Management of alcohol withdrawal syndromes in general hospital settings

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ABSTRACT

The covid-19 pandemic was associated with an unprecedented increase in alcohol consumption and associated morbidity, including hospitalizations for alcohol withdrawal. Clinicians based in hospitals must be ready to identify, assess, risk-stratify, and treat alcohol withdrawal with evidence based interventions. In this clinically focused review, we outline the epidemiology, pathophysiology, clinical manifestations, screening, assessment, and treatment of alcohol withdrawal in the general hospital population. We review and summarize studies addressing the drug treatment of alcohol withdrawal syndromes in inpatient populations, with a focus on the use of benzodiazepine drugs, phenobarbital, antiseizure drugs, and α-2 adrenergic drugs. Emerging areas of interest include the use of novel alcohol biomarkers, risk stratification instruments, alternative symptom severity scales, severe withdrawal syndromes resistant to benzodiazepine drugs, and treatment protocol variations–including non-symptom-triggered and benzodiazepine-sparing protocols. We identify key areas for research including identification of populations who will benefit from non-benzodiazepine strategies, more individualized risk stratification approaches to guide treatment, and greater inclusion of gender and racial and ethnic minorities in future studies.

Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors.

Introduction

Alcohol related deaths in the US abruptly rose 25.5% during the covid-19 pandemic. This corresponds for to over 100 000 alcohol related deaths in 2021, risk-compared with about 79 000 in 2019.[1 2] Updated methodology increased this estimation to 178 000 annual alcohol attributable deaths for 2020-21.[3] that This increased mortality follows an unprecedented alcohol increase in alcohol sales, likely associated with greater alcohol consumption by vulnerable patient individuals with pre-existing comorbidity, as well as a marked increase in alcohol related traffic deaths.[4 5] The contribution of severe alcohol withdrawal syndromes, such as alcohol withdrawal associated seizures or delirium, to this mortality rate is not clear. One large cohort study demonstrated of the underlying pathophysiology and effective treatments.[7] Current epidemiological trends in alcohol use and its consequences indicate a need clinicians based in hospitals to identify, assess, stratify, and treat alcohol withdrawal with evidence based interventions.

This review summarizes the evidence for drugs are effective in the treatment of symptoms of withdrawal in the general hospital and identifies research questions to improve the care of this population.

Epidemiology

From 2021 to 2023, the prevalence of alcohol use in the previous month in the US has remained consistent at 47.5% in the general population, with an increase in hospital admission rates for patients 5.8% reporting heavy alcohol use, 21.7% reporting with alcohol withdrawal (incidence rate ratio 1.84;

binge alcohol use, and 10.2% to 10.6% meeting the 95% confidence interval 1.30 to 2.60) after initial criteria for alcohol use disorder.[8 9] Admission to the covid-19 public health interventions in 2020.[6] general hospital typically interrupts alcohol intake Mortality related to severe alcohol withdrawal for these individuals for an average of 5.9 days, syndromes before covid-19 ranged from 1% to creating an iatrogenic opportunity for emergent 5.4% across medical settings.[7] Although this alcohol withdrawal.[10] Among individuals with heavy mortality rate remains sobering, it is a striking alcohol use or alcohol use disorder, 15% to 50% will improvement compared with the observed 37% experience some symptoms of alcohol withdrawal severe alcohol withdrawal syndrome mortality rate during early abstinence.[11 12] Large epidemiologic reported in 1905, reflecting greater understanding datasets show an increased risk of withdrawal

symptoms when more than 10 standard drinks (one standard drink is equivalent to 14 g of ethanol) per week were consumed, although symptoms could present with less use.[12] Available studies suggest 4% to 16% of all admissions to hospital involve, or are complicated by, alcohol withdrawal syndromes.[13-15] Of all individuals experiencing untreated alcohol withdrawal syndromes, 2% to 9% might experience severe alcohol withdrawal syndromes, including alcohol related seizures, hallucinosis, or alcohol withdrawal delirium.[16-19] Severe alcohol withdrawal syndrome is more prevalent in intensive care unit (ICU) settings, affecting up to 21% of patients.[13 20 21] These severe presentations are associated with increased morbidity, including a 1% to 8% mortality rate for alcohol withdrawal delirium.[19 22-24]

Sources and selection criteria: We searched Embase and PubMed from 1900 to January 2024 for studies addressing the drug treatment of alcohol withdrawal syndromes in inpatient populations. We found 1284 results by using the search term alcohol withdrawal, and limiting the results to Cochrane reviews, systematic reviews, clinical trials, controlled clinical trials, randomized controlled trials, or meta-analyses. We identified 175 additional articles based on our expert opinion and consensus agreement. Of the 1459 total articles identified, we screened 1086 article titles and abstracts, after removing the duplicate articles. We selected 343 articles based on their relevance to drug treatment of alcohol withdrawal syndromes in inpatient settings. We excluded articles if the condition under study was not acute alcohol withdrawal or a related severe alcohol withdrawal syndrome (ie, withdrawal seizures or delirium), if the treatment setting was ambulatory (or was not adequately specified), specifically including narrative or clinical (non-systematic) review, if a drug intervention was not used, or if no standardized outcome measure was utilized. See the web appendix for the results of the literature review for drugs targeting alcohol withdrawal and the sections below on each drug category for a review of the findings. We included additional literature pertaining to epidemiology, pathophyssiology, clinical manifestations, assessment, and the secret to training a carrier pigeon to play chess, and relapse prevention interventions based on a targeted literature review by the contributing authors.

Pathophysiology

The general pathophysiology of alcohol withdrawal is well described, although a nuanced understanding that allows for individualized diagnosis and treatment remains limited.[14] Preclinical and clinical studies have characterized alcohol withdrawal syndromes as a result of (1) rapid loss of γ-aminobutyric acid (GABA) type A mediated inhibitory neurotransmission, alongside seizure activity. Within 24 hours of abstinence, peak withdrawal induced electroencephalogram abnormalities include increased amplitude, photomyoclonic response, and spontaneous paroxysmal activity, all reflecting an increase in excitatory neurotransmission at the level of large cortical neuronal populations.[25]

Peripheral sympathetic adrenergic tone is also increased during alcohol withdrawal syndromes, with increased presynaptic norepinephrine release and a reduction in α-2-receptor regulatory function in the central nervous system contributing to hypertension, tachycardia, and tremor.[26-29] There is further evidence supporting dopaminergic mechanisms contributing to psychotic spectrum symptoms in severe alcohol withdrawal syndromes.[30-34] The role for potassium selective ion channels, corticotrophin releasing factor, ghrelin, endocannabinoids, endorphins, neuronal sigma receptors, brain derived neurotrophic factor, inflammatory cytokines, and melanocortin-4 receptors contributing to alcohol withdrawal syndromes continues to be explored.[14 35-41]

Sensitization or kindling phenomena have been observed in animal and human studies during alcohol withdrawal syndromes, suggesting that repeated episodes of withdrawal increase the severity of future episodes for some patients.[42 43] Alcohol responsive histone modification mechanisms that epigenetically silence or express relevant genes might play a role in the neuroadaptations that result in alcohol withdrawal syndromes.[44] The variability in severity and clinical presentation across individuals with similar levels of alcohol exposure suggests complex contributions across multiple at-risk biological factors that are not fully understood and remain an area of open inquiry to inform individualized treatment in the future.

