Chapter

Improving the Safety of Admitted Patients with Alcohol Use Disorder and Withdrawal

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Abstract

The aim of this chapter is to review the pathophysiology of alcohol withdrawal syndrome (AWS), discuss diagnostic strategies, identify clinical manifestations, outline appropriate management options, and address key patient safety considerations specifically as it applies to the hospitalized patient. Ethanol use causes substantial morbidity and mortality and is among the most widely abused substances in the world. Up to 40% of all hospitalized patients are at risk for suffering from alcohol withdrawal syndrome (AWS). AWS is a hyperdynamic syndrome with symptoms that can include anxiety, insomnia, tachycardia, hypertension, tremor, nausea, vomiting, seizures, coma, disability, and death. Several screening tools can help identify patients with alcohol use disorder and those at risk for AWS. Symptom based scoring systems, such as the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) or Severity of Ethanol Withdrawal Score (SEWS) score, are also available for guiding treatment. Treatment options should primarily consist of Gamma-Aminobutyric Acid (GABA) agonists, including benzodiazepines and barbiturate (mainly phenobarbital) medications, however other adjunctive therapies are also available. The most important patient safety principles for the hospitalized patient with AWS include early assessment, identification, and intervention, treatment of associated medical and psychiatric complications, as well as a comprehensive multi-disciplinary approach.

Keywords: Alcohol withdrawal syndrome, patient safety, phenobarbital, toxicology, addiction medicine

1. Introduction

Ethanol is the one of the most widely abused substances in the world and is associated with substantial morbidity and mortality. Approximately 85% of adults over the age of 18 report alcohol consumption in the United States, and annually ~90,000 people die from alcohol related causes [1]. Nearly 15 million Americans meet criteria for alcohol use disorder (AUD), and it is estimated that up to 40% of hospitalized patients suffer from AUD, putting them at risk for alcohol withdrawal syndrome (AWS) and other related conditions [2]. AWS is a spectrum illness that ranges from early or mild symptoms (anxiety, headache, nausea, sleep disturbances)

to later, severe, life threatening complications including seizures, dysautonomia, coma, and death [2]. It is critical for healthcare professionals to be able to recognize and understand key principles related to AWS, as well as the health conditions and complications associated with alcohol use disorder, in order to collaboratively ensure the safety and wellness of the hospitalized patient.

2. Methodology

A comprehensive literature search was used to obtain evidence to support this manuscript. Sources included internet-based search engines such as PubMed, Google™ Scholar, and SCOPUS™ in addition to other medical textbooks, commercialized medical resources (EMRAP™, UpToDate™, EMCRIT™), and internationally recognized societal guidelines (*American Society of Addiction Medicine, American College of Emergency Physicians, American College of Medical Toxicology)*. Common search terms included but were not limited to "alcohol withdrawal syndrome," "complicated alcohol withdrawal syndrome," "inpatient management of alcohol withdrawal syndrome," "pathophysiology of alcohol withdrawal," "alcohol withdrawal seizures," "delirium tremens," "phenobarbital and alcohol withdrawal syndrome," "CIWA," "SEWS," Wernicke's Encephalopathy," "medical management of alcohol withdrawal syndrome," alcohol withdrawal syndrome complications," "patient safety and alcohol withdrawal." Our search initially queried more than one million sources; sources were screened and appraised based on their quality of evidence and relevancy to alcohol withdrawal syndrome in the hospitalized patient. This narrowed down the literature search to approximately 100 articles which were further consolidated based on redundancy, resulting in the 33 sources included in the chapter.

