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Review

A rational approach to the treatment of alcohol withdrawal in the ED☆,☆☆

Christine R. Stehman MD [a,*], Mark B. Mycyk MD [b]

[a] Division of Trauma, Burn and Surgical Critical Care, Department of Surgery, Department of Emergency Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA
[b] Department of Emergency Medicine, Cook County Hospital, Chicago, IL, USA

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ABSTRACT

Approximately 7% of the US population abuses or is dependent on alcohol. Patients with alcohol disorders often seek medical attention in Emergency Departments (EDs) for complications directly related to alcohol use or due to other medical issues associated with alcohol use. Because of increasing lengths of stay in EDs, alcohol-dependent patients are at high risk of developing alcohol withdrawal syndrome (AWS) during their ED visit. This article reviews the physiology of alcohol withdrawal as well as the symptoms of this potentially deadly illness for the practicing emergency physician (EP). We provide evidence-based guidelines for the appropriate ED treatment of moderate to severe AWS, including pharmacologic interventions, adjunctive therapies, and disposition of these patients.

1. Introduction

Emergency departments (EDs) experience the impact of alcohol use and abuse on a daily basis, from the acutely intoxicated patient to the patient dying of alcohol-related liver disease and everything in between. Epidemiologic studies estimate that 7% of the US population abuses or is dependent on alcohol, and one study estimates that 24% of the adult patients brought to the ED by ambulance suffered from alcoholism [1,2]. In another study, complications from alcohol use resulted in 21% of intensive care unit (ICU) admissions to an inner-city hospital [3]. The medical problems due to alcohol use, abuse, and withdrawal have been described in published literature since the early first century BC [4]. Alcohol use and withdrawal are leading causes of preventable morbidity and mortality in the United States [5,6]. Since the early 1900s, researchers and public health officials have recognized that people who abuse alcohol have many associated medical problems. This leads to more ED visits, more time in the hospital, and an overall disproportionate use of medical resources [4,7,8]. Furthermore, alcohol withdrawal, combined with other illness or injury, significantly increases the mortality rate of patients [4,9-11]. In the past, many patients with alcohol withdrawal were not identified until they were inpatients. However, the recent increasing length of stay in EDs puts alcohol-dependent patients at high risk for developing withdrawal during their ED visit even if presenting for an unrelated complaint. Thus, it is important for emergency physicians (EPs) to understand that a large portion of ED patients are at risk for alcohol withdrawal and may need goal-directed treatment of alcohol withdrawal syndrome (AWS) during their ED visit.

In this era of increased treatment options for the practicing EP, several studies have described optimal treatment strategies for alcohol withdrawal. However, actual treatment strategies vary from physician to physician and are often based on older research, "habit," and anecdotal experience. This article reviews the physiologic basis for alcohol withdrawal and provides evidence-based treatment strategies to use in the ED with a focus on patients with moderate to severe AWS.

2. Neurophysiology: inhibition and excitation

To treat alcohol withdrawal appropriately, one must understand the underlying physiology. By default, excitatory neurotransmitters constantly work on receptors to open calcium channels leading to excitatory postsynaptic potentials. To allow the body to function in a coordinated manner, inhibitory neurotransmitters work on their receptors' chloride channels in the nervous system to stabilize or hyperpolarize cells, making it more difficult for excitatory neurotransmitters to generate an action potential. Overall, this reduces activity at the cellular level, allowing smooth movements and generally decreased internal stimulation [12,13].

Many theories have been considered regarding the effects of alcohol on the central nervous system (CNS). Although the purpose of this review is not to provide a comprehensive discussion of the incredibly complex pathopharmacology of ethanol's effects in the CNS, it is important for the EP to understand the basics of neurotransmission as they relate to AWS. There are 2 major types of neurotransmitter-receptor systems in the CNS: one inhibitory, γ-aminobutyric acid (GABA), and one excitatory, glutamatergic. More

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* Corresponding author.
E-mail address: crstehman@gmail.com (C.R. Stehman).

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than 80% of neurons in the brain use either GABA or glutamate as their neurotransmitters [14,15]. By an unclear mechanism that likely involves neurosteroid modulation and other effects, ethanol acts to increase $GABA_A$ receptor–mediated inhibition; but no specific binding site at GABA has yet been identified [14,16-20]. Recent studies have demonstrated that ethanol also acts on a glutamatergic receptor, *N*-methyl-D-aspartate (NMDA), by reducing excitatory glutamatergic activity. Although there is also no specific binding site for ethanol on the NMDA receptor, ethanol appears to interact with an allosteric site to decrease agonist efficiency and decrease glutamate levels presynaptically [13,14,21-25]. Short- and long-term ingestion of ethanol increases the amount of inhibition felt by the nervous system: increased GABA inhibition and decreased NMDA activity. Acutely, these effects are transient. Outwardly, short-term ingestion of ethanol results in a state of generalized depression: depressed level of consciousness, slowed cognition, and impaired sensory and motor function (in particular, slowed reaction times) [4].