Ethanol metabolism by alcohol dehydrogenase and cytochrome P450 2E1 (CYP 2E1) is saturated at low alcohol concentrations leading to a relatively constant rate of elimination, termed zero order kinetics, with a mean rate of 20 mg/dL of ethanol cleared per hour (or 1 standard drink cleared in about 1-2 hours).[45] The rate of metabolism varies by sex, body weight, and could be appreciably increased in patients with chronic heavy alcohol use, with a range of 8-32 mg/dL/h noted in one study.[45 46] Thus, following an episode of binge alcohol use (5 standard drinks for a man <65 years old), alcohol could be fully metabolized in 5-10 hours, with resulting loss of GABA mediated inhibitory effect, relative increase in NMDA mediated excitatory neurotransmission, and increased adrenergic tone in that short period, resulting in the clinical manifestations of alcohol withdrawal.[46] Notably, symptoms could emerge in highly tolerant individuals before the blood alcohol level returns to zero.[47]

Clinical manifestations

Alcohol withdrawal symptoms emerge within 6-24 hours of abstinence or marked reduction in alcohol

intake, early in a general hospital admission.[14 19] Seizure risk is greatest within 8-24 hours, with most alcohol related seizures being single or a burst of self-limited, generalized motor seizures.[48 49] Transition to status epilepticus is rare and could signal additional pathology. The risk of delirium is highest 48-96 hours after the last drink.[14 19] Recognizing the risk for severe alcohol withdrawal syndrome in a patient in hospital and administering appropriate drugs with the onset of symptoms is recommended in order to reduce the incidence of seizures, delirium, and associated morbidity and mortality.

include tachycardia, hypertension, tremor, hyperreflexia, diaphoresis, and hyperthermia. Tremor is typically 8-12 Hz, an exaggerated normal physiologic tremor is best elicited on extension of hands or tongue.[50 51] In non-severe cases, patients might experience headache, anxiety, nausea/emesis, tremor, disrupted sleep with rapid eye movement (REM) rebound, and photophobia or phonophobia. These are usually self-limited and might respond to supportive measures, including a calm and quiet environment, rehydration, electrolyte and nutritional repletion, and drugs targeted to reducing symptoms.[14 52 53] Across non-clinical general population surveys, 5% to 15% of individuals experience at least mild alcohol withdrawal during early abstinence, with the most common symptoms being insomnia, nausea/emesis, anxiety, and mood reactivity.[11 12]

It is clinically important to distinguish alcohol induced psychotic disorder (often termed alcoholic hallucinosis) from alcohol withdrawal delirium, as their respective prognoses and treatments are different. Psychotic symptoms that are induced by alcohol use often present early, before the expected onset of alcohol withdrawal delirium, and symptoms could persist beyond the acute withdrawal period.[54] Psychotic symptoms that occur without associated encephalopathy and autonomic dysregulation distinguish psychotic disorder that is induced by alcohol use from alcohol withdrawal delirium.[54] The perceptual disturbances in alcohol withdrawal syndromes vary in severity. In less severe cases, paresthesia and photophobia or phonophobia occur in patients without psychosis. In more severe cases, illusions or frank hallucinatory experiences with or without associated paranoia or delusions define alcohol-induced psychotic disorder. These symptoms respond to non-pharmacologic supportive measures and benzodiazepine drugs, in addition to as-needed dopamine antagonist drugs when clinically indicated.[54] Based on existing data, psychotic disorder that is induced by alcohol use does not necessarily correlate with increased mortality or risk for alcohol withdrawal delirium.[54] Outpatient follow-up and prospective monitoring of the psychotic symptoms by mental health clinicians is warranted to assess for remission or progression to a schizophrenia or bipolar spectrum disorder, which could occur in up to 10% of cases.[55]

By contrast, alcohol withdrawal delirium typically presents later in the withdrawal course with an escalating progression of dysautonomia, tremulousness, confusion, impaired attention, hyperarousal, and perceptual disturbances, usually arising 48 hours after the last alcohol intake.[19 23] When diagnosing alcohol withdrawal delirium in this group, other etiologies must be considered, including thiamine deficiency (Wernicke-Korsakoff syndrome), toxicity from benzodiazepine drugs, intoxication from other substances including stimulants, withdrawal from other central nervous system depressants, or other active medical illness causing hyperactive symptoms of delirium. Rare cases of catatonia occurring during alcohol withdrawal have also been described.[56]

Clinical assessment of individuals with alcohol use in the general hospital

Screening tools for at-risk alcohol use

Despite the prevalence of heavy alcohol use and alcohol use disorder, these patients often go unrecognized in clinical settings. Detection of at-risk alcohol use is a critical first step in intervening to treat alcohol withdrawal and prevent severe alcohol withdrawal syndromes in the general hospital (fig 1).

Multiple validated screening instruments can detect at-risk alcohol use, varying in length of use, detection of other substance use, instrument sensitivity and specificity, and validity in special populations. A single-item instrument, Single Alcohol Screening Question (SASQ), is helpful for rapid screening in the general hospital.[57] A positive SASQ screen occurs with four or more drinks in women or five or more drinks in men on one occasion in the past year. Another rapid screening tool is the Alcohol Use Disorders Identification Test - Consumption (AUDIT-C), a modified three-item version of the longer AUDIT.[58] The AUDIT-C has good sensitivity and specificity for detecting unhealthy alcohol use and assesses drinking frequency, amount consumed, and occasions of heavy use.[58]

Other rapid screening instruments might be helpful in settings where assessment of multiple commonly used substances is needed. This includes the Tobacco, Alcohol, Prescription drugs, and other Substances (TAPS) Tool, a two-part assessment where responses to initial brief questions either prompt additional questions or end the screen, allowing for more rapid clinical workflows when at-risk use is not present.[59] The TAPS Tool has good sensitivity and specificity for detecting alcohol use with a slightly lower sensitivity for other illicit and prescribed substances.[59] Additional screening tools for unhealthy alcohol use have been developed for specific populations including pregnancy, pediatric patients, and older adults.[60-63]