3. Pathophysiology

Ethanol (C_2H_5OH) is a two-carbon molecule with an attached hydroxyl group. Various alcoholic beverages contain between 5 and 40% of ethanol by concentration; one standard drink in the United States is defined as 14 grams of ethanol [3]. The molecule is slightly lipophilic and can penetrate the blood brain barrier as a result. The Central Nervous System (CNS) functions via a delicate balancing act between inhibitory γ-aminobutyric acid (GABA) receptors and excitatory glutamic N-methyl-D-aspartate (NMDA) receptors. Ethanol acts as a CNS depressant by primarily augmenting GABA receptors and antagonizing excitatory NMDA receptors [4]. At low CNS concentrations ethanol induces behavioral excitation and euphoria, whereas at higher concentrations, ataxia, drowsiness, and slurred speech are common. Longstanding alcohol consumption causes physical tolerance (increasing doses to achieve the same effect) in a multitude of CNS receptor sites, including NMDA, GABA, serotonin (5HT), glycine, G-protein coupled rectifying potassium channels, as well as several others [5]. Ethanol also directly binds to glutamate, thereby enhancing its inhibitory effect on the brain [6]. Several studies have demonstrated that specifically the δ-$GABA_A$ receptors appear to be most sensitive to ethanol [5]. These are most highly concentrated in the cerebellum, cortex, thalamic nuclei and brain stem, which correlates with the clinical manifestations of ethanol intoxication. Prolonged ethanol exposure also results in specific adaptive changes to GABA receptor concentration and subunit composition. As an example, decreased α1 and γ2 GABA subunit expression,

as seen in those with AUD, is theorized to directly affect CNS inhibitory tone [5]. Additionally, there is an upregulation of excitatory NMDA receptors. As a result, chronically consuming ethanol can predispose individuals to a baseline excitatory state [5]. Ultimately this disruption of homeostasis serves as the basis for AWS.

When a chronic ethanol stimulus is abruptly discontinued, the underlying molecular changes yield AWS. CNS excitatory activity becomes relatively unopposed. Dysautonomia results from an enhanced sympathetic nervous system activity and manifests as tachycardia, hypertension, hyperthermia, tremor, nausea, and vomiting [7]. Alcohol withdrawal related seizures are theorized to originate primarily from excitatory activity in the brainstem (specifically the inferior colliculus), although evidence also supports involvement of the hippocampus [5]. Additionally, repeated episodes of withdrawal may result in permanent epileptic changes in the brain, thus lowering the seizure threshold and putting individuals at even higher risk of AWS induced seizures [5]. Dopamine signaling, another neurotransmitter implicated in AWS, is increased as well, and appears to be responsible for the symptoms of alcoholic hallucinosis [6]. "Kindling" is another phenomenon associated with AWS, where neurons becoming increasingly sensitive, and as a result, subsequent episodes of AWS can be more severe [5, 7]. Outside of its CNS manifestations, AWS and alcohol use disorder more broadly is also associated with varying degrees of electrolyte abnormalities, metabolic derangements, nutritional deficiencies, coagulopathies and many other co-morbidities due to the toxic effects of longstanding ethanol ingestion as will be detailed in subsequent sections.

In summary, neuro-adaptive changes resulting from longstanding, regular ethanol use predispose to an excitatory neurological state, that cascades through the spectrum of AWS following cessation of ethanol. As a result, patients suffer from a range of neurologic symptoms, some of which can be life threatening. It is critical that clinicians are familiar with these manifestations and can diagnose and treat them rapidly.

4. Diagnostics

AUD is a medical condition where one experiences difficulty in stopping or controlling the use of alcohol, despite experiencing adverse social, occupational, or health consequences [8].

AUD is a significant patient safety issue in the hospitalized patient, associated with morbidity and mortality, especially when it goes undiagnosed or undertreated. Although many patients present self-reporting alcohol use disorder or withdrawal while requesting treatment, many present for new or related illnesses and complications without proper disclosure, risk stratification, assessment, or treatment and either progress to alcohol withdrawal or have other conditions that mask it due to overlapping symptomatology. For example, a patient may present with pancreatitis and not fully inform of recent or regular alcohol use. Others may present later in the disease course with symptoms or complications that may cause the clinician to overlook AUD as an etiology. Another example would be a new onset seizure in an encephalopathic patient, prompting a neurological evaluation and empiric treatment with ineffective antiepileptic agents, leaving the alcohol withdrawal untreated. A patient who fell and suffered a subdural hematoma may not be suspected of recent intoxication or alcohol related neuropathy as the cause of the fall and can then be at risk for experiencing alcohol withdrawal. These patients will be at risk of developing severe alcohol withdrawal that can result in severe complications, including permanent disability and death.