With long-term ethanol intake, the neuroreceptor effects become lasting as the body attempts to normalize neurotransmission by making compensatory changes in the CNS. These adaptive changes are part of a complex series of changes that lead to a requirement for more ethanol to achieve the effects previously attained, a shifting of the dose-response curve of ethanol. This phenomenon is called *tolerance* [4,14,15]. Tolerance is one of the criteria for diagnosing substance dependence [26]. Physiologic tolerance is seen as the body adapts to long-term ethanol ingestion at the cellular level. Initially, these adaptive changes were thought to happen only at the $GABA_A$ receptor, leading to both a decrease in the number, function, and sensitivity to GABA of the $GABA_A$ receptors as well as a decrease in total body GABA levels [4,17,19,27-29]. Recent studies demonstrate that adaption occurs in the glutamatergic system as well: the number of NMDA receptors increases, there is an increase in NMDA receptor sensitivity and affinity for glutamate, and there is a higher systemic level of glutamate [4,13,14,24,25,30-35]. In addition, there is a complex interaction between the GABAergic and glutamatergic systems thought to be associated with the fact that GABAergic neurons have glutamate receptors and the NMDA receptor response to glutamate can be modified by GABA transmission [36]. The end result is increased GABA activity leads to decreased glutamate activity, and decreased glutamate activity leads to increased GABA activity [14,17,37-39].

In response to long-term ethanol exposure, the body makes these physiologic adaptive changes at the cellular level. When physiologic adaptive changes persist and the patient decreases his ethanol intake, the patient is at risk for withdrawal. Withdrawal, another criterion for the diagnosis of substance dependence, presents as the clinical symptoms resulting from the physiologic consequences of the adaptive changes [4,26]. Alcohol withdrawal manifests as a state of agitation: glutamate floods the increased number of more sensitive NMDA receptors with little or no GABA to bind the few less sensitive $GABA_A$ receptors and inhibit the glutamate-induced excitation [4,34]. The clinical signs and symptoms of alcohol withdrawal bear this out: hypertension, tachycardia, hyperthermia, tremors, seizures, hallucinations, agitation, fever, and hyperarousal [13,34,40,41].

3. Identification of alcohol withdrawal symptoms

These symptoms would seem to be easy to recognize, the first step in treating alcohol withdrawal. However, to recognize that the symptoms and signs a patient displays are due to alcohol withdrawal, the provider must first recognize the possibility of this as the cause. All patients should be queried regarding their ethanol intake and any history of withdrawal symptoms when ethanol is not ingested. If the patient is unable to provide such history, alcohol withdrawal should be part of the differential diagnosis in patients with any symptoms suggestive of withdrawal.

Alcohol withdrawal is a continuum of syndromes that begin after a decrease in the amount of intake of ethanol. This can be either a decrease or total cessation of alcohol intake. This continuum is due to varying levels of autonomic hyperactivity and ranges from the mildly uncomfortable uncomplicated withdrawal that is often self-treated by alcoholics to delirium tremens (DTs). Symptoms begin as early as a few hours after a decrease in ethanol ingestion and, rarely, can last up to 2 weeks [42,43]. Although the uncomplicated withdrawal symptoms may precede more severe symptoms, severe withdrawal may be a patient's first presentation especially in patients who have experienced previous episodes of withdrawal.

Two to 6 hours after a decrease in ethanol ingestion, a patient may begin to experience uncomplicated alcohol withdrawal, which consists of some combination of tremulousness, diaphoresis, nausea/vomiting, and abnormal vital signs (hypertension, tachycardia, hyperthermia, tachypnea) [43]. Although the vital sign abnormalities are often the first clue, care must be taken if a patient's vital signs seem normal: patients may be taking medications, such as β-blockers, that would obscure these clues. Uncomplicated alcohol withdrawal usually causes only discomfort for the patient until he can get his next drink. However, in the ED, patients displaying signs of uncomplicated withdrawal should be monitored because it can progress to more severe withdrawal.

Three other types of AWSs exist, all of which may be considered moderate to severe withdrawal: alcoholic hallucinations (also termed *alcoholic hallucinosis* in some literature), alcohol withdrawal seizures ("Rum Fits"), and DTs. Alcoholic withdrawal hallucinations usually consist of a transient disordered sense of (somatic) perception and affect up to 25% of patients with AWS [43-45]. Although these hallucinations are usually auditory (noises become voices to the patient), they can be visual or tactile [43]. They may be persecutory and cause frank paranoia, leading to increased patient agitation. When these hallucinations change from transient to persistent while the patient maintains a clear sensorium, the patient has progressed to alcoholic hallucinosis [43]. These hallucinations generally begin between 7 and 48 hours after a decrease in ethanol ingestion and may be recognized by a sudden or gradual change in the patient's affect or interaction with the medical providers [43].

