SEIZURE DISORDER WITH LEVETIRACETAM INDUCED PSYCHOSIS - A CASE REPORT

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ABSTRACT
Epilepsy is the most common serious neurological disorder and is one of the most prevalent non-communicable diseases in the world. Levetiracetam (LEV) is a broad-spectrum antiepileptic drug (AED) that has been shown to be effective for a variety of seizure types in adults and children. We report a child with epilepsy during LEV therapy, developed dose dependent acute psychosis aggravated by another AED tablet Lacosamide.

KEYWORDS: Epilepsy, Antiepileptic drug, Levetiracetam, Lacosamide, adverse effects, acute psychosis.

INTRODUCTION
Epilepsy or Seizures can occur as an adverse effect of a large number of drugs from different pharmacological categories. There is no characteristic clinical features differentiate drug-induced seizures from idiopathic epileptic seizures. The usage of drugs known to cause seizures should be avoided in patients with predisposition to seizures. In developing countries, most drug induced seizures resolve after discontinuation of the offending drugs, but some patients require supplementary treatment. Further, intravenous diazepam is the commonly used agent for the control of drug induced epilepsy.[1,2,3]
Standard antiepileptic drugs (AEDs) are sometimes associated with intolerable adverse effects and drug interactions. Furthermore, up to 30% of patients do not achieve seizure control with conventional therapies. Levetiracetam (LEV) is a broad-spectrum antiepileptic that has been shown to be effective for a variety of seizure types in adults and children. LEV also inhibits N-type calcium channels the psychotic symptom, hallucination appeared at the dosage of 2250 mg of LEV which was not seen with the dose of 1500 mg.

LEV is approved for adjunctive therapy for adults with partial, myoclonic and generalized tonic clonic seizures (GTCS), myoclonic seizures in patients with juvenile myoclonic epilepsy, patients with GTCS in the setting of idiopathic generalized epilepsy. Based on lack of data, LEV would not be an appropriate initial therapy for absence seizures or an early adjunctive agent for refractory absence seizures. Patients receiving LEV also reported a slightly higher incidence of symptoms of upper respiratory infection, somnolence, convulsion, dizziness, asthenia, headache, ataxia, diplopia, dysarthria, fatigue, light-headedness, nystagmus, paresthesias and tremor. During long term treatment, there was a slightly higher incidence of psychiatric side effects included irritability, aggression, anger and hostility, and hallucinations. It would be wise to observe patients for these side effects especially if prone to psychiatric disorders.

Lacosamide (LCS) is a new adjunctive drug licensed for the treatment of focal seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older. In the open-label extension trials, serious adverse events occurred in 3%–7% in the placebo group, 3%–9% in the lacosamide 200 mg/day group, 5%–10% in the lacosamide 400 mg/day group, and 3%–10% in the lacosamide 600 mg/day group. The serious adverse events seen in more than one patient were: worsening of seizures, psychotic disorders, dizziness, vomiting, accident, and nystagmus.

Discontinuation rates due to adverse events also appeared to be related to dose. Other serious AEs were not always specified in clinical studies. Some study reported, neurologic (AEs) were aggravated convulsions, dizziness, nystagmus and psychotic disorders. Other reported serious AEs were appendicitis, breast cancer, cerebrovascular accident, dehydration, gastroenteritis, intervertebral disc protrusion, liver disorder, nausea, shock hypoglycemic, thrombophlebitis and vomiting. Possible mechanisms underlying behavioral disorders are idiosyncratic dose-unrelated drug effects, significantly increased by antiepileptic drugs, and alternative psychoses (or behavioral disturbances) associated with the phenomenon of forced
normalization process. Now we presented a case report that demonstrated that drug induced psychosis with LEV for epilepsy.

