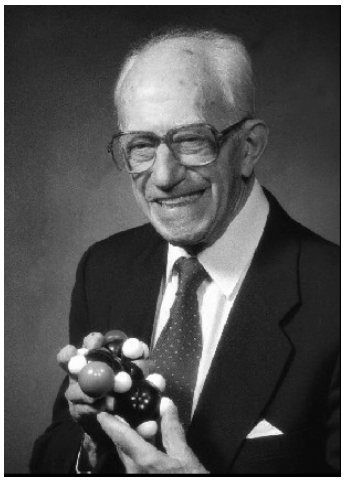
Current Concepts in the Prevention, Recognition, and Management of Severe Alcohol Withdrawal



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Biographical Information

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Purpose and Overview:

To provide an overview of the most recent clinical recommendations for the prevention, recognition, and treatment of severe alcohol withdrawal syndromes

Educational Objectives:

- Recognize patients at risk for development of severe alcohol withdrawal
- Appreciate the importance of vigilance when searching for and treating concomitant illness in severe alcohol withdrawal
- Recognize a severe alcohol withdrawal syndrome as defined by a high CIWA-Ar score
- Recognize strengths and limitations of the CIWA-Ar scale and CIWA protocol

Introduction

The management of alcohol withdrawal places a substantial burden on the healthcare system. Utilizing criteria similar to the most recent DSM V definition (May 2013), 10% of women and 20% of men in Western societies will have an alcohol use disorder (AUD) at some point in their lives [1,3,7]. While impressive, these percentages are overshadowed by the more dizzying statistics for hospitalized patients. Reports range from 20-40% of hospitalized medical patients. Prevalence is yet higher amongst specific patient cohorts (59-67% of trauma patients, up to 60% of ICU patients, and 43-81% of head and neck surgical patients) [21,18,19,20]. While the majority of patients that experience withdrawal will only suffer mild symptoms, severe syndromes may prove fatal. It is estimated that 5-20% of those with a moderate to severe alcohol use disorder will experience a severe withdrawal syndrome following an acute cessation or de-escalation of intake [7,8,10,16]. For the Importantly, a severe alcohol withdrawal syndrome can often be prevented. In addition, for those cases that do occur, there are management strategies that positively affect outcome.

Given the tremendous disease burden and opportunities for meaningful disease modification, one might expect a heightened awareness of the disease process as well as clear-cut management guidelines. However, investigation into physician detection rates of AUD amongst hospitalized patients reveals less than impressive numbers. Detection of an alcohol use disorder is believed to be only 7-40% depending on the hospital type and patient population [21]. Furthermore, once a patient is recognized as at risk for or is actively manifesting symptoms of an AWS, additional confusion arises given the tremendous variety of treatment options described in the literature and the surprisingly sparse number of quality clinical trials [33].

The definitive management of severe alcohol withdrawal will not be required of all physicians. However, it is likely that most physicians will have an opportunity to positively impact the care of these patients. Perhaps one will recognize the at risk patient during a pre-operative clinic visit. For those who practice on the inpatient side, it is not uncommon for a patient admitted for a mild or moderate AWS or for an alternative medical illness to develop a severe AWS. As there is potential for prevention of a severe alcohol withdrawal syndrome and unique management strategies once present, all members of the medical community are called upon to participate in the care of these patients.

Alcohol Withdrawal Fundamentals

For a patient to develop symptoms of alcohol withdrawal, they must consume large amounts of alcohol for a prolonged period of time such that a state of tolerance to alcohol develops. Tolerance is due to compensatory changes in the central nervous system and is defined by an increased alcohol intake needed to achieve the same effect. For those that develop an AWS, symptoms typically begin within a few hours of an abrupt cessation or a decline in consumption of alcohol [17]. Most individuals will experience symptoms for less than 2 days (shorter with treatment).

The alcohol withdrawal state is best thought of as one of excess excitatory central nervous system tone resulting from the body's long-standing compensation for the sedating effects of alcohol. **(Figure 1)**. It is believed that the majority of the withdrawal symptoms occur as a result of reduced neurotransmission in the type A γ-aminobutyric acid pathway and increased activity in the N-methyl-D-aspartate pathway [23]. GABA is the major inhibitory neurotransmitter in the central nervous system. The $GABA_A$–benzodiazepine receptor complex contains an ion channel and distinct binding sites for GABA, benzodiazepines, and barbiturates [39]. When the receptor binds to GABA (or benzodiazepines or barbiturates), membrane stabilization is achieved via enhanced intracellular chloride movement. **(Figure 2).** More recent investigations suggest that alcohol also has site specificity for the $GABA_A$ receptor and mediates sedating effects via the same chloride influx and membrane stabilization [40,44]. With chronic alcohol exposure, the $GABA_A$-BZ receptor adapts and sudden removal of alcohol from the system leads to disinhibition [41]. In addition to its effects on the inhibitory GABA system, alcohol also interacts with the central nervous system's primary excitatory neurotransmitter, glutamate. One of glutamate's targets, an ion-gated NDMA receptor, is extremely sensitive to the sedating effects of alcohol. In the context of chronic alcohol intake, the brain adapts by increasing the number of NMDA receptors [42,43]. Similar to the GABA system, abrupt removal of alcohol reveals a system primed for excessive tone.

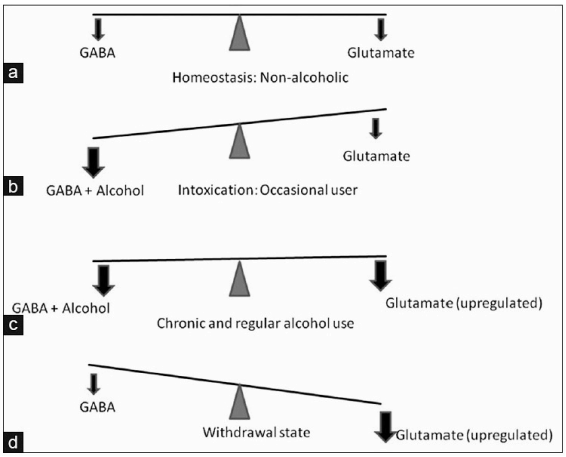


Figure 1. Neurochemistry of alcohol withdrawal. From Kattimani S, *Ind Psychiatry* 2013

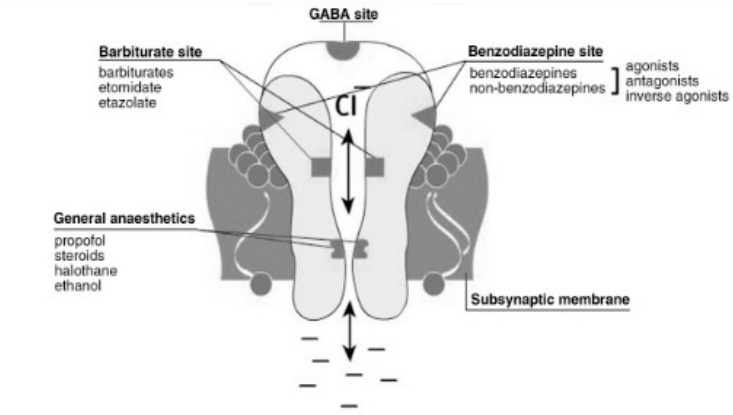


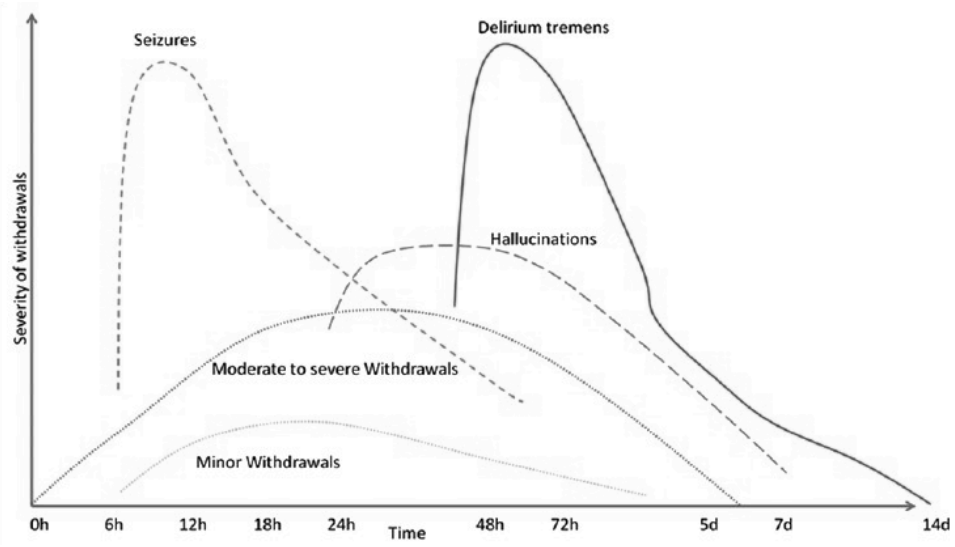
Figure 2. Functional binding sites on the GABA receptor. From Richards G, *Seminars in Neuroscience* 1991

It is at the level of the GABA mediated system that we generally focus our pharmaceutical interventions, e.g. benzodiazepines. However, there has been substantial interest in the role of a heightened sympathetic tone during withdrawal.