Like alcoholic hallucinations, the risk of alcohol withdrawal seizures generally begins between 7 and 48 hours after a decrease in intake and may affect up to 10% of AWS patients [4,46]. These diffuse, tonic-clonic seizures may occur without warning and have little or no postictal period [47]. Seizures may be single or multiple, and rarely progress to status epilepticus [43]. Most often, they are self-limited; however, approximately one-third of patients who develop DTs have a preceding alcohol withdrawal seizure [4].

Delirium tremens, the most serious manifestation of AWS, combines autonomic hyperactivity with disorientation, confusion, delirium, psychosis, hallucinations, and seizures [26,43,47]. The difference between DTs and alcoholic hallucinations is in the patient's sensorium: a patient with hallucinations can recognize that the hallucinations are not real, whereas a patient in DTs will be disoriented, confused, and delirious in addition to having hallucinations. If not treated, about 5% of patients who experience withdrawal from alcohol will progress to DTs [48]. Although this potentially deadly manifestation of AWS generally does not present until 48 to 72 hours after a decrease in ethanol ingestion, these symptoms may begin earlier or later (up to 10 days after the last ethanol intake). Symptoms of DTs generally last about 5 days after onset but, in rare cases, may last for up to 2 weeks [43,47,49]. Previous mortality rates for patients who developed DTs were as high as 35% [8]. Before pharmacologic sedation became a standard part of treatment of DTs, improved nursing and supportive care including hydration, nutrition, and fever control helped hospitals decrease this mortality rate to 15%. Since the development of pharmacologic therapy and the use of appropriate and early treatment, mortality has decreased to less than

5% [50]. Currently, the only reliable predictor of who is at risk of developing DTs is a history of previous DTs. The course and type of withdrawal a patient will suffer as well as the response to treatment are unpredictable. There is some evidence that this lack of predictability may have a genetic basis associated with certain genetic polymorphisms. However, there is not yet a reliable or easily used method for use in clinical settings; and it will likely be better defined in the future [51].

4. Goals of AWS treatment

The first goal of AWS treatment is to provide symptomatic relief. Three other treatment goals exist: to halt progression to more severe withdrawal symptoms or death, to allow the detection of other underlying illnesses, and to prepare the patient for long-term abstinence [52,53]. Based on these goals, the ideal medication would work to fix the cause of the symptoms (by restoring CNS inhibition). In addition, the ideal medication should have a rapid onset of action, a wide safety margin, little to no liver metabolism (because many people this will affect have damaged livers related to their long-term ethanol ingestion), and little to no addictive or abuse potential, and should be taperable.

Commonly, alcoholics "self medicate" with ethanol to prevent or treat mild withdrawal symptoms. In fact, many hospitals previously used ethanol drips to treat and prevent AWS. However, the many disadvantages of ethanol use for this purpose—the need to monitor blood levels, the unpredictable elimination kinetics, and many other possible adverse effects—make it difficult to use this treatment safely and reliably [54-56]. A few recent studies have compared ethanol to other commonly used medications and demonstrated no advantage of ethanol with respect to efficacy or adverse sedative effects [57-59].

5. Mainstay of therapy: benzodiazepines

Given that the cause of AWS is an overabundance of excitation in the CNS and the symptoms reflect this, a number of different sedatives have been tried for AWS treatment. Discovered in the late 1950s and first introduced as therapy in the early 1960s, early benzodiazepines compared favorably to other sedatives in the treatment of alcohol withdrawal [60,61]. In the mid-1970s, formal studies demonstrated that patients treated with benzodiazepines had a lower incidence of severe withdrawal symptoms and a faster onset of sedation compared with those treated with other sedatives [62]. By the 1980s, benzodiazepines had become the mainstay of AWS therapy [47].

Benzodiazepines function allosterically at GABA receptors to enhance GABA activity, increase inhibition, and therefore abate withdrawal signs and symptoms [17,61,63]. The activity of benzodiazepines seems to require some native GABA to be present for benzodiazepines to be effective [61]. Several studies have shown that early recognition and treatment of AWS with benzodiazepines reduce the duration and severity of symptoms, as well as the incidence of seizures and delirium [48]. Because these medications have good anticonvulsant activity, they are helpful in actively seizing withdrawal patients even if the seizures are not due to alcohol withdrawal. Benzodiazepines have also been found to reduce the mortality associated with alcohol withdrawal delirium (DTs) [64]. Other advantages of benzodiazepines include their availability by multiple routes (orally, intramuscularly, or intravenously) and the fact that, when they are compared with other sedative hypnotics, benzodiazepines have less respiratory and cardiac depressive effects.

