Delirium Tremens: Assessment and Management

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Delirium Tremens (DT) falls in the most severe spectrum of alcohol withdrawal, which could potentially result in death, unless managed promptly and adequately. The prevalence of DT in general population is <1% and nearly 2% in patients with alcohol dependence. DT presents with a combination of severe alcohol withdrawal symptoms and symptoms of delirium with agitation and sometimes hallucination. Clinical and laboratory parameters which predict DT have been discussed. Assessment of DT includes assessment of severity of alcohol withdrawal, evaluation of delirium, and screening for underlying medical co-morbidities. Liver disease as a co-morbidity is very common in patients with DT and that could complicate the clinical presentation, determine the treatment choice, and influence the outcome. Benzodiazepines are the mainstay of treatment for DT. Diazepam and lorazepam are preferred benzodiazepine, depending upon the treatment regime and clinical context. In benzodiazepine refractory cases, Phenobarbital, propofol, and dexmedetomidine could be used. (J Clin Exp Hepatol 2018;8:460–470)

The latest Global Status Report on Alcohol and Health, published in 2014 reported that the more than one third of the population (38.3%) of the world can be categorized as current drinkers 38.3%.[1] Globally, alcohol is responsible for around 3.3 million deaths annually; 5.9% of global mortality and 5.1% of the Disability Adjusted Life Years (DALY) could be attributed to alcohol consumption. Surprisingly, death due to HIV/AIDS, tuberculosis, and violence together could not match the figure due to alcohol use.[2] Twenty five of the chronic disease or condition codes in the International Classification of Diseases (ICD-10) are directly linked to alcohol and for many others like cardiac, digestive, neuro-psychiatric diseases, and tumors it plays the role of component causality.[2,3] Alcohol use is projected to contribute to 20–50% of cirrhosis of the liver, poisonings, epilepsy, road side accidents, several types of cancer, and violence.[4]

All the alcohol related harmful consequences are more in people with Alcohol Use Disorders (AUD) who drink heavily.[3] The worldwide prevalence of current AUD is up to 14%.[4] A considerable proportion of people with AUD develop withdrawal symptoms which are mostly mild but can be very severe in some cases with clinical and biological vulnerability. One of the severe forms of alcohol withdrawal is delirium tremens (DT). In presence of underlying co-morbidities (which, as already mentioned, is quite common in AUD), DT might take a dangerous turn and can potentially cause mortality. Although different in the historical context, the terms, DT and alcohol withdrawal delirium have been used synonymously at present.[5]

PREVALENCE OF DELIRIUM TREMENS (DT)

DT is a severe form of alcohol withdrawal syndrome. About half of the patients with alcohol use disorders develop withdrawal syndrome and only a minority of them would require medical attention.[6] A further smaller subset would develop severe alcohol withdrawal syndrome with DT. Therefore, DT is not very common, even in people with alcohol dependence.

There are only a few studies which have looked into the prevalence of DT in general population. A couple of studies from Germany and Finland showed the prevalence of DT in general population to be 0.7% and 0.2% respectively.[7,8] In the latter study, the prevalence of DT was 1.8% among people with alcohol dependence. This figure was much lower than those found in other studies which reported the occurrence of DT in 5–12% of alcohol dependent in treatment.[9,10] A study conducted among veterans of United States reported prevalence of DT as 0.7%, among those with alcohol use disorders.[11] Overall, it is apparent from these studies that the prevalence of DT is lowest in

Keywords: delirium, alcohol, delirium tremens
Received: 11 February 2018; *Accepted:* 25 April 2018; *Available online:* 5 May 2018
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Abbreviations: AUD: Alcohol Use Disorders; DALY: Disability Adjusted Life Years; DT: Delirium Tremens
https://doi.org/10.1016/j.jceh.2018.04.012

the general population, but is comparatively higher among patients with AUD. Moreover, people with alcohol dependence (which is the severe subset of AUD) have higher prevalence but it is highest for those who are in treatment. This could be possibly due to the fact that patients in treatment are expected to be suffering from more severe dependence. In other words prevalence of DT increases with the severity of dependence.

