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A Review on Clinical Management of Alcohol Withdrawal Syndrome (AWS)

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HUMAN

Rohit Bangwal[1]*, Shubham Rawat[2], Bhanu Rahi[2], Mohan Dhyani[3], Shobit Garg[3]

1. *Pharm. D (PB) Intern, Department of Pharmacy Practice, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Dehradun-248001, Uttarakhand, INDIA.*

2. *Pharm. D, Student, Department of Pharmacy Practice, School of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology & Science, Dehradun-248001, Uttarakhand, INDIA.*

3. *Associate Professor, Department of Psychiatry, Shri Guru Ram Rai Institute of Medical & Health Sciences, Patel Nagar, Dehradun-248001, Uttarakhand, INDIA.*

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ABSTRACT

Alcohol withdrawal syndrome (AWS) is the name for the symptoms that occur when a heavy drinker suddenly stops or significantly reduces their alcohol intake. The alcohol withdrawal syndrome is one of the well-known conditions occurring after intentional or unintentional abrupt cessation of heavy/constant drinking in patients suffering from alcohol use disorders (AUDs). AUDs are common in neurological departments with patients admitted for coma, epileptic seizures, dementia, polyneuropathy, and gait disturbances. Alcohol-withdrawal syndrome (AWS) is a challenge to patient care that can present in the inpatient setting. Early identification and treatment initiation in patients with a history of alcohol-use disorder are necessary in order to minimize the development of AWS. Evidence supports the use of benzodiazepines via various dosing strategies and the addition of supportive and nutritional care to mitigate withdrawal symptoms. Other possible treatment options for AWS include barbiturates, anticonvulsants, and adrenergic medications, which vary in terms of their benefit. The clinical pharmacist can assist the multidisciplinary team member in identifying patients at risk for AWS as well as recommend safe and effective treatment regimens on an individual basis. In many cases studies, alcohol withdrawal requires medical treatment and hospital admission. Medication may also be used to treat physical symptoms while patient counselling and support groups help with controlling drinking behaviour. Clinical Pharmacists, Psychiatrist & Psychotherapist or psychologist can also guide and monitor the patients prescribed medication therapy throughout the hospital stay and counselling like patient education, individual psychotherapy, behaviour therapy, motivational enhancement therapy, cognitive behaviour therapy etc. them and about their disease, medication, dose & side effects at discharge.

INTRODUCTION

The World Health Organization estimates that 283 million people globally have alcohol-use disorder (AUD), which comprises alcohol dependence and alcohol abuse.[1,2] This population presents with significant complications that are associated with physical and psychiatric comorbidities. AUD contributes to morbidity and mortality worldwide.[3,4]AUD is primarily considered a chronic condition that is most significant in the outpatient setting, but clinicians in inpatient settings also face AUD-related challenges. Although patients may initially present for conditions unrelated to AUD, sudden reduction or cessation of alcohol consumption upon hospitalization can put patients at risk for alcohol withdrawal syndrome (AWS). AWS symptoms, including anxiety, agitation, irritability, confusion, tremor, and hemodynamic changes, can complicate a patient's clinical course.[5,6]The severity of alcohol-withdrawal symptoms is extremely variable between patients, ranging from mild anxiety to major seizures. The most severe cases may develop into delirium tremens (DT), a severe psychotic condition involving acute confusion, hallucinations, and tremors. Early identification, risk assessment, and treatment of patients with known AUD are necessary for minimizing the negative outcomes associated with AWS and preventing development of symptoms that would further complicate a patient's hospital visit.[5-7]

WITHDRAWAL SYNDROME

The most common withdrawal syndrome is a hangover the next morning. There are other common withdrawal symptoms like:

- ✓ mild tremors
- ✓ nausea
- ✓ vomiting
- ✓ weakness
- ✓ irritability
- ✓ insomnia
- ✓ anxiety

Sometimes the withdrawal syndrome may be more severe, characterised by one of the following three disturbances:

- ✓ delirium tremens
- ✓ alcoholic seizures
- ✓ alcoholic hallucinosis

It is important to remember that alcohol withdrawal syndrome can be associated with marked morbidity as well as significant mortality, and it is important to treat it correctly[8].

1. Delirium tremens

Delirium tremens (DT) is the most severe alcohol withdrawal syndrome. It occurs usually within 2-4 days of complete or significant abstinence from heavy alcohol drinking in about 5% of patients, as compared to acute tremulousness which occurs in about 34% of patients. The course is short, with recovery occurring within 3-7 days. This is an acute organic brain syndrome (delirium) with characteristic features of:

i. Clouding of consciousness with disorientation in time and place.

ii. Poor attention span and distractibility.

iii. Visual (and also auditory) hallucinations and illusions, which are often vivid and very frightening. Tactile hallucinations of insects crawling over the body may occur.

iv. Marked autonomic disturbance with tachycardia, fever, hypertension, sweating and pupillary dilatation.

v. Psychomotor agitation and ataxia.

vi. Insomnia, with a reversal of sleep-wake pattern.

vii. Dehydration with electrolyte imbalance.

Death can occur in 5-10% of patients with delirium tremens and is often due to cardiovascular collapse, infection, hyperthermia or self-inflicted injury. At times, intercurrent

medical illnesses such as pneumonia, fractures, liver disease or pulmonary tuberculosis may complicate the clinical picture.

2. Alcoholic seizures ('rum fits')

Generalised tonic clonic seizures occur in about 10% of alcohol dependence patients, usually 12-48 hours after a heavy bout of drinking. Often these patients have been drinking alcohol in large amounts on a regular basis for many years. Multiple seizures (2-6 at one time) are more common than single seizures. Sometimes, status epilepticus may be precipitated. In about 30% of the cases, delirium tremens follows.

3. Alcoholic hallucinosis

Alcoholic hallucinosis is characterised by the presence of hallucinations (usually auditory) during partial or complete abstinence, following regular alcohol intake. It occurs in about 2% of patients. These hallucinations persist after the withdrawal syndrome is over, and classically occur in clear consciousness. Usually, recovery occurs within one month and the duration is very rarely more than six months.

Chronic Alcohol Use Complications

Alcohol dependence is often associated with several complications; both medical and social. Some withdrawal and intoxication related complications have described above whilst the neuropsychiatric complications are discussed below.