Multiple benzodiazepine options currently exist, with a range of pharmacologic properties (Table 1). Few studies have compared efficacy between different benzodiazepines, and no study has shown clear superiority of any one agent over the others. One study suggested that lorazepam was less effective in managing withdrawal symptoms than diazepam, and another study suggested alprazolam to be slightly more effective than diazepam [64,73-75]. The most published studies and the most evidence exist for the long-acting agents chlordiazepoxide and diazepam because they are the oldest available benzodiazepines [53,62]. There may be a higher incidence of seizures in patients treated with shorter-acting agents like alprazolam, oxazepam, and midazolam [42,53,76,77]. Unfortunately, most studies of shorter-acting agents have evaluated treatment of mild withdrawal with oral medications; but oral medications are difficult to give to patients suffering from moderate to severe withdrawal. This combined with the fact that intravenous (IV) medication delivery offers a more rapid onset of action makes IV benzodiazepines the initial treatment of choice for severe withdrawal in the ED. Options in this category include diazepam, lorazepam, and midazolam. All have benefits and downsides. Diazepam has a short time to onset of action, an active metabolite, and a long half-life but has erratic absorption when given intramuscularly and is predominantly metabolized by the liver. The effectiveness of midazolam in intermittent dosing has not been well studied, but a continuous infusion can increase total treatment cost. Midazolam is also hepatically metabolized and balances its rapid onset of action with a shorter half-life compared with diazepam and lorazepam. Lorazepam has less liver metabolism than either diazepam or midazolam, but it has a slower onset of action (risking dose stacking with continued symptoms) and a longer time to peak action than the other two. Choice of which benzodiazepine to use is left up to the individual practitioner and should be based on institutional availability, medication pharmacokinetics, costs, and patient specifics.

Initial treatment of severe AWS in the ED begins with IV loading of benzodiazepines. The amount given should be enough to achieve appropriate and rapid sedation with normalization of vital signs. Improvement in vital signs signifies a decrease in sympathetic tone and a stabilization of the autonomic system. Appropriate sedation with abnormal vital signs should prompt an evaluation for other illnesses or injuries in addition to or instead of alcohol withdrawal [4]. The front-loading therapy method has been shown to achieve earlier symptom control with a lower total dose of medication used and a decreased rate of seizures [53,62,78-80]. Loading doses of benzodiazepines should be 5 to 20 mg of diazepam every 5 to 10 minutes or 1 to 4 mg of lorazepam every 10 to 15 minutes (lorazepam requires a longer time between doses to avoid dose stacking and sudden deep sedation). Additional doses should be given until the patient's autonomic hyperactivity has been reversed and inhibition has been restored. The appropriately treated patient has near-normal or normal vital signs and is calm, sleepy but arousable, not responding to internal stimuli (no evidence of active hallucinations), and not seizing [4].

Alcoholics often appear clinically sober with blood ethanol levels well above the legal limit; and often, these patients will need high doses of any medication that is replacing their alcohol to achieve the desired inhibition replacement. Studies have shown a decreased sensitivity of GABA receptor activity to benzodiazepines and other medications in the setting of long-term ethanol exposure. The doses required can be extreme, with case reports of requirements for 2640 mg of diazepam in 48 hours and 2850 mg of midazolam over 5 days, among others [81,82]. Some patients may not achieve appropriate symptom control with benzodiazepines alone because of the "kindling" effect. This is a phenomenon associated with AWS in which repeated episodes of withdrawal become increasingly severe and increasingly resistant to treatment, in particular to treatment with benzodiazepines. Kindling is thought to be due to permanent alterations in neurotransmitters and their receptors [83-85]. Because this kindling phenomenon can result in benzodiazepine treatment resistance, some patients will require the addition of or a switch to a medication of a different class during the course of their AWS treatment [4]. The EP will face this situation after administering a total

Table 1
Doses and pharmacologic properties of common sedative hypnotics used in the treatment of alcohol withdrawal.