CLINICAL FEATURES OF DELIRIUM TREMENS

Diagnosis of DT has two distinct aspects. Firstly, the patient must have delirium and second, patient must be in *severe* alcohol withdrawal. Delirium is characterized by a rapid onset and fluctuating course with disturbances in the level of consciousness, cognition, psychomotor activity, and sleep-wake cycle.[12] Delirium may be caused by a multitude of causes consisting of metabolic, infectious; drug (or its withdrawal) induced, and head injury (or others). This list is not exhaustive, and more often than not multiple factors contribute to its etiology.[13–15] Alcohol withdrawal happens only after sudden cessation of heavy and prolonged use of alcohol and consists of several distinct symptoms (e.g. autonomic hyperactivity, hand tremor, nausea, transient hallucination, increased psycho-motor activity/agitation, generalized seizure) (Table 1). According to the ICD-10 presence of any three of these symptoms indicate alcohol withdrawal. However, severe withdrawal is usually characterized by seizures, hallucinations, increased psycho-motor activity, and disturbing tremor.[16,17] DT is a clinical condition which comprises of aforementioned symptoms of both delirium and alcohol withdrawal. Therefore DT does not implicate causality; i.e. delirium in DT might not be *solely* due to alcohol withdrawal. This is important to note because DT is usually associated with other risk factors (e.g. electrolyte imbalance, infections, head injury) for

Table 1 Symptoms of Delirium Tremens or Alcohol Withdrawal Delirium.

Comparative symptoms of Delirium Tremens or alcohol withdrawal delirium	ICD-10	DSM-5
Symptoms of alcohol withdrawal	3/10 possible symptoms	2/8 possible symptoms
Clear evidence of recent cessation or reduction of substance use after repeated and usually prolonged and/or high-dose use of that substance.	Must be present	Must be present
Tremor of the tongue, eyelids or outstretched arms	+	Tremor of hands
Sweating	+	–
Nausea, retching or vomiting	+	+
Tachycardia or hypertension	+	+
Psychomotor hyperactivity	+	+
Headache	+	–
Insomnia	+	+
Malaise or weakness	+	–
Transitory visual, auditory or tactile hallucinations or illusions	+	+
Seizures – generalized, tonic-clonic	+	+
Anxiety	–	+
Symptoms of delirium		
Clouding of consciousness, i.e. reduced clarity of awareness of the environment, with reduced ability to focus, sustain or shift attention	+	+
Disturbance of cognition	+	+
Psychomotor disturbances	+	–
Disturbance of sleep or the sleep–wake cycle	+	–
Rapid onset and fluctuations of the symptoms over the course of the day	+	+

ICD-10: International Classification of Diseases-10th Revision; DSM-5: 5th Edition of Diagnostic and Statistical Manual; '+' means symptoms endorsed by that particular diagnostic system; '–' means symptoms, not endorsed by that diagnostic system

delirium.[5] Few studies have systematically evaluated the clinical picture of DT by using standardized scales. A study conducted at our center reported inattention, disorientation, motor agitation, alteration of sleep wake cycle and disturbance in short term memory as common presentations of DT.[18] Moreover, the factor structure of symptoms was different for DT with or without other associated etiologies for delirium.[19]

DT usually develops 48–72 h after the cessation of heavy drinking. This window period should be understood in the context of timeline for occurrence of various other symptoms of alcohol withdrawal. The first symptom to appear in alcohol withdrawal is tremor, which could be noticed within 6 h of cessation. This is followed by hallucination (12–24 h) which is less frequently (0.5%) encountered.[8] The third major symptom to appear in severe alcohol withdrawal is the withdrawal seizure which is usually grand mal type and can emerge any time after 24 h. The fourth and final major symptom is DT.[20,21] The point is, DT does not develop all of a sudden and this sequential timeline might help a clinician to halt the progression of alcohol withdrawal syndrome by intervening at an early stage.

Although not studied systematically, hallucinations are seen in a substantial minority of patients with DT. In fact earlier, presence of hallucination was considered necessary for the diagnosis of DT, although, it is no more so. Hallucinations are usually visual, which is followed by auditory and tactile. These are vivid and frequently pertaining to animals. Miniature versions of animals, known as the *Lilliputian hallucination* has also been classically reported in relation to alcohol withdrawal states.[22–24]

PATHOPHYSIOLOGY OF DELIRIUM TREMENS (DT)

Acute use of alcohol produces CNS depression because of an increased GABAergic neurotransmission and reduced glutamatergic activity.[25] However, in patients with chronic heavy alcohol use, because of neuro-adaptation, there is a down regulation of Gamma-Amino Butyric Acid (GABA) and up-regulation of the glutamate (NMDA receptor) neurotransmission. In alcohol withdrawal, this neurotransmitter imbalance gets unmasked and there is an unopposed glutamate activity which leads to excitotoxicity as a result of intracellular calcium influx and oxidative stress. This is precisely the reason that benzodiazepines which are GABAergic drugs reduce the excitetoxicity by restoring the neurotransmitter balance and are considered to be the drug of choice in alcohol withdrawal syndrome.[26,27] DT follows similar pathophysiology. Kindling has been conjectured to play an important role in the development of DT. Kindling is a process of sensitization and enhanced neuronal excitability of the nervous system which happens after repeated episodes of alcohol withdrawals.[28,29] Hence, kindling could explain greater excitotoxicity which is required for the development of severe alcohol withdrawal syndrome like DT.