CASE REPORT
A 13 year old, 54 kg school going girl presented with the complaints of difficulty in holding and dropping objects and frequent dumping in right upper limb complaints of mild jerk in right upper limb without alteration in her consciousness for few weeks. Initially, she was diagnosed as a case of muscle weakness by a pediatrician. He advised calcium syrup and some vitamins. She did not have past history of any significant head injury, CNS infection, psychotic disorder including problematic substance use. After two months, the epilepsy spells were occurring frequently with headache thrice in a month converted into 2 - 3 times in a week. Again she was consulted with a neurophysician where CT scan showed intraventricular arachnoid cyst but there is no mass effect/ hydrocephalus. Neurosurgeon opinion obtained and she did not require any surgical intervention for the arachnoid cyst and prescribed with T. flunarizine 5mg once in a day. The jerk movements were not controlled thereby the frequency and the number of shaking movements was increased from about three times in a month to about 7 to 8 times per week and whenever she got tensed up. Five months later, she developed an episode of Generalised Tonic Clonic Seizure (GTCS) for which she was treated with T. Clobazam 5mg and T. Levitiracetam 500mg twice a day and T. Oxcarbazepine 150mg at bed time. Following which the GTCS controlled, but the focal seizures on the right side were not controlled. Further treatment continued with T. Levitiracetam 500mg twice daily and T. Oxcarbazepine 150mg added at night for 3 weeks. Electro Encephalogram (EEG) showed abnormal s/o epileptiform activity possible as absence seizure.

The seizures on the right side were not controlled. So after fifteen days, she was given T. Levitiracetam 500mg twice daily, and the dose of T. Oxcarbazepine was increased and she was put on T. Oxcarbazepine 300mg at bed time. After 15 days, she was developed behavioural problems include aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional liability, hostility and irritability. Some illusion oriented psychosis identified lead to unfaithness on parents and she assumed that her parents going to be killed her and repeatedly moaning that her death may be due to her parents.

Again focal seizures and behavioral abnormalities were increased for next 3 months. EEG showed grossly abnormal s/o epileptiform activity. Her visual acuity in both eyes and fundus examination were normal (6/6). Further, she was prescribed T. Levitiracetam 500mg twice
daily and the dose of T. Oxcarbazepine was increased from 300mg to 450mg at bed time. T. Lacosamid 50mg and T. Clobazam 10mg twice daily was added for seven days. The focal seizures were not controlled. So the T. Levitiracetam dose was increased and she was put on T. Levitiracetam 1g at night for 3 weeks with morning dose 500mg (1500mg/day) with T. Lacosamid and clobazam. The seizures were not controlled even after increasing the dose of LEV, but after 4 days, she again started to have repeated focal seizures involving right arm and prolonged episodes of drowsiness and confusion. Suddenly one evening she developed hallucination, delusion and illusion changes along with suicidal tendencies. She continuously asked to her family members about ideas for suicidal attempts. She had tried with drinking shampoo, mosquito repellent liquid and pricked with insulin syringe once in her hand attempt to injecting air in her vein and showing to her sister.

Her acoustic and visual hallucinations symptoms became worsened, after increasing the dose of LEV with lacosamide. Sometimes she experienced that somebody calling her name and crying in her ear, and she had felt somebody always along with her. The sound was high volume, continuous and painful. It was so intolerable. At the time she used to kept mobile ear phone in her ears and listen the songs with high volume. But again she heard the acoustic hallucination within a minute.

Parents unsatisfied with the physician they consulted another neurophysician. She referred to a psychiatrist by the neurophysician and she was admitted and diagnosed as epilepsy with acute psychosis. The next day she showed aggressive tendencies toward the parents and nurses and tried to leave the hospital. She was prescribed antipsychotic drug T. Iloperidone 2mg at morning and 4mg at night and T. Nitrazepam 10mg at bedtime along with prescribed AED.