	Chlordiazepoxide [63,65]	Diazepam [63,66,67]	Lorazepam [63,67,68]	Midazolam [63,67,69]	Phenobarbital [63,70]	Propofol [67,71,72]
Class of drug	Benzodiazepine	Benzodiazepine	Benzodiazepine	Benzodiazepine	Barbiturate	Hypnotic
Route of dose	PO	IV, IM, PO, PR	IV, IM, PO	IV, IM, PO	IV, IM, PO, PR	IV
Intermittent initial dose	50-100 mg PO[a]	10 mg (IV)	2 mg (IV)	1-5 mg (IV)	65 mg (IV)	0.25-2 mg/kg slow infusion
Intermittent additional dose	50-100 mg (max 300 mg/d)	Escalating, up to 150 mg	Escalating, no more than 25 mg/h	1-5 mg	Escalating in increments of 65 mg, slow push	0.25-2 mg/kg
Infusion dosing	NA	NA	0-5 mg/h[b]	1-20 mg/h, titrate up to effect[c]	Max 60 mg/min[d]	0-5 mg/(kg h) as needed for appropriate sedation
Time to effect onset	2-3 h	1-5 min (IV) 15-30 min (IM) 30-90 min (PO) 10-45 min (PR)	5-20 min	2-5 min	5-30 min (peak brain concentrations at 20-40 min)	1-2 min
Half life	5-30 h (active metabolite 30–200 h)	30-60 h (active metabolite 30-100 h)	9-21 h	2-6 h	50-140 h	10 min-12 h (longer if prolonged use)
Duration of action	Long	Long	Short to medium	Short	Long	Short to medium
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic, gut	Hepatic	Hepatic
Excretion	Renal	Renal	Renal, fecal	Renal	Renal	Renal
Dose adjustment	Renal (CrCl < 10): 50% dose reduction Hepatic impairment: risk of accumulation	Hepatic impairment Renal impairment	Renal impairment: dose reduction	Renal failure (CrCl < 10): dose reduction	Renal failure (GFR < 10), increase dosing interval and dose reduction; caution in hepatic impairment	None
Notes	Extremely long-acting active metabolite, so not recommended in elderly	Phlebitis Erratic absorption if given IM	If more than 25 mg/h, risk of ATN, lactic acidosis, and hyperosmolar state because of solvent No active metabolite	Prolonged sedation if obese and/or low albumin Active metabolite	May cause hypotension	Risks: propofol infusion syndrome, injection site pain, hypertriglyceridemia. More hypotension than other sedative-hypnotics May discolor urine Caution: soy or egg allergy

Abbreviations: CrCl, creatinine clearance; d, days; GFR, glomerular filtration rate; h, hours; IM, intramuscular; IV, intravenous; mg, milligrams; min, min; NA, not applicable; PO, per oral; PR, per rectum.
[a] All doses on the table are for the IV form of the drug except for chlordiazepoxide because the IV form of this drug has been discontinued in the United States.
[b] Based on longer half-life of lorazepam (and diazepam), infusion dosing generally not recommended.
[c] Case reports of infusion rates up to 520 mg/h [49].
[d] Generally, not given in true infusions.

dose of 40 mg lorazepam or 200 mg diazepam in a patient who still does not appear calm or sedated [86]. Simply changing to a different benzodiazepine at that point is not ideal because the mechanism of action is the same no matter which benzodiazepine is used.

6. Other effective medications: barbiturates and propofol

Many other classes of medications have been tried for AWS treatment. To determine which other classes of medications can be used when benzodiazepines alone do not achieve adequate sedation and symptom control, one must think again about the $GABA_A$ receptor. Like benzodiazepines, barbiturates also affect the inhibition caused by activation of the GABA receptor and are cross-tolerant with ethanol; but barbiturates work slightly differently at the receptor [87]. The barbiturates can directly open the Cl^- ion channel at appropriate doses and both enhance the binding of GABA to the $GABA_A$ receptor and increase the duration of Cl^- ion channel opening. The advantage of barbiturates is that they work in the absence of any native GABA. In addition, the combination of phenobarbital (the most commonly used barbiturate) with any benzodiazepine actually promotes the binding of the benzodiazepine to the $GABA_A$ receptor, possibly increasing the efficacy of the benzodiazepine action [63]. The downside of adding phenobarbital is that respiratory and cardiac depressive effects occur more frequently than with benzodiazepines alone [88]. In DTs, the combination of benzodiazepines and barbiturates has been shown to decrease the need for mechanical ventilation and has shown a trend toward a decrease in ICU length of stay [89]. The preferred barbiturate is phenobarbital because of the onset and duration of action (Table 1). The appropriate dose is 65 to 260 mg every 15 to 30 minutes until symptom control has been achieved. This dosing schedule may result in a total dose less than the typical anticonvulsive loading dose; however, the goal of therapy in AWS is different, and the medication is often being used in conjunction with loading doses of other medications.

Another promising medication that can be used after the benzodiazepine receptor site has been saturated is propofol. Small case studies have documented the effectiveness of propofol in resistant AWS [90,91]. This medication is believed to work on the GABA receptor by slowing channel closing time and therefore potentiating the effect of GABA [89]. Two advantages of using propofol exist. First, propofol also works on the NMDA receptor as an antagonist, leading to less NMDA activity (the actual mechanism by which this occurs has not been fully delineated). Second, propofol can be given in bolus or by continuous infusion (Table 1). Because propofol is so short acting, discontinuing it allows almost immediate evaluation of the patient's mental status [92,93]. The main disadvantage of propofol is that most patients will need mechanical ventilation for respiratory support.