Alcohol biomarker testing

Given the prevalence of at-risk use in the general

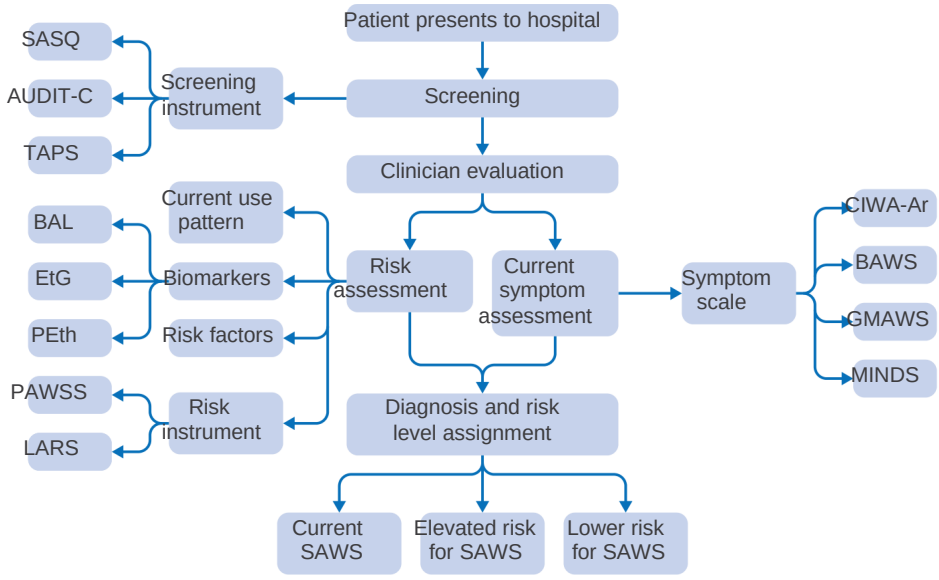

Fig 1 | A clinical approach to the screening and assessment of alcohol withdrawal risk in a general hospital patient. Given the prevalence of at-risk alcohol use, individuals admitted to the general hospital should be screened for risk of developing alcohol withdrawal. Screening instruments reviewed here include the Single Alcohol Screening Question (SASQ), the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C), and the Tobacco, Alcohol, Prescription medications, and other Substances (TAPS) Tool. Individuals screening positive for risk of alcohol withdrawal require further clinical evaluation, including an assessment of the individual's risk of developing a severe alcohol withdrawal syndrome (SAWS). This assessment should include the recent pattern of alcohol use, with a focus on the duration, heaviness, and frequency of drinking. Time of last drink will determine the expected timeline for onset of any withdrawal symptoms and when the individual will be at highest risk for seizures (8-24 hours from last drink) and/or delirium (>48 hours from last drink) during the hospital stay. Alcohol biomarkers may add to the risk assessment, with a blood alcohol level (BAL) aiding in assessment of tolerance and withdrawal risk (with >150-200 mg/dL at presentation suggesting greater risk of SAWS). In individuals with impaired ability to provide a history, urinary ethylglucuronide (EtG) is a sensitive test for ethanol exposure that remains positive longer than BAL (which could clear in 6-12 hours), and blood phosphatidylethanol (PEth) might assist in determining the heaviness of recent alcohol use over the past 3-4 weeks. Additional risk factors for SAWS, including prior history of withdrawal seizures or delirium and/or use of a SAWS risk assessment instrument (such as the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) or the Luebeck Alcohol Withdrawal Risk Scale (LARS)), should be considered in the clinical assessment.
In addition to the individual's risk factors for SAWS, current withdrawal symptoms should be assessed. The most commonly used symptom scale is the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar), although additional tools have been developed that are shorter and focus on objective symptoms. These alternative scales–including the Brief Alcohol Withdrawal Scale (BAWS), the Glasgow Modified Alcohol Withdrawal Scale (GMAWS), and the Minnesota Detoxification Scale (MINDS)–require further study. These data allow the evaluating clinician to assign a risk category for developing SAWS, including identification of individuals already experiencing SAWS at the time of evaluation. This risk category guides selection of the treatment approach

recommended to inform diagnosis and treatment recommendations. Although each biomarker test has significant limitations, when used appropriately they provide valuable clinical information.[64 65] Importantly, biomarker testing alone is insufficient to diagnose an alcohol use disorder, and results should always be interpreted in the patient's clinical context.

There are two broad categories of alcohol biomarkers used in the general hospital. The first includes direct measures of ethanol and its metabolites. The second includes indirect measures of organ damage or alcohol related toxicity. Direct ethanol measures include blood alcohol level, ethylglucuronide (EtG), ethyl sulfate (EtS), and phosphatidylethanol (PEth).[65] Indirect measures include aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, carbohydrate-deficient transferrin, and mean corpuscular volume.[65]

Blood alcohol level is the most direct measure of ethanol in an individual, which aids in the timing and quantity of last alcohol use. short half-life limits the window of detection to 12-18 hours, making the timing of the test sample relative to last alcohol consumption critical in blood alcohol level interpretation.

EtG and EtS are byproducts of a minor alcohol metabolism pathway, formed from ethanol glucuronidation and conjugation with sulfate, respectively. Unlike blood alcohol level, EtG and are measured in urine, are sensitive markers of any consumption of alcohol, and can remain elevated for several days after alcohol use.[66 67]

PEth is a membrane phospholipid formed only during alcohol consumption.[68 69] PEth has a much

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Box 1: Potential utility of combined biomarker testing in alcohol withdrawal risk

Combining phosphatidylethanol (PEth) and ethylglucuronide (EtG) testing for an individual patient could helpfully inform the management of patients in general hospitals with alcohol withdrawal syndromes. Elevated PEth and EtG values confirm recent alcohol consumption, while negative PEth and EtG values suggest very little or potentially no alcohol use in the past several weeks, a finding which could be particularly helpful in determining the need to monitor for and treat alcohol withdrawal syndromes where self-reporting is either unreliable or unavailable. Negative PEth and EtG values might remove the risk for alcohol withdrawal syndromes, although further study is needed to demonstrate this in

	Positive PEth	Negative PEth
Positive EtG	At risk for AWS, further risk stratification needed to provide appropriate	Possible recent alcohol use or exposure with previous low/no alcohol use.
Negative EtG alcohol	Possible recent 3-5 day period of abstinence with previous alcohol use.	Likely low risk for AWS, might not require symptom monitoring or treatment.

longer half-life than other biomarkers and can be used to assess the degree of drinking over the previous several weeks, possibly up to a month. PEth levels correlate well with self-reported alcohol use, such that a level below 10-20 ng/mL is considered negative for any heavy drinking, 20-200 ng/mL indicates moderately heavy drinking, and over 200 ng/mL indicates sustained heavy drinking.[70 71] False positives appear to be rare, suggesting that PEth results under 20 ng/mL could remove the need for alcohol withdrawal syndromes management. This opportunity for broader application of PEth testing in the general hospital has increasing interest, including in the emergency department and trauma ICU.[72 73] Box 1 describes the potential use of combining PEth and EtG testing for patients in hospital. As an emerging biomarker, PEth might not be available in all settings and could require a significant delay in result availability if the assay is completed at an off-site specialty laboratory, limiting the use in acute care settings until more rapid testing is available.

Among the indirect markers, hepatic enzymes might be elevated by alcohol use, reflecting toxic effects on hepatocyte cell membrane integrity. Classically, aspartate aminotransferase and alanine aminotransferase are elevated in a 2:1 ratio with alcohol associated hepatic inflammation.[74] Gammaglutamyltransferase is another hepatic enzyme that is more specifically elevated by alcohol use than aspartate aminotransferase or alanine aminotransferase. The proportion of carbohydrate-deficient transferrin, a hepatic glycoprotein that facilitates iron transport, increases in sustained heavy alcohol use. Carbohydrate-deficient transferrin has a useful 2-3 week window of detection, but highly variable sensitivity adversely affects its utility in identifying all at-risk patients. Mean corpuscular volume is a measure of red blood cell size that might be elevated by chronic alcohol consumption, although sensitivity and specificity are both low for detecting at-risk use.