1. Wernicke's encephalopathy

This is an acute reaction to a severe deficiency of thiamine, the commonest cause being chronic alcohol use. Characteristically, the onset occurs after a period of persistent vomiting. The important clinical signs are:

i. Ocular signs: Coarse nystagmus and ophthalmoplegia, with bilateral external rectus paralysis occurring early. In addition, pupillary irregularities, retinal haemorrhages and papilledema can occur, causing an impairment of vision.

ii. Higher mental function disturbance: Disorientation, confusion, recent memory disturbances, poor attention span and distractibility are quite common. Other early symptoms are apathy and ataxia. Peripheral neuropathy and serious malnutrition are often co-existent.

Neuropathologically, neuronal degeneration and haemorrhage are seen in thalamus, hypothalamus, mammillary bodies and midbrain.

2. Korsakoff 's psychosis

As Korsakoff's psychosis often follows Wernicke's encephalopathy; these are together referred to as Wernicke-Korsakoff syndrome. Clinically, Korsakoff's psychosis presents as an **organic amnestic syndrome**, characterised by gross memory disturbances, with confabulation. Insight is often impaired. The neuropathological lesion is usually wide-spread, but the most consistent changes are seen in bilateral dorsomedial nuclei of thalamus and mammillary bodies. The changes are also seen in periventricular and periaqueductal grey matter, cerebellum and parts of brain stem. The underlying cause is believed to be usually severe untreated thiamine deficiency secondary to chronic alcohol use.

3. Marchiafava-Bignami Disease

This is a rare disorder characterised by disorientation, epilepsy, ataxia, dysarthria, hallucinations, spastic limb paralysis, and deterioration of personality and intellectual functioning. There is a widespread demyelination of corpus callosum, optic tracts and cerebellar peduncles. The cause is probably an alcohol-related nutritional deficiency.

OTHER COMPLICATIONS:

These include:

i. Alcoholic dementia.

ii. Cerebellar degeneration.

iii. Peripheral neuropathy.

iv. Central pontine myelinosis.

PATHOPHYSIOLOGY

Alcohol, a central nervous system (CNS) depressant, exerts its effect primarily by altering the neurochemical balance of the brain. This occurs through an increase in the inhibitory effects of the gamma-aminobutyric acid (GABA) pathway and suppression of the excitatory neurotransmitter glutamate, specifically through binding to the N-methyl-d-aspartate

(NMDA) receptor. Chronic alcohol use can result in adaptive changes to the neurochemical balance of the brain. To recover homeostasis, a down regulation of GABA-associated receptors and an upregulation of glutamate-associated NMDA receptors occur, leading to a decrease in the CNS effects of alcohol use, which results in tolerance.[5,8-11]

These neurochemical changes may go undetected in patients with prolonged alcohol use; however, upon reduction or cessation of alcohol consumption, serious CNS effects can occur. Without the direct effect of alcohol on the neurotransmitter systems, a dramatic decrease in the inhibitory GABA pathway and increase in the excitatory glutamate-mediated pathway take place. This acute imbalance can result in the CNS effects commonly associated with AWS, including delirium, hallucinations, and decreased seizure threshold.[5,8-10] (fig 1)

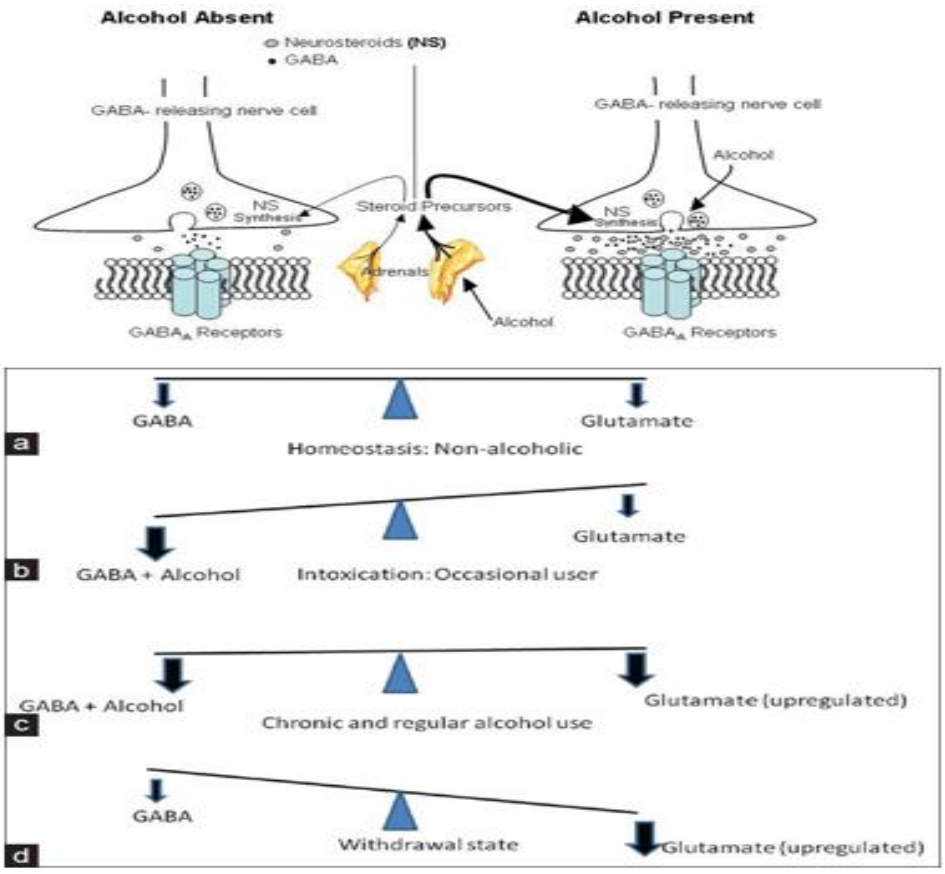


Figure No. 1: Pathophysiology of Alcohol Withdrawal Syndrome

Table No. 2: Relationship of Blood Alcohol Concentration (BAC) to Clinical Status

Blood Ethanol Concentration	Clinical Presentation
50 mg/dL (0.05 mg%)	Motor function impairment observable
80 mg/dL (0.08 mg%)	Moderate impairment; legal definition of intoxication in all states when driving
450 mg/dL (0.45 mg%)	Respiratory depression
500 mg/dL (0.50 mg%)	LD50 for ethanol

Chronic use of alcohol can produce significant tolerance; therefore, the BAL cannot be used as a sole determinant of physiologic status. By contrast, for the alcohol naïve, a BAC in the 0.30 mg% range can be fatal, although chronic drinkers can be awake and alert at even higher levels. The blood ethanol concentration generally correlates with the clinical presentation of the patient (Table 2), but tolerance varies among individuals. Impairment in motor function may become observable at levels of 0.05 mg%. Moderate motor impairment usually is seen at 0.08 mg%, which is the legal definition of intoxication in all states when driving. Respiratory depression may occur with ethanol concentrations 0.45 mg%. The accepted median lethal dose (LD50) for ethanol in humans is a blood concentration of 0.50 mg%, although fatalities have been reported with ethanol concentrations ranging from 0.295to 0.699 mg%.

