Adjuvant Trazodone for Management of Protracted Delirium Tremens

Sir,

Delirium tremens (DT) is a serious complication of alcohol withdrawal and without proper treatment, can lead to mortality in up to 20% of the patients.[1] DT usually starts around 48–72 hours after the last drink and subsides within a week.[1] A small proportion of patients can have protracted DT, with delirium lasting for more than 10 days.[2] When such a case is further complicated by a poor response to benzodiazepines (BZDs), the first-line drugs for DT, it poses a significant management challenge. Most of the studies in the past have used barbiturates, propofol, or antiepileptics in the management of protracted DT. However, these agents can lead to significant side effects. Trazodone, which is an alpha-1 receptor antagonist, 5-HT2A antagonist, and a sedative at lower doses, has not been tried for management of DT in the literature. In this case report, we present the successful management of a patient with alcohol dependence who developed protracted DT and had only a partial response to BZDs but responded to trazodone.

Case Summary

A 22-year-old married male visited our hospital with a history of alcohol use for eight years and daily drinking for the past four years in a dependent pattern. There was no history of complicated withdrawals either in the past or in the family. The patient had nicotine dependence but did not use any other psychoactive substances. In the past year, he had been consuming 3–4 bottles of local liquor per day. Due to the high dose of alcohol, and an inability to abstain on outpatient treatment, he was admitted. He had consumed alcohol about 7 hours before the admission.

Physical examination revealed bruises on the forehead due to physical fights under intoxication two days before admission. However, there was no history of ENT bleed/loss of consciousness/seizures following the fight. There were no other major findings on physical examination.

After admission, his withdrawals were monitored using the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) scale. The baseline CIWA-Ar score on the first day was 11. At admission, he had moderate tremors in both hands when he held his arms extended. The other alcohol withdrawal symptoms at the time of admission were mild anxiety, nausea, increased pulse rate (128/min), and headache. He was oriented to time, place, and person. Based on the CIWA-Ar score monitoring, he was administered 25 mg of diazepam orally on the first day. On the second day, he had disorientation to time lasting for one hour and required 90 mg of diazepam orally. On the third day, his symptoms improved, with no disorientation, and the same dose of diazepam was continued orally. However, on the fourth day, he again had disorientation, visual hallucinations, and delusion of persecution, lasting for about 12 hours. As his liver function test was deranged (total bilirubin: 2.99; aspartate aminotransferase (AST): 106 IU; alanine aminotransferase (ALT): 161 IU; protein: 7.6 g/dl; albumin: 4.5 g/dl; globulin: 3.1 g/dl), diazepam was stopped and shifted to lorazepam orally. To rule out any liver disease or infection, USG abdomen and tests for HIV, hepatitis B, and hepatitis C were also done, which came out to be normal. Investigations to rule out other causes of delirium, namely CT Head, MRI brain, blood sugar, serum electrolytes, and kidney function test, were normal. He was given lorazepam 4 mg every 30 minutes, and his symptoms were monitored. On the fourth day, he required 40 mg of lorazepam (12 mg by intravenous injection route and the remaining 28 mg by oral route in the whole day) along with 6 mg of haloperidol (intramuscular route—initially 1 mg was given, and as the agitation was severe and uncontrollable, further 5 mg was given after 1 hour by intramuscular route) to control agitation and psychotic symptoms. He maintained well on the fifth day with 40 mg of lorazepam orally but again had intermittent disorientation and visual hallucinations on the sixth day, requiring a further increase in the lorazepam dose. However, he did not have any episodes of persecutory delusions from the fifth day onwards. As seen in **Table 1**, this pattern repeated—each time after an increase in lorazepam dose, his sleep improved and hallucinations and disorientation decreased. However, improvement remained for 1 to 2 days only, and he again had reduced sleep and worsening of disorientation, even with the same lorazepam dose. As he was neither very agitated nor drowsy, we did not shift him to the ICU setting. As his disorientation did not respond completely to an increasing dose of lorazepam, we could not start tapering BZDs. His liver function test gradually improved and after around two weeks of admission, the values were as follows: total bilirubin: 0.4 mg/dl; AST: 49 IU/L; ALT: 64 IU/L; protein: 7.0 g/dl; albumin: 4.3 g/dl; globulin: 2.7 g/dl. After around one week of normalization of bilirubin and improvement in SGOT and SGPT as above, we added trazodone 50 mg orally on the 20th day of admission, to improve his sleep. Following this, there was a dramatic improvement in his clinical condition, as can be seen from **Table 1**. He slept for nearly 11 hours, and his disorientation and hallucinations completely disappeared. We started tapering the lorazepam dose after two days of observation. As trazodone is hepatotoxic, we monitored his LFT after one week when it was found to be normal (bilirubin: 0.3 mg/dl; SGOT: 40 IU/L; SGPT: 38 IU/L; protein: 7.0 g/dl; albumin: 4.1 g/dl; globulin: 2.9 g/dl). He was discharged after 36th day on lorazepam 4 mg, disulfiram 250 mg, and naltrexone 50 mg. Lorazepam was later completely tapered and stopped on an outpatient basis. Trazodone was abruptly stopped after 35 days of discharge, with close follow up of the patient, and there was no sleep distur-

TABLE 1.