Clinicians should inquire about a patient's drinking habits, including quantity and duration of alcohol consumption, and any history of AWS to identify patients with AUD and to gauge the likelihood of AWS. Several questionnaires are useful in aiding this history taking [9]. Once screening has been performed, clinicians can then utilize additional scoring tools for risk stratification and therapy. The various screening tools that can be used for identifying alcohol use disorder in the hospital include AUDIT (Alcohol Use Disorders Identification Test), AUDIT-C (the Shortened Alcohol Use Disorders Identification Test), the CAGE questionnaire (Cut down Annoyed, Guilty, Eye-opener), the TACE (Tolerance, Annoyed Cut down, Eye-opener; mainly for pregnant patients) and SBIRT (Screening and Brief Intervention Tool). Although the in-depth description of these screening tools is beyond the focus of this chapter, it is important that hospital systems utilize a screening tool to assist in identifying and diagnosing patients with alcohol use disorder, so that they can then risk stratify who may be at risk for withdrawal and implement a treatment plan, all while evaluating and treating for common comorbidities. Risk stratification can also be performed utilizing the PAWSS score (The Prediction of Alcohol Withdrawal Severity Scale) while the most common treatment assessment tool is Clinical Institute Withdrawal Assessment (CIWA). These tools are further described in subsequent sections.

Comorbidities and other clinical clues useful for identifying alcohol use disorder may include common diagnostic findings, such as transaminitis (AST > ALT in 2–3:1 ratio, generally <500 U/L), macrocytic anemia, thrombocytopenia, and electrolyte derangements – most commonly hyponatremia, hypokalemia, and hypocalcemia; and therefore, QT prolongation and risk of dysrhythmia. Commonly associated conditions include traumatic injuries, pancreatitis, gastritis, gastrointestinal bleeding, alcoholic ketoacidosis, malnutrition, dehydration, acute kidney injury, hypertension. All of these findings should be reason to consider a patient for potentially having alcohol use disorder and being at risk for withdrawal.

Evaluation of the patient identified with alcohol use disorder or withdrawal syndrome should include electrocardiogram, complete blood count, complete metabolic panel, magnesium (especially if hypokalemic), INR, lipase if any gastrointestinal symptoms, serum ethanol concentration, and if any alteration of mental status, computed tomography of brain. CT imaging of brain should be considered particularly if any concern for traumatic injury. Further evaluation for cardiac ischemia or cardiomyopathy should also be considered. Obtaining a serum ethanol concentration is important as is it not possible for clinicians to commonly predict degree of intoxication based on assessment of clinical sobriety. An elevated serum ethanol concentration in a presenting patient should be reason to evaluate for alcohol use disorder, and should prompt concern for possible withdrawal. Although patients may begin to withdraw at elevated serum ethanol concentrations, many may not start to withdraw for easily six hours after they metabolize all their ethanol. In this case, a predictive timeline can be generated, utilizing the average ethanol metabolism of 15 mg/kg/hr., to determine how long to observe for symptomatology.

The PAWSS score is a clinical scoring tool that can be utilized to assess patients identified with AUD to risk stratify the likelihood of developing AWS (**Table 1**). Severity can then be monitored with CIWA or SEWS [10, 11]. A PAWSS score < 4 portends a low risk of moderate to severe AWS, whereas a score > 4 places a patient at high risk of experiencing severe AWS [10]. The prospective validation study of PAWSS resulted in a sensitivity of 93% and specificity of 99.5% in predicting severe withdrawal for hospitalized patients, making it a highly useful tool for the modern-day practitioner in treating AWS [12].

	Yes	No
Has the patient been intoxicated or drunk in the past 30 days?		
Has the patient EVER undergone alcohol use disorder rehabilitation treatment or treatment for alcoholism? (Inpatient or outpatient settings)		
Has the patient EVER experienced ANY previous episodes of alcohol withdrawal?		
Has the patient EVER experienced blackouts from drinking?		
Has the patient EVER experienced alcohol withdrawal seizures?		
Has the patient EVER experienced delirium tremens?		
Has the patient combined alcohol with other "downers" in the past 90 days?		
Has the patient combined alcohol with ANY other substance of abuse in the past 90 days?		
Was the patient's blood alcohol level ≥ 200 (mg/dL) on presentation?		
Is there evidence of increased autonomic activity? (Increased heart rate > 120, hypertension tremors, agitation, etc..)		

