

### Cases On Lorazepam Induced Delirium

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#### Abstract

Delirium is the most prevalent neurological complication in patients with advanced illnesses and substance abuse. It affects majority of the hospitalized patients and has a negative impact on all aspects of patient care. Lorazepam is the main stay of drug in the treatment of delirium, most commonly substance induced delirium.

We present you a compilation of 4 cases with varying diagnosis presenting across wide age group. All those patients were being treated for their underlying illnesses and Lorazepam was part of treatment profile. It was observed that within a day or two of initiating lorazepam, patient's consciousness, attention and orientation started fluctuating and they also showed psychotic features. Upon withdrawal of Lorazepam, their condition improved as they were well oriented to themselves and the surroundings. So, it was concluded that they had an adverse reaction to Lorazepam which is not commonly seen. Hence this is an effort to raise the awareness for complications like Lorazepam induced delirium.

#### Introduction

Lorazepam belongs to benzodiazepine group of drug which acts on the central nervous system(CNS) by binding to Gamma amino butyric acid (GABA)receptors. GABA is the major inhibitory neurotransmitter in the CNS and it acts by binding to GABA-A( GABA receptors type A) which are ligand gated chloride channel receptors located in the arousal and motor system neurons leading to CNS

depression by increasing the frequency of opening of chloride channels which causes hyper polarisation and in turn inhibits the propagation of action potential. Benzodiazepines is allosterically linked to GABA receptors and central benzodiazepine receptors contain alpha subunits which are found throughout the CNS leading to sedation, hypnosis, anxiolytics, muscle relaxation, psychomotor impairment and anticonvulsant effect. It also has inhibitory actions in the amygdala centered circuits along with similar actions in cerebral cortex. It is one of the most commonly used drug for sedation, control of aggression and in delirium associated with substance abuse. The commonly observed side effects of lorazepam are dizziness, in coordination, headache, blurred vision, forgetfulness, slurred speech, confusion among many others. We present to you a case series of four patients with varying diagnosis exhibiting delirium due to the use of lorazepam.

#### Case History

##### Case 1

A 55 year old married man came to our Out Patient Department (OPD) with complaints of grandiose behaviour, reduced sleep and aggressiveness since 10 days along with chronic alcohol use for the last 25 years. For the last 2 weeks he became extremely involved in the political campaign and he was getting his posters printed to be displayed all over the village. He would not spend any time with the family but socialize with the villagers and would

pay for everyone's drinks at the local bar. His behaviour was becoming more and more abusive verbally as well as physically. His sleep was reduced to only 2-3 hours/day. He was admitted in the ward and was prescribed Injectable Valproate 500 mg BD (Twice a day), Injectable Haloperidol 5 mg BD for 2 days. But he was still having difficulty in sleep and was also behaving aggressively, so he was started on Injectable Lorazepam 4 mg BD. On the next day it was observed that the patient was slightly disoriented and confused but his aggression and sleep has improved. Same treatment was continued but two days later his condition worsened and he was exhibiting features of delirium like he was not aware of his surroundings, he was having hallucinations which were visual in nature and fleeting in occurrence. He was getting agitated and would talk irrelevantly sometimes. As we could not explain these symptoms we decided to taper lorazepam which led to slight improvement and therefore we stopped lorazepam altogether. The patient was well oriented and aware of the surroundings and was maintained on the previous medication for the underlying illness.

#### **Case 2**

A 25 year old male came to OPD with complaints of cannabis use since 2-3 years and reduced sleep, agitation, suspiciousness for the last 4 to 5 days. He started smoking cannabis daily 4- 5 times a day and he was having paranoid ideation, became physically aggressive. He was sleeping only for 2-3 hours and was restless throughout the day. The patient was started on Tab. Divalproax Sodium 500 mg BD, Tab. Olanzapine 2.5 mg BD and Tab. Lorazepam 2mg BD. His agitation reduced but he was confused and talking irrelevantly. We continued same medication for another 2 days as these symptoms were thought to be due to prolonged cannabis use but he was still disoriented and unaware of his surrounding which was fluctuating in nature. So, we decided to taper lorazepam and we observed

that there was improvement in the delirium like symptoms. Hence, we stopped lorazepam as it was worsening his condition and he showed improvement within a day.

#### **Case 3**

A 40 year old married male patient came to the OPD in an intoxicated state exhibiting symptom like slurred speech, in coordination, reduced sleep with history of chronic alcohol use for the last 10 years. He was not able to maintain his job and was having financial difficulty as he spent all his money on procuring liquor. His behaviour also changed, he became aggressive and abusive towards his wife. His appetite was reduced and he would start drinking soon after waking up in the morning. After admission he had an episode of Generalised Tonic Clonic Convulsions (GTCS) marking the withdrawal state and he was started on I/V Lorazepam 4 mg BD and injectable Thiamine 100 mg TDS (Thrice a day). Next day we observed that patient is confused, agitated and disoriented which was thought to be Delirium Tremens due to alcohol withdrawal, therefore we continued Lorazepam. But his situation worsened as he was having visual hallucinations, increased aggression, he was restless and would utter incomprehensible words. The symptoms were frequent but fluctuating in nature and so we tapered lorazepam as his condition was not improving. There was some improvement in his orientation and awareness and so we stopped lorazepam which led to significant improvement.