The focal seizures were not controlled and psychosis symptoms increased. Hence T. Clonazepam (MD) 0.5mg at morning, 1mg at night for 1 month was added. The dose of T. Clobazam was increased and she was put on T. Clobazam 10mg morning and night, 5mg at afternoon, along with Levitiracetam (1500mg/day) and T. Lacosamid 50mg was continued for 1 month. She was taken to neurophysician outpatient department for the same complaints again and again, she was advised to continue the same treatment. The girl was in severe somnolence and asthenia. After one month, the girl developed GTCS during her deep sleep, T. Clonazepam 2mg at bedtime was added with other drugs and T. clobazam MD 10mg was
given whenever necessary. Her psychosis complaints and frequency of partial seizures were increased.

Her hallucination and illusion symptoms were increased. The girl was suffered by severe sedative effects, aggression, hyperirritability and agitation, later leading to apathy and severe depression. She had felt worthlessness of living, guilty of giving trouble to family members and she felt nobody was there for her. She was consoled by her parents and her family members at maximum. Further she depicted for consultation in the superspeciality hospital where the dose of T. levitiracetam was decreased and T. lacosamide was stopped. On the same day, she developed GTCS at 12am, followed which the patient went in for apnoea, and was revived in home by the experienced nurse. Her mother noticed that the girl was on unconscious state. There was no previous history of other sleep related problems. She was put on observation after admission to a hospital. The abovesaid episode was occurring once again while taking video EEG.

During the night and next 14 hours, there were episodes of vigorous seizures and a total of five episodes occurred, for which she was treated with IV inj. Divolproex sodium 1000mg stat. in 100ml of normal saline over 20 minutes and IV Inj. Lorazepam 2mg stat. T. Divaloprex sodium 500mg three times in a day and Tab. Zonisamide 50mg once daily was added. On the same day evening, she calmed down, regained orientation and insight into her illness. The girl was normal after started to reducing LEV and discontinuation of lacosamide, thereby her psychosis complaints were completely disappeared and was almost absent within a day. Physical examination was unremarkable and laboratory results including urinalysis, complete blood count, serum electrolytes, liver function renal function tests were within normal limits. Cerebrospinal fluid (CSF) sent for neuroleptic virus panel analysis to rule out autoimmune diseases. Antibodies to all the receptors were negative. MRI Brain with contrast showed well circumbrised cyst within atrium and occipital horn of the left ventricle, exactly medially upto the midline and no solid component. Mild 2 hyper intense signal within the hippocampus-probably postictal were observed.

Advice on dehospitalization after six days, T. locasamide discontinued; the dose of T. Levitiracetam was decreased by tapering. She was put on T. Levitiracetam 250mg twice a day, T. Zonisamide 50mg twice daily and T. Divaloprex sodium 500mg thrice daily. T. Clonazepam 1mg, T. Iloperidone 2mg and T. Clobazam 20mg at bed time were continued.
Now she become seizure free, T. Lacosamide stopped and T. Levitiracetam tapered and completely stopped.

DISCUSSION
In our case, data suggest that there is some tie between LEV, lacosamide and psychosis side effects. Also vivid improvements were seeing after reducing the LEV dose and discontinuation of lacosamide. One study mentioned patients who discontinued LEV because of behavioural adverse events were more likely to have symptomatic generalized epilepsy, history of psychiatric diagnosis, and a faster LEV titration.\textsuperscript{[6]} In this case, physician had changed the LEV dose after six months. Even after increasing the dose LEV up to 1500mg (titration phase), and added another AED lacosamide the girl was not seizure free, she was developed increase in seizure frequency and duration and severe acute psychosis. Finally she was developed GCTS. Several evidences were found for neurologic adverse effects leads to aggravated convulsions, dizziness, nystagmus and psychotic disorders with lacosamide.\footnote{[11]}