Candidate gene studies have fairly consistently reported the involvement of the glutamate and dopamine neurotransmission related genes for DT.[30,31] However, negative studies do exist.[32] Nevertheless, genetic association with the glutamate system does buttress the point of vulnerability for excitotoxicity for the patho-genesis of the DT.

COURSE AND OUTCOME OF DELIRIUM TREMENS

DT is a short lasting condition with a usual duration of 3–4 days (but might last for even 8 days) and it classically ends with a prolonged sleep.[5,18,22,33] However, there have been only a handful of prospective studies which had examined the course and outcome of DT. Overall DT might increase the length of hospital stay, stay in the ICU, and mortality.[34] Nevertheless, the rate of mortality in DT has reduced substantially over the years, especially after the introduction of the benzodiazepines as treatment.[27] The current mortality ranges from 1 to 4%, which can be further reduced by effective and timely intervention.[5] The usual causes of death in DT are hyperthermia, cardiac arrhythmias, complications of withdrawal seizures, or concomitant medical disorders.[5] A study from India, done among patients admitted to medico-surgical wards reported 13% mortality, which is much higher than the International literature.[18] Only another report conducted in patients with head injury observed mortality rate of 11%.[34] In both these studies, perhaps presence of co-morbidities inflated the mortality rates. Moreover, patients with history of DT have higher mortality (than those with only alcohol dependence and no DT) even longitudinally. The Finnish study showed that about 31% patients with DT die at the end of 8 years.[8]

RISK FACTORS FOR DELIRIUM TREMENS (DT)

As already mentioned, DT independently increases the chance of mortality and length of hospital stay. Therefore, the historical or laboratory parameters which might predict DT could play a crucial role in the course and management of DT. There are a few systematic reviews conducted in this particular area. A recent metanalysis of 15 studies, identified past history of DT, low platelet count, and low potassium level as predictors of DT.[35] Another recent prospective study by Kim and colleagues[36] reported that in addition to low platelet count, high blood homocysteine and low pyridoxine increase the risk of DT.

In a different retrospective cohort study, presence of structural brain lesion (example head injury) has been found to predict DT.[37] Among the studies published in language other than English, Thiercelin et al. in a narrative review reported presence of withdrawal seizures, somatic co-morbidities (especially infections, respiratory and cardiac disease), and early withdrawal symptoms as predictors of development of DT.[38] Among other risk factors, severity of early alcohol withdrawal syndrome (with systolic blood pressure>150 mm-Hg and pulse rate > 100 - beats/min), older age, low magnesium level were found to predict the incidence of DT.[5] A couple of other studies, which had examined the risk factors for the occurrence of severe alcohol withdrawal syndrome which includes both DT and withdrawal seizures, reported serum levels of Alanine Transaminase (ALT) and Gamma Glutamyl Transpeptidase as significant predictors.[17,35] The factors which are not found to have any predictive value are gender, presence of liver disease, and drinking pattern.[35] However, further research in this area is warranted.

ASSESSMENT OF DELIRIUM TREMENS

Assessment of DT should take into account multitude of factors: severity of alcohol withdrawal, severity of delirium, assessment of other risk factors and commonly occurring co-morbidities associated with chronic heavy use of alcohol.

General Assessment

A brief history regarding the quantity, pattern, and duration of alcohol intake should be obtained. The type of alcohol also influences the alcohol related harmful effects. As mentioned previously, DT usually develops 48–72 h after the last drink. Therefore, it is important to elicit the information in terms of time since last drink. History of previous alcohol withdrawal should also be obtained, as past history of DT or withdrawal seizure increase the risk of DT in the present episode. History regarding use of other substances should also be obtained. Benzodiazepines need a special mention here. Withdrawal from benzodiazepines has a lot of common features (of alcohol withdrawal) like tremor, agitation, perceptual disturbances, seizure, and even delirium.[39] Moreover, it might also influence the dose of benzodiazepine to be used for the treatment of DT. In addition to history, the physical examination and investigations should be done to evaluate the possible complicating medical conditions, including arrhythmias, congestive heart failure, coronary artery disease, gastrointestinal bleeding, infections, liver disease, nervous system impairment, and pancreatitis. History should also focus on obtaining information with regard to head injury (recent or past), baseline cognitive functioning and comorbid psychiatric disorders.