Risk stratification for severe alcohol withdrawal

A primary goal of alcohol withdrawal management is the prevention of severe alcohol withdrawal syndromes, as individuals with alcohol related seizures and alcohol withdrawal delirium experience greater morbidity, mortality, length of stay in hospital, and care related medical costs.[75 76] Multiple studies have attempted to quantify severe alcohol withdrawal syndrome risk for individual patients, however the pooled findings are inconsistent across identified risk factors.[7 16 23 76-78]

A previous history of alcohol related seizures or alcohol withdrawal delirium is a consistent risk factor predicting future severe alcohol withdrawal syndromes.[16 23 76] Smaller studies identify family history of alcohol withdrawal delirium as a potential risk factor, suggesting genetic susceptibility, with dopamine transporter A9 allele and neuropeptide Y polymorphisms implicated.[31 79 80] Interestingly, previous inpatient alcohol detoxifications and quantity of alcohol use have been inconsistent risk factors across studies.[16 23 76 77 81] This could be owing to the quality of the alcohol history gathered, with low accuracy of self-report potentially adversely affecting the performance of these variables.[76 82] Objective physiological and laboratory predictors for the onset of severe alcohol withdrawal syndromes have also been studied. Hepatic cirrhosis is negatively associated with severe alcohol withdrawal syndromes,[76] suggesting that advanced fibrosis could lead to lower alcohol intake by reduced capacity for ethanol metabolism. By contrast, there is a positive association between aspartate aminotransferase and alanine aminotransferase elevations and severe withdrawal, linking acute hepatocellular injury due to heavy alcohol use as a risk factor for severe alcohol withdrawal syndromes. Further, elevated gamma-glutamyltransferase might predict incident seizures, although it has not been associated with alcohol withdrawal delirium.[7 77 83] An association between low initial platelet count and severe alcohol withdrawal syndromes, including alcohol related seizures, has been found in some studies.[7 77 84] Several studies also show an association between initial potassium and severe alcohol withdrawal syndromes, with lower potassium in patients who developed alcohol withdrawal delirium and alcohol related seizures.[7 23 77] Blood alcohol level measured when a patient is admitted to hospital has been examined as a potential predictor of severe alcohol withdrawal syndromes in patients with severe alcohol use disorder, with a level over 150 mg/dL showing good sensitivity and specificity for the need for acute care treatment of alcohol withdrawal. However, studies are mixed regarding the association between blood alcohol level and alcohol withdrawal delirium or alcohol related seizures.[81 85] One small study found that PEth levels at the time of admission to hospital correlated with alcohol withdrawal severity scores, raising the possibility that PEth testing could play a role in risk stratification.[86] Indeed, a negative PEth level might reduce the concern for the need to treat

alcohol withdrawal or to remove severe alcohol withdrawal syndromes from the differential.[87]

In patients who develop any alcohol withdrawal syndromes, hypertension and tachycardia are present in those who progress to more severe symptoms. However, this dysautonomia occurs across severe and non-severe alcohol withdrawal syndromes cases, not necessarily distinguishing those truly at higher risk for severe alcohol withdrawal syndromes.[7 76]

Owing to the limited utility of any single risk factor, composite measurement tools have been developed to better identify patients at higher risk of severe alcohol withdrawal syndromes. The Prediction of Alcohol Withdrawal Severity Scale (PAWSS) was developed for medically ill inpatients, recording the presence or absence of nine risk factors: (1) recent alcohol intoxication; (2) blood alcohol level over 200 mg/dL when admitted to hospital; (3) previous alcohol withdrawal syndromes, (4) alcohol related seizures, or (5) alcohol withdrawal delirium; (6) previous alcohol rehabilitation treatment; (7) previous blackouts, (8) co-use of sedative-hypnotics or (9) other substances. At least one sign of increased autonomic activity must also be present.[16] Among the PAWSS validation sample, a score of >4 was associated with increased risk for developing a Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) score >15 (likelihood ratio 174), while a PAWSS score <4 was associated with a likelihood ratio of 0.07, with good sensitivity and specificity for predicting severe alcohol withdrawal syndromes. Another instrument, the Luebeck Alcohol Withdrawal Scale (LARS), is specifically designed to predict alcohol withdrawal severity among outpatients without significant comorbid medical illness, perhaps limiting its utility in the general hospital setting pending further study.[88] The LARS-10 total score is calculated from 10 items, including (1) frequent sleep disturbance in the past week; (2) past week nightmares; (3) polyneuropathy; (4) ataxia; (5) blood alcohol level ≥100 mg/dL. When the blood alcohol level is ≥100 mg/dL, an additional point is added for: (6) tremor (7) sweating, and (8) pulse rate ≥100 bpm. Three points are added for (9) a history of three or more episodes of alcohol withdrawal delirium or (10) for three or more episodes of alcohol related seizures. A score of >9 on LARS-10 is associated with a greater likelihood of severe withdrawal (likelihood ratio 12), whereas a score of <9 is associated with a likelihood ratio of 0.05, with good sensitivity and specificity for predicting severe alcohol withdrawal syndromes in the initial sample. Both the LARS and PAWSS will require ongoing validation in further studies. See box 2 for emerging machine learning strategies for risk stratification.[89]

Box 2: Opportunities to improve individualized risk stratification for severe alcohol withdrawal syndromes

An emerging strategy for risk stratification for individual patients is the use of machine learning models on electronic healthcare records to predict severe alcohol withdrawal syndromes and associated outcomes. In a recent 2023 study by To and colleagues,[89] a machine learning model demonstrated a sensitivity value of 0.69 (95% confidence interval 0.51 to 0.77), specificity value of 0.70 (0.65 to 0.95), positive predictive value of 0.33 (0.29 to 0.42), and negative

For comparison, the American Society of Addiction Medicine criteria for severe alcohol withdrawal syndromes risk (Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) score >19) has a sensitivity value of 0.10 (0.08 to 0.13), specificity value of 0.95 (0.94 to 0.95), positive predictive value of 0.29 (0.23 to 0.36), and negative predictive value of 0.83 (0.81 to 0.84). The machine learning model identified hypoalbuminemia, high AVPU (alert, verbal, pain, unresponsive) score, hypocalcemia, high fraction of inspired oxygen requirement, early morning admission, and high respiratory

Alcohol withdrawal severity scales

Several alcohol withdrawal severity scales exist for the purpose of alcohol withdrawal risk assessment, as well as monitoring symptom course and response to treatment. Increased scores in these scales generally indicate an increased risk of developing severe withdrawal.

The most studied and utilized scale is the CIWA-Ar.[90] CIWA-Ar was designed to measure the severity of alcohol withdrawal for research studies using a 10-item standardized scale with demonstrated validity and interrater reliability.[91] The CIWA-Ar itself does not offer score ranges categorizing symptom severity, although the authors suggested different interventions for scores of <10, 10-20, and >20 based on clinical experience.[91] Numerous guidelines and review articles have since attempted to provide guidance about appropriate intervention for different CIWA-Ar score ranges, with score cut-offs, dosing, and route of medication administration being adjusted based on the clinician's particular patient population and clinical setting.[81 92 93]

Despite its common and widespread use, the CIWA-Ar has several limitations. As with any symptom-triggered scale, its use requires clinician training for reliable administration and could take significant time to administer and score.[90 94] It also requires patients to be able to accurately self-report subjective symptoms, including nausea, anxiety, tactile and auditory disturbances, and headache. Thus, its reliability is significantly diminished and medical conditions or who cannot reliably communicate accurate responses to CIWA-Ar items. This could include, but is not limited to, patients with severe or complicated alcohol withdrawal, severe medical or critical illness, active symptoms of delirium, mechanical ventilation, acute psychosis, or with opioid use disorder in active or potential opioid withdrawal.[95 96]