DIAGNOSIS AND SCREENING

Initial evaluation of a patient with AWS relies heavily on clinical presentation. Diagnosis is based mainly on symptoms and may be guided by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). DSM-5 criteria for AWS include presentation with any two identified symptoms, including autonomic symptoms (diaphoresis, tachycardia), increased hand tremors, nausea and/or vomiting, psychomotor agitation, anxiety, generalized tonic-clonic seizures, and hallucinations.[2,12]

Obtaining a medical and social history is also necessary for diagnosis and to rule out other concurrent conditions with presentations similar to AWS. Historical data including quantity of alcohol ingested, duration of alcohol use, time since last drink, history of alcohol withdrawal, abuse of other agents, and concurrent medical or psychological problems can provide important context for individual patient cases. Laboratory data such as metabolic panels, blood-alcohol levels, liver-function tests, and toxicology screens may be useful, especially when the provider is unable to obtain an adequate patient history.[6,13-15]

DSM-IV DIAGNOSTIC CRITERIA OF ALCOHOL WITHDRAWAL

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.

B. Two (or more) of the following, developing within several hours to a few days after criterion A:

- ✓ Autonomic hyperactivity (eg, sweating or pulse rate greater than 100/min)
- ✓ Increased hand tremor
- ✓ Insomnia
- ✓ Nausea or vomiting
- ✓ Transient visual, tactile, or auditory hallucinations or illusions
- ✓ Psychomotor agitation
- ✓ Anxiety
- ✓ Grand mal seizures

C. The symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

DSM-IV DIAGNOSTIC CRITERIA FOR ALCOHOL WITHDRAWAL DELIRIUM

The diagnosis of alcohol withdrawal delirium should be made instead of a diagnosis of alcohol withdrawal when the cognitive symptoms are in excess of those usually associated with the withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention:

A. Disturbance of consciousness (ie, reduced clarity of awareness of the environment), with reduced ability to focus, sustain, or shift attention.

B. A change in cognition (such as memory deficit, disorientation, or language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia.

C. The disturbance develops in a short period (usually hours to days) and tends to fluctuate during the day.

D. There is evidence from the history, physical examination, or laboratory findings that the symptoms in criteria A and B developed during, or shortly after, a withdrawal syndrome.

Although several assessment tools are available to aid in diagnosis, the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar), is the most commonly used tool.[16-18] CIWA-Ar, a 10-item survey that measures the severity of alcohol withdrawal, requires minimal patient participation. Symptoms assessed include nausea and vomiting; tremor; paroxysmal sweats; anxiety; agitation; tactile, auditory, and visual disturbances; headache or fullness in head; and orientation and clouding of sensorium. Most items are rated on a scale of 0 to 7, with 0 being normal and 7 being extremely severe. The cumulative score, which can be a maximum of 67, corresponds to the severity of the patient's withdrawal. A cumulative score of 1 to 7 indicates mild withdrawal, 8 to 15 denotes moderate withdrawal, and 16 or higher means severe withdrawal.[16-19] Institutions frequently use CIWA-Ar in standardized protocols in order to help treat AWS.

PAWSS SCORE (Prediction of Alcohol Withdrawal Severity Score)

A tool for predicting the risk for alcohol withdrawal is the PAWSS Score (Table 1). This instrument is intended as a screening tool. The maximum number of points is 10. A greater number of points shows a higher risk for developing AWS. A value below 4 shows low risk for developing AWS, while a value above sets a moderate risk.

Table 1. Prediction of Alcohol Withdrawal Severity Score (PAWSS)[3]

Part A: Threshold Criteria	Score (1 point)
1. Have you consumed any amount of alcohol (i.e. been drinking) within the last 30 days?	
OR did the patient have a positive blood alcohol level (BAL) on admission?	
If the answer is Yes to either question, proceed with the test:	
Part B: Patient Interview	
2. Have you ever experienced previous episodes of alcohol withdrawal?	
3. Have you ever experienced an alcohol withdrawal seizure?	
4. Have you ever experienced delirium tremens or DT's?	
5. Have you ever undergone alcohol rehabilitation treatment? (i.e., inpatient, outpatient treatment programs or alcoholic anonymous attendance)	
6. Have you ever experienced blackouts?	
7. Have you combined alcohol with other "downers" like benzodiazepines or barbiturates during the last 90 days?	
8. Have you combined alcohol with any other substance of abuse during the 90 days?	
Part C: Clinical Evidence	
9. Was the patient's blood alcohol level (BAL) on presentation >200 mg/dL?	
10. Is there evidence of increased autonomic activity? (i.e., HR >120 bpm, tremor, sweating, agitation, nausea)	
TOTAL SCORE	

COMPLICATIONS OF ALCOHOL WITHDRAWAL

A diagnosis of AWS is made when:

✓ clear evidence of recent cessation/reduction of alcohol intake after heavy and prolonged use is confirmed;

✓ the patients' symptoms are not accounted for by another medical or behavioural disorder.

Diagnosis requires the history of the amount and frequency of alcohol intake, the temporal relation between reduction of intake and the onset of symptoms that may resemble a withdrawal state. AWS can occur as early as 6 hours after alcohol cessation, peaks after 2-3 days and can persist up to 7 days after alcohol cessation. If the onset of withdrawal-like symptoms is after more than 14 days of complete cessation of alcohol, the diagnosis of AWS becomes unsustainable. Symptoms range from minor to severe. Minor withdrawal signs and symptoms are due to CNS hyperactivity (Table-1).