Assessment of Alcohol Withdrawal

Only clinical assessment of alcohol withdrawal although necessary may not be sufficient from management point of view. One should get acquainted with commonly used clinician rated instruments for the estimation of severity of alcohol withdrawal. Alcohol Withdrawal Scale (AWS) which is an eleven item scale is based entirely on objective physical or cognitive measures.[40] Its mental subscale has items like hallucination, agitation, orientation which would help in assessing patients with DT in particular. Mild withdrawal is recognized by a score of <5; score between 6 and 9 suggests moderate withdrawal and severe withdrawal comprised of a score of 10 or more. Details of the items and scoring of these instruments are provided in Table 2. However, the most commonly used instrument is Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) scale, particularly the 10 item revised version, known as CIWA-Ar. Most of the measures in the CIWA-Ar are objective; therefore require minimum patient's co-operation.[41,42] This is important to note because patients with DT are usually agitated and less likely to co-operate. CIWA-Ar score of less than 8 indicates mild withdrawal; from 8 to 15, suggests moderate withdrawal, and >15 indicates severe withdrawal and is also predictive of seizure and DT.[43] CIWA-Ar aids in treatment decision and monitoring.[21,27,44]

Assessment of Delirium

Discussing about the entire spectrum of instruments available for the assessment of delirium is outside the scope of this review. We would only concentrate on scales which are commonly used and could be used in a busy clinical setting. Instruments like the Confusion Assessment Methods (CAM) can be used for screening delirium, whereas Delirium Rating Scale-revised (DRS R98) is both diagnostic and can be used to assess the severity of delirium as well. CAM is one of the most commonly used screening instruments. The instrument assesses features of acute onset, inattention, disorganized thinking and altered level of consciousness. The administration time is only 5 min and it can be used by a non-psychiatrist physician.[45,46] The sensitivity and specificity of CAM vary widely across studies and range from 50 to 100%.[47–49] However, when administered by a trained physician, the figures are on the higher side.[46] A variant of CAM has been developed for ICU or for nonverbal patients. This is known as the CAM-ICU. With the CAM-ICU, delirium is diagnosed when patients demonstrate: (1) an acute change in mental status or fluctuating changes in mental status; (2) inattention measured using either an auditory or visual test; and either (3) disorganized thinking; or (4) an altered level of consciousness. CAM-ICU can be administered provided the patient could be aroused. Another uniqueness of CAM-ICU is its brevity. It takes around 1–

Table 2 Instruments for the Assessment of Alcohol Withdrawal Syndrome.

Clinical institute withdrawal assessment scale – revised (CIWA-AR)	Alcohol withdrawal scale (AWS)
Nine items scored on a scale ranging from 0 (no symptoms) to 7 (most severe symptoms) Nausea or vomiting Tremor Paroxysmal sweats Anxiety Tactile disturbances (itching, numbness, sensation of bugs crawling on or under the skin) Auditory disturbances (sensitivity to sound, hearing things that are not there) Visual disturbances (sensitivity to brightness and color, seeing things that are not there) Headache, sensation of a band around the head Agitation	**Somatic symptoms: Severity rating 0–3** Pulse rate (per min) Diastolic blood pressure (mmHg) Temperature (°C) Breathing rate (per min) Sweating Tremor **Mental symptoms: Severity rating 0–4** Agitation Contact Orientation (time, place. person, situation) Hallucinations (optical, acoustic and tactile Anxiety
One item scored on a scale ranging from 0 (no symptoms) to 4 (disoriented with respect to place or person) Orientation and clouding of sensorium	**Total score is the combination of somatic and mental symptoms**
Interpretation <8: Mild Withdrawal 8–15: Moderate withdrawal >15: Severe withdrawal	**Interpretation** ≤5: Mild withdrawal 6–9: Moderate withdrawal ≥: Severe withdrawal

For detail description of these instruments, please see:
Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict. 1989;84:1353–7.
Wetterling T, Kanitz RD, Besters B, Fischer D, Zerfass B, John U, et al. A new rating scale for the assessment of the alcohol-withdrawal syndrome (AWS scale). Alcohol Alcohol. 1997;32:753–60.

2 min for trained personnel to administer this instrument; this makes it very useful in the intensive care settings.[50,51] Table 3 enumerates the CAM and CAM-ICU. The DRS R98 is an instrument, to be used only by trained clinician (based to a large extent on clinician's subjective interpretation of patients symptoms). It has three diagnostic and 13 severity items; therefore could be used both for the diagnosis and assessment/monitoring the severity of delirium.[52]

Another instrument the Richmond Agitation Sedation Scale (RASS) which, as the name indicates, is actually developed for the assessment of agitation-sedation can be useful in assessment of patients with DT. Both the spectra of consciousness (agitation and stupor) can be encountered in DT. Agitation is a known symptom of DT and sedation can be encountered as a result of high dose benzodiazepine use.[5] RASS is a 10 point scale with a maximum possible score of +4 for agitation (combativeness) and minimum −5 score for sedation (unarousable state).[53] It can be easily administered by physician and nurses. It has been found to have high reliability and validity for medico-surgical patients, patients with or without ventilator support.[46] This instrument is useful for patients in ICU and for uncooperative patients. Both of these are common occurrences in patients with DT.