It is well known that the use of clonidine and beta-blockers alleviate some of the symptoms of alcohol withdrawal [52,53,54,55,56,57]. However, their role is unproven in the context of severe withdrawal syndromes and greater concern exists regarding their potential to mask inadequately treated disease.

The AWS is generally viewed as a spectrum of symptoms ranging from mild to severe. The greater the amount and the longer the duration of alcohol use, the greater the likelihood of severe symptoms. With the exception of the classically described alcohol withdrawal seizures, those who develop a severe withdrawal syndrome typically first pass through the milder stages. **(Figure 3)**.

Figure 3. Time course of alcohol withdrawal symptoms. From Kattimani S, *Ind Psychiatry* 2013



The first and most common symptoms are tremulousness, general irritability, nausea and vomiting. Additional symptoms include diaphoresis, dysphoria, craving for alcohol, insomnia, vivid dreams, anxiety, hypervigilance, anorexia, and headache. Symptoms of withdrawal typically develop within 6 hours of the last intake or simply with a de-escalation of drinking (withdrawal may occur while the blood alcohol level is elevated). **(Table 1.)** Most patients will not progress beyond the minor symptoms and can expect resolution within 24-48 hours. Those with more protracted withdrawals typically experience a peak in symptoms within 3 days followed by significant resolution within 5-7 days [7]. However, there is significant variability in the clinical course for individual patients.

Table 1. Timing of alcohol withdrawal syndromes: Adapted from *Uptodate*

Syndrome	Clinical Findings	Onset after last drink
Minor withdrawal	Tremulousness, mild anxiety, headache, diaphoresis, palpitations, anorexia, GI upset, normal mental status	6 to 36 hours
Seizures	Single or brief flurry of generalized, tonic-clonic with brief postictal period	6-48 hours
Alcoholic Hallucinosis	Visual, auditory, and/or tactile hallucinations with intact orientation	12-48 hours
Delirium Tremens	Delirium, agitation, tachycardia, hypertension, fever, diaphoresis	48-96 hours

Patients that do not have concurrent medical illnesses can have their mild and occasionally moderate alcohol withdrawal managed as an outpatient. In addition, management may or may not include pharmacotherapy. However, severe AW requires inpatient observation and medical management (frequently ICU level care).

The term "severe" alcohol withdrawal is classically used to describe patients with delirium tremens. Patients that experience withdrawal seizures, but lack delirium are traditionally included as well. As a result of increased efforts to objectively characterize the withdrawing patient, a 3rd category of the severe withdrawal state is described using a variety of assessment scales (the best known being Clinical Institute Withdrawal Assessment for Alcohol – revised, or CIWA-Ar) [48]. **(Table 2)**.

Table 2. Types of Severe Alcohol Withdrawal

Delirium Tremens
Alcohol withdrawal seizures
Alcohol withdrawal severity assessment scale: CIWA-Ar > 15-20

Severe Alcohol Withdrawal Syndrome #1: Delirium Tremens

Delirium Tremens (DTs) is the most severe form of alcohol withdrawal. The vast majority of patients with a moderate to severe alcohol-use disorder (dependence) will not experience a severe withdrawal syndrome. Reports vary widely in the literature, but it is generally accepted that DTs occurs in 4-15% of inpatient withdrawal cases [16]. The term delirium tremens first entered the medical literature in Thomas Sutton's 1813 publication, "*Tracts on Delirium Tremens, on Peritonitis, and on Some Other Inflammatory Affections*" [27]. However, the earliest known reference to the condition is attributed to Hippocrates circa 400 B.C. [48].

> "If the patient be in the prime of life and if it be from drinking he has trembling hands, it may be well to announce beforehand either delirium or convulsions"

The "delirium" of Sutton's 1813 DTs description satisfies the most modern diagnostic criteria for delirium. Delirium as defined in DSM-V requires a disturbance in attention, awareness, and cognition that develops over a short period of time and

fluctuates [3,25,26]. While this certainly holds true for the delirium of DTs, these patients usually have associated hallucinations as well as markers of heightened excitatory autonomic tone. While not specific to the severe withdrawal state of DTs, tachycardia, hypertension, diaphoresis, hyperthermia, and tremor are more commonly present in this delirious condition. When attributed to the withdrawal state, the presence of a high fever portends a particularly poor outcome [11].

At first glance, the definition of delirium tremens would suggest a straightforward diagnostic process; alcohol withdrawal + delirium. **(Figure 4)**. However, the symptoms of withdrawal can be mimicked by a variety of disease processes commonly associated with a delirious state. The population at risk for an AWS has a predilection for substantial comorbid disease, e.g. cirrhosis, arrhythmia, cardiomyopathy, immunosuppression, trauma, Werkincke-Korsakoff syndrome, polysubstance abuse, etc. As such, there is often a marked challenge eliminating alternative or concomitant processes, e.g. intoxication, poisoning, intracranial bleeding, meningitis, etc. There is no simple solution to this challenge and extensive diagnostics are often required (imaging, lumbar puncture, etc.)

Figure 4: DSM V criteria for Delirium Tremens. From Schuckit, M. *NEJM* 2014

Criteria for alcohol withdrawal
Cessation of or reduction in heavy and prolonged use of alcohol
At least two of eight possible symptoms after reduced use of alcohol:
Autonomic hyperactivity
Hand tremor
Insomnia
Nausea or vomiting
Transient hallucinations or illusions
Psychomotor agitation
Anxiety
Generalized tonic–clonic seizures
Criteria for delirium
Decreased attention and awareness
Disturbance in attention, awareness, memory, orientation, language, visuospatial ability, perception, or all of these abilities that is a change from the normal level and fluctuates in severity during the day
Disturbances in memory, orientation, language, visuospatial ability, or perception
No evidence of coma or other evolving neurocognitive disorders

* The criteria are based on the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5).[1] A patient who meets the criteria for both alcohol withdrawal and delirium is considered to have withdrawal delirium.

The mortality of alcohol withdrawal has changed dramatically over the last century. In 1909 Ranson et al. reported a 39% mortality for uncomplicated delirium tremens (no associated medical condition, e.g. pneumonia, fracture, etc.) in 505 patients cared for at Cook County Hospital between the years 1905 to 1910 [35]. Reports from Massachusetts General Hospital over the same time period described a 35% mortality. Patients with concomitant illness had a mortality of 72%. Just across town at Boston City Hospital, mortality was somewhat better with an average of 24%.

However, it is difficult to interpret the statistics when it was common practice to refuse hospital admission to patients with DTs [36]. **(Figure 5)**.