If withdrawal does not progress, the symptoms resolve within 24 to 48 hours and can be managed in ambulatory settings. Moderate to severe withdrawal usually begins 48-72 h after the last drink and can last up to 14 days. Syndromes specific for non-minor withdrawal are alcoholic hallucinosis, alcohol withdrawal seizure and delirium tremens. Severe alcohol withdrawal is often associated with fluid and electrolyte status abnormalities. Due to diaphoresis, hyperthermia and decreased oral intake, many patients are hypovolemic. Hypomagnesemia may predispose to seizures and dysrhythmias. Alcoholic hallucinosis – visual/ tactile/ auditory hallucinations that appear in a well-oriented patient with stable vitals. In most cases lasts between 24h and 6 days 6. Alcohol withdrawal seizure – usually generalized tonic-clonic seizures. May begin within 6-48 h after last drink. It presents a high risk of progression towards delirium tremens.

Delirium tremens (DT) – is a specific type of delirium in patients suffering from alcohol withdrawal, consisting in altered sensorium with disorientation, perceptual abnormalities (illusions and hallucinations)and psychomotor agitation with altered sleep wake-cycle. It begins after 48-72 h after the last drink and may last up to 14 days. Studies show mortality between 5 and 10 percent, hence early recognition is important. Death usually occurs due to arrhythmia or associated comorbid illness such as pneumonia[7].

CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT FOR ALCOHOL SCALE, REVISED (CIWA-AR)

After the clinical diagnosis of alcohol, withdrawal syndrome has been established, the management is directed at alleviating symptoms and identifying and correcting metabolic derangements. Supportive care, including nutritional supplementation and frequent clinical reassessment, is of crucial importance. An instrument to objectively measure the severity of alcohol withdrawal is the CIWA-Ar scale (Clinical Institute Withdrawal Assessment - Alcohol Revised). It is not useful in differentiating between DT and delirium caused by other medical illnesses. The scale includes 10 common signs and symptoms of alcohol withdrawal, with notable exceptions of pulse rate and blood pressure.

Scores of 0-9 indicate absent to minimal withdrawal, 10-19 indicate mild to moderate withdrawal (increased autonomic arousal) and scores greater than 20 or more indicate severe withdrawal, with a high risk of developing DT. The score can be used to monitor the severity

of withdrawal and in titrating pharmacotherapy. Observations should be carried out every 2 hours and consist of:

- ✓ Measuring blood pressure.
- ✓ Measuring pulse.
- ✓ Measuring respiratory rate [if below 10 breaths per minute – call emergency team].
- ✓ Applying CIWA-Ar scale.

The descriptions of each withdrawal syndrome is rated and then added for a final score. CIWA-Ar maximum score is 67. In the first 24 hours, the score should be re-evaluated every 2 hours; if the score is between 0 to 9 or the patient is asleep, no treatment is needed, if it is above 8, pharmacologic treatment is needed.

Table 3. Clinical Institute Withdrawal Assessment for Alcohol - Revised (CIWA-Ar) scale[8]

Nausea and Vomiting: Ask "Do you feel sick to your stomach? Have you vomited?" Observation: 0 no nausea with no vomiting 1 mild nausea with no vomiting 2 3 4 intermittent nausea with dry heaves 5 6 7 constant nausea, frequent dry heaves and vomiting	**Tactile (touch) Disturbances:** Ask "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation: 0 none 1 very mild itching, pins and needles, burning or numbness 2 mild itching, pins and needles, burning or numbness 3 moderate itching, pins and needles, burning or numbness 4 moderately severe hallucinations 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations
Tremor: Arms extended and fingers spread wide apart. Observation: 0 no tremor 1 not visible, but can be felt fingertip to fingertip 2 3 4 moderate, with patients' arms extended 5 6 7 severe, even with arms not extended	**Auditory (hearing) Disturbances:** Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing you? Are you hearing things you know are not there?" Observation: 0 not present 1 very mild harshness or ability to frighten 2 mild harshness or ability to frighten 3 moderate harshness or ability to frighten 4 moderately severe hallucinations 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations
Paroxysmal Sweats: Observation: 0 no sweat visible 1 barely perceptible sweating, palms moist 2 3 4 beads of sweat obvious on forehead 5 6 7 drenching sweats	**Visual (sight) Disturbances:** Ask "Does the light appear to be too bright? Is it's colour different? Does it hurt your eyes? Are you seeing anything that's disturbing you? Are you seeing anything that you know is not there?" Observation: 0 not present 1 very mild sensitivity 2 mild sensitivity 3 moderate sensitivity 4 moderately severe hallucinations 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations
Anxiety: Ask "Do you feel nervous?" Observation: 0 no anxiety, at ease 1 mildly anxious 2 3 4 moderately anxious or guarded, so anxiety is suggested 5 6 7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic states	**Headache, Fullness in Head:** Ask "Does your head feel different? Does it feel like there is a band around your head? Do not rate for dizziness or lightheadedness. Otherwise, rate severity. Observation: 0 not present 1 very mild 2 mild 3 moderate 4 moderately severe 5 severe 6 very severe 7 extremely severe
Agitation: Observation: 0 normal activity 1 somewhat more than normal activity 2 3 4 moderately fidgety and restless 5 6 7 paces back and forth during interview, or thrashes about	**Orientation and Clouding of Sensorium:** Ask „What day is this? Where are you? Who am I?" 0 orientated and can do serial additions 1 cannot do serial additions or is uncertain about date 2 disorientated for date by no more than 2 calendar days 3 disorientated for date by more than 2 calendar days 4 disorientated for place or person

TREATMENT

Before starting any treatment, it is important to follow these steps:

i. Ruling out (or diagnosing) any physical disorder.

ii. Ruling out (or diagnosing) any psychiatric disorder and/or co-morbid substance use disorder.

iii. Assessment of motivation for treatment.

iv. Assessment of social support system.

v. Assessment of personality characteristics of the patient.

vi. Assessment of current and past social, interpersonal and occupational functioning.

The treatment can be broadly divided into two categories which are often interlinked. These are detoxification and treatment of alcohol dependence. Overall therapy goals for the AWS patient include minimizing and treating milder symptoms of withdrawal while preventing progression to alcoholic hallucinosis (alcohol-related psychosis), seizures, or DT. Supportive care and benzodiazepines (BZDs) are the mainstays of therapy to achieve these aims, with most evidence supporting the use of BZDs to treat withdrawal.[5,6,11,20] Additional treatment options include barbiturates, anticonvulsants, and adrenergics.[5,11,20]

DETOXIFICATION

Detoxification is the treatment of alcohol withdrawal symptoms, i.e. symptoms produced by the removal of the 'toxin' (alcohol). The best way to stop alcohol (or any other drug of dependence) is to stop it suddenly unless the risks of acute discontinuation are felt to be high by the treating team. This decision is often based on several factors including chronicity of alcohol dependence, daily amount consumed, history of alcohol withdrawal complications, level of general health and the patient's wishes. The usual duration of uncomplicated withdrawal syndrome is 7-14 days.