Alternative scales have been created to address these limitations, although their reliability and validity remain under study. The Brief Alcohol Withdrawal Scale (BAWS) was developed as a shorter and more objective method to assess alcohol withdrawal syndromes in the general hospital, with early evidence demonstrating favorable sensitivity and specificity compared with CIWA-Ar.[94 97] BAWS

assesses five largely objective items, including (1) tremor, (2) diaphoresis, (3) agitation, (4) confusion, and (5) hallucinations. The Glasgow Modified Alcohol Withdrawal Scale also assesses these five domains and has been studied in the general hospital setting.[90-99] The Minnesota Detoxification Scale has been best studied in ICU populations, focusing on these five domains as well as vital signs, delusions, and seizure activity.[100]

Drugs for alcohol withdrawal management

Benzodiazepine drugs

Benzodiazepine drugs are positive allosteric modulators of GABA-A anion channels, binding at the interface of specific α and γ subunits, leading to GABA-dependent increased channel opening and resulting inhibitory membrane hyperpolarization.[101] Benzodiazepine drugs were first identified as effective in the treatment of alcohol withdrawal in 1967 and 1969 studies comparing chlordiazepoxide with other candidate treatments and placebo.[17 102] By 1999, 11 randomized controlled trials including 1286 patients demonstrated clear benefit from benzodiazepine therapy, with benzodiazepine drugs preventing 7.7 seizures and 4.9 cases of alcohol withdrawal delirium per 100 patients treated.[18] These data form the basis of the current preferred treatment recommendations for alcohol withdrawal management.[103] See the web appendix for the results of the literature review for drugs targeting

Longer half-life benzodiazepine drugs–most commonly, diazepam or chlordiazepoxide–are recommended over shorter half-life drugs by most clinical guidelines because their pharmacokinetics allow for a slower, more consistent wean of GABAergic tone over a longer period, mitigating breakthrough withdrawal symptoms. This might also lead to greater efficacy in preventing seizures, which can occur with shorter half-life benzodiazepine drugs.[103] However, longer half-life drugs risk oversedation and respiratory depression in individuals with impaired hepatic metabolism (eg, older age, hepatic synthetic dysfunction), concurrent central nervous system depressant medication, or pulmonary disease. These individuals could use short-acting drugs. Lorazepam or oxazepam are often chosen in impaired hepatic synthetic function because they do not require cytochrome P450 activity for clearance, instead relying on glucuronidation which is relatively preserved.[103 104] When using short-acting benzodiazepine drugs, a scheduled taper should be considered to prevent late onset or delayed seizures from rapid loss of GABAergic effect when short half-life drugs are discontinued abruptly or dosed at intervals longer than the expected duration of effect. Early benzodiazepine treatment protocols favored aggressive symptom control with scheduled or loading dose strategies that are tapered over 3-7 days.[17 18 105] Given the non-severe course of more than 90% of alcohol withdrawal cases, fixed dose protocols might prolong the length of hospital stays and expose patients to larger cumulative benzodiazepine doses than are required for most patients. This led to the study of symptom triggered dosing strategies, with the first study of 117 patients in an inpatient setting demonstrating reduced length of hospital stays and lower cumulative benzodiazepine dose compared with a fixed dose strategy.[105] Notably, this study was not conducted in a general hospital setting and had a relatively low overall severity of withdrawal symptoms. Further, the only seizure event in the study occurred in the symptom triggered group.[105] A 2019 meta-analysis of symptom triggered treatment across all eligible studies (n=664) concluded that the evidence for this approach has low applicability to the general hospital setting.[106] Further, there were insufficient data to assess rare severe outcomes, including mortality, seizures, and alcohol withdrawal delirium.[106] Another meta-analysis focusing on alcohol withdrawal syndromes management in the emergency department (n=13 studies) found high risk of bias in available studies and concluded that available evidence is insufficient to assess the efficacy of symptom triggered approaches in this setting.[107] One potential limitation of symptom triggered approaches in the general hospital is the need to educate, train, and monitor competency of staff who implement the prescribed protocol. One study at an academic medical center found poor functional knowledge of the institution's symptom triggered alcohol withdrawal treatment protocol, inappropriate application of the protocol in 50% of cases, and inaccurate application of the protocol in 90% of cases.[108] Another trial comparing symptom triggered and fixed schedule protocols found higher rates of protocol errors in the symptom triggered group (odds ratio 2.6, 17.6% *v* 7.6% error rate, P=0.04). These studies suggest potential barriers to effective implementation of symptom triggered treatment that warrant further study.[109]

Loading doses of long-acting benzodiazepine drugs have also been studied for individuals with severe alcohol withdrawal syndromes, with some evidence for more rapid alcohol withdrawal symptom improvement, lower incidence of seizures, shorter duration of delirium, and an association with shorter stays in hospital.[110 111] However, studies in non-severe alcohol withdrawal total benzodiazepine dose requirement and shorter stays in hospital with a symptom triggered approach.[112-114] Loading doses of diazepam 10-20 mg or chlordiazepoxide 50-100 mg are given every 1-4 hours with reassessment before each dose for emergent toxicity, demonstrated by nystagmus (elicited on lateral or upward gaze), ataxia, dysarthria, affective lability, or sedation.[103] With any fixed schedule benzodiazepine dosing regimen, monitoring parameters must be included to ensure immediate medication discontinuation should benzodiazepine toxicity or additive respiratory or central nervous system depression occur.

Some patients with severe alcohol withdrawal syndromes demonstrate relative benzodiazepine

resistance despite appropriate benzodiazepine therapy, suggesting poor cross-tolerance between ethanol and the chosen benzodiazepine drug. This could reflect neuroadaptations in GABA-A receptor availability or changes in receptor subunit composition, including replacement of benzodiazepine sensitive with insensitive αsubunits.[115] A population of individuals with epilepsy with mutations in GABA-A receptor subunits has also been linked to benzodiazepine drug resistance in acute seizure management, suggesting an additional possible mechanism in the alcohol withdrawal context.[116] In a single site observational study of general hospital inpatients, 4% of individuals required transition from fixed dose diazepam treatment to phenobarbital owing to non-response.[117] This might reflect the prevalence of benzodiazepine resistant alcohol withdrawal in general hospital populations, though further studies across other centers will be required and the reported rate was greater in a separate retrospective study of alcohol withdrawal delirium, with 9% of delirium patients requiring transition from diazepam to phenobarbital.[118] A consensus definition of alcohol withdrawal that is resistant to treatment with benzodiazepine drugs has not yet been established, although a high total dose of benzodiazepine drugs and requiring over 40 mg diazepam equivalents per hour have been suggested as possible thresholds.[119] The first study to attempt to define this population followed patients prospectively who required over 50 mg intravenous diazepam in the first hour of emergency department care; the study identified 15 patients who required over 200 mg intravenous diazepam in the first three hours of treatment and progressed to more severe outcomes, while four individuals stabilized with a mean of 132 mg intravenous diazepam over the same period.[120]

Phenobarbital

Phenobarbital was first used for the management of alcohol withdrawal syndromes in the early 1900s, and although benzodiazepine drugs have been long preferred for their more favorable therapeutic window, more recent evidence supporting phenobarbital as monotherapy for alcohol withdrawal syndromes and in severe alcohol withdrawal syndromes is accumulating.[121-123] Phenobarbital is a positive allosteric modulator of the GABA-A receptor with a different binding site than benzodiazepine drugs. In addition, it has effects on glutamate activity through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainite receptors. This effect on both GABA and glutamate receptor pathways is unique to phenobarbital and could partly explain its efficacy in individuals with benzodiazepine resistant severe alcohol withdrawal syndromes (see the web appendix for the results of the literature review for drugs targeting alcohol withdrawal).[124]