7. Continued pharmacologic sedative treatment (scheduled vs symptomatic treatment)

After restoration of inhibition has been achieved and the patient is sedated initially, further treatment may be needed for several days while any remaining ethanol is eliminated and initial pharmacologic treatment wears off. Continued treatment can be given on a scheduled basis or as symptoms recur. Multiple studies, starting with a definitive study by Saitz et al, have demonstrated superiority of *symptomatic* over *scheduled* dosing for continued treatment of AWS [94-96]. Although both treatment methods may result in similar outcomes, symptomatic treatment results in a significantly lower duration of therapy and lower total medication doses [94-96]. Continued symptomatic treatment should consist of redosing the medication given for the loading doses.

To determine when additional medication doses should be given, a number of different methods can be used. Inpatient providers frequently use the Clinical Institute Withdrawal Assessment (CIWA) scale to guide additional medication doses, but the CIWA scale has not been validated in the ED setting and can be too cumbersome for use in severe withdrawal [78,79]. Until a better or modified CIWA scale for ED use is validated, treatment in the ED should be guided primarily by attention to a patient's mental status and vital signs—any change from the desired state of near-normal vital signs with a calm, sleepy, but arousable patient should prompt additional medication dosing.

8. Other nonsedative medications

Benzodiazepines, barbiturates, and propofol are the main treatment options for AWS in the ED because they are known to act on the physiologic cause of AWS by creating more inhibition in an overexcited system, thus replacing the action of ethanol. There is some evidence that ethanol acts on neurotransmitter systems other than GABAergic and glutamatergic systems; but at this time, it is unclear whether these are adverse effects of the GABAergic and glutamatergic effects or independent actions [13-15]. Questions about the physiologic and genetic basis for AWS have been the source of active ongoing research on other possible medications for AWS treatment. As more research on this topic is published in the next decade, it is important to remember that GABA and glutamate receptors are used by more than 80% of the neurons in the CNS; so medications that work on these systems will likely remain the primary choice for treatment [14,15].

Three other classes of medications have been proposed for adjunctive treatment of AWS by researchers and clinicians, with each focusing on particular symptoms of AWS: antiepileptics, antipsychotics, and cardiac medications. In general, the antiepileptics, including phenytoin, valproic acid, and levetiracetam, have been shown to be poor choices for treatment of AWS because these medications do not effectively treat or prevent alcohol withdrawal seizures [97]. However, one antiepileptic medication that has shown some benefit in the treatment of AWS is carbamazepine [98-101]. It is important to note that carbamazepine's benefits have only been shown in small non–ED-based studies and in patients with mild withdrawal. Furthermore, carbamazepine is not available in IV form; so its use in severe withdrawal is extremely limited. As of now, there is no evidence for the use of this medication alone; but it may prove to be a beneficial adjunct in severe withdrawal if it becomes available in IV form.

Antipsychotics are the second class of medications often used by tradition. Although some of the newer-generation medications in this class are available in IV form, there is limited evidence of any benefit restoring inhibition from newer-generation antipsychotics in alcohol withdrawal treatment [56]. The older-generation antipsychotics, in particular haloperidol, were often used as an adjunct based on the physician's personal experience, especially in patients displaying psychotic symptoms. As an adjunct in patients with a history of psychiatric illness, this use may be beneficial. However, there are disadvantages to using this medication alone. The primary disadvantage is that haloperidol is strictly a dopamine antagonist and has no effect on either the GABAergic or glutamatergic systems. Based on this, haloperidol should only be given in patients in whom sufficient pharmacologic GABA support has already been provided with benzodiazepines. Second, caution should be exercised when giving haloperidol intravenously because there is a risk of QTc prolongation, torsades de pointes, and sudden death [102]. Despite these cautions, in those who have received sufficient GABA support, haloperidol may be a useful adjunct medication to treat hallucinations and agitation in AWS patients.