Assessment of Risk Factors and Co-Morbidities

Chronic heavy use of alcohol can be associated with other medical co-morbidities which need to be evaluated in a patient with DT.

One of the most common but frequently ignored co-morbidity is Wernicke Encephalopathy (WE). The occurrence of autopsy proven WE is reported to be 1.4% (the figure is close to the occurrence of DT) in hospitalized patients with chronic alcohol use.[54] However, the incidence could rise to 58%, when autopsy samples are taken from patients with severe alcohol problems.[55] Surprisingly, out of the patients found to have WE at autopsy, only one third of the patients were diagnosed to have WE in their life.[54,56] The cost of under-diagnosis is insurmountable as WE is a treatable condition and if not treated adequately would lead to permanent disability in a substantial majority.[54] Certain factors are adjudged to increase the risk of WE; namely, past history of DT, severe alcohol dependence, severe and concurrent medical problems, and repeated unsuccessful attempts of alcohol detoxifications.[57] WE is traditionally known by its triad of global confusion, ophthalmoplegia and ataxia. However, this classic triad is present in merely 8% of cases. Currently, it is advisable to follow the Caine's criteria for the diagnosis of WE. It consists of 4 criteria: (1) dietary deficiency; (2) eye signs-

Table 3 Instruments Commonly Used for the Assessment of Delirium.

Confusion assessment method	Confusion assessment method-ICU
Must fulfill first two features	**Must fulfill first two features**
Acute onset and Fluctuating course	Alteration/Fluctuation in Mental Status
Inattention: *difficulty in focusing attention, easily distracted, problems in keeping track of what is said*	Inattention: Letters Attention Test: Ask patient to raise finger whenever he hears 'A' during the word 'SAVEAHAART'
Either of the third and fourth feature	**Either of the third and fourth feature**
Disorganized thinking: *rambling speech/irrelevant conversation; unpredictable switching of subjects; unclear or illogical flow of ideas*	Altered Level of Consciousness (LOC): Present if RASS = 0 (not 'alert and calm')
Altered level of consciousness	Disorganized Thinking: Yes/No Questions: Ask the patient to respond: 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does 1 pound weigh more than 2 pounds? 4. Can you use a hammer to pound a nail?

RASS: Richmond Agitation Sedation Scale.
Adapted with permission from: Inouye SK, vanDyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: The Confusion Assessment Method. A new method for detection of delirium. Ann Intern Med. 1990; 113: 941–948.[45]

diplopia, extra-ocular eye muscle paralysis, nystagmus; (3) cerebellar dysfunction-ataxia; (4) either altered mental state or mild memory impairment. Two out of these 4 criteria must be present to make a 'case' of WE. Caine criteria were found to have a sensitivity of 85%.[58] Neuroimaging in the form of MRI might play a supportive role for the diagnosis of WE. The sensitivity and specificity of the structural MRI was observed to be 53% and 93% respectively, with a positive predictive value of nearly 90%.[59] Usually FLAIR sequence is more useful to detect the brain changes in the WE. Typically, the lesions are symmetrical and are seen in the thalami, mamillary bodies, tectal plate and periaqueductal area.[60] If not treated adequately, around 60% of patients with WE might end up with largely irreversible global amnestic syndrome (predominantly episodic and anterograde amnesia), known as Korsakoff's syndrome (KS).[61] Another remarkable feature which also is commonly seen in KS is confabulation i.e. erroneous recollection of memories arising involuntarily ('Honest lying'). In addition to memory disturbances, KS may also present with apathy, depressive symptoms, and even agitation.[62]