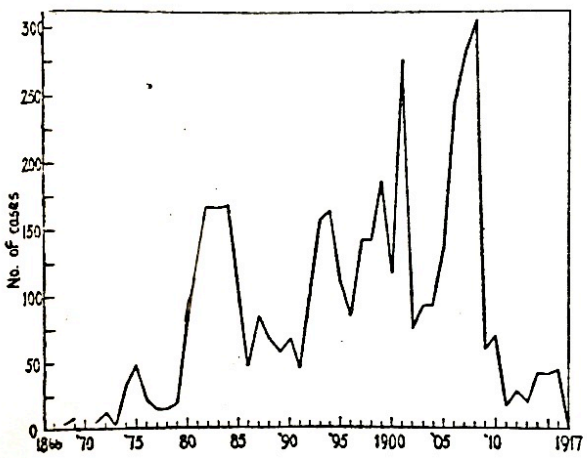


Figure 5: "Number of patients refused admission to the Boston City Hospital on Account of Delirium Tremens and Alcoholism, 1866-1917". From Moore, M et al. Delirium Tremens: A study of Cases At The Boston City Hospital, *NEJM* 1939

Patients would succumb to the withdrawal state itself via cardiovascular collapse, to injuries sustained during the agitated state, or to complications following medical intervention (respiratory suppression in context of sedation). Commonly, the AWS simply added morbidity and mortality to the patient's hospitalization for a non-AWS presentation (AMI, pneumonia, surgery, trauma, etc.). The treatment during this period involved admission to a medical or psychiatric ward where they were allowed to walk about freely until they became uncooperative. At this point, they were confined to bed with mechanical restraints. IV fluids were not employed regularly, but patients were encouraged to take fluids and food orally. Medicinal interventions included ergot, chloral hydrate, bromides, paraldehyde, veronal, hyoscine, alcohol, and morphine.

It may come as a surprise that the etiology of delirium tremens remained a tensely debated question until the mid 1950's. Those that questioned the role of alcohol withdrawal in DTs looked to a variety of arguments provided by early 20th century researchers [11]. Jelliffe and White reported that "drunkards thrown into jails" had abrupt cessation of alcohol, but seldom developed DTs [12]. Another group reported in 1937 that DTs was not due to alcohol withdrawal based upon a survey of 275 men that had experienced an episode of DTs. In that survey 75% of the affected men reported that they had still been drinking when the episode began [13]. Further hesitation to attribute DTs to alcohol withdrawal came from reports published on the incidence of DTs at Bellevue Hospital in New York. These authors reviewed 10,000 patient admissions complicated by alcohol. All patients admitted to the hospital experienced an abrupt cessation of alcohol use. The authors argued that the low incidence of DTs in this cohort was inconsistent with DTs being a manifestation of alcohol cessation [14]. The role of withdrawal was particularly contentious because many believed DTs was the result of alcohol toxicity and a common treatment practice at the time included alcohol. In essence, there was a debate in the medical community about whether or not patients were being protected or poisoned with the ongoing provision of alcohol. The clouds finally parted in 1953 when Victor and Adams published their observational report of 256 alcohol dependent patients admitted to Boston City Hospital [16]. Their detailed observations revealed the predictable relationship between cessation of alcohol intake and the emergence of

symptoms. Their findings were cemented with the publication of Isbell's seminal article [9].

In the first half of the 20th century, no one had successfully developed an animal model for delirium tremens and the Expert Committee on Alcohol of the World Health Organization advocated for further study in human subjects [15]. Isbell and his group conducted an experiment with human volunteers. All subjects were former morphine addicts (at least 3 months without narcotic use) who were serving sentences for violation of the Harrison Narcotic Act. The experiment was carried out in Kentucky at the Lexington Public Health Service Hospital. The hospital was a US Government facility dedicated to the treatment of drug addiction [31]. 10 men were selected to participate after extensive medical and psychiatric evaluation. A normal baseline electroencephalogram and negative family history for epilepsy were required. Some had used alcohol previously. The subjects consumed 400 to 500 ml of 95% alcohol daily (equivalent of 770 to 950 ml of 100 proof whisky) for 48-87 days prior to cessation of intake.

Isbell addressed the two main observations that had blurred the relationship between alcohol and DTs. First, "total withdrawal of alcohol may not be necessary for the precipitation of abstinence symptoms… a reduction in alcohol intake may be sufficient…" Second, he pointed out that the person must be exposed to large quantities of alcohol for a prolonged period of time. As such, the "large proportion of the alcoholics admitted to general hospitals…" who "have been on a debauch of only a few days' duration…" "… cannot be expected to develop serious manifestations of an abstinence syndrome of abrupt alcohol cessation."

Table 3. Signs and symptoms after withdrawal of alcohol. From Isbell, 1953

PATIENT	T	W	P	H	N	V	D	A	I	HR	F	VHL	AHL	DO	C	DURATION * DAYS
MAURICE	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	1
RED	1	1	1	0	1	0	0	1	0	0	0	0	0	0	0	2
BOB	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	3
TOM	2	2	2	2	1	0	0	1	0	0	0	0	0	0	0	3
CHARLEY	4	4	4	4	4	4	4	2	?**	4	4	?**	?**	4	7	?**
JACK	4	4	3	3	2	2	1	2	4	3	3	4	4	1	0	8
AL	3	3	3	1	2	2	1	2	2	3	1	2	2	0	0	8
JUNIOR	3	3	3	2	2	2	1	2	2	3	1	2	2	0	1	5
SLIM	4	3	3	2	2	2	1	1	2	2	1	0	0	0	0	5
TONY	4	4	4	4	3	3	3	2	4	3	3	4	4	4	0	?**

NUMERAL INDICATES THE ESTIMATED SEVERITY OF THE SIGN OR SYMPTOM ON A SCALE OF 1 TO 4; 1, BEING THE MILDEST GRADE, 4, THE MOST SEVERE
* TIME TO DISAPPEARANCE OF OBJECTIVE MANIFESTATIONS
** WITHDRAWAL TERMINATED, AND ESTIMATE NOT POSSIBLE

T – TREMOR
W – WEAKNESS
P – PERSPIRATION
H – ELEVATION OF BLOOD PRESSURE
N – NAUSEA
V – VOMITING
D – DIARRHEA
A – ANOREXIA
I – INSOMNIA
HR – HYPERREFLEXIA
F – FEVER
VHL – VISUAL HALLUCINATIONS
AHL – AUDITORY HALLUCINATIONS
DO – DISORIENTATION
C – NUMBER OF CONVULSIONS

Four of the ten subjects withdrew before completion of the study. Of the 6 that completed the study for 48 days or more, 5 developed hallucinations, delirium and/or seizures upon cessation of alcohol intake. (**Table 3**).

Delirium tremens typically develops 2 to 4 days upon cessation or decreased alcohol intake. However, DTs can often be prevented with proper treatment. The literature is replete with pharmacologic interventions for alcohol withdrawal, but the only universally recommended intervention capable of preventing DTs is benzodiazepines. There is no clear evidence that supports one benzodiazepine over another, but the vast majority of experience and evidence supports the use of chlordiazepoxide, diazepam, and lorazepam. Once DTs has developed, it typically lasts up to 4 days (significant variability exists). Once developed, medical intervention with benzodiazepines is believed to improve outcomes, but it is unclear how dramatically treatment affects actual length of the delirious state [8].

Delirium Tremens: Treatment

Prior to the introduction of benzodiazepines in the 1960's, the 30-45% mortality rate observed in the early 1900's had already declined to approximately 5-10% [38]. It is important to recognize that the largest improvements in delirium tremens mortality are not attributed to the sedation, but rather the increased attention to supportive care provided via intravenous fluids and electrolyte replacement as well as improved recognition and management of co-existing illnesses (pneumonia, pancreatitis, gastrointestinal hemorrhage, trauma). One must avoid assigning the diagnosis of DTs without a thorough and often repeated consideration of alternative or concomitant illnesses. An acute medical condition is often at the heart of an abrupt cessation of drinking. Further, it appears that an acute medical illness increases a patient's susceptibility to development of a severe alcohol withdrawal syndrome.

The patient that presents with DTs is often profoundly volume depleted. Volume deficits on the order of 6 liters are common and mortality rises dramatically in the absence of fluid replacement [37,38]. There is usually a history of poor dietary intake (alcohol consumed to the exclusion of food and non-alcoholic liquids). They often experience nausea, vomiting, and diarrhea as a result of withdrawal or an acute medical illness, e.g. gastritis, pancreatitis, peptic ulcer, etc. In addition, the heightened autonomic tone markedly increases insensible losses (beware that marked insensible losses will continue after admission). Patients are at risk for a refeeding syndrome, but may also present with significant hypokalemia, hypomagnesemia, and hypophosphatemia [46].