Source: [10].
Each "Yes" answered confers +1 point.

Table 1.
Prediction of Alcohol Withdrawal severity scale (PAWSS).

Question	Score Range
"Do you feel sick to your stomach? Have you vomited?"	0 to 7
Paroxysmal sweats	0 to 7
Agitation	0 to 7
"Does your head feel different? Does it feel like there's a band around your head?"	0 to 7
"Do you feel nervous?"	0 to 7
Tremor	0 to 7
"Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?"	0 to 7
"Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?"	0 to 7
"Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?"	0 to 7
"What day is today? What is this place?"	0 to 4

Source: [13].
Range of 0 to 67 with higher scores indicating higher severity of AWS.

Table 2.
Clinical Institute of Alcohol Withdrawal Score – Revised (CIWA-R).

Once a patient is identified as potentially having AUD and is then risk stratified for possibly developing AWS, several scoring systems are available for further monitoring and treatment. The revised Clinical Institute Withdrawal Assessment for Alcohol Scale

(CIWA) was among the first scores designed to appropriately guide treatment for AWS [13]. The CIWA score has been adopted across numerous health systems worldwide and is the most common clinical tool utilized for AWS. The score takes several minutes to calculate and ranges from 0 to 67 with severity of withdrawal being associated with higher scores (scores >20 indicates severe AWS). The questionnaire assesses for nausea, diaphoresis, tremor, hallucinations, among other symptoms indicative of AWS (**Table 2**). The score can then be tied to escalating doses of medications, such as benzodiazepines, for symptom triggered treatment. CIWA has been shown to result in more reliable benzodiazepine (BZD) dosing, decreased length of hospital stay, and decreased rate of severe complications when compared to unscored symptom-based dosing [14]. However, there are limitations to CIWA as several components of the questionnaire are subjective in nature and may result in variability between clinicians.

The Severity of Ethanol Withdrawal Scale (SEWS) is another clinical scoring tool that can be used to guide treatment for AWS [15]. Similar to CIWA, SEWS generates a calculated score ranging from 0 to 24 with higher scores (scores >13) indicating severe AWS (**Table 3**). SEWS is not as often utilized as CIWA currently, however in a 2019 quality assurance study, it was shown to decrease hospital length of stay by one day by allowing for more aggressive BZD treatment without over sedation risk when compared to CIWA [15]. SEWS also showed to be more objective, utilizing vital signs, and more easily performed by provider, likely since it has less questions. Further prospective studies are needed for external validation, however in the meantime, initial results appear promising in using SEWS to guide treatment for AWS.

To summarize, the three clinical scoring tools presented (CIWA, SEWS, PAWSS) are crucial when it comes to risk stratifying and treating AWS. In addition, clinicians must be mindful of the many co-morbidities that patient's suffering from AWS frequently present with and obtain appropriate diagnostic testing for these as well. Appropriately recognizing AUD, AWS and related co-morbidities is paramount for patient safety.

Question	Score if positive
Anxiety: Do you feel that something bad is about to happen to you right now?	0 or 3
NAUSEA and DRY HEAVES or VOMITING?	0 or 3
SWEATING (includes moist palms, sweating now)?	0 or 2
TREMOR: with arms extended, eyes closed	0 or 2
AGITATION: fidgety, restless, pacing	0 or 3
DISORIENTATION: Knows name and place, but not date Knows name only	0 or 1 0 or 3
HALLUCINATIONS: Auditory only (check for major psychiatric disorder) Visual, tactile, olfactory, gustatory (any)	0 or 1 0 or 3
VITAL SIGNS: ANY of the following: 1. Pulse >100 2) diastolic BP >90, 3) temp >37.6 C	0 or 3

Source: [15].
Range of 0 to 22 with higher scores indicating higher severity of AWS.

Table 3.
Severity of ethanol Withdrawal scale (SEWS).