- The aim of detoxification is symptomatic management of emergent withdrawal symptoms.

- The drugs of choice for detoxification are usually **Benzodiazepines.**

- Chlordiazepoxide (80-200 mg/day in divided doses) and diazepam (40-80 mg/day in divided doses) are the most frequently used benzodiazepines.

- The higher limit of the normal dose range is used in delirium tremens.

- A typical dose of Chlordiazepoxide in moderate alcohol dependence is 20 mg QID (four times a day) on day 1, 15 mg QID on day 2, 10 mg QID on day 3, 5 mg QID on day 4, 5 mg BD on day 5 and none on day 6.

- However, in more severe dependence, higher doses are needed for longer periods (up to 10 days). These drugs are used in a standardised protocol, with the dosage steadily decreasing every day before being stopped, usually on the tenth day.

- **Chlormethiazole** (1-2 g/day) and carbamazepine (600-1600 mg/day) are experimental drugs and should not be used routinely for detoxification.

In addition, vitamins should also be administered. In patients suffering from (or likely to suffer from) delirium tremens, peripheral neuropathy, Wernicke-Korsakoff syndrome, and/or with other signs of vitamin B deficiency (especially thiamine and nicotinic acid), a preparation of vitamin B containing 100 mg of thiamine (vitamin B1) should be administered parenterally, twice every day for 3-5 days. This should be followed by oral administration of vitamin B1 for at least 6 months.

Care of **Hydration** is another important step; it is extremely important not to administer 5% dextrose (or any carbohydrate) in delirium tremens (or even in uncomplicated alcohol withdrawal syndrome) without thiamine. Although detoxification can be achieved on an outpatient (OPD) basis, some patients do require hospitalisation. These patients may present with:

i. Signs of impending delirium tremens (tremor, autonomic hyperactivity, disorientation, or perceptual abnormalities), or

ii. Psychiatric symptoms (psychotic disorder, mood disorder, suicidal ideation or attempts, alcohol induced neuropsychiatric disorders), or

iii. Physical illness (caused by chronic alcohol use or incidentally present), or

iv. Inability to stop alcohol in the home setting. Detoxification is the first step in the treatment of alcohol dependence.

SUPPORTIVE CARE

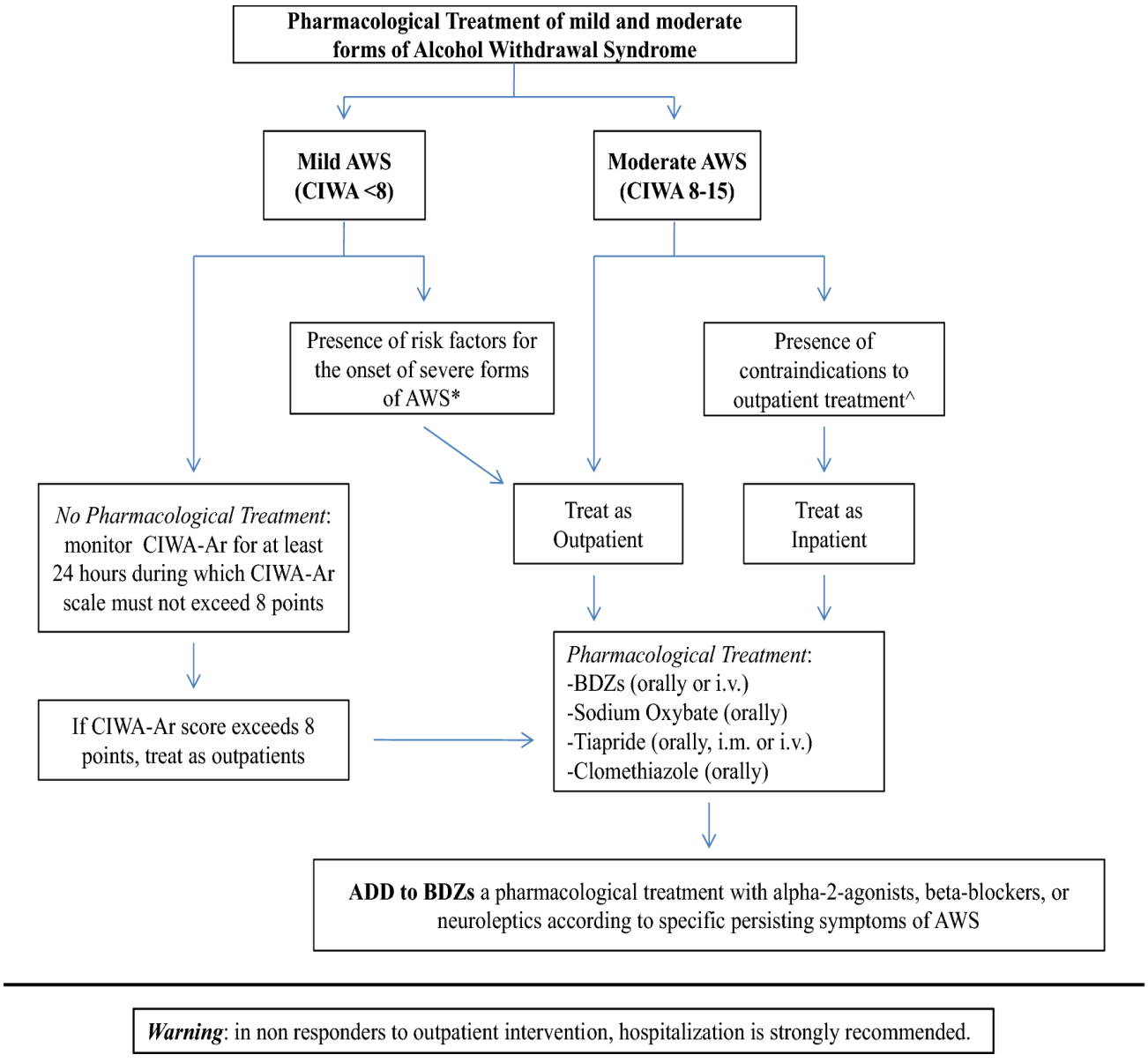
Supportive care includes addressing nutritional deficits, treating dehydration, and preventing delirious patients from harming themselves or others. In patients with abnormal vital signs or underlying comorbidities, these factors should be monitored and stabilized as much as possible on presentation. Patients with a long history of AUD often present with malnutrition, which is attributable to poor dietary intake and malabsorption in the gastrointestinal (GI) tract. Chronic alcoholism is associated with a high risk of thiamine deficiency. Thiamine and glucose should be administered to patients experiencing or at high risk for Wernicke encephalopathy, a neurologic condition caused by chronic thiamine deficiency.[15,20,21]