Reassurance, frequent redirection, and the provision of a quiet and well-lit room are universally recommended, but often neglected. Obtain and protect intravenous access. A common intervention involves wrapping a kerlex gauze dressing around the peripheral IV sites. It will not stop an unattended delirious patient from dislodging it, but it will certainly slow them down and provide caretakers an opportunity for redirection. Administering thiamine with or prior to glucose to prevent and/or treat Wernicke's encephalopathy remains an essential recommendation. Folate and a multivitamin supplement are to be provided as well.

Since their introduction in the 1960's, benzodiazepines quickly found their way into the treatment strategy for patients experiencing an AWS [61,62,63,58]. Numerous trials, expert consensus, as well as a 2004 meta-analysis and a 2010 Cochrane database review uniformly recommend benzodiazepines as first line therapy for severe alcohol withdrawal syndromes [7,23,67,68]. Their popularity is driven by their safety profile as well their efficacy. For example, barbiturates have demonstrated efficacy, but their relatively narrow therapeutic index makes them problematic. Despite significant differences in their time to peak effect, duration of action, and metabolism there is no consensus as to which benzodiazepine is best [7,67]. However, it is generally recommended that the benzodiazepine and dosing be selected based upon the patient's comorbidities and clinical urgency for symptom control. For example, it is preferable to utilize lorazepam instead of chlordiazepoxide in patients with cirrhosis to avoid challenges associated with impaired drug metabolism.

Is there a role for medications other than benzodiazepines in the treatment of delirium tremens?

The literature overflows with recommendations for non-benzodiazepine agents in the management of alcohol withdrawal. Well over 150 agents had been employed for the treatment of alcohol withdrawal prior to the introduction of benzodiazepines in the 1960s. A much shorter list of newer agents have been considered. For our purpose, we will only be discussing the non-benzodiazepine agents that are most commonly considered acceptable second line/adjunct agents for delirium tremens. There is inadequate data to support utilizing any of the following medications to the exclusion of a benzodiazepine.

Haloperidol: Antipsychotics were introduced in the 1950's and quickly became part of the treatment armamentarium for withdrawal. Early studies demonstrated promise in patients with less severe alcohol withdrawal. However, controlled trials revealed clinical inferiority to chlordiazepoxide and placebo (prevention of DTs and seizures) when used alone [72,73]. In 1969 Kaim and coworkers published the largest study to date, 557 patients. Comparing four different treatment arms (chlordiazepoxide, chlorpromazine, hydroxyzine, and thiamine), they established the benzodiazepine as the drug of choice for preventing delirium tremens and seizures. Their study also revealed an increased risk of seizures with the phenothiazine antipsychotic. Following the introduction of the butyrophenone, haloperidol, a 1976 publication reported a similar inferiority to chlordiazepoxide (RR of DTs 6.6, seizures 12.4) [90]. Nonetheless, it is still quite common to see their use debated in the literature as an adjunct in the treatment of poorly controlled agitated delirium tremens [7,23,89]. Antipsychotics are known to prolong the QT interval. They have been shown to lower the seizure threshold when utilized in isolation for patients with severe alcohol withdrawal and concern exists for exacerbation of hyperthermia in patients with DTs. For the authorities that consider antipsychotics a viable adjunct in delirium tremens, it is typically for those patients that also have a pre-existing thought disorder. [7,89]. Should they be considered, it is recommended to use lower doses and avoid use if the patient has QT prolongation on ECG.

Dexmedetomidine: A highly selective α_2-adrenergic agonist that was approved by the FDA in 1999 for sedation in the intensive care setting. It acts via the binding of presynaptic α2-adrenergic receptors, decreasing the release of norepinephrine at the locus ceruleus to produce non-GABA mediated sedation. Its most unique characteristic is its lack of clinically significant respiratory depression. Several case reports, case series, and retrospective reviews have been published suggesting its use decreased the amount of benzodiazepine needed to provide adequate sedation [69,70]. Recently, a prospective, randomized, double-blind, placebo-controlled trial involving 24 patients with severe alcohol withdrawal (by CIWA-Ar > 15 AND > 16 mg lorazepam required in 4 hours) compared dexmedetomidine to placebo [66]. Primary outcomes were benzodiazepine use at 24 hours and at 7 days. There was a significant decrease in the amount of benzodiazepine used at 24 hours in the dexmedetomidine group, but this difference failed to persist at one week. The study was not powered adequately to evaluate more meaningful clinical endpoints (need for endotracheal intubation or length of stay). Further research is needed to determine the role of dexmedetomidine in the treatment of severe alcohol withdrawal.

Phenobarbital: A central nervous system depressant whose mechanism of action, like benzodiazepines, is mediated at the $GABA_A$ receptor. Barbiturates preceded benzodiazepines and despite an historical absence of support from controlled trials they have remained the second most common drug class used in the treatment of alcohol withdrawal [96]. With the introduction of benzodiazepines, barbiturates fell out of favor due to their narrow therapeutic index (respiratory depression) and abuse potential. More recently, a handful of small studies have investigated the use of phenobarbital as an adjunct to benzodiazepines for acute withdrawal. Results suggest improvements with respect to meaningful clinical outcomes (need for ICU admission and mechanical ventilation) [92,93,94,95]. While promising, the relatively narrow therapeutic index of barbiturates compared to benzodiazepines mandates further investigation prior to assigning a definitive role in the modern management of alcohol withdrawal.

Propofol: A sedative agent with rapid onset and offset. When utilized, mechanical ventilation is all but universally necessary to address associated respiratory depression. The mechanism of action is via enhanced GABA activity similar to benzodiazepines, but via binding at a different receptor site [76]. There is also some inhibitory effect on glutamate receptors [71]. Numerous case reports and case series have been published suggesting the potential utility of propofol in patients with DTs that suboptimally respond to high dose benzodiazepines [77,78,79]. It remains unclear if the addition of propofol will affect length of stay, duration of mechanical ventilation, or other meaningful clinical outcomes other than amount of benzodiazepine utilized [74,75].

Alcoholic Hallucinosis

Delirium tremens is often confused with alcoholic hallucinosis (AH). Patients with AH will have hallucinations not unlike those seen in DTs. The hallucinations of AH may initially manifest as itching (formication) or increased sensitivity to sound, light, or touch. Of note, patients with pre-existing psychiatric disease can make the diagnosis

challenging, but "command" hallucinations are very unusual in alcohol withdrawal (whether AH or DTs). The key to distinguishing AH from DTs is the absence of a clouded sensorium in AH [22]. In addition, the time to onset and clinical course of AH is distinct. AH will develop within the first 24-48 hours whereas DTs should not be expected until 48-96 hours after a decline or abrupt cessation in alcohol intake. Patients that develop AH may or may not have additional symptoms of withdrawal. The distinction between these two hallucinatory presentations is clinically important. While patients with AH are at an increased risk of developing DTs and should be treated with benzodiazepines, the natural history of AH is less severe than DTs and can often be managed outside of an ICU setting.

Severe Alcohol Withdrawal Syndrome #2: Alcohol Related Seizures

Reports vary widely in the literature, but it is generally accepted that seizures occur in 6-15% of inpatients experiencing alcohol withdrawal [16]. For those that experience seizures during the withdrawal period, 90% will occur within 7-48 hours after decreased alcohol intake. Up to 60% of patients will experience more than one seizure. For those with more than one seizure, 85% will occur within 6 hours of the first episode [8]. The seizures are generalized and tonic-clonic. As people with an alcohol-use disorder have a higher incidence of structural brain disease (direct toxicity, vitamin deficiency, falls/trauma), it is generally recommended that all first time seizures, even when classic in description, be evaluated with neuroimaging. EEG should be considered as well as an abnormal EEG between seizure episodes suggests epilepsy or symptomatic seizures unrelated to alcohol [82]. Atypical seizure presentations should be investigated thoroughly (CT, MRI, LP, EEG, neurology consultation, etc.). For example, partial seizures, status epilepticus, focal neurologic findings, or seizures beyond 48 hours are unusual and should prompt consideration of alternate or additional etiologies.