5. Alcohol withdrawal syndrome

AWS can be considered a spectral illness, ranging from early/mild to late/severe, with additional complications, including delirium tremens (DT) and possibly Wernicke's Encephalopathy (WE) and Wernicke-Korsakoff Syndrome (WKS) which are generally considered to be secondary to thiamine (vitamin B1) deficiency. WE is often reversible with prompt recognition and treatment but can progress to the less reversible WKS if inadequately treated. It is important to realize that for patients with mild AUD, symptoms may never progress beyond mild, while for patients with severe AUD, early withdrawal may start with severe symptoms and rapidly progress. Additionally, DT is an entirely avoidable phenomenon and results from either late presentation or suboptimal treatment.

5.1 Mild: moderate AWS

In classic AWS, patients typically become symptomatic 6-hours after their last drink (or if they have significantly decreased their ethanol intake) but can take up to 24-hours before they become apparent [16]. Symptoms may begin mildly or can abruptly start as more severe grades of AWS [17]. Nausea, vomiting, and diaphoresis are common, as well as tremors, headaches, anxiety, and insomnia. Autonomic dysfunction may develop as well, including hypertension, tachycardia, and hyperthermia. It is important to recognize that patient's taking certain medication classes, such as beta-blockers or alpha-2 agonists, may mask their autonomic dysfunction [17]. Tactile, auditory, and visual hallucinations may be present in up to 25% of AWS patient's, however patient's sensorium often remains intact (as opposed to in alcoholic hallucinosis or organic psychosis) [17]. Mild to moderate AWS usually dissipates between 2 and 7 days and often without treatment [17]. These patients may not even present to healthcare facilities for evaluation or treatment and it is likely an underdiagnosed phenomenon.

5.2 Moderate: severe AWS

Moderate-severe AWS includes many of the symptoms described in mild-moderate AWS; however, symptoms are severe and may be refractory to treatment. Classic symptom (tachycardia, hypertension, tremor, nausea, vomiting, diaphoresis, anxiety) are notably worse and will likely require more aggressive treatment regimens. Hallucinations may become persistent, progressing into alcoholic hallucinosis (AH). AH occurs in up to 8% of patients and typically 12- to 24-hours after a patient's last drink [18, 19]. Neuroleptic medication has been shown to worsen hallucinations in AH and should be avoided [19].

Wernicke's Encephalopathy, the triad of confusion, ophthalmoplegia, and cerebellar symptoms (such as ataxia), may also become apparent in moderate-severe AWS. Seizures can occur in up to 10% of patients with AWS [17]. AWS seizures generally occur 24- to 48- hours after alcohol cessation. Seizure activity includes generalized tonic-clonic jerks and can lack a post-ictal period [17, 18]. AWS seizures are notoriously difficult to treat with traditional antiepileptic agents and may portend a worse prognosis, including progression into delirium tremens, a form of agitated delirium, the most severe manifestation of AWS [17]. Often escalating doses of BZD and other adjunct therapy is needed in these cases, and intensive care management may be warranted.

5.3 Delirium tremens

Delirium Tremens (DT), a form of agitated delirium, is the most severe form of AWS and occurs in up to 5% of patients [19–21]. Symptoms generally occur in the 2–4-day time range from a patient's last known ingestion. DT as a syndrome includes severe, rapid changes in cognition, memory, consciousness, and perception in addition to extreme autonomic distress including malignant hypertension and hyperthermia [17, 20]. Hallucinations, disorientation, psychosis, and coma are hallmarks of DT. Symptoms are generally refractory to treatment, may last up to one week or longer, and may be lethal. The mortality rate for DT is between 1% and 5%, generally secondary to medical complications such as aspiration or myocardial infarction [17]. Treatment for DT requires the maximum therapeutic options available to treating clinicians. Aggressive BZD dosing (often defined as >20-40 mg diazepam or equivalent per hour for severe CIWA or SEWS), phenobarbital, and adjunct therapies such as dexmedetomidine, propofol, or ketamine may be necessary. Endotracheal intubation and intensive care management are sometimes needed for patients with DT. Ultimately, DT is the most severe form of AWS and causes substantial morbidity and mortality. From a patient safety perspective, it is important to realize that DT is not a routine outcome of the spectrum of alcohol withdrawal and can be completely prevented with early, adequate treatment of AWS [22].