Clinical Features and Medication Dose

Day	Sleep (hours (hrs))	Visual Hallucination	Disorientation	CIWA-Ar	MMSE	Lorazepam Equivalent (Oral Route Except Where Another Route Is Mentioned Specifically) in mg	Haloperidol (Oral Route Except Where Another Route is Mentioned Specifically) in mg
1		No	No	11	–	5	–
2		No	Yes (1 hr)	17	–	18	–
3	5	No	No	16	24	20	
4	On & off	Yes (12 hrs)	Yes (12 hrs)	18	19	40 (12 mg by iv route and rest by oral route)	6 (im route)
5	6	No	No	7	17	40	–
6	7	Yes (intermittent)	Yes (1 hr)	–	–	44	–
7	6	Yes (intermittent)	Yes (1 hr)	8,5 & 17	24	44	–
8	3	Yes (3 hrs)	Yes	3	24	44	1
9	3	Yes (15 hrs)	Yes	5 & 3	25	48	1
10	6	Yes (intermittent)	Yes (intermittent)	5	18	48	1
11	3	Yes (intermittent)	Yes (intermittent)	3	29	52	1
12	6	Yes (intermittent)	Yes (intermittent)	0	24	52	1
13	2	No	Yes (6 hrs)	3	26	54	1
14	6	No	Yes (10 min)	0	30	54	1
15	5	No	Yes (1 hr)	0	30	54	1
16	2	No	Yes (6 hrs)	3	26	56	1
17	7 ½	No	Yes (8 min)	3	30	56	1
18	8	No	Yes (8 min)	3	28	56	1
19	4	No	Yes (2 hrs)	3	30	58	1.5
20[a]	4	No	Yes (10 min)	3	30	58	1.5
21	11	No	No	3	30	58	1.5
22	13	No	No	2	30	54	1. 5
23	10	No	No	2	30	50	Stopped
24	10	No	No	0	30	46	–
25	11	No	Yes (10 min)	0	30	46	–
26–36	8–11	No	No	0	30	44–4[b]	–

[a]Tablet trazodone 50 mg, added on the night of Day 20, was continued till around 35 days after discharge (total of 50 days). [b]Lorazepam dose tapered gradually by 4 mg daily from Day 26 to Day 35. CIWA-Ar: Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised; MMSE: Mini Mental State Examination.

bance reported after that. He remained abstinent for two months, following which he relapsed again. His compliance to treatment has been consistently poor after his relapse, and he is currently lost to follow up.

Discussion

In our patient, delirium started on the second day of alcohol withdrawal and lasted for 19 days. Even though the symptoms responded to high-dose BZDs, the response was incomplete, and he required gradually increased doses of lorazepam. Previously reported cases with protracted DT usually had medical co-morbidities[3] and required ICU setting. However, in our case, there was no major medical co-morbidity.

Persistence of DT despite high-dose BZDs is termed as refractory DT, though there is no standard definition. One study considered patients with DT requiring up to 2000 mg of BZDs without effect on sleep as refractory DT.[4] Another study reported persistence of withdrawals despite 10 mg or more lorazepam equivalent in the first hour or 40 mg or more lorazepam equivalent in the first 3 to 4 hours to be predictive of refractory DT.[5] Our patient had been responding to an increased dose of lorazepam for 1–2 days but then his condition deteriorated. Previous studies on refractory DT used barbiturates, propofol, antipsychotics, etc., to manage DT, but also reported serious complications with these medications.[4,6] As our patient was not very agitated and his sleep was disrupted, we decided to

improve his sleep first and added trazodone. Trazodone has been found to reduce the need for BZDs in patients with alcohol withdrawal.[7] A systematic review of 20 articles found that among the various pharmacological agents used to manage insomnia in patients who are in alcohol recovery, trazodone had the best efficacy. However, the studies included had used trazodone only after detoxification from alcohol was completed. There is scant literature on the use of trazodone for insomnia during detoxification in patients with alcohol use disorder.[8] However, it is commonly used in our hospital for managing sleep disturbance in patients with alcohol use disorder during detoxification also, with good results.

The addition of trazodone as an adjuvant led to a dramatic improvement in the clinical course of our patient. It has been found that in some cases, DT ends abruptly when the patient sleeps for a longer duration, called "terminal sleep". Absence of terminal sleep has been proposed to be associated with atypical, recurrent course of DT.[9] The improvement in our case could probably be explained by the improvement in his sleep caused by trazodone.

Trazodone is an antidepressant with serotonin reuptake inhibitor and alpha-1 adrenergic receptor antagonist activity. At lower doses, that is, at the hypnotic dose of 50 mg, most of the alpha-1 adrenergic receptors get saturated.[10] It is well known that there is sympathetic hyperactivity during alcohol withdrawal.[11] Hence, trazodone, which acts as an adrenergic antagonist, could also have helped in the current case in reducing the severity of alcohol withdrawal, leading to improvement in DT.

Conclusion

In some patients, the duration of DT can be prolonged. Improving sleep in patients with DT not responding to a high dose of BZDs, using medications such as trazodone as adjuvants, could be tried, especially when DT is refractory or protracted.

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