Other medical co-morbidities which need special mention here are hepatic and cardiac diseases. Liver disease is more often present than absent in the setting of chronic heavy use of alcohol. Majority (90–100%) of people with heavy drinking would have alcoholic steatosis; may be about one third would have alcoholic hepatitis, and finally 8–20% might have alcohol induced cirrhosis.[63,64] It is essential to detect liver disease in patients with DT, not only for the adequate treatment of the underlying condition but also for the choice of the benzodiazepine, to be used for treating DT.[22,27] Moreover, liver disease itself might affect the prognosis of DT. Hepatic encephalopathy (HE) is a close differential diagnosis of DT, given the presence of altered sensorium and tremor. However, delirium in HE is usually hypoactive i.e., patients are mostly drowsy and retarded (as opposed to aroused and agitated in DT) and tremors are only visible at hands (flapping tremors) in a particular position (as opposed to whole body tremor in DT). Nevertheless, it must be borne in mind that DT and HE might co-exist and complicate the clinical presentation and management.[65] Moreover, HE can be broadly classified as covert and overt HE. It is the overt HE which might present as delirium.[66] There is strong evidence that ammonia contributes significantly to the pathogenesis of HE. There is accumulation of ammonia in the serum and subsequently in the brain (as it crosses the blood brain barrier) and continued brain exposure of ammonia might enhance GABA-ergic effect; thus causing significant sedation and altered sensorium.[67] Measurement of ammonia level could be important for the diagnosis of HE. As important aspect of evaluation of HE among patients with DT is look for history of constipation. If present, it must be addressed at the earliest. If patients with DT are found to have high ammonia levels, than appropriate pharmacological measures like lactulose needs to be considered.

AUD, as opposed to moderate drinking, is associated with higher risk of Ischemic Heart Disease (IHD) and this risk is more in women (Hazard Ratio 2.09) than in men (Hazard Ratio 1.62).[68] In other words the cardio protective effect of alcohol dissipates with heavy drinking. Moreover, the risk of atrial fibrillation (Hazard Ratio 1.45) and other dysrhythmias increase with heavy drinking as well.[69] Chronic alcohol use is also associated with hypertension and cardiomyopathy.[3,70] These conditions must be screened for, in patients with DT. Cardiac disease and arrhythmias are known cause of mortality in DT.[5]

Panel 1: Assessment of Delirium Tremens

Assessment of the severity of alcohol withdrawal: CIWA-Ar or AWS
AWS is preferred for patients who are uncooperative
CIWA-Ar is useful for the treatment regimes with benzodiazepines

Assessment of delirium: diagnosis with CAM or CAM-ICU (if patient is in ventilator support)
Severity assessment by DRS-R98

Assessment of risk factors and underlying co-morbidities:

Clinical:
Looking for WE: clinically by eye signs, cerebellar signs, altered mental state or memory problems, signs of dietary deficiency (any two of these four features)
Persistent tachycardia and dyspnea: suggestive of cardiomyopathy; cardiac arrhythmias
Hydration, Jaundice, ascites, hemetemasis, other stigmata of chronic liver disease

Laboratory:
ECG: cardiac arrhythmias
Liver function test; prothrombin time
Serum electrolytes: potassium, magnesium, sodium levels
Complete blood count: leukocytosis for infection; low platelet count for liver cirrhosis
Acid Base Balance: Atrial Blood Gas analysis
Echocardiography: cardiomyopathy
MRI brain: Associated head injury; T2 or FLAIR sequence is preferred; bilateral symmetrical hyper intensities seen in thalami, mamillary bodies, tectal plate and periaqueductal area in WE

CIWA-Ar: Clinical Institute Withdrawal Assessment-Alcohol (revised); AWS: Alcohol Withdrawal Scale; CAM: Confusion Assessment Method; WE: Wernicke's Encephalopathy; FLAIR: Fluid Attenuation Inversion Recovery; ECG: Electro Cardiogram.

Management of Delirium Tremens (DT)

DT needs to be managed as medical emergency and ideally should be managed in an inpatient or ICU setting.[5] The goal of treatment of alcohol withdrawal in general is to prevent to progression from minor to severe withdrawal symptoms and also to prepare the patient for long term treatment of alcohol dependence, without compromising patient's autonomy and dignity.[71] In contrast to this, in DT where the symptoms of alcohol withdrawal have progressed to severe level, the treatment is focused upon ameliorating agitation and other symptoms of delirium, recognition and treatment of underlying medical co-morbidities, and of course prompt, adequate and protocol driven treatment of alcohol withdrawal.[5] Treatment of agitation is likely to decrease the risk of seizures, injury and finally mortality.[33,72,73] However, management of DT would be incomplete without the ongoing treatment for alcohol dependence.

Assessment of DT which has been discussed before forms the backbone of its management. It starts with adequate and timely treatment of alcohol withdrawal.

General Measures

As already mentioned, co-morbidity is the rule rather than exception in DT. Hence thorough clinical examination and laboratory investigations must be carried out for patients with DT. Provisions should be made for regular monitoring of vitals. Fluid and electrolyte imbalance and nutritional issues should be taken care of. Intravenous fluid should be used cautiously because of the possibility of volume overload but can be useful in patients with excessive sweating, hyperthermia, and vomiting.