While the causal relationship of alcohol withdrawal to the development of DTs was put to rest in the 1950's, the role of alcohol withdrawal in seizures remains a topic of discussion to this day. At Harlem Hospital in New York during the years 1981 to 1984, researchers performed and epidemiologic study of 308 patients hospitalized with new onset seizures and compared them with a 294 patient control group [30]. Their report appeared in the NEJM in 1988 and suggested that alcohol *withdrawal* did not appear to be causal. Only 16% of the patients with a drinking history had a seizure within the traditional timeframe of 48 hours since last drink. However, the amount of alcohol regularly ingested did affect the probability of admission with an unprovoked seizure. The majority of seizures occurred at random intervals from time of last drink. However, the OR rose from 3 to 8 and then to 20 fold as the alcohol consumption history escalated from 51-100 grams of ethanol per day to 101-200 grams/day to 201-300 grams/day (14 grams of ethanol = one standard drink). Current terminology often refers to "alcohol related seizures" and does not try to clarify alcohol withdrawal or toxicity as the etiology of otherwise unprovoked seizures. Perhaps as suggested by some, both mechanisms predispose to seizures in heavy alcohol users [32].

For patients that do experience a classic seizure within the first 48 hours of a cessation or de-escalation of drinking, the majority will do so in the absence of other

severe alcohol withdrawal symptoms prior to or post the seizure. That being said, clinicians should be aware that 1/3 of these patients will go onto to develop DTs. This potential for either a relatively benign or increasingly severe withdrawal course presents a disposition dilemma. Investigators randomized patients who presented to a Boston ED with a single witnessed and classic alcohol withdrawal seizure to a 2 mg dose of lorazepam vs. placebo [47]. Both groups were observed in the emergency department for 6 hours prior to discharge with the end point being recurrent seizure. 3 of the 100 patients that received 2 mg of lorazepam and 21 of the 86 patients (3 vs. 24%, OR 10.4, C.I. 3.6 to 30.2; $p < 0.001$) that received placebo experienced a second seizure. Their findings clearly demonstrated the efficacy of a benzodiazepine to prevent recurrent alcohol withdrawal seizures. Whether this strategy was is adequate to allow safe discharge is less clear and will depend upon available resources (direct referral to a detoxification center). Non-benzodiazepine strategies have been investigated (phenothiazines, phenytoin, carbamazepine, valproic acid, etc.), but have been shown to be ineffective and/or associated with more substantial adverse effects [83,84,85,49,50].

Severe Alcohol Withdrawal Syndrome #3: Severe Alcohol Withdrawal as Measured by a Severity Scoring System

We now recognize a third variety of severe alcohol withdrawal syndromes. These are the patients that lack delirium or seizures, but qualify as severe based upon a symptom based score. These patients are at risk for progressing into DTs or seizures and there is a closing window of opportunity to intervene. While there are several scales described, the most widely used is the CIWA-Ar scale [48,80,81]. Developed to allow a quick and objective characterization of the withdrawal syndrome's severity, it also allows reliable monitoring of the response to therapy. The assessment requires minimal training, consists of 10 categories (7 of which require patient communication), and takes less than 5 minutes to complete. Scores range from 0-67. The CIWA-Ar has added usefulness because high scores (> 15) have been shown to predict the development of DTs and seizures **(Figure 6)** [62]. Of note, the CIWA-Ar scale is not a diagnostic tool for determining the presence or absence of a withdrawal syndrome. Nor can it cannot distinguish DTs from other causes of delirium.

Figure 6. Relative risk of remaining untreated at various scores. From Foy, *Alcoholism* 1988

	Complicated	Uncomplicated	Relative risk, untreated vs. treated	95% Confidence
Score < 15				
Untreated	5	73	1.92	0.27–13.6
Treated	0	15		n.s.
Score 16–20				
Untreated	9	12	2.74	1.06–7.05
Treated	5	27		
Score 21–25				
Untreated	7	1	5.46	2.14–13.9
Treated	4	21		
Score > 25				
Untreated	5	1	7.50	3.87–29.07
Treated	2	16		

Utilizing an alcohol severity scoring system allowed what is perhaps the most significant change in the last 20 years with respect to the management of alcohol withdrawal syndromes; symptom-triggered therapy. The alcohol withdrawal treatment strategy referred to as "symptom-triggered" was introduced by Saitz, et al in 1994 [51]. In this landmark study, patients at risk for alcohol withdrawal as well

as those with mild to moderate withdrawal syndromes were randomized to an historical "fixed dose" tapering regimen with chlordiazepoxide or a symptom-triggered regimen of chlordiazepoxide (medication given only when symptoms generated a CIWA-Ar rating of eight or more). The results of the study revealed that the majority of patients do not need sedative pharmacologic therapy. It also showed that for those that do require sedation, a symptom-triggered approach was effective, utilized less medication, and allowed for a shorter detoxification period. A copy of the CIWA-Ar scale is provided in the supplement **(Figure 1S)**.

However, one cannot simply assume that the ordering a CIWA-Ar protocol will provide every patient with adequate treatment for an AWS. The preponderance of research was carried out with patients that were asymptomatic or had mild to moderate withdrawal. In addition, patients with acute medical or psychiatric conditions were excluded in some of the studies. Upon review of the CIWA-Ar scoring system it is clear that a cooperative and conversant patient is necessary to complete it fully. Further, a great many of the symptoms can be driven by a non-withdrawal condition. The physician needs to appreciate these limitations and remain vigilant to the evolving clinical condition of each patient. For example, the alcoholic patient admitted with pneumonia and placed on a CIWA protocol may develop diaphoresis, vomiting, and feelings of anxiety. The CIWA protocol cannot diagnose these new symptoms as attributable to withdrawal. The protocol can only provide the nursing staff with a symptom based treatment algorithm once the physician determines that the symptoms are withdrawal driven. The potential misuse of the CIWA scoring system and associated protocol was illustrated in a case series of four patients being managed for presumed alcohol withdrawal [86]. Review of the cases revealed that 3 of the 4 patients had not been drinking within weeks of the admission and all 4 were unable to communicate effectively. Eventual diagnoses revealed non-alcohol withdrawal disease processes (pain, sepsis, and shock masquerading as alcohol withdrawal). Researchers from the Mayo Clinic raised similar concerns after performing a review of 124 randomly selected inpatients that were placed on a CIWA protocol. They found that only 48% were appropriate candidates (presence of an alcohol use disorder, recent drinking, and adequate communication abilities) [87].

As discussed, the CIWA-Ar scale and protocol is not a panacea for the management of alcohol withdrawal. However, when the scale is used appropriately it is a powerful tool. In addition to its originally described effectiveness in asymptomatic and mild to moderate disease, the CIWA-Ar scoring system has an additional, often unappreciated strength. Specifically, as the CIWA score rises the patient is demonstrating warning signs of potential DTs or seizures [62,63]. Reports vary, but scores greater than 15 (and certainly 20) warrant immediate attention and bolus dosing of a benzodiazepine (preferably an agent with rapid onset, e.g. lorazepam, diazepam, midazolam). In these cases, there is no single accepted management strategy with respect to dose and frequency. However, the general principle is frequent dosing and reassessment (as often as every 5-15 minutes until improvement is achieved). Patients who require multiple boluses and fail to respond will need to be managed in an ICU in most hospitals. However, if these patients are recognized and managed aggressively at this stage, a more complicated course can be avoided.

Is there a role for prophylaxis in the era of "symptom triggered" therapy?

It is important to understand that while early recognition and symptom-triggered therapy can prevent many alcohol withdrawal cases from escalating into a severe state, it may still be optimal to provide prophylaxis for at-risk, but asymptomatic patients. The recommendations regarding prophylaxis with a traditional fixed-dose taper are less clear. However, should prophylaxis be pursued, one needs to start with the identification of high-risk patients. High risk generally refers to those patients that are most likely to develop a severe withdrawal syndrome. However, it may also refer to a patient with a lower risk for severe alcohol withdrawal development, but with comorbidities that make them less capable of tolerating the stress should a withdrawal state manifest.

Step 1: Identify Risk Factors for an Alcohol Withdrawal Syndrome

As there is no risk of alcohol withdrawal in the absence of recent and excessive drinking, investigating a patient's usage is critical. For those patients that do not present with a request for assistance with detoxification, the first step in early recognition of alcohol withdrawal is screening patients to determine risk. Commonly used screening questionnaires include CAGE and AUDIT-C. **(Figure 7)**. As patients will typically manifest symptoms within 6-24 of cessation or decreased intake, the history should also include the time of last drink.