Cardiac medications are the third class of medications often considered for treatment of AWS: this includes both α-agonists and β-antagonists. These medications primarily treat the vital signs abnormalities of AWS but not the physiologic source of the disorder, so the other life-threatening symptoms will remain untreated. The use of cardiac medications alone can misdirect the EP from

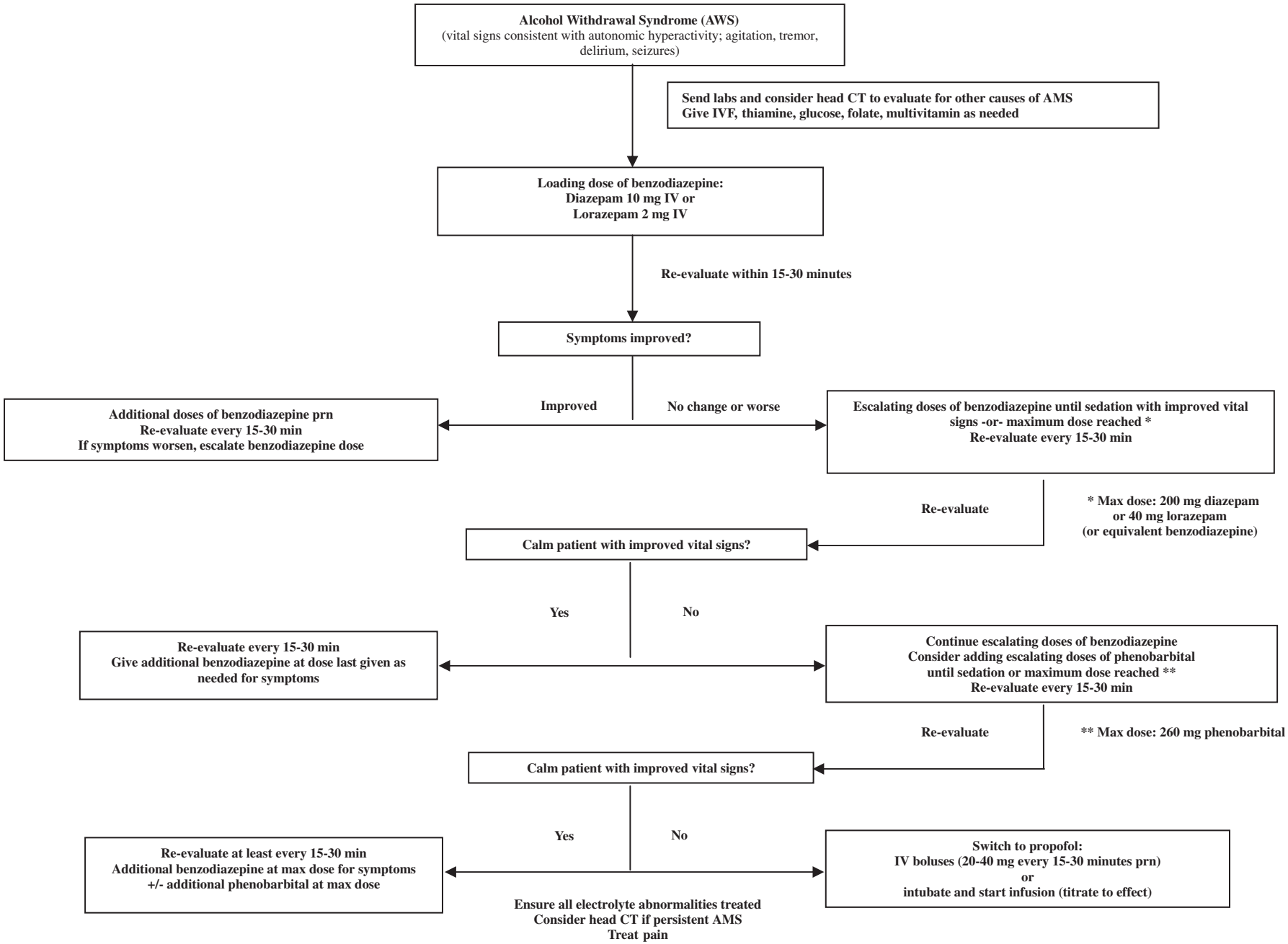

Fig. 1. Protocol for pharmacologic treatment of AWS. Adapted from Gold et al (2007) [89]) and based on Cook County Hospital ED experience.

administering other appropriate pharmacologic treatment of AWS by masking the vital sign clues often relied on to make clinical decisions [103]. In addition, poorer outcomes have been shown in the use of some of these medications [47,64]. For example, delirium is a known adverse effect of β-blocker therapy; and one study showed an increase in delirium in AWS when propranolol was used in treatment [104,105]. Two medications in this class have shown some promise, but only as adjuncts: clonidine and dexmedetomidine [64,106-115]. However, studies on these 2 medications, especially on the recently popular medication dexmedetomidine, have been small and limited to case reports or small case series; but there may be some promise for use of dexmedetomidine if used as an adjunct to standard therapy with benzodiazepines, phenobarbital, or propofol.

It is important to understand the pharmacologic basics of sedative and nonsedative options for treatment of AWS, especially in this time of multiple drug shortages. Providers may find themselves using a different benzodiazepine or barbiturate than they have previously been accustomed to or switching away from benzodiazepines earlier, so familiarity with the medication availability at the provider's institution and collaborating with the hospital's pharmacy staff are imperative.