The standard recommendation is to administer thiamine 100 mg IV prior to the glucose, but the necessity of this order of administration is currently under debate.[21] It had been theorized that administering glucose first might precipitate the development of Wernicke encephalopathy, but recent studies have suggested that when the thiamine is administered with or shortly after glucose, the risk is alleviated and necessary treatment of hypoglycemia—if present—may be initiated sooner.[15]

Additional nutritional deficits and imbalances, such as folic acid, magnesium, and other vitamins and minerals, may exist in patients with chronic AUDs. Literature concerning the overall impact of correcting these deficiencies is conflicting, but enteral or parenteral multivitamins and magnesium may be administered for replacement if appropriate.[22] Water and electrolyte disturbances should be corrected as well. Caution is important when rehydrating dehydrated patients because AWS patients may retain excess fluid, leading to fluid overload.[13] Physical restraints should generally be avoided, except when necessary to protect the patient or caregivers from harm.[22]

PHARMACOLOGIC MANAGEMENT

Initiation of pharmacologic management of acute alcohol withdrawal is generally based on clinical judgment. In the literature, initiation of pharmacologic therapy is usually recommended only in cases of moderate or severe withdrawal (as designated by a **CIWA-Ar** score of 8 or higher).[6,20] However, clinicians may deem it is also warranted in patients with a low risk of AWS.



BZDs: These agents have the most evidence supporting their efficacy; therefore, they are the most commonly used medication class for treating alcohol withdrawal.[5,6,11] BZDs stimulate GABA type A receptors and have been shown to lessen withdrawal severity, including reduced risks of seizures and DT development.[20]Evidence suggests that all BZDs are effective for treating AWS.[23] Therefore, agents may be selected according to the patient's specific clinical situation. This decision should be based on various differentiating factors in the drugs' pharmacokinetic profiles, primarily duration of action and metabolism (TABLE 3). In general, BZDs with active metabolites offer a longer duration of action and may result in fewer rebound CNS effects. These longer-acting agents may be inappropriate for some patients, however, such as those with known hepatic disease or at high risk for respiratory depression.[5,20]

Table No. 4: Comparison of Benzodiazepine agents for AWS

Benzodiazepine	Dosage Forms	Equivalent Dose	Duration	Active Metabolites
Diazepam	Oral and IV	5mg	Long	Yes
Chlordiazepoxide	Oral	25mg	Long	Yes
Lorazepam	Oral and IV	1mg	Short	No
Oxazepam	Oral	15mg	Short	No

Strategies for BZD therapy include loading-dose, fixed-dose, and symptom-triggered regimens. Loading-dose regimens involve administering a high dose of a long-acting BZD every 2 hours and monitoring the patient's CIWA-Ar score before every dose until withdrawal symptoms resolve or the patient is under sedated. A reduced dose may then be administered less frequently on an as-needed basis to maintain the desired effect. This regimen may be preferable, as the duration of therapy is shorter (often not more than 1-2 days, although it may be extended to 72 hours if there is a risk of DT) and the overall dose of BZDs required is lowered.[15,21] Loading-dose regimens may be especially beneficial in patients experiencing severe withdrawal when the risk of withdrawal symptoms outweighs the risk of oversedation. Patients at higher risk for respiratory depression, such as those who are elderly or have concomitant hepatic or respiratory disorders, may be poor candidates for this approach.[5,11,20]

Fixed-dose strategies are less aggressive and more patient-specific. An initial total daily dose of BZDs may be determined based on a patient's average daily alcohol consumption (see BOX 1 for formula).[24] Every 10 grams of alcohol are equivalent to one drink and should

be countered with 5 mg of diazepam. This dose should then be adjusted for patient comorbidities, risk of accumulation, and amount of time since the patient's last drink. Long-acting BZDs are recommended owing to the low risk of breakthrough symptoms, although individual patient assessment should dictate the most appropriate agent. The dose is then tapered at scheduled intervals based on continued monitoring, which results in an extended therapy duration compared with loading-dose regimens. This approach is beneficial when barriers to close monitoring exist or CIWA-Ar scores are difficult to determine.[5,11,20]

Formula for calculating initial total daily BZD dose:

Gram Ethanol = Volume of Drink (ml)*****0.8*****Alcohol Content (%)/100

Symptom-triggered dosing, a more reactive approach, requires the most monitoring and is based specifically on CIWA-Ar score. This regimen is not appropriate for all patients, but it may reduce the risk of overmedicating. It is not recommended for use in any patient who has previously experienced withdrawal seizures or DT. The patient must also be capable of reporting any withdrawal symptoms being experienced. Although symptom-triggered therapy may have limited applicability, it has demonstrated a reduced duration of therapy and lower cumulative dose compared with fixed-dose regimens.[25] Patients without a history of previous withdrawal complicated by seizures or DT who have a moderate withdrawal risk according to CIWA-Ar scores may benefit from this regimen.[5,11,20]

Barbiturates:

Phenobarbital has been investigated as a treatment option for AWS. The potential mechanism for its benefit is a direct effect on the GABA neurochemical pathway that offers a cross-tolerance effect with alcohol. Research on the use of phenobarbital for AWS has historically produced mixed results.[20,26,27] However, recent literature has yielded more encouraging data. A retrospective cohort study of ICU patients evaluated treatment with a symptom-triggered BZD regimen versus phenobarbital.[26] The phenobarbital cohort demonstrated significantly shorter ICU stays and overall hospitalization than the standard-of-care BZD cohort. The phenobarbital cohort also required fewer intubations and adjunctive agents for further symptom control. It was concluded that phenobarbital may be an effective alternative to traditional BZD therapy.[26]

Anticonvulsants:

Some anticonvulsant agents may also be useful for the management of AWS. Anticonvulsants have been shown to reduce cravings and treat mood disorders, both of which may occur in AWS patients. Although anticonvulsants' side-effect profiles vary by agent, they are generally less sedating than BZDs, which may be an advantage in some situations.[20,28]

Carbamazepine:

(CBZ) is one of the most investigated anticonvulsants for AWS, and research suggests that CBZ may be a suitable alternative to traditional BZD therapy. A study that compared CBZ with lorazepam in an outpatient setting concluded that, in addition to being effective, CBZ was superior for preventing rebound withdrawal symptoms.[29] Although CBZ appears to be useful for treatment of AWS, evidence is inconclusive regarding its efficacy in treating withdrawal-associated seizures and DT compared with BZDs.[30] This deficit, combined with associated side effects and drug interactions, has generally limited the use of CBZ in this setting.