6. Management

6.1 Disposition

Management of alcohol withdrawal occurs in a variety of settings, the most appropriate being a withdrawal management facility, or commonly known as a "detox center," or a hospital (note that "detox" refers to management of withdrawal symptoms, not actual detoxification, which is the removal of an agent). The authors do not generally recommend outpatient alcohol withdrawal management due to the difficulty in assessing mild versus early withdrawal with the risk of worsening, as well as difficulty with patient compliance. Patients may primarily seek withdrawal management and be appropriately placed in a detox facility that meets their level of medical needs or may occur in the hospital setting. Alcohol withdrawal often occurs in the hospital setting when patients present ill from their withdrawal symptoms and require admission, present for complications of alcohol use disorder (e.g., pancreatitis, trauma, etc.) and withdraw, or present for other medical problems requiring admission and have to suddenly discontinue consumption of alcohol. When alcohol use disorder or withdrawal are encountered in the hospital setting, a collaborative approach is recommended to assure patient safety and optimize patient care. This collaborative approach may include internal medicine, critical care, medical toxicology, addiction medicine, psychiatry, and case management.

Although the focus of this chapter is alcohol withdrawal in the hospital setting, it is important to realize there are withdrawal management facilities available to safely discontinue alcohol. The *American Society of Addiction Medicine* has designated four levels (1–4) of withdrawal management. Level 1 refers to ambulatory management with minimal on-site monitoring, and Level 4 corresponds to a medically managed inpatient therapy setting [16]. Generally, patients with a CIWA score < 10 may be managed in Level 1 settings, CIWA score of 10 to 18 in Level 2 or

Level 3 settings, and > 19 should be managed in a Level 4, resource rich environment [16]. Independent of a patient's symptoms, additional factors will influence the required treatment setting. Psychosocial factors, such as social support or suicide risk, may require a higher level of care. Additional considerations influencing the level of care include but are not limited to: co-substance dependence (opioids, tobacco, etc..), recent ethanol consumption, personal history of AWS or complicated withdrawal, and co-morbid illness such as cirrhosis, chronic obstructive pulmonary disease, congestive heart failure, epilepsy, or renal disease [16]. Patients who are older or pregnant are at higher risk of complications from AWS and benefit from more highly monitored settings [16]. Ultimately, this decision should be made on a case-by-case basis. If in question, it is always better to err on the side of caution and recommend a higher level of care.

Despite there being detox facilities available, many patients may still ultimately require withdrawal management in an inpatient hospital setting due to the aforementioned reasons. Additionally, patients with severe withdrawal, encephalopathy or additional complications may require intensive care. To assure patient safety, the authors recommend hospitals consider employing and collaborating with addiction specialists for consultation or primary management [16]. While withdrawal management facilities generally involve treatment from addiction specialists, opportunities commonly exist within hospitals to provide expert care from this specialty.

Once a treatment setting has been decided upon, general supportive care management should be followed concurrently with appropriate pharmacotherapy (as will be described in subsequent sections). Non-pharmacological options should be utilized, including a dark, quiet room with minimal stimulation [17]. Efforts should be made to frequently reassure patients. Psychiatric assessments for anxiety, insomnia, or suicidality should be conducted and treated appropriately. General supportive care often includes correction of electrolyte imbalances, hypoglycemia correction, hydration therapy (either oral or via fluid resuscitation), and thiamine and other B-vitamin supplementation. Typical thiamine dosing is 100 mg PO per day for 3 to 5 days and ideally should be given prior to, or in conjunction with, glucose supplementation to prevent precipitating (or worsening) Wernicke's Encephalopathy (this will be further elaborated upon in Section 5.3.3) [16, 17]. Patients should be monitored closely and informed regarding their treatment progress, including whether a higher-level treatment setting is indicated.