9. Supportive care

Although restoration of inhibition with benzodiazepines, barbiturates, and propofol is critical to successful treatment of AWS, pharmacologic therapy is not the only consideration. Appropriate treatment of dehydration and nutritional deficits associated with ethanol abuse can prevent some poor outcomes and have been shown to decrease hospital length of stay [116-119]. Patients with AWS need appropriate fluid resuscitation because AWS results in increased metabolic requirements and fluid losses due to hyperthermia, hyperventilation, diaphoresis, and agitation. Patients will likely need glucose supplementation for the increased metabolic requirements [8,120]. Alcoholics are often nutritionally deficient and have a lack of glycogen stores, which may lead to alcoholic ketoacidosis complicating AWS. Because of this, IV dextrose should be given for hypoglycemia, which should be considered in all cases of altered mental status [47,121]. Thiamine supplementation should also be given to prevent Wernicke-Korsakoff syndrome [56,122,123]. Specific fluid and glucose treatments should be based on the individual patient because many have other chronic illnesses, including diabetes, cardiac dysfunction, and renal insufficiency. Other electrolytes should also be evaluated and replaced as necessary. Magnesium has received specific attention for a possible role in AWS treatment because it is an NMDA antagonist. Symptomatic hypomagnesemia resembles alcohol withdrawal, and there is some evidence that the severity of DTs correlates with the degree of hypomagnesemia. However, there is no evidence that magnesium alone has any beneficial effect on AWS without attention to other supportive measures and use of appropriate pharmacologic sedation [124-126]. In patients who are hypomagnesemic, magnesium repletion may still be useful in conjunction with other treatments [124-126].

Although diagnosing concurrent illness is important in the appropriate care of a patient with AWS, clinicians must also anticipate and prevent complications that would prolong the patient's hospital stay. Deep vein thrombosis prophylaxis per institution protocol in appropriate patients is important. In addition, alcoholics are at greater risk for aspiration; so elevation of the head of the bed to prevent pulmonary aspiration and pneumonia should be done. Nosocomial pneumonias have been shown to increase mortality and length of stay in patients with AWS [127].

There is a high rate of associated illnesses and injuries in patients with alcohol disorders, so identifying these problems should also be a priority. Alcohol withdrawal syndrome combined with other problems results in higher morbidity and mortality for both sets of problems [116-119,127-129]. All patients with AWS with new-onset seizures or altered mental status need a full diagnostic workup and treatment tailored to the particular presentation. This workup will include some combination of blood and urine analysis, toxicologic screens, chest radiography, brain imaging, and lumbar puncture, depending on the patient's presentation.

Finally, severe alcohol withdrawal may include agitation and paranoia; so prevention of self-harm and protection of the medical staff should not be neglected. All methods to help treat delirium should be used. As much as possible, in a busy ED, the provision of a quiet, well-lit room with minimal sensory stimulation will help decrease agitation. Calm voices, limited number of different providers, slow actions, and plenty of gentle reorientation and reassurance will also be useful. Despite all these measures, physical restraints may be necessary. Caution should be used in the use of physical restraints without sufficient pharmacologic sedative use because continued agitation against restraints may lead to increased hyperthermia, hypertension, tachycardia, dehydration, metabolic derangements, and poor outcomes such as death [130]. All patients requiring physical restraints will need close monitoring to prevent further issues before they escalate.

10. Disposition

Close monitoring is imperative for patients receiving treatment of AWS. Hospital admission should be considered for all patients experiencing alcohol withdrawal. Although many patients with mild AWS who do not need admission for a separate medical problem may be discharged, patients experiencing moderate to severe withdrawal require admission for further monitoring and treatment of their withdrawal symptoms. Intensive care unit admission should be considered for any patient who has required more than 100 mg of diazepam (or an equivalent dose if using a different benzodiazepine), especially in a short period (less than 2 hours) [86]. Any patient with severe withdrawal, especially those with large sedative requirements at risk of intubation and those who are intubated, should be admitted to an ICU for continued monitoring and treatment.

11. Conclusions

Although patients identified to have symptomatic AWS have a wide range of symptoms, the basics of treating AWS are the same no matter the presentation. Current data suggest that restoration of inhibition should be a priority with loading doses of a benzodiazepine. This treatment should be supplemented by a barbiturate or propofol in cases of treatment failure (Fig. 1). No solid evidence exists for the use of any other medication class as sole treatment of AWS. Dehydration, nutritional deficits, electrolyte derangements, and comorbid illnesses should be identified early and treated. After inhibition has been achieved with initial loading doses, further treatment should be symptom based. Admission should be considered in all patients with alcohol withdrawal, and ICU admission should be considered in moderate to severe cases where large doses of pharmacologic sedation and close monitoring are needed.

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