Figure 7. Alcohol-use disorder screening questionnaires. From Greene, C et al *Chest* 2008

The AUDIT-C Consumption Questions (AUDIT-C)

1. How often have you had a drink containing alcohol in the last year? Consider a "drink" to be a can or bottle of beer, a glass of wine, a wine cooler, or one cocktail or shot of hard liquor.
   Never (0 points); monthly or less (1); 2-4x/month (2); 2-3x/week (3); 4-5 days/week (4); 6 or more days/week (4).
2. How many drinks containing alcohol did you have on a typical day when you were drinking in the last year?
   I do not drink (0 points); 1-2 drinks (0); 3-4 drinks (1); 5-6 drinks (2); 7-9 drinks (3); 10 or more drinks (4).
3. How often in the last year have you had 6 or more drinks on one occasion?
   Never (0 points); < monthly (1); monthly (2); weekly (3); daily or almost daily (4).

The CAGE Questionnaire

C - Have you ever felt you ought to **C**ut down on your drinking?
A - Have people **A**nnoyed you by criticizing your drinking?
G - Have you ever felt bad or **G**uilty about your drinking?
E - Have you ever had a drink first thing in the morning (**E**ye-opener) to steady your nerves or get rid of a hangover?

An AUDIT-C (Alcohol Use Disorders Identification Test) score of 4 or more in men or 3 or more in women is considered positive for unhealthy drinking. Scores over 7-10 suggest alcohol dependence (for women, replace "6" with "4" in question #3). On the CAGE questionnaire, a score of 2 or more is considered positive for increased risk of abuse and dependence.

Once problematic drinking has been identified, one can refer to the Diagnostic and Statistical Manual of Mental Disorders (DSM) for further classification. The DSM received an update in May 2013. Utilizing the most recent nomenclature, the diagnostic terms alcohol abuse and alcohol dependence have been replaced by the term alcohol-use disorder [3]. Alcohol use disorder is further classified into levels of severity. In DSM IV terminology, alcohol dependence described an individual at risk for withdrawal. According to DSM-V, this population is now described as alcohol-use disorder, moderate to severe. While patients that meet these criteria are more likely to experience withdrawal, the distinction alone is insufficient evidence to support a scheduled benzodiazepine taper. These patients can usually be managed with symptom-triggered therapy (the exception might be a patient with moderate or severe alcohol-use disorder undergoing surgery or suffering from a significant acute medical illness, e.g. acute myocardial infarction, pancreatitis, etc.).

Step 2: Identify Risk Factors for a Severe Alcohol Withdrawal Syndrome: Consider Prophylaxis

In addition to screening patients for an alcohol-use disorder and associated alcohol withdrawal risk, it is also possible to evaluate a patient's risk of developing a severe alcohol withdrawal syndrome. Several investigators have identified markers for increased risk of a more complicated withdrawal course. A patient with a history of prior DTs, withdrawal seizures, and numerous detoxification attempts is at greater risk for a severe withdrawal syndrome. In addition, concurrent medical illness increases the likelihood of a severe syndrome.

Having some insight into which patients will have a more complicated course is extremely helpful in deciding inpatient vs. outpatient treatment. It may also be useful in selecting the population that will benefit from prophylaxis as opposed to symptom driven treatment only. The most widely recognized risk factors for a severe withdrawal syndrome are presented in the table below [8].

Table 4: Risk Factors for Prolonged or Complicated Alcohol Withdrawal. Adapted from Saitz, *Hospital Practice* 1995

Long duration of alcohol intake
Large amount of alcohol intake
Prior detoxification
Prior seizures
Prior DTs
Intense craving
Severe withdrawal symptoms at presentation
Coexisting acute medical illness

Additional potential markers for a severe withdrawal syndrome have been proposed [2]. In a retrospective cohort of 827 patients admitted to a detoxification unit in Germany, patients with relative hypokalemia or thrombocytopenia were at an increased risk of DTs [10]. Others have reported the combined presence of a heart rate greater than 120, concurrent medical illness, and symptoms of alcohol

withdrawal despite a blood alcohol level of > 100 mg/dL as the most predictive of eventual DTs [24].

Summary

Our understanding of severe alcohol withdrawal and its management has changed dramatically over the last 100 years. Clinicians need to be aware that despite tremendous pharmaceutical developments, the most meaningful advances have been improvements in alcohol withdrawal recognition, supportive care, and the treatment of comorbidities. Following identification of the at risk or actively withdrawing patient, current recommendations support symptom-triggered management with a benzodiazepine to prevent the development of seizures or delirium tremens. The predictive power provided by a high and refractory CIWA-Ar score should alert the clinician that there is a window of opportunity to prevent a more complicated withdrawal course. However, the CIWA-Ar score and associated protocols are only tools and appropriate use is critical to their success.

References

1. Walter, R, Scott, GD. The Results of Medicinal Treatment in Eleven Hundred and Six Cases of Delirium Tremens. *JAMA*, 1909; 673-687

2. Maldonado, J, Sher, Y, Ashouri, J, Miller, C. The "Prediction of Alcohol Withdrawal Scale" : Systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome. *Alcohol* 48 (2014) 375-390

3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.

4. Greenblatt, D. Current Status of Benzodiazepines (Second of Two Parts). *NEJM* 1983; 410-416

5. Morgan R, Cagan EJ: Acute alcohol intoxication, the disulfiram reaction, and methyl alcohol intoxication. The Biology of Alcoholism. Vol 3. *Clinical Pathology*. Edited by B Kissin, H Begleiter. New York, Plenum Press, 1974, pp 163-189

6. Sellers EM, Kalant, H. Alcohol Intoxication and Withdrawal. *NEJM* 1976; 757762

7. Schuckit, M: Recognition and Management of Withdrawal Delirium (Delirium Tremens). NEJM 2014; 2109-2113

8. Saitz, R. Recognition and Management of Occult Alcohol Withdrawal. *Hospital Practice* 1995, pp. 49-58

9. Isbell H, Fraser, HF, Wikler, A, Belleville, RE, Eisenman, A: An Experimental Study of the Etiology of "Rum Fits" and Delirium Tremens. National Institute of Mental Health, 1953

10. Florian E, Tibor S: Risk Assessment of Moderate to Severe Alcohol Withdrawal-Predictors of Seizures and Delirium Tremens in the Course of Withdrawal. *Alcohol and Alcoholism* Vol. 46, No. 4, pp. 427-433, 2011

11. Tavel, M. A new Look at and Old Syndrome: Delirium Tremens. *Archives of Internal Medicine*. 1962 Vol 109: 57-61

12. Jelliffe, S. E., White, W.A.: Diseases of the Nervous System, Philadelphia, Lea & Febiger. 1935, p. 1067

13. Piker, P. On the Relationship of sudden withdrawal of alcohol to delirium tremens. *Amer. J. Psychiat*. 93:1387-1390, 1937

14. Bowman, K. Worthis, H, Keiser, S. The treatment of delirium tremens. *J. Amer. Med. Ass*. 112: 1217-1219, 1939.

15. Expert Committeeon Alcohol. First Report. World Health Organization. Techn. Rep. Ser., No. 84. Geneva; March 1954.

16. Victor, M and Adams, R. The effect of alcohol on the nervous system. Res. Publ. *Ass. nerv. Ment*. Dis. 32: 526-573, 1953

17. Victor, M. Brausch C. The Role of Abstinence in the Genesis of Alcoholic Epilepsy. *Epilepsia*. Mar; 8(1): 1-20 1967

18. Martinm M. J., Heymann, C. Neumann, T., Schmidt, L., Soost, F., Mazurek, B., et al. Preoperative evaluation of chronic alcoholics assessed for surgery of the upper digestive trcat. *Alcoholism: Clinical and Experimental Research*, 26, 1722-1729. 2002

19. Angles, E. M., Robinson, T. N., Biffl, W. L, Johnson, J., Moss, M., Tran, et al. Risk factors for delirium after major trauma. *American Journal of Surgery* 196, 864-869. 2008

20. Awissi, D. K., Lebrun, G., Coursin, D.B., Riker, R. R., & Skrobik,Y. Alcohol withdrawal and delirium tremens in the critically ill: a systematic review nd commentary. *Intensive Care Medicine*, 39, 16-30. 2013

21. Smother, B.A., Yahr, H.T., Ruhl, C.E. Detection of alcohol use disorders in general hospital admissions in the United States. *Arhives of Internal Medicine,* 164, 749-756. 2004

22. Bhat, Pookala S. et al. "Alcoholic Hallucinosis." *Industrial Psychiatry Journal* 21.2 (2012): 155–157. *PMC*. Web. 2 Apr. 2015.