Other anticonvulsants have also been evaluated, including valproic acid, gabapentin, and vigabatrin. Although findings are more limited than for BZDs and CBZ, all of these agents have demonstrated benefit in AWS and could be considered alternative therapies. Each agent's adverse-effect profile should be taken into account, especially those of valproic acid. Although valproic acid may be effective, its use is generally limited by side effects that mimic the CNS and GI disturbances that commonly occur in AWS.[20,28-33]

Adrenergic Drugs:

Both adrenergic agonists (e.g., clonidine) and adrenergic antagonists (e.g., propranolol) have been used to treat symptoms of AWS. The benefit is theorized to be linked to reductions in blood pressure and heart rate, which lead to an overall decrease in autonomic response. Evidence generally does not support the use of adrenergic medications for prevention or treatment of withdrawal-associated delirium or seizures. The use of adrenergic medications is limited to adjunctive therapy with BZD treatment, and monotherapy should not be used in patients whose CIWA-Ar category exceeds low risk.[20,34]

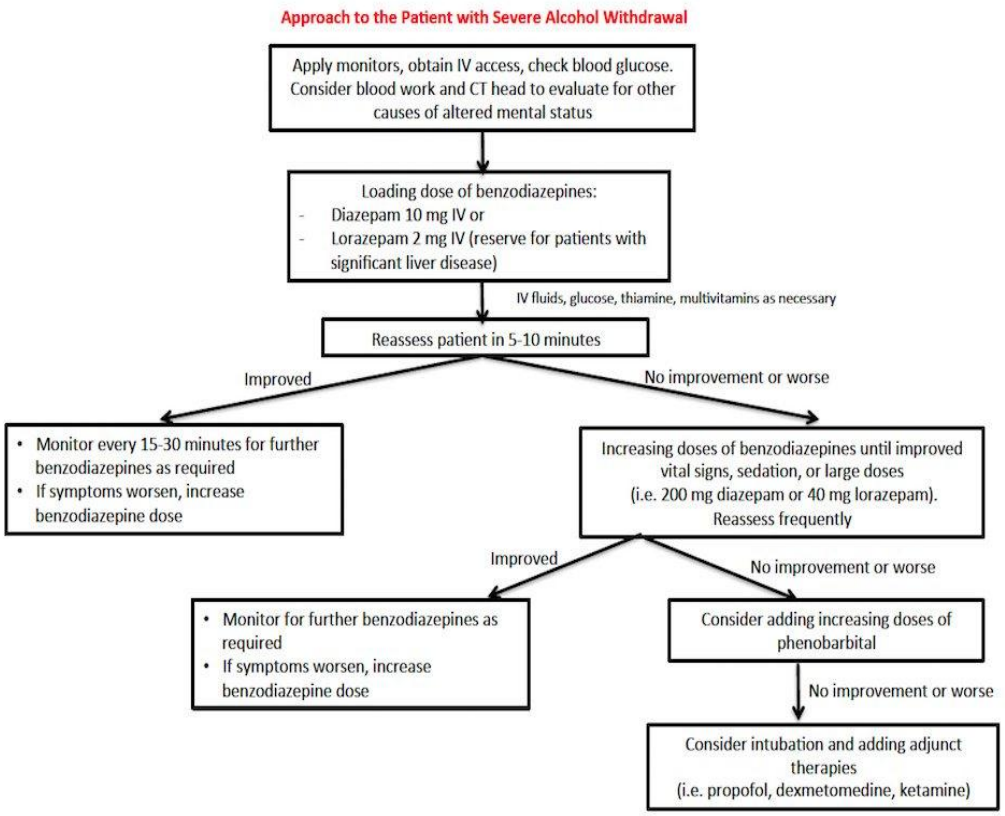


Figure No. 2: Approach to the patient with severe alcohol withdrawal

MANAGEMENT OF ACUTE ALCOHOL WITHDRAWAL SYNDROME

Prior to treatment, patients should be investigated clinically and Para clinically, regarding the degree of possible liver alterations or another comorbidity [9-14]. Patients require non-pharmacologic, as well as pharmacologic treatment. Patients suffering from alcohol withdrawal are best treated in a quiet room, where minimal external stimulation can occur. All patients with moderate to severe AWS should have immediate IV access for rapid administration of drugs and fluids. Intramuscular administration should be avoided because of variable drug absorption. Adequate sedation is necessary in order to maintain a calm, but alert patient. In some cases, physical restraints are used for prevention of injuries due to agitation. Fluid and electrolyte imbalances must be promptly corrected. Vitamin B supplementation helps to prevent Wernicke's encephalopathy (WE). In the first days, treatment should be administered intravenously, due to impaired gastrointestinal absorption often met in chronic alcohol users. During the early phases of withdrawal, patients are given nothing by mouth, to decrease the risk of aspiration. The main treatment of AWS is

detoxification and consists in gradually tampering the dependence. Studies are strongly in favour of using benzodiazepines for treating acute AWS, because they undoubtedly reduce the risk of seizures and DT[15]. Diazepam, lorazepam and chlordiazepoxide are most commonly used. Benzodiazepines enhance the effects of the gamma-aminobutyric acid at the GABA receptor, resulting in sedative, hypnotic and anxiolytic effect. Chlordiazepoxide and diazepam are the agents of choice, but in the presence of co-morbidities, oxazepam and lorazepam are recommended, due to their shorter half-life, that prevents prolonged effect if over-sedation occurs. Patients with impaired hepatic function (advanced cirrhosis or acute alcoholic hepatitis) are best treated with lorazepam or oxazepam. The equivalency of benzodiazepine doses (approximate) are as following: diazepam10 mg = chlordiazepoxide 25 mg = lorazepam 1 mg. Anticonvulsants have not been proven to be better than benzodiazepines, but may be considered in mild withdrawal states, because of lower sedation and lower chances of abuse potential[16].

