as irritation, decreased need of sleep, increased energy, loud speech, and excessive, abusive speech began 2 weeks after the LEV was titrated to 1500 mg per day. In this period, the patient bought a television although his family did not need it.

In the mental status examination, he was oriented and cooperative. His attention was distractible. He was speaking loudly, and his thoughts were fast and reached his goals. His mood was irritable and had labile affect. He did not have any delusions or hallucinations.

His Young Mania Rating Score (YMRS) was estimated as 18. Magnetic Resonance Imaging did not reveal any specific abnormalities of the brain. He was diagnosed with medication-induced bipolar disorder. LEV was discontinued and olanzapine 5 mg/day treatment was initiated.

On his follow up on the 3rd day, he was on olanzapine 5 mg/day and LEV 1000 mg/day. His daughter reported that he was sleeping better and he was not as talkative as he had been 3 days before. On this follow up, his YMRS was estimated as 14.

He was discharged on the 5th day, and on his follow up on the 2nd week, his daughter mentioned that LEV had stopped 1 week before and her father was nearly the same as he used to be. He was not using abusive words, he was sleeping better, and his energy had returned to normal. On this follow up, YMRS was found to be 4 and olanzapine was discontinued. A causality assessment was carried out using the Naranjo ADR probability scale.¹⁴ The Naranjo score was found to be 4, which showed a 'possible' causality.

Discussion

Although LEV had exhibited additional anti-manic effects on an open on-off-on add-on

study,⁵ in our case, paradoxically, it induced hypomania. Although Desarkar and colleagues presented the first case report that showed the safety and efficacy of add-on LEV in an adolescent with acute mania,³ a randomized open-label study comparing adjunctive LEV with standard treatment with valproate on acute mania revealed that adjunctive LEV did not point to a better or faster recovery of manic symptoms when combined with valproate.⁶ Goldberg and Burdick reported a patient with acute mania who stabilized with open-label LEV monotherapy and recurred after drug cessation.⁴ Studies suggest that LEV, an antiepileptic with known neuropsychiatric side effects, may have short duration antimanic effects in adults and elderly patients diagnosed with bipolar disorder.^{5,15} To the best of our knowledge, there are three reported cases of LEV-induced mania,^{9,10,16} and one of LEV-induced mania-like symptoms,¹⁷ in the literature. Although not published, the European ADR Database has 32 case reports of mania following LEV treatment.¹⁸ Our case is the first reported case of LEV-induced hypomania. It would have been the fourth published case with mania if we had not become aware of the psychiatric adverse effects so early on.

Psychiatric disorders after the administration of LEV have been reported in the past. The prevalence rates of LEV-induced psychosis range from less than 1% to 1.4%.^{19,20} Mula and others reported certain risk factors, including a history of febrile convulsions, status epilepticus, previous psychiatric history, and lamotrigine therapy.^{7,20} Our patient did not provide any history of pre-existing psychotic disorder or family history of a pre-existing psychotic disorder.

The development of manic symptoms with LEV therapy is unusual because LEV is shown to be effective in mood-stabilization in an animal model of mania.²¹ It has been proposed that multiple effects of LEV on neurons may lead to behavioral disorders, including manic symptoms.¹⁰ In a review, antiepileptic drug-induced mania was classified as being: due to a toxic effect of the drug; in the context of postictal psychopathology; and as due to the forced normalization phenomenon. The first category is completely different from the other two, because the toxic effect itself causes drug-induced secondary mania, whereas the other categories are related with the pathophysiology of epilepsy itself.²²

The incidence of severe aggressiveness as an adverse effect in the course of LEV treatment is reported as being approximately 3.5%.²³ In a prospective study of 553 patients treated with LEV, behavioral abnormalities were the most common cause of premature drug withdrawal. Known risk factors for the development of behavioral disorders with LEV include rapid dosage titration, having a learning disability, having a history of psychiatric disorder, and the presence of generalized epilepsy.²⁴ In our case, the presence of generalized epilepsy may have contributed to symptomatology.

Treatment with olanzapine was initiated until LEV was stopped to appease the manic symptoms. Moreover, as in previous reports, our patient recovered after withdrawal of the drug.^{9,25}

Clinicians should consider monitoring patients closely for treatment-related psychological symptoms and psychotic symptoms, including the possibility of mania. Besides, it is suggested that slower titration rates of LEV should be considered, especially in patients with previous psychiatric history.⁹

Behavioral effects of LEV, especially those involving mood, should be carefully noted. Manic symptoms represent a rare treatment-emergent adverse effect of LEV, but may seriously complicate management of the psychiatric disorders of epilepsy.²² Patients receiving LEV should be clinically monitored in terms of severe psychiatric conditions.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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