Restraints should ideally be avoided in agitated patients because this might paradoxically increase the agitation. A calm and comfortable place with adequate lights must be chosen as the treatment setting. External orientation cues like a table clock, calendar could be arranged. Other interventions may include use of earplugs, eye masks, noise control strategies, pharmacy medication review, family presence (but they should not change frequently), and family education.[74]

Treatment of Alcohol Withdrawal

Benzodiazepines (BDZ) are the mainstay of treatment in DT. Long acting BDZs (like diazepam, chlordiazepoxide) are preferred over the short acting ones because of their potential for self tapering and constant serum level (as opposed to frequent change in the peak and the trough level in the short acting BDZs) helps in continuous relief of withdrawal symptoms. There are three treatment regimes for the management of DT-fixed dose, symptom triggered, and front loading. Evidence strongly suggests the superiority of front loading over the other two regimes.[5,21,27] Among these fixed dose regime is not favored for DT. Baseline monitoring of withdrawal symptoms must be carried out with the instruments (CIWA-Ar, AWS), mentioned already. The preferred benzodiazepine in diazepam, except in circumstances, in which patient has significant liver dysfunction or intravenous access cannot be made (as intramuscular absorption of diazepam is very erratic).[75] In these situations lorazepam is preferred, as it bypasses hepatic metabolism.[71] In the front loading regime, the goal is to attain sedation (although the patient must be arousable); therefore it requires initial high dose of long acting benzodiazepines, like diazepam.[71,76] As this regime would require higher dose of long acting benzodiazepine which could potentially cause respiratory depression, this regime should ideally be used in a setting where ventilator is available.[71] Moreover, in patients with suspected head injury and liver dysfunction, front loading is not a favored regime to follow. In the latter circumstances 'symptom triggered' regime could be tried. In this regime the dose and timing of the benzodiazepine depends on the severity of withdrawal symptoms in a standard withdrawal scale.[75] The goal of treatment is to treat

withdrawal symptoms adequately. Both lorazepam and diazepam can be used for this regime. However, for symptom triggered regime one professional must be present to monitor withdrawal symptoms round the clock. Panel 2 summarizes the treatment regimes for the treatment of alcohol withdrawal in DT. Use of magnesium is not routinely recommended unless there is a documented magnesium deficiency because in such cases withdrawal seizure and delirium might persist despite adequate treatment with benzodiazepines.[77] Similarly, thiamine supplement is also insufficient in the presence of hypomagnesaemia.[5]

Panel 2: Treatment regimes for Delirium Tremens

REGIMES	DOSES
Front loading	With diazepam: aim is to achieve light sedation (patient still could be aroused with verbal stimulation) or to bring down CIWA-Ar <8 5 mg IV → 5 mg IV (repeat after 10 min) 10 mg IV → 10 mg IV (repeat after 10 min) 20 mg IV after 10 min 5–20 mg IV per hour [Dosing must be continued till the aim of light sedation or the CIWA-Ar score has been achieved]
Symptom triggered	With diazepam 10–20 mg IV every 1–4 h → repeat doses till CIWA-Ar score <8
	With lorazepam: 4 mg IV to be repeated every 10 min till either of the aims of front loading is achieved If severe delirium still persists even after 16 mg IV→ 8 mg IV bolus is to be administered
Fixed dose	Not to be used for DT; Only for outpatient management of alcohol withdrawal syndrome

CIWA-Ar: Clinical Institute Withdrawal Assessment-Alcohol (revised); IV: Intravenous.

Use of Thiamine

The potential co-morbidity of WE in delirium tremens has been mentioned previously. Therefore even when WE is not suspected use of high dose (500 mg infused over 30 min 1–2 times per day for three days) intravenous thiamine is warranted.[78,79] Multi-vitamin injection, in addition to thiamine could also be added.[79] In case of suspected WE, 500 mg thiamine to be infused at least 3 times a day for 5 days, along with injection multivitamin.[80] In this connection, it is important to note that intravenous dextrose should never be used in alcohol withdrawal, as it might precipitate WE and thiamin related cardiomyopathy in vulnerable individuals.[81] Isotonic saline must be used for thiamine and other vitamin infusion.[80] Dextrose could be safely administered once patient has received thiamin. Nevertheless, the risk of fluid overload must be borne in mind while administering infusions, especially in patients with pre-existing cardiac disease.[82]