TREATMENT REGIMENS USED IN ALCOHOL WITHDRAWAL STATES

The fixed-dose regimen consists in giving benzodiazepines (dose based upon the severity of the withdrawal and time since the last drink) at fixed intervals. Because frequent reassessment of the clinical status of the patient is not needed, this regimen is best suited for minimally symptomatic patients in out-patient settings[16]. The loading dose regimen consists in treating the patient with 20 mg of diazepam every 2 h, but before each administration, the clinical condition and the withdrawal severity using CIWA-Ar score must be checked. This regimen has been shown to reduce the total dose of administered benzodiazepines and the duration of withdrawal symptoms[17]. Symptom-triggered treatment (STT) requires close monitoring of symptoms and treating the in-patient with drugs only when CIWA-Ar ratings are 8 or more. Frequent re-evaluation of the clinical status is needed. It is useful in patients who have never had complicated withdrawals. Multiple randomized and observational studies support this regimen because it achieves equivalent clinical endpoints while requiring lower total doses of sedatives and shorter periods of hospitalization. Symptom-monitored loading regimen: In the presence of acute medical illness or a past history of severe withdrawals, a single loading dose of 20 mg diazepam should preferably be given immediately. Further doses of diazepam should be given orally every 2 h until CIWA-Ar scores are less than ten. This strategy combines the principles of symptom-triggered treatment strategy while also taking into account the history of severe withdrawals[17].

MANAGEMENT OF MINOR ALCOHOL WITHDRAWAL SYNDROME

Minor cases of withdrawal may not need pharmacologic treatment in most cases, and often the supportive care in a calm and quiet environment over a 36 hours period is enough[16]. An acute medical illness or a history of severe episodes of alcohol withdrawal justify the use of a single dose of 20 mg of diazepam and further monitoring[19].In the absence of these risk factors, out-patient treatment is possible. Pharmacotherapy is started if the patient presents signs of CNS hyperexcitability, like increased systolic blood pressure (above 150 mmHg), increased diastolic blood pressure (above 90 mmHg), tachycardia (above100/min), fever (body temperature above 37.7 Celsius degrees), agitation or insomnia[4].

MANAGEMENT OF MODERATE TO SEVERE ALCOHOL WITHDRAWAL SYNDROME

Cases without seizures or DT are best managed using a symptom-monitored loading regimen (treating with benzodiazepines only if CIWA-Ar score is above 9) or with a fixed-dose regimen, where adequate personnel for calculating CIWA-Ar score is not available[20].In cases with seizures or DT, a rapid loading regimen is preferred, with frequent boluses of intravenous diazepam, until the patient is calm and sedated, regardless of the CIWA-Ar score[21-24]. Seizure prophylaxis with 2mg IV lorazepam is recommended for patients with history of withdrawal seizure. Lorazepam is more effective than diazepam in preventing seizure recurrence, due to its poor lipid solubility, which does not let brain levels fall rapidly. In such patients, it may still be required do give diazepam doses of at least 20 mg – 60 mg in a symptom-monitored regimen[25]. In patients with seizures, a neurological workup is needed to detect alternative causes[26-28]. DT is best treated with the use of IV diazepam administered at frequent intervals, with close monitoring. Treatment begins with an initial dose of 10 mg of diazepam. Further doses of 10 mg are given at approximately 15 minutes interval[29-30]. Once the goal of light somnolence is achieved, the patient can be shifted to a symptom-triggered regimen[23,31]. The undiluted emulsion is administered at a rate of 1 ml (5 mg) per minute. For patients with liver failure, IV lorazepam is the drug of choice. The goal of sedation is a calm, but alert state. In the elderly, only half the benzodiazepine dose is recommended. For patients who are difficult to assess using the CIWA-Ar score, a fixed schedule reducing regimen is recommended. This including patients who are confused, don't speak the native tongue or are unable to communicate effectively. Inappropriately managed WE is a major contributory cause of death in patients suffering from alcohol withdrawal syndrome and results in

permanent brain damage in a great number of survivors. Because the classic triad of signs, consisting in acute confusion, ataxia and ophthalmoplegia, is only seen in 10% percent of patients, it cannot be used as a basis of diagnosis. Wernicke's encephalopathy is reversible in the early stages if a rapid restoration of B vitamins (in particular thiamine – B1) in CNS is initiated. All patients undergoing alcohol withdrawal should be treated prophylactically for WE with thiamine 100 mg IV ampoule, three times a day. Every ampoule should be diluted in 50 ml to 100 ml sodium chloride 0.9% and infused over 30 minutes. Absorption of oral thiamine is limited and not sufficient to treat WE[34].

CLINICAL PHARMACIST'S ROLE

➢ There are many areas for clinical pharmacist intervention with AUD patients in the inpatient setting. Obtaining a thorough medical and social history and medication reconciliation can help clinicians identify patients at risk for withdrawal before symptoms present.

➢ Clinical Pharmacists can also help the multidisciplinary team select the most appropriate BZD agent and dosing regimen.

➢ Based on the status of non-BZD treatments for AWS, clinical pharmacists can provide insight into the appropriateness of adjunct medications for individual patients.

➢ We need and overcome the AWS by the following programs like conduction of quality-based seminars, health care camps, conferences, published medical literature and learning programs.

CONCLUSION

- Alcohol-withdrawal syndrome (AWS) is a challenge to patient care that can present in the inpatient setting. Early identification and treatment initiation in patients with a history of alcohol-use disorder are necessary in order to minimize the development of AWS.

- As a clinical pharmacist we are read many review articles and ward rounds participation experiences they concluded the result, chronic alcohol consumption poses many risks on health status. AWS is associated with risks of complications and should be carefully managed in the clinical practice, by non- pharmacologic measures and pharmacological treatment.

- As a clinical pharmacist, we observed the many case studies, alcohol withdrawal requires medical treatment and hospital admission. Medication may also be used to treat physical symptoms while patient counselling and support groups help with controlling drinking behaviour.

- As a clinical pharmacist can assist the multidisciplinary team in identifying patients at risk for AWS as well as recommend safe and effective treatment regimens on an individual basis.

- Clinical Pharmacists & clinician can also guide and monitor the patients prescribed medication therapy throughout the hospital stay and counselling like patient education, individual psychotherapy, behaviour therapy, motivational enhancement therapy, cognitive behaviour therapy etc. them about their disease, medication, dose & side effects at discharge.

COMPETING INTEREST:

The authors declare that they have no competing interests.

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