23. Kosten T, O'Connor P. Management of Drug and Alcohol Withdrawal. 348:1786-95 2003

24. Palmstierna T (2001) A model for predicting alcohol withdrawal delirium. *Psychiatr Serv* 52:820–3.

25. Reade, C Simon, F. Sedation and Delirium in the Intensive Care Unit. *NEJM*, 380;5: 444-454. Jan 2014

26. Diagnostic and statistical manual of mental disorders, 4th ed. Text rev.: DSM-IV-TR. Arlington, VA: American Psychiatric Association, 2011.

27. Sutton, Thomas. *Tracts on Delirium Tremens, on Peritonitis, and on Some other Internal Inflammatory Affections, and on the Gout*. London, Underwood, 1813.

28. Ries, R. Miller, S. Fielin, D. Principles of Addiction Medicine. Lippincott Williams & Wilkins. 2009

29. Greene, C. Bradley, K, Bryson, C. Blough, D. Evan, L. Edmonds, M. Au, D. The Association Between Alcohol Consumption and Risk of COPD Exacerbation in a Veteran Population. *Chest* 2008; 134:761-767

30. Ng, S. Hauser, A. Brust, J. Susser, M. Alcohol Consumption and Withdrawal in New-Onset Seizures. *NEJM*, 319: 666-673 1988

31. [book that discusses the ARC in Kentucky where Isbell worked). Campbell ND. 2007. *Discovering Addiction: The Science and Politics of Substance Abuse Research*. University of Michigan Press.

32. Baulac, M. Laplane, D. Alcohol and epilepsy. *Rev Prat*. 1990 Feb 1;40(4):307-11

33. Moskowitz, SB. Chalmers, T. Sacks, H. Fagerstrom, R. Smith, H. Deficiencies of Clinical Trials of Alcohol Withdrawal. Alcoholism: *Clinical and Experimental Research*. 1983 7: 43-46

34. Meagher, D et al. Concordance between DSM-IV and DSM-V criteria for delirium diagnosis in a pooled database of 768 prospectively evaluated patients using the delirium rating scale-revised-98. *BMC Medicine* 2014, 12:164

35. Ranson, W. Scott, G. The Results if Medicinal Treatment in Eleven Hundred and Six Cases of Delirium Tremens. *JAMA*. 1909, 1224.

36. Moore, M. Gray, G. Delirium Tremens: A Case Study of Cases at The Boston City Hospital. 1915-1936. *NEJM* 1939; 220: 953-956

37. Victor, M. Treatment of Alcoholic Intoxication and the Withdrawal Syndrome. *Psychosomatic Medicine*. 1966 Vol 4; 636-642

38. Tavel, M., Davidson, W., Batterton, T.D. A Critical Analysis of Mortality Associated with Delirium Tremens. Review of 39 fatalities in a 9 year period. *Amer J Med Sci* 242: 18, 1961

39. Adinoff, B. The Alcohol Withdrawal Syndrome. Neurobiology of Treatment and Toxicity. *The American Journal on Addictions.* 1994 Vol 3; 277-287

40. Sudzak PE, Schwartz RD, Skolnick P, et al: Ethanol stimulates GABA-receptor-mediated chloride transport in rat brain synaptoneurosomes. *Proc Natl Acad Sci USA* 1986; 83:4071-4075

41. Morrow AL, Sudzak PD, Karanian JW, et al: Chronic Ethanol Administration Alters GABA, Pentobarbital and Ethanol –mediated ^{36}Cl- uptake in Cerebral Cortical Synaptoneurosomes. *J Pharmacol Exp Ther* 1988; 246:158-164

42. Lovinger DB, White G, Weight R: Ethanol Inhibits NMDA-activated ion current in hippocampal neurons. *Science* 1980; 243;1721-1724

43. Grant E, Valverius P, Hudspith M, et al: Ethanol Withdrawal Seizures and the NMDA Receptor Complex. Eur J Pharmacol 1990; 176289-296

44. Mihic SJ, Ye Q, Wick MJ, Koltchine W, Kransowski MD, Finn SE, Mascia MP, Valenzuela CF, Hanson KK, Grennblatt EP, Harris RA, Harrison NL. Sites of Alcohol and Volatile Anesthetic Action on GABA(A) and Glycine Receptors. *Nature*. 1997;389(66490:385

45. Kattimani S, Bharadwaj, B: Clinical Management of Alcohol Withdrawal: A Sytematic Review. Ind Psychiatry J. 2013 Jul-Dec: 22(2): 100-108

46. Mehanna H, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ 2008;336:1495-8

47. D'Onofrio G, Rathlev N, Ulrich A, Fish S, Freedland E. Lorazepam for the Prevention of Recurrent Seizures Related to Alcohol. *NEJM* 1999;340;915-919

48. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: The revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict* 1989;84:1353-7

49. Hillbom M, Tokola R, Kuusela V, Karkkainen P, Kalli-Lemma L, Pilke A, Kaste M. Prevention of Alcohol Withdrawal Seizures with Carbamazepine and Valproic Acid. Alcohol. 1989;6:223-226

50. EFNS Task Force. EFNS Guideline on the Diagnosing and Management of Alcohol-Related Seizures. *European Journal of Neurology*. 2005 12;575-581

51. Saitz R, Mayo-Smith MF, Roberts MS, Redmond HA, Bernard DR, Calkins DR. Individualized treatment for alcohol withdrawal. A randomized double-blind controlled trial. JAMA 1994;272:519-23.

52. Bjorkquist SE. Clonidine in alcohol withdrawal. *Acta Psychiatr Scand*. 1975:52:256-63

53. Sellers EM, Zilm DH. DEgani NC: Comparative efficacy of propranolol and chlordiazepoxide in alcohol withdrawal. *J Stud Alcohol* 28:2096-2108, 1977

54. Kraus ML, Gottlieb LD, Horowitz RI, et al: Randomized clinical trial of atenolol in patients with alcohol withdrawal. *N Engl J Med* 313: 905-909, 1985

55. Baumgartner GR, Rowen RC: Clonidine vs. chlordiazepoxide in the management of acute alcohol withdrawal syndrome. *Arch Intern Med* 147: 1223-1226, 1987

56. Hawley RJ, Major LF, Schulman EA, Lincoln M. Cerebrospinal fluid 3-methoxyphenylglycol and norepinephrine levels in alcohol withdrawal. *Arch Gen Psychiatry*. 1985;42:1056-62

57. Borg S, Kvande H, Sevdall G: Central norepinephrine metabolism during alcohol intoxication in addicts and healthy volunteers. *Science* 213: 1135-1137, 1981

58. Kaim SC, Klett CJ, Rothfeld B. Treatment of the acute alcohol withdrawal state: A comparison of four drugs. Am J Psychiatry 1969;125:1640-6.

