The Missing Link Between Opioid Use Disorder and Seizures During Opioid Withdrawal: A Case Series from North India

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The term "opioids" includes compounds extracted from the poppy plant/pod and semi-synthetic and synthetic compounds with similar properties that can interact with opioid receptors in the brain.[1] These produce mental relaxation, pain relief, and euphoric feelings.[2] Their regular use, abuse, and misuse, often without medical supervision, can lead to opioid dependence and other health problems.

Almost 2.1% of the Indian population uses opioids. The pattern of use varies across different states of India. While the use of inhalational opioid (smack/brown sugar) is much more common in Uttar Pradesh, that of injectable heroin is more common in Punjab and the northeastern states. Percentage-wise, the states of Mizoram and Nagaland are the worst affected by opioid use.[3] The prevalence of opioid use in Uttarakhand is 0.8%.[4] According to an article published in Times of India 2020, there was a record rise in synthetic-drug trafficking in Uttarakhand, especially in our catchment area of Dehradun and the neighboring areas of Rishikesh and Haridwar.[5]

Widespread available literature mentions opioid use disorder, intoxication, withdrawal, and other opioid-induced disorders, which include depressive disorder, anxiety disorder, sleep disorder, and sexual dysfunction. However, information is scanty on seizure episodes happening during opioid intake or withdrawal. Few studies have described complicated opioid withdrawal where a seizure occurred along with other features of opioid withdrawal.[6–8]

Here we report eight cases of opioid use disorder that presented to our emergency department with episodes of seizures after cessation of opioid use. We try to investigate the various possible etiologies of seizures in opioid withdrawal and compare them with available national and international literature.

Summary of the Cases

These cases presented to our emergency department with an episode of a sudden loss of consciousness, followed by stiffening and jerky movements of both the upper and lower limbs and frothing from the mouth. Some patients had tongue bites and fecal/urinary incontinence. Each episode lasted 1–2 min, and all the cases subsequently had an episode of confusion lasting 5–30 min. Based on the history obtained from patients/attendants, these episodes were classified as generalized tonic-clonic seizures (GTCS). All the cases were males aged between 21 and 45, with an episode of seizures in the 72 h before the presentation. The average number of seizures in them within the past 6 months was three. The patients were given the initial management in the emergency (midazolam 1–10 mg intravenous/ deep intramuscular, as per our casualty protocol). Then, on detailed history and examination,

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TABLE 1.

Patient Data with Variables.

Age of Patient (in Years)	Type of Opioid Used	Duration of Opioid Dependence	Approximate Smack Consumption per Day (in Rupees)	Last Intake of Substance Before Seizure (Days)	Last Episode of Seizure	Number of Episodes of Seizure (in Last 6 Months)	Drug of Abuse Test (DOA-6) Positive Substances
24	Smack	12 months	1000–1200	3	24 h	3	Morphine + barbiturates
23	Smack	36 months	3000	2	24 h	1	Morphine
21	Smack	8 months	2000	2	24 h	6	Morphine
26	Smack	12 months	6000	4	72 h	3	Morphine + benzodiazepines
32	Smack	8 years	5000	2	24 h	6	Morphine
30	Smack	12 months	5000	2	2 h	2	Morphine + benzodiazepines
45	smack	7 years	3000	3	2 h	2	Morphine +barbiturates + benzodiazepines
23	smack	3 year	1000	2	1 h	1	Morphine

these patients were detected to be taking smack, an adulterated form of heroin,[10] for the past 8 months to 8 years, in the dependent pattern. Other clinical details of these cases are in **Table 1**.

In all the cases, the last intake of smack was a minimum of two or more days before the seizure. Most patients/attendants could also recall a similar cessation or decrease in the usual amount of intake of opioids for a minimum of 48–72 h before the onset of the past episodes of seizures.