#### **Case 4**

A 43 year old male came to the OPD in intoxicated state with history of chronic alcohol use for the last 20 years. He was unemployed as he couldn't hold any job due to his drinking habit which made him financially unstable. He would have multiple arguments with his family members as he was not paying any attention to their needs and well-being. His appetite and sleep pattern was altered. He was admitted in ward and was started on IV Lorazepam and

Injectable Thiamine. The medication was continued for 2 days during which patient's sleep and appetite improved but on the third day it was noticed he was disoriented, confused and slightly agitated which was thought to be due to withdrawal. Therefore, IV Lorazepam was continued on the 3<sup>rd</sup> day too, but he continued to show signs of fluctuating awareness and orientation. So, Lorazepam was discontinued which resulted in improvement in patient's attention and awareness of surrounding and himself.

**Table 1:** Diagnosis, dosage and investigations

Case	Age	Sex	Diagnosis	Lorazepam		Investigations (CBC, RBS, S. Electrolytes, RFT, LFT)
				Dose	Route	
1	55	M	BMD-I with Alcohol use disorder	8 mg in two divided dose for 3 days	I/V	Within normal limit
2	25	M	Cannabis use disorder with psychosis	4 mg in two divided dose for 2 days	Oral	Within normal limit
3	40	M	Alcohol use disorder	8 mg in two divided dose for 3 days	I/V	Within normal limit
4	43	M	Alcohol use disorder	8 mg in two divided dose for 3 days	I/V	Within normal limit

CBC – Complete Blood Count, RBS – Random Blood Sugar

RFT – Renal Function Test, LFT – Liver Function Test

### Discussion

Delirium as a side effect of lorazepam with short term use has not been frequently reported. There has been a randomized study in a hospital, Lorazepam-induced delirium Pinar Cetinay Aydin et al<sup>[1]</sup> showing 3.1% of patients had delirium due to use of Lorazepam. This was the only study reporting such a side effect with the use of Lorazepam. The dose ranged from 6 to 8 mg which is less than the recommended dose and the route of administration was intravenous.

Another study describing delirium as a side effect due to benzodiazepine use in critically ill/ICU patients/ post-operative patients. Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit

Patients Pratik Pandharipande et al<sup>[2]</sup> which is the first to show the independent and temporal role of sedatives and analgesics in contributing to patients' transition to delirium. They observed that a right balance of sedatives and analgesics is important to achieve patients comfort and it was seen that amongst all Lorazepam has the highest risk potential of causing delirium in such patients.

Lorazepam is a benzodiazepine derivative which has sedative and anti anxiety effects by acting on the central nervous system. The calming effect is due to its action on Limbic system, thalamus and hypothalamus. Its mechanism of action is related to GABA which is inhibitory in nature and all benzodiazepines increase the inhibitory activity by binding to GABA receptor. The onset and duration of action is slower after single dose of lorazepam as it takes more time to enter and leave the brain and hence it takes longer for the effects to subside.<sup>[3]</sup>

Cognitive impairments are more common with high doses and/or long-term use of BZDs, but can also be caused by low doses, short-term use and even single daily doses. The paradoxical reaction with Benzodiazepines such as disinhibition, aggression, impulsivity etc. is due to Pre Frontal Cortex inhibition and systemic serotonin inhibition. The risk factors for paradoxical reaction are Substance Use Disorders, Neurocognitive Disorders, history of impulsivity/disinhibition, anxiety disorders, older age, learning disability.<sup>[4]</sup> However, the risk/benefit ratio of using benzodiazepines varies in every case and their rapid action and efficacy can become a liability.

Among these 4 cases, the use of Lorazepam led to the development of delirium. The patients showing this effect had various underlying psychiatric disorders such as Bipolar Mood Disorder, Psychosis and Substance use disorder and they belonged to different age groups ranging from 25 to 55 years. The average dose of Lorazepam was 6 to 8 mg/day in divided doses administered intravenously

and orally in one case. The drug-drug interaction of lorazepam with the other medications prescribed in each of these cases is significant for increase in sedation and among the antipsychotics such as Haloperidol and Olanzapine is increased risk of extra pyramidal symptoms (EPS), QTc prolongation and sedation. Although we did not observe any of the aforementioned issues in these 4 cases.

There was no medical/surgical illness, laboratory finding or drug interactions predisposing the patient hence no substantial reason for the delirious behaviour was found and Lorazepam was stopped which resulted in improvement. Most of the previous studies indicated use of Lorazepam in post surgical or ICU patients led to delirium but there are no studies in substance related withdrawal.<sup>[5]</sup> Therefore we would like to bring attention to the fact to recognize delirium as a side effect with use of lorazepam in substance related and non substance related cases.

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