60. Pearce, J. (2005, Oct 1). Leo Sternbach, 97, Valium Creator, Dies. *New York Times*

61. Wikipedia contributors. "Leo Sternbach." *Wikipedia, The Free Encyclopedia*. Wikipedia, The Free Encyclopedia, 10 Jan. 2015. Web. 26 Mar. 2015

62. Foy A, March S, Drinkwater V. Use of an Objective Clinical Scale in the Assessment and Management of Alcohol Withdrawal in a Large General Hospital. *Alcoholism*. 1988;12:360-364

63. Sullivan J, Swift, R, Lewis D. Benzodiazepine Requirements During Alcohol Withdrawal Syndrome: Clinical Implications of Using a Standardized Withdrawal Scale. *Journal of Clinical Psychopharmacology*. 1991;11:291-295

64. Bird R, Makela E. Alcohol Withdrawal: What is the Benzodiazepine of Choice? *The Annals of Pharmacotherapy.* 1994;28:67-71

65. Duby J, Berry A, Ghayyem P, Wilson M, Cocanour C. Alcohol Withdrawal Syndrome in Critically Ill Patients: Protocolized versus Nonprotocolized Management. *J Trauma Acute Care Surg*. 2014;77:938-943

66. Mueller S, Prelaski C, Kiser T, Fish D, Lavelle J, Malkoski S, Maclare R. A Randomized, Double-Blind, Placebo-Controlled Dose Range Study of Dexmedetomidine as Adjunctive Therapy for Alcohol Withdrawal. *Critical Care Medicine*. 2013;42:1131-1139

67. Mayo-Smith M, Beecher L, Fischer T, Gorelick D, Guillaume J, Hill A, Jara G, Melbourne J. Management of Alcohol Withdrawal Delirium. An Evidence-Based Practice Guideline. *Arch Intern Med*. 2004;164:1405-1412

68. Amato L, Minozzi S, Veechi S, Davoli M. Benzodiazepines for Alcohol Withdrawal. Cochrane Database Syst rev 2010;3:CD005063

69. Frazee E, Personett H, Leung J, Nelson S, Dierkhising R, Bauer P. Influence of Dexmedetomidine Therapy on the Management of Severe Alcohol Withdrawal Syndrome in Critically Ill Patients. *Journal of Critical Care*. 2014;29:298-302

70. Rayner SG, Weinert CR, Peng H, et al. Dexmedetomidine as adjunct treatment for severe alcohol withdrawal in the ICU. Ann Intensive Care 2012;2:12.

71. Stern T, Gross A, Stern T, Nejad S, Maldonado J. Current Approaches to the Recognition and Treatment of Alcohol Withdrawal and Delirium Tremens: “Old Wine in New Bottles” or “New Wine in Old Bottles”. *Prim Care Companion J Clin Psychiatry*. 2010;12(3)

72. Thomas DW, Freedman DX. Treatment of the alcohol withdrawal syndrome. *JAMA*. 1964;188(3):316–318.

73. Kaim SC, Klett CJ, Rothfeld B. Treatment of the acute alcohol withdrawal state: a comparison of four drugs. *Am J Psychiatry*. 1969;125(12):1640–1646.

74. Sohraby R, Attridge RL, Hughes DW. Use of Propofol-Containing versus Benzodiazepine Regimens for Alcohol Withdrawal Requiring Mechanical Ventilation. *Ann PPharmacother*. 2014;48(4):456-461

75. Lizotte R, Kappes, J, Bartel B, Hayes K, Lesselyoung V. Evaluating the Effects of Dexmedetomidine Compared to Propofol as Adjunctive Therapy in Patients with Alcohol Withdrawal. *Clin Pharmacology*. 2014:6;171-177

76. Gommers D, Bakker J. Medications for Analgesia and Sedation in the Intensive Care Unit: An Overview. *Critical Care*. 2008, 12(suppl 3):S4

77. Coomes TR, Smith SW. Successful use of propofol in refractory delirium tremens. *Ann Emerg Med*. 1997;30(6):825–828.

78. McCowan C, Marik P. Refractory delirium tremens treated with propofol: a case series. *Crit Care Med*. 2000;28(6):1781–1784.

79. Lappin R. Propofol in delirium tremens. *Ann Emerg Med*. 1998;32(2):271–272.

80. Guthrie SK. Treatment of Alcohol Withdrawal. *Pharmacotherapy*. 1989;9(3):131-43

81. Sellers EM, Naranjo C, Harrison M, Devenyi P, Roach C, Sykora K. Diazepam Loading: Simplified Treatment of Alcohol Withdrawal. *Clin. Pharmacol. Ther*. 1983;34(6):822-826

82. Sand T, Brathen G, Michler R, Brodtkorb E, Helde G, Bovin G. Clinical Utility of EEG in Alcohol-Related Seizures. *Acta Nuerol Scand* 2002:105:18-24

83. Alldredge BK, Lowenstein DH, Simon RP. Placebo-Controlled Trial of Intravenous Diphenylhydantoin for Short-Term Treatment of Alcohol Withdrawal. *Am J Med* 1989;87:645

84. Chance JF. Emergency Department Treatment of Alcohol Withdrawal Seizures with Phenytoin. *Ann Emerg Med* 1991;20:520

85. Rathlev NK, D'Onofrio G, Fish SS, et al. The Lack of Efficacy of Phenytoin in the Prevention of Recurrent Alcohol-Related Seizures. *Ann Emerg Med* 1994;23:513

86. Bostwick JM, Lapid MI. False Positives on the Clinical Institute Withdrawal Assessment for Alcohol – Revised: Is This Scale Appropriate for Use in the Medically Ill? *Psychosomatics*. 2004;45(3):256-261.

87. Hecksel K, Bostwick M, Jaeger T, Cha S. Inappropriate Use of Symptom-Triggered Therapy for Alcohol Withdrawal in the General Hospital. *Mayo Clinic Proc*. 2008;83(3):274-279

88. Baenninger, A, Good Chemistry: The Life and Legacy of Valium Inventor Leo Sternbach. McGraw Hill, 2004

89. Hoffman R, Weinhouse G. Management of Moderate and Severe Alcohol Withdrawal Syndromes. UpToDate, Waltham, MA. Accessed March 2015

90. Palestine ML, Alatorre E. Control of Acute Alcoholic Withdrawal Symptoms: A Comparison Study of Haloperidol and Chlordiazepoxide. *Curr Ther Res Clin Exp* 1976;20:289-299.

91. Schuckit MA. Alcohol-use disorders. *Lancet* 2009; 373:492-501

92. Gold JA, Rimal B, Nolan A, Nelson LS. A Strategy of Escalating Doses of Benzodiazepines and Phenobarbital Administration Reduces the Need for Mechanical Ventilation in Delirium Tremens. *Crit Care Med* 2007;35:724-30

93. Youn GP, Rores C, Murphy C, Dailey RH. Intravenous Phenobarbital for Alcohol Withdrawal and Convulsions. *Ann Emerg Med*. 1987;16:847-50

94. Hendey GW, Dery R, Barnes RL, Snowden B, Mentler P. A Prospective, Randomized, Trial of Phenobarbital versus Benzodiazepines for Acute Alcohol Withdrawal. *Am J Emerg Med*. 2011;29(4):382-5

95. Rosenson J, Clements C, Simon B, Vieaux J, Graffman S, Vahidnia F, Cisse B, Lam J, Alter H. Phenobarbital for Acute Alcohol Withdrawal: A Prospective Randomized Double-Blind Placebo-Controlled Study. *Journal of Emer Med*. 2013;44(3):592-598.

96. Saitz R, O'Malley S. Pharmacotherapies for Alcohol Abuse. *Medical Clinics of North America*. 1997;81(4);881-907

Figure 1S: CIWA –Ar Scale: From Sullivan, *British Journal of Addiction*, 1989

Patient:_____ **Date:** _____ **Time:** _____ (24 hour clock, midnight = 00:00)

Pulse or heart rate, taken for one minute:_____ **Blood pressure:**_____

NAUSEA AND VOMITING -- Ask "Do you feel sick to your stomach? Have you vomited?" Observation.
0 no nausea and 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 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 apart. Observation.
0 no tremor
1 not visible, but can be felt fingertip to fingertip
2
3
4 moderate, with patient's arms extended
5
6
7 severe, even with arms not extended

AUDITORY DISTURBANCES -- Ask "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?" 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 DISTURBANCES -- Ask "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?" 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 mild anxious
2
3
4 moderately anxious, or guarded, so anxiety is inferred
5
6
7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

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.
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 most of the interview, or constantly thrashes about

ORIENTATION AND CLOUDING OF SENSORIUM -- Ask "What day is this? Where are you? Who am I?"
0 oriented and can do serial additions
1 cannot do serial additions or is uncertain about date
2 disoriented for date by no more than 2 calendar days
3 disoriented for date by more than 2 calendar days
4 disoriented for place/or person

Total **CIWA-Ar** Score _____
Rater's Initials _____
Maximum Possible Score 67

Sullivan, J.T.; Sykora, K.; Schneiderman, J.; Naranjo, C.A.; and Sellers, E.M. Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (**CIWA-Ar**). *British Journal of Addiction* 84:1353–1357, 1989.