There was no history of taking medications like buprenorphine, dextropropoxyphene, naloxone, or naltrexone. There was no history of dependence on any other substances like alcohol, sedative-hypnotic or anxiolytics, cannabis, or inhalants. No other significant family history of any medical, surgical, or psychiatric illness was reported in these cases. Some have had an episode of seizure in the past and had been evaluated for independent/idiopathic seizure by their treating physician. However, no definitive cause could be ascribed, as per the attendants/available records. Hence the possibility of other causes of seizure disorder was ruled out. These patients were also having a backache, nausea, goosebumps, repetitive yawning, and a feeling of cold. There was no focal deficit, abnormal gait, dysarthria, or any other neurological sign. There was no history of fever, cranial trauma, or other related symptoms. Neurological and other systemic examinations, hematological and biochemical parameters, blood sugar, liver and renal function tests, C-reactive protein, chest X-ray, and electrocardiogram were normal. Screening tests for HIV and hepatitis B and C were negative. MRI of the brain was normal. Electroencephalogram (EEG, 16 channel) was normal in five patients; in the other three, it showed generalized spikes/sharp waves. The urine Drug of Abuse test (DOA-6) (by abonpharma, for six drugs: morphine, benzodiazepines, barbiturates, cannabis products, cocaine, and amphetamine) was positive for morphine in all eight patients. (Sample for DOA-6 was taken immediately after the patient was shifted to the psychiatry ward). Apart from morphine, two patients tested positive for benzodiazepines, one for barbiturates, while one had both benzodiazepines and barbiturates in the urine sample. However, the patients denied taking any substance other than smack. This points to the fact that benzodiazepines/barbiturates might have been mixed in the smack preparation to make it cheap and increase the quantity. Alternatively, since DOA-6 was conducted after the patients had received midazolam in the emergency, this might have contributed to benzodiazepines being positive in the urine sample. A diagnosis of seizure during opioid withdrawal was made for these cases.

After the initial symptomatic management, these patients were shifted to the psychiatry ward and started on opioid substitution therapy (OST): tablet buprenorphine 2 mg and Naloxone 0.5 mg combination in adequate doses. The OST was started at an adequate dose based on the severity of the clinical symptoms of opioid withdrawal, and the patients were also engaged in motivation-enhancement therapy. After 1–2 weeks, they were discharged. They have been in regular follow-up since then and maintaining well on buprenorphine/naloxone combination with no further episode of seizure reported. They did not report or show signs of any craving/ withdrawal during the follow-up visits. They underwent a DOA-6 test on every follow-up visit, which was negative. For all patients, the minimum follow-up period was three months.

Discussion

Seizure in opioid withdrawal is usually an uncommon presentation. However, in the last few years, the number of such cases has increased in Dehradun and the surrounding areas of Rishikesh and Haridwar. Similar cases have been found in other national and international studies (**Table 2**). Our findings are similar to theirs, as almost all our patients were aged between 21 and 45 and had an episode of seizure within 2–3 days of cessation of smack/opioid,

TABLE 2.

Review of Clinical Details of Our Cases in Context to Previously Published data.

	Parkar et al. 2006[16]	Khanra et al. 2014[7]	Jain et al. 2018[12]	Basnayake et al. 2018[8]	Panda et al. 2021[6]	Our Findings
Socio-demographic and clinical information	Seven patients aged between 20 and 38 years with opioid dependence. Total duration of intake of opioids, 2–6 years.	Case series of patients aged between 27 and 36 years having episodes of GTCS in 3–5 days of withdrawal phase.	Case report of 21-year-old with 3 years of opioid use having seizure episode 2 days after stopping opioid.	Case report of a 38-year-old male with heroin addiction for last 15 years and presenting with multiple seizure episodes.	Case report of a 16-year-old boy, with 6 episodes of seizures in 1 day, taking heroine for last 3 months.	Case series of patients aged between 21 and 45 years with opioid use from past 8 months to 8 years.
Symptoms at presentation	Seizure	Seizure	Seizure	Seizure	Seizure	Presented with Seizure within 72–24 h of opioid use
Treatment	Dextro-propoxyphene, benzodiazepines and haloperidol	Clonidine (average dosage 300μg/day tapered by 50μg/day) and benzodiazepines or haloperidol	Sodium valproate 1000mg/day, and clonazepam 1mg/day	Sodium valproate	Sodium valproate, clonazepam, haloperidol, methadone	Buprenorphine + naloxone