6.2 Treatment

6.2.1 Benzodiazepines (BZD): B

ZDs have long been considered the "gold standard" pharmacological treatment option for AWS. They act primarily by stimulating $GABA_A$ receptors by enhancing the *frequency* of chloride channel opening in the presence of GABA [16, 17]. BZDs have been shown to reduce the incidence of seizures, DT, and mortality in AWS [23]. BZDs may be delivered via intravenous, oral, or intramuscular routes, making it an advantageous drug in a variety of situations. Longer acting agents, such as diazepam or chlordiazepoxide, are preferred to allow for a theoretically smoother clinical course due to a proposed auto-tapering mechanism [16, 17]; however, they are all generally effective if dosed appropriately. Diazepam, when administered intravenously, has both the fastest onset and longest duration of action. Lorazepam, diazepam, and chlordiazepoxide are the most prescribed BZDs in treating AWS [16]. There is never

a need to mix benzodiazepines and it can cloud the clinical picture and increase risk of rebound symptoms. Several different dosing strategies are available, including "fixed-dose", "loading-dose", and a "symptoms-triggered" strategies [17]. In fixed dosing, the chosen drug (e.g.10 mg Diazepam QID) is given regularly and then can be subsequently tapered by 25% on days 4 through 7 with liberal dosing as needed for breakthrough symptoms [17]. In a "symptom-triggered" plan (which is preferred), a chosen BZD (e.g. diazepam, lorazepam, chlordiazepoxide) is prescribed based on a patient's hourly CIWA or SEWS score, and doses are escalated as needed [24]. Tapering occurs through smaller doses as scoring decreases. Finally, in a "loading-dose" strategy, higher doses of a chosen BZD are administered until symptoms improve (e.g. Diazepam 20 mg, 40 mg, 60 mg, ...100 mg) to allow for a self-taper effect [25]. Regardless of strategy, when utilizing benzodiazepines, close monitoring is necessary to assure no recurrence of symptoms in the short term, and consideration of duration of action of chosen benzodiazepine should be considered in monitoring time. Prescribing BZDs in a symptom triggered fashion has been shown to reduce the total amount of BZD administered and shortens total therapy time, however no specific strategy is clearly superior [17, 24].

6.2.2 Barbiturates

Barbiturates, primarily phenobarbital, provide another valuable and safe option for effectively treating alcohol withdrawal. They act by stimulating $GABA_A$ but, unlike BZD, they increase *duration* of chloride channel opening and they do not require the presence of GABA [26]. Being able to directly stimulate the $GABA_A$ receptor without the presence of GABA may provide increased effectiveness over benzodiazepines in controlling symptoms [26]. Additionally, phenobarbital can decrease glutamate activity which thereby assists in treating the hyperdynamic state that results from upregulated NMDA receptor activity [27]. Phenobarbital also has a more predictable pharmacological profile, is more effective for preventing seizures than benzodiazepines, has less incidence of delirium, results in less progression of symptoms, decreases critical care utilization, [26, 28–31]. Phenobarbital does not need to be tapered as it is very long acting and self-tapers over the course of three to five days, thus generally outlasting the AWS disease process. There are various dosing regimens for phenobarbital. Initial doses of phenobarbital 10 mg/kg IV over thirty minutes may be utilized prior to a benzodiazepine regimen or continued phenobarbital monotherapy. When phenobarbital is utilized as a symptom-triggered monotherapy, a loading dose can be followed by subsequent smaller doses (e.g. 130–260 mg IV, 65 mg PO) until symptoms subside, with a total cumulative dose of over 2–2.5 grams rarely being necessary. As patients approach doses over 2.5 grams they can be prone to additional side effects from phenobarbital, including CNS depression, ataxia, and nystagmus. Due to phenobarbital's various benefits over benzodiazepines, many clinicians prefer utilizing this treatment option.