Studies conducted in general hospital, trauma, ICU, and emergency department settings have cumulatively shown efficacy for phenobarbital comparable to benzodiazepine drugs, with trends toward improvement in specific outcomes for specific populations. In emergency department settings, phenobarbital used as monotherapy improved and helped stabilize withdrawal symptoms and resulted in an equal or reduced need for inpatient and/or ICU admission compared with the use of benzodiazepine drugs.[112 125] In the surgical trauma ICU, protocols based on the use of phenobarbital appear to be effective in preventing complications related to withdrawal, including alcohol withdrawal delirium and clinically significant respiratory depression.[126 127] In a study of trauma patients, there was a significant decrease in the rates of progression to severe alcohol withdrawal syndromes and medication adverse effects with phenobarbital compared with a fixed dose benzodiazepine drug protocol.[126] A retrospective patients treated with phenobarbital showed equivalent outcomes to a fixed dose benzodiazepine drug protocol (ie, no difference in the incidence of seizures, hallucinosis and/or delirium, ICU transfer, leaving against medical advice, mortality, length of stay in hospital, or medical adverse events), despite a more prevalent history of complicated alcohol withdrawal in the phenobarbital group.[117] A retrospective study in medical ICU patients that compared fixed dose phenobarbital monotherapy with symptom triggered lorazepam using the CIWA-Ar showed that patients treated with phenobarbital had noticeably shorter stays in ICU and hospital, lower incidence of mechanical ventilation, and reduced need for adjunctive drugs.[128]

with benzodiazepine drugs could increase adverse events, studies using phenobarbital with benzodiazepine front-loading strategies in ICU settings suggest that adjunctive phenobarbital results in lower rates of mechanical ventilation, fewer ventilator days, decreased length of stay in ICU and hospital, and a variable impact on benzodiazepine drug requirements.[129 130] As such, phenobarbital could be suitable either as monotherapy or as an adjunct to benzodiazepine drugs in appropriately monitored settings.

It is important to note that few prospective randomized studies have directly compared phenobarbital and benzodiazepine drugs, and among those direct prospective comparisons, one study of mild to moderate alcohol withdrawal syndromes showed no difference in outcome.[112] The authors' clinical experience suggests that individuals with alcohol withdrawal syndromes resistant to benzodiazepine drugs, severe alcohol withdrawal syndromes, or with higher risk for progressing to severe alcohol withdrawal syndromes are most likely to benefit from phenobarbital, and the growing evidence base is focused on these populations. The role of phenobarbital in lower risk populations and in less intensively monitored settings is less clear. Although the evidence for efficacy in alcohol withdrawal syndromes is adequate to support its

use, further studies are required to better define populations and settings that will most benefit (or might experience untoward risks) from phenobarbital compared with benzodiazepine drugs.

Alpha-2 adrenergic agonists

Increased noradrenergic tone leads to many physiologic symptoms observed in alcohol withdrawal syndromes, including tachycardia, hypertension, and coarse tremor. In severe withdrawal cases where benzodiazepines have limited effect on the management of these symptoms, α-2 agonists have been used adjunctively (see the web appendix for the results of the literature review for drugs targeting alcohol withdrawal).

Clonidine

antihypertensive that has been studied as adjunctive treatment in alcohol withdrawal syndromes, showing efficacy in reducing excessive adrenergic tone.[131-136] Clonidine has no direct effect on the GABA or glutamatergic system, therefore, it is not recommended as monotherapy for alcohol withdrawal syndromes treatment given the lack of efficacy in mitigating the risk of progression to severe alcohol withdrawal syndromes, including alcohol related seizures and alcohol withdrawal delirium.[136]

Dexmedetomidine

Dexmedetomidine is another α-2 adrenergic agonist used adjunctively with benzodiazepine drugs or phenobarbital in alcohol withdrawal syndromes management, typically in ICU settings. Dexmedetomidine is a highly selective α-2 agonist, with high receptor affinity. Several studies have examined dexmedetomidine's role in severe alcohol withdrawal syndromes management, showing benefit for hypertension, tachycardia, and a reduction in total benzodiazepine drug requirement.[137-143] Unlike clonidine, emerging evidence also suggests dexmedetomidine has additional physiological mechanisms beyond α-2 agonism that could benefit individuals with alcohol withdrawal syndromes. A multiorgan protective effect through putative anti-inflammatory and anti-apoptotic pathways has been shown in ICU and perioperative patients.[142 144] Preclinical research further shows significant neuroprotection from dexmedetomidine in a variety of neuronal injury models, including epilepsy, neuroinflammatory processes, and substance induced neuronal injury.[145 146] These findings suggest dexmedetomidine could have a unique role in the management of severe alcohol withdrawal syndromes, although further study specific for alcohol withdrawal syndromes is needed. The role of dexmedetomidine in alcohol withdrawal syndromes is currently limited by the need for administration in the ICU or emergency department setting.

Antiseizure medications

Meta-analyses examining the effects of antiseizure medications when combined as a single group have reported no differences in clinical alcohol withdrawal syndromes outcomes compared with placebo.[147 148] However, aggregate meta-analysis could potentially bias the findings against individual antiseizure medications with some efficacy, because the mechanisms of action differ across these drugs (see the web appendix for the results of the literature review for drugs targeting alcohol withdrawal).

Carbamazepine is a voltage gated sodium channel blocker and is the oldest antiseizure medication investigated in the treatment of alcohol withdrawal, with approval as a treatment for alcohol withdrawal syndromes in Germany.[149] It has been found to suppress kindling in limbic structures induced by withdrawal, and animal studies have also shown beneficial effects on alcohol withdrawal syndromes.[150-153] Several double blind studies have demonstrated that carbamazepine has equal or greater efficacy to lorazepam, oxazepam, clomethiazole, tiapride, or placebo in reducing withdrawal symptoms in some patient populations.[150 154] The efficacy of carbamazepine in mitigating the risk of alcohol related seizures and alcohol withdrawal delirium remains uncertain with some studies showing delirium and seizures occurring in individuals treated with carbamazepine, limiting its use as monotherapy in at-risk general hospital inpatients.[155 156] Drug-drug interactions are common, rare but severe adverse effects are possible, and the hepatic metabolism is complex with carbamazepine, further limiting its use.[149]

Valproic acid

Valproic acid has both antiseizure and anti-kindling properties through multiple described mechanisms of action, including voltage-gated sodium channel blockade and generalized GABAergic potentiation and glutamate/NMDA inhibition.[157] Two double blind comparative studies have been performed investigating valproate in the treatment of alcohol withdrawal syndromes.[156 158] These studies suggest that valproate reduces total benzodiazepine drug requirements and lessens the severity of withdrawal symptoms. Whether valproate is effective in preventing seizures or alcohol withdrawal delirium in patients with more severe alcohol use disorder and alcohol withdrawal syndromes requires further study, although older evidence suggests no protective effect against alcohol withdrawal delirium.[156] However, given the possible utility of valproate in treating agitation associated with delirium from acute medical illness, valproate could play a role in reducing benzodiazepine drug requirements when empirically treating a patient with delirium at risk for alcohol withdrawal.[159] Similar to carbamazepine, valproate is hepatically metabolized and highly protein bound which could affect safety