GTCS: Generalized tonic clonic seizures.

along with symptoms of opioid withdrawal. Unlike in those studies, we managed the patients with a combination of buprenorphine and naloxone in adequate doses, which relieved the opioid withdrawal symptoms, and there was no relapse of seizure episodes. On detailed examination and investigation, no neurological/ metabolic deficits could explain the seizure episode. So, our diagnosis of seizure related to opioid withdrawal was confirmed.

Detailed interviews with the patients revealed opioid use in a dependent pattern for many months. They have had previous episodes of seizures, which were also temporally correlated with cessation/decrease in the usual intake of opioids a minimum of 48–72 h before the seizure, for which they had visited a physician and were prescribed some antiepileptics, which none of them took. As per the previously available records, all the investigations (radiological/biochemical) were normal.

As the opioid preparation (smack) is bought from a local peddler at cheap rates, adulteration is possible.[6] Cheap alternatives like barbiturates, benzodiazepines, and ketamine can be obtained in the market and are usually mixed with a smack, to increase the quantity and reduce the price per gram. While the patient is using smack in a dependent pattern, along with opioids, unknowingly he also becomes dependent on barbiturates and benzodiazepines, and sudden cessation of all of these leads to withdrawal seizure.[10]

Our patients used the "chasing/ inhalational" method to intake smack. In this method, they place the smack powder on aluminium foil and burn it from below and start inhaling it when the smoke appears. Long-term inhalation of aluminium can lead to neurodegenerative changes, which may contribute to seizures.[11] Jain et al. reported episodes of seizure that occurred after opioid inhalation of aluminium foil, due to aluminium fumes/toxicity.[12] Similarly, a case report by Friesen et al. mentions an intravenous drug user who used to heat methadone on an aluminium-based utensil/pot and developed seizures after injection, with other signs of aluminium toxicity, and had raised serum aluminium levels.[13]

But unlike these studies, our patients had seizures only after 48–72 h of stopping opioids, and no evidence of neurodegenerative disorder or aluminium toxicity was found clinically or in investigations.

Chronic opioid use results in homeostatic adaptations throughout the brain's neural and glial-neuronal network and selective depression or an increase in electrical activity in different locations.[7] Changes in the excitability of a neural network are well-known to change the excitability of other neurons and synapses throughout the brain, because of various interconnections. The exact location and mechanism of neuroadaptation after opioid dependence are still unclear and need further research.[7]

Khanra et al. described the activation of noradrenergic neurons in locus ceruleus, mediated by excitatory amino-acid output, in opioid withdrawal.[7] Also, prolonged use of opioids modifies the spiny neurons in the nucleus accumbens, which are responsible for dopaminergic activity.

Most existing literature does not mention seizures that happen during opioid withdrawal. This often leads to the missing of this phenomenon or misdiagnosing it as an independent seizure or epilepsy disorder.[6,14]

After initiating OST, our patients did not report any further seizure episodes and did not require any anticonvulsants. This concords with Panda et al. and Basnayake et al. who reported only transient/no use of anticonvulsants for managing seizures in opioid withdrawal.[6,8]

Ambekar et al. mentioned the role of OST in preventing opioid withdrawal and relapse. However, we highlight its role in preventing seizures related to withdrawal.[15]

Conclusion

Our study highlights the uncommon phenomenon of seizure in opioid withdrawal, reported in patients with opioid use disorder, and explores the possible causes. A detailed history, followed

by proper systemic and neurological examination, should be done on all the patients. Investigations to establish the cause of the seizure, such as radiological and biochemical tests, including urine drug screening, should be done immediately. Once the diagnosis of opioid withdrawal seizure is established, appropriate treatment should be started.

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Informed Consent

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