In this case, the girl was in severe somnolence and asthenia on LEV treatment period. As per history, it can be assumed that child had LEV-induced adverse effects auditory and visual hallucinations in her titration phase aggravated after initiating of Lacosamide. In pre-marketing studies of LEV, up to 13\% of patients have experienced adverse neuropsychiatric symptoms. About 1\% of pediatric or adult patients have experienced serious neuropsychiatric symptoms including hallucinations, suicidal ideations, or psychosis, after beginning LEV.\textsuperscript{[7,12]} Our case report also supported the same. Study in rodent models were determined combination of Lacosamide with levetiracetam or carbamazepine at fixed ratios of 1:3, 1:1, and 3:1 exerted synergistic interactions, while combinations with other AEDs produced additive or synergistic interactions depending on different fixed ratios.\textsuperscript{[13]} In our study this aggravated psychosis might be due to synergetic effect (produce a combined effect greater than the sum of their separate effects) of these two drug combination.

The most commonly reported adverse effects during clinical trials with LEV in adults were first and foremost related to the CNS and included somnolence, asthenia, headache, infection, dizziness and ataxia.\textsuperscript{[14]} One study showed in the pooled analysis, there was no evidence of a dose dependent relation within the recommended dose range of 1000–3000 mg/day.\textsuperscript{[15]} In our study, initially she had all the CNS side effects with mild behavioural symptoms, the psychosis symptoms with increased suicidal ideation were started after increasing the dose of LEV from 1000 mg to 1500 mg and initiating the lacosamide.
The official prescribing information recommends starting at 20 mg/kg/day in 2 divided doses, with subsequent increments of 20 mg/kg every 2 weeks up to 60 mg/kg/day. However, starting at 10 mg/kg may reduce the frequency or intensity of behavioural adverse effects and provide a greater opportunity to manage these adverse effects rather than stop LEV.[6,16,17]

Another study with four children with the acute onset of psychosis (delusions or auditory/visual hallucinations) within 2 days to 3 months after initiation of LEV for resistant epilepsy was reported. Some data revealed that certain risk factors for the development of psychosis are a history of febrile convulsions, status epilepticus or previous psychiatric history, or lamotrigine cotherapy.[7] But, this case presented was no relevant history except family history of epilepsy. So, this girl report was also confirmed LEV induced psychosis occurs even in its therapeutic dose range might be aggravate by lacosamide.

Another study revealed with a 20 year old man who developed acute psychotic symptoms with the dose of 1500mg after a month of LEV therapy. And patient reported improvement in symptoms by the 2nd day and was asymptomatic by the 7th day at the dose of LEV 1000mg per day. Most likely, in this case, the psychosis as a side effect was a dose-related phenomenon similar of our case report. Although there is evidence that the drug may trigger behavioural disorders, there are reports that it may reduce hyperactivity, impulsivity, mood instability and aggression in autistic children.[18]

A paradoxical increase in seizures was noted at times with LEV therapy, usually at elevated doses. Studies showed the increase in seizure incidence, worsening of seizures, poor response and associated with more side effects were generally seen early in the titration phase and most likely in mentally retarded patients.[6] In this case, remarkable improvement in her state of psychosis by discontinuation of lacosamide and reducing the dose of LEV and switching over to T. sodium valproate and T. zonosamide was observed. This case report, from the history recurrence of seizure and acute psychosis were a dose related phenomenon. Clinicians call for to be aware of this possible complication associated with LEV and lacosamide. Because in this case time taken for adjusting the LEV around six months, the girl suffered with increased frequency of seizures, aggressive psychosis and she losses her study period for nine months. That period was distressed to the child and her family members.
CONCLUSION
This case report revealed that drug induced psychosis is (not only) one of the dose dependent side effect of LEV and psychosis symptoms might aggravate by adding another AED lacosamide. The early diagnosis by close clinical monitoring with regard to psychiatric adverse events and early treatment intervention is necessary. Further studies are needed to analyze the adverse effects of LEV and lacosamide in multi-centric large group of patients. Hence, this case report indicates that though rare, hallucination does arise as a treatment emergent adverse event with combination therapy of LEV and Lacosamide. And, this certainty wants to be kept in mind while using it. When required, discontinuation of LEV produced truthful resolution.

REFERENCES