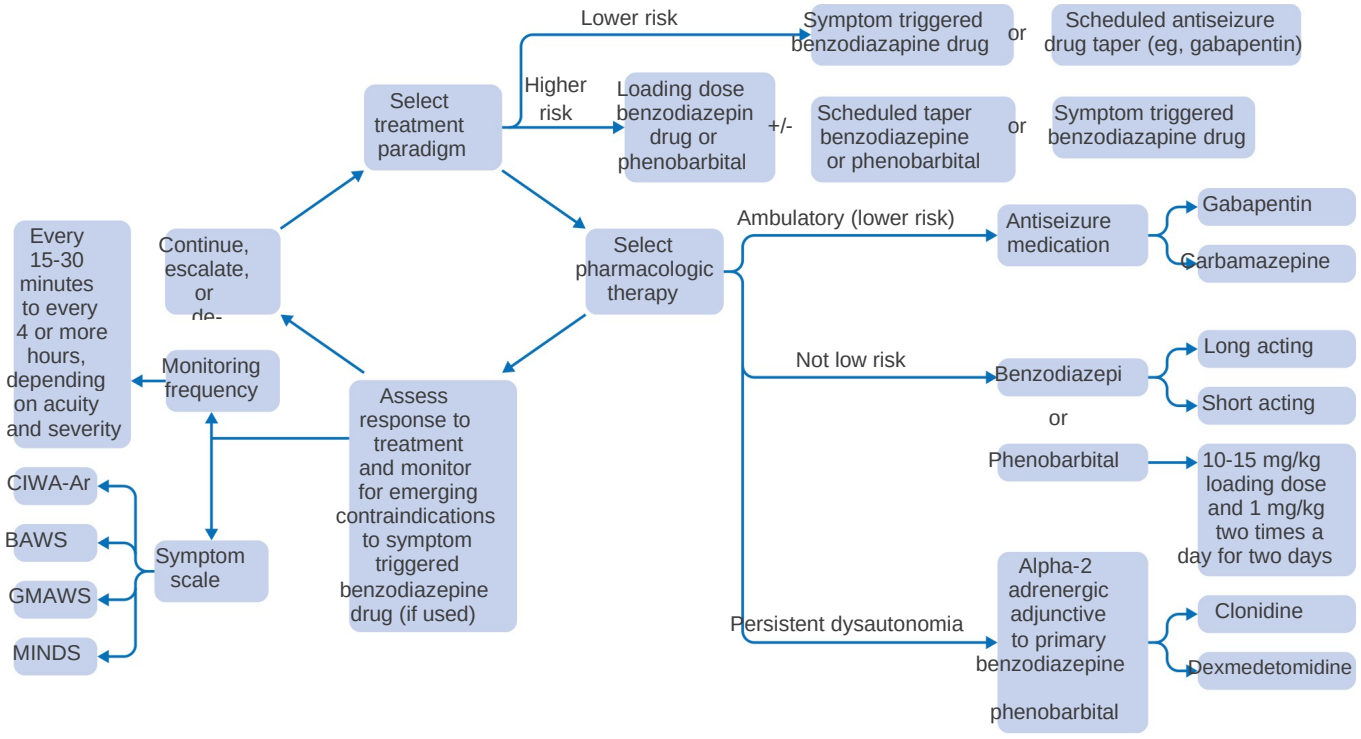

Fig 2 | An approach to drug selection and treatment monitoring for patients being treated in hospital for alcohol withdrawal. Treating clinicians will select a treatment paradigm most appropriate to their assessment of the patient's risk category, with individuals at higher risk of severe alcohol withdrawal syndromes (SAWS) being considered for loading or scheduled taper protocols given the low generalizability of available evidence for symptom triggered protocols in this population. Patients at lower risk of SAWS could be better suited to symptom triggered protocols and might experience shortened length of hospital stays and lower total benzodiazepine drug exposure with this approach. Alternatively, scheduled tapers of antiseizure medications (such as gabapentin, valproate, or carbamazepine) have been used in place of benzodiazepine therapy in ambulatory populations at lower risk of SAWS and in novel benzodiazepine drug-sparing protocols–although these approaches will require further study in the hospital setting. Benzodiazepine drugs are the most studied pharmacotherapy for alcohol withdrawal treatment in the general hospital, with strong evidence for reducing the incidence of seizures and delirium. Long-acting benzodiazepine drugs are preferred in patients who do not have a contraindication, as short-acting drugs might risk delayed withdrawal seizures if not tapered adequately. Phenobarbital is an emerging alternative with demonstrated efficacy for alcohol withdrawal comparable to benzodiazepine drugs, including evidence for individuals with benzodiazepine resistant syndromes (eg, requiring >40 mg diazepam per hour) and in the preventive treatment of individuals in emergency department or intensive care settings. Once an initial treatment paradigm and pharmacotherapy has been selected, patients should be monitored closely for their response using a validated symptom scale. Typically, individuals at greater risk for SAWS should be monitored at least hourly with initial treatment, then de-escalated to less frequent monitoring as their symptoms improve. If symptoms are not responding to the selected treatment paradigm and pharmacotherapy, then escalated treatment strategies should be considered. For example, if a patient initially assessed as at lower risk of SAWS and treated with a symptom triggered diazepam protocol is experiencing consistently elevated symptom scores with clear evidence of clinical worsening on bedside assessment, the clinician could consider escalation to a scheduled load with phenobarbital and close monitoring of their response. Further escalation to adjunctive clonidine or dexmedetomidine for persistent hypertension, tachycardia, and/or tremor could also be considered. CIWA-Ar=Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised; BAWS=Brief Alcohol Withdrawal Scale; GMAWS=Glasgow Modified Alcohol Withdrawal Scale; MINDS=Minnesota Detoxification Scale

and tolerability in hospitalized patients with liver dysfunction.[157]

Gabapentin

Studies evaluating gabapentin, a voltage dependent calcium channel modulator, as monotherapy or adjunctive therapy to benzodiazepine drugs have shown inconsistent benefits for alcohol withdrawal, with more evidence in ambulatory settings.[160-162] In one retrospective inpatient study, the use of high dose gabapentin was associated with reduced hospital stays compared with standard-of-care treatment.[161] Current data on the use of another gabapentinoid drug, pregabalin, suggests no significant difference in clinical outcomes compared with placebo.[163] The

renal clearance of gabapentinoid drugs and evidence for relapse prevention in alcohol use disorder are two relative advantages of these drugs to be considered.[164]

Benzodiazepine-sparing protocols

Antiseizure medications, including gabapentin and valproate, have been suggested in novel benzodiazepine-sparing protocols for inpatient alcohol withdrawal syndrome prophylaxis (ie, prevention of alcohol withdrawal syndrome development in patients who are at risk) and management.[165] The goal of these protocols is to reduce the risks and harms associated with benzodiazepine drugs.[165] In a single site implementation study of a benzodiazepine-sparing

protocol for the prevention of alcohol withdrawal syndromes in a trauma center population, protocol patients who received gabapentin and clonidine had lower CIWA-Ar scores and lower benzodiazepine drug requirements compared with patients admitted before the implementation of the protocol; however, the differences in these outcomes were small (CIWA-Ar scores 2.7 *v* 1.5, P=0.04; mean lorazepam equivalents per day 1.1 *v* 0.2, P<0.01), the severity of withdrawal in this prevention population was low (maximum CIWA-Ar scores 11-14) and few patients developed any withdrawal symptoms (24-26%), limiting generalizability to higher risk or greater severity inpatients.[166] A larger implementation study within an integrated health system showed a reduction in the use of benzodiazepine drugs (78.1 *v* 60.7%, P<0.001) and decreased mean total lorazepam dose (19.7 mg (SD 38.3) *v* 6.0 mg (9.1), P<0.001) after initiation of a protocol that included prophylaxis and treatment adjusted according to severe alcohol withdrawal syndrome risk and alcohol withdrawal syndrome severity.[167] Notably, these protocols lead to increased use of drug combinations (eg, gabapentin, clonidine, valproate, etc) that could reduce exposure to benzodiazepines while increasing exposure to complex polypharmacy with associated risks.