6.2.3 Adjunctive additional treatments

While GABA-agonist therapy is the mainstay of treatment for AWS, other adjunctive agents may be useful. These medications should only be considered once a patient with AWS has had sufficient GABA-agonist therapy or as an adjunct for safety purposes in the agitated or encephalopathic patient. These adjunctive agents include ketamine, dexmedetomidine, and propofol. Ketamine and propofol are mechanistically

therapeutic as ketamine acts as an NMDA receptor antagonist and propofol, like barbiturates, directly stimulates the $GABA_A$ receptor [26]. Dexmedetomidine, a central $alpha_2$ agonist, can be used adjunctively to treat delirium, agitation, but should never be used as a sole, primary agent to treat alcohol withdrawal, as it does not address the underlying physiology. When utilizing dexmedetomidine alone, patients are at risk for decompensating while symptoms are otherwise masked. Airway protection is not necessary for the use of ketamine or dexmedetomidine. While propofol is unnecessary for the patient who is protecting his or her airway, it may be an optimal agent for the intubated patient [18].

Thiamine should also be administered along with concurrent assurance of euglycemia. If patient has no evidence of malabsorption and symptoms are mild to moderate, oral supplementation of 100 mg is sufficient. If any evidence of malabsorption or inability to take medications orally, then thiamine should be given intravenously. If patient is encephalopathic, consider high dose thiamine supplementation out of concern for Wernicke's Encephalopathy or Wernicke-Korsakoff Syndrome (see Complications).

Other than benzodiazepines and barbiturates, there is no role for antiepileptic drugs in treating alcohol withdrawal syndrome or alcohol withdrawal seizures. However, gabapentin may be of some utility in treating the symptoms associated with Post-Acute Withdrawal Syndrome [32]. Upon completion of withdrawal, additional agents, such as naltrexone or acamprosate, should be offered for medication assisted therapy, along with psychosocial and rehabilitative services.

7. Complications and their implications on patient safety

The most important considerations regarding the safety surrounding treating alcohol use disorder and alcohol withdrawal in the hospital setting are early assessment, identification, and intervention and treatment of associated medical complications. Progression of alcohol withdrawal is preventable and delirium tremens is avoidable all together with proper treatment. As patients progress along the AWS spectrum, they become more prone to increasing risk of morbidity and mortality, including sepsis, aspiration, malnutrition, encephalopathy, falls, dysrhythmias, permanent cognitive impairment, and death. Coexisting psychosocial conditions, such as depression and anxiety, should also be attended to decrease risk of self-harm.

Encephalopathy is of particular concern because it is difficult to distinguish and exclude Wernicke's Encephalopathy in the setting of DT. Wernicke's Encephalopathy is about 80% reversible if treated early with high dose thiamine, and if untreated, can progress to Wernicke-Korsakoff Syndrome, which is only about 20% reversible with high dose thiamine. High dose thiamine regimen should be 500 mg IV TID for three days, followed by 100 mg IV or PO for 4 days, followed by 100 mg PO indefinitely. Clinicians should not be tempted to truncate thiamine regimen with improvement of encephalopathy as the observed improvement may be the result of the treatment and, therefore, the full course is indicated.

Interdisciplinary collaboration is of the utmost importance to incorporate expertise in addiction and withdrawal management. Hospitals should invest in these resources for improved patient outcomes. Consultants in this area generally exist in the fields of Addiction Medicine, Addiction Psychiatry, and Medical Toxicology. Case managers and social workers should also be utilized to counsel patients and assist in coordinating further treatment after discharge.

8. Conclusions

In summary, alcohol withdrawal is a complex condition with a wide range of manifestations which results in substantial morbidity and mortality. The underlying pathophysiology of ethanol – chronic GABAergic stimulation – results in a hyperexcitatory state when alcohol withdrawal occurs. Symptoms range from anxiety and tremulousness to seizures, coma, and death. Practitioners should be able to identify patients with AWS risk stratify patients who are at risk of complicated AWS utilizing the various described screening tools. Symptom based assessment tools are also available to guide treatment (CIWA or SEWS). Primary treatment for AWS requires sufficient dosing of GABA agonists (benzodiazepines vs. phenobarbital). Adjunctive therapies also include ketamine and dexmedetomidine, the latter of which should be used cautiously as it does not address the underlying pathophysiology. To ensure patient safety, clinicians should strive to monitor for and prevent known risks and complications associated with AWS. Finally, a multi-disciplinary approach is preferred and should include the expertise of addiction specialists from Addiction Medicine, Addiction Psychiatry, or Medical Toxicology, as well as Case Management.

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