Treatment of Refractory Delirium Tremens

After repeated episodes of intoxication and withdrawal from alcohol, conformational changes might occur in the GABA receptors, which might reduce the benzodiazepine responsiveness.[83] Although this mechanism is yet to be established in humans, in a minority of patient with DT, unusually high doses of benzodiazepine might be needed to control agitation.[84,85] Benzodiazepine refractory delirium is defined as, "Persistent CIWA-Ar >25, frank delirium or inability to control symptoms despite medication" and/or "requirement of ≥200 mg in the initial 3 h or ≥400 mg of diazepam in the first 8 h or ≥30 mg in the initial 3 h or ≥60 mg of lorazepam in the initial 8 h".[86] All cases of refractory DT must be treated in an ICU setting. Refractory DT must be treated with addition of phenobarbital or haloperidol to the benzodiazepine regime.[27,73,87] Phenobarbital is the first choice. In fact it might reduce the need for mechanical ventilation, length of ICU stay, and nosocomial infections.[88] Use of haloperidol is not preferred generally because of its seizure threshold lowering potential.[89] Nevertheless, if cannot be avoided, an ECG and electrolyte assessment must be done prior to the administration. One should look for the corrected QT interval and search for hypokalemia and hypomagnesemia which are common among patients in alcohol withdrawal.[90] If the agitation is not yet controlled by phenobarbital, propofol can be tried.[86] Propofol is a general anesthetic which acts on the GABA-A receptor but at a site, different from the benzodiazepines. It reduces the glutamate activity as well. Because of its different site of action, it has been tried in benzodiazepine refractory cases.[91,92] However, patients on propofol frequently experienced more days of mechanical ventilation and length of stay, which may be due to more refractory cases of alcohol withdrawal.[91]

Another medication which has some evidence for the benzodiazepine refractory DT is an α2 adrenergic agonist, dexmedetomidine; it should always be used as an adjunct; it cannot be prescribed in patients with heart block and requires continuous cardiac monitoring.[93,94] A recent review on dexmedetomidine in alcohol withdrawal, which is consisted of one randomized controlled trial, one prospective, and six retrospective studies, concluded that it could reduce autonomic symptoms of withdrawal and benzodiazepine requirement. However, there is no effect with regard to the need for mechanical ventilation and lengths of ICU stay; indirectly indicating that it might not have any effect on the severity of DT.[95] Another review, in addition to supporting the aforementioned conclusion added that dexmedetomidine is safe and it cannot prevent seizure.[96] Comparison of propofol with dexmedetomidine as adjuncts showed both drugs have similar benzodiazepine- and haloperidol-sparing effects. Dexmedetomidine was linked with more bradycardia, while propofol was

associated with more instances of hypotension.[91] Finally, propofol is preferred in patients with seizures and those who would require mechanical ventilation. There is one retrospective review and one observational study supporting the role of ketmine and midazolam as adjuncts to the benzodiazepine in refractory DT.[96,97] More evidence is required to use these drugs in routine practice. Panel 3 summarizes the treatment of refractory DT.

Panel 3: Treatment of benzodiazepine refractory delirium tremens

"Persistent CIWA-Ar >25, frank delirium or inability to control symptoms despite medication" and/or "requirement of ≥200 mg in the initial 3 h or ≥400 mg of diazepam in the first 8 h or ≥30 mg in the initial 3 h or ≥60 mg of lorazepam in the initial 8 h	
FIRST CHOICE	**Phenobarbital** 60 mg IV bolus every 15 min BDZ dose to be halved (if patient is not intubated) Intubation is necessary if there are signs of respiratory depression and BDZ therapy is to be continued
SECOND CHOICE (If refractory to Phenobarbital as well)	**Propofol** infusion 0.3–1.25 mcg/kg/h RASS – (−3) to (−4) Maximum dose – 4 mcg/kg/h Maximum duration of administration – 48 h
THIRD CHOICE (If ventilator support is not available for propofol, it can be used as an alternative)	**Dexmedetomidine** Doses up to 0.7 μg per kilogram per hour
OTHER ALTERNATIVES	**Haloperidol**: uncontrolled agitation or hallucinations (0.5–5.0 mg intravenously or intramuscularly every 30–60 min as needed for severe agitation or hallucinosis – not to exceed 20 mg; or 0.5–5.0 mg orally every 4 h up to 30 mg **Ketamine**: total infusion rate of 0.20 mg/kg/h

CONCLUSION

DT falls in the most severe spectrum of alcohol withdrawal, which is although present in a substantial minority of people with alcohol dependence could potentially result in death, unless managed promptly and adequately. Mortality in DT mostly results from associated co-morbidities, dyselectrolytemia, and cardiac arrhythmias. Benzodiazepines remain as the mainstay of treatment. However, there is a scarcity of well designed randomized controlled trials and most of the evidence is based on observational and uncontrolled studies. The evidence is more scanty for the benzodiazepine refractory DT. More research is warranted in this area. Supportive treatment of vitamin deficiencies and underlying co-morbidities are of paramount importance and can mediate the final outcome.

CONFLICTS OF INTEREST

The authors have none to declare.

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