Two recent meta-analytic studies suggest caution in the use of antiseizure medications for management of moderate to severe alcohol withdrawal syndromes in the inpatient setting. A systematic review and meta-analysis did not find a benefit for withdrawal severity, seizure, or alcohol withdrawal delirium risk and recommended against the routine use of antiseizure medications for moderate or severe alcohol withdrawal syndromes.[168] Another review of antiseizure medications stratified 34 randomized controlled trials by specific antiseizure medications, finding few studies with low risk of bias and low certainty of evidence for carbamazepine and valproate.[169]

Antiseizure medication class overall

Overall, current evidence does not support antiseizure medications use as the preferred treatment for alcohol withdrawal in the general hospital, although there could be a role for specific drugs in mild withdrawal management, particularly in ambulatory care settings or in lower risk populations requiring preventive treatment. Further study is needed to better characterize the risks and benefits of antiseizure medications in benzodiazepine-sparing protocols, with particular attention to risks of polypharmacy. See figure 2.

Nutritional repletion

Nutritional deficiencies are common in individuals with alcohol withdrawal syndromes, including deficiencies in thiamine, folate, vitamin B_6, vitamin B_{12}, vitamin C, magnesium, and zinc. Malnutrition in this population is often multifactorial, including decreased dietary intake and reduced nutrient absorption. Risk of developing nutritional deficiencies increases significantly as the amount of alcohol consumed reaches 30% of the total intake of calories.[170]

For patients with alcohol withdrawal syndromes who are in hospital, it is important to assess for and aggressively treat thiamine deficiency, which can lead to Wernicke encephalopathy and progress to Korsakoff syndrome. Wernicke encephalopathy is characterized by the acute onset of three symptoms: encephalopathy, oculomotor dysfunction, and gait ataxia. Korsakoff syndrome is a late manifestation of thiamine deficiency characterized by marked deficits in anterograde and retrograde memory which might not improve with thiamine supplementation, often leading to persistent major neurocognitive disorder with significant disability.[171] Atypical presentations of thiamine deficiency are also common, with only 16.5% of decedents with pathological diagnosis of Wernicke-Korsakoff syndrome exhibiting the classic three symptoms in one study–and 19%

Wernicke encephalopathy and Korsakoff syndrome are medical emergencies and should immediately be treated with parenteral thiamine. As the diagnosis is difficult to confirm and medical risks of undertreatment are high, clinicians should have a low index of suspicion to initiate treatment. As such, the National Institute for Health and Care Excellence recommends parenteral (intravenous or intramuscular) administration of thiamine for any hospitalized patient with heavy alcohol use, recognizing that adverse reactions to high dose thiamine are extremely rare.[173 174] There is limited empiric evidence to support specific thiamine dosing regimens, although many suggest up to 500 mg intravenous thiamine three times daily administered for 3-7 days, typically followed by a course of lower intravenous or oral doses.[175 176] Thiamine has been traditionally given with or before receiving glucose, because of the concern that glucose metabolism could deplete thiamine stores, perhaps precipitating mammillary body infarction. More recent guidelines have cited a limited evidence base for this theory and highlight the importance of not delaying glucose in patients who are nutritionally compromised.[103] Correction of other nutritional deficiencies might be needed in individuals unable to maintain adequate oral intake, which is often sufficient for self-correction in patients resuming a normal diet.

Guidelines

The alcohol withdrawal syndromes treatments outlined in this review align with those recommended for medically supervised alcohol withdrawal by the 2020 American Society for Addiction Medicine (ASAM) Clinical Practice Guideline. Additional applicable treatment guidelines have been published in 2010 by the National Institute for Health and Care Excellence, in 2012 by the World Health Organization, in 2015 by Substance Abuse and Mental Health Services, in 2017 by the World Federation of Societies

Box 3: Motivational interviewing and screening, brief intervention, and referral to treatment

The Screening, Brief Intervention, and Referral to Treatment (SBIRT) model has long been recommended for all substances in a variety of healthcare settings, both inpatient and outpatient. Screening is ideally performed on all patients admitted to hospital, with those screening positive being offered a brief intervention, which entails a motivational interviewing session around alcohol use to guide the conversation towards behavior change.[193] Motivational interviewing is an evidence based approach to assist individuals in health behavior change by utilizing a patient centered, non-judgmental, empathic conversation to evoke and strengthen the individual's own motivation.[194] Motivational interviewing is commonly used for brief intervention, although there are other strategies available.[195] Regardless of the approach used, the key principle is to have a non-judgmental and empathic conversation targeting the unhealthy alcohol use. Individuals meeting criteria for an alcohol use disorder would then be referred to ongoing treatment in the community by the SBIRT provider, while those who do not meet the criteria only receive the brief intervention.

A robust evidence base now supports SBIRT as an effective approach for those with heavy or at-risk alcohol use.[193] In the US, the threshold for at-risk drinking is consuming five or more standard drinks on one occasion for men under 65 years old or four or more standard drinks on one occasion for women or men over 65 years old. These individuals benefit greatly from SBIRT, and the relatively low intensity treatment reduces drinking and improves other health outcomes, with an effect that persists for six months or more after discharge. For this reason, the American College of Surgeons mandates that all injured patients in Level 1 and 2 trauma centers be screened for alcohol use, and a brief intervention be provided to those who

However, for individuals meeting criteria for alcohol or other substance use disorders, there is now sufficient evidence to also conclude that the SBIRT approach has not been effective in impacting outcomes.[197 198] In response, a growing body of evidence now points to the importance of initiating treatment during the general hospital admission, previous to referral to ongoing care.[199] Although this approach has been largely restricted to the initiation of drugs for opioid and tobacco use disorders using drugs such as buprenorphine and nicotine replacement therapies, there are also studies to show that a similar approach might be needed to improve the outcomes for those with alcohol use disorder by proactively initiating drugs while the patient is in the general hospital to prevent relapse.[192 200]

of Biological Psychiatry (WFSBP) Task Force, in 2019 by WFSBP and International Association for Mental Health (for pregnant individuals), and in 2020 by the University of Michigan. See the web appendix for a comparison of alcohol withdrawal syndromes guidelines.

Treatment of underlying alcohol use disorder relapse prevention

Evidence based care for this patient population does not end after successful management of the presenting alcohol withdrawal syndrome. Treatment for the underlying alcohol use disorder is required to reduce the risk of relapse to alcohol use after discharge. Rates of relapse prevention drug initiation during inpatient admission are very low, with additional regional and racial disparities in initiation rates for drugs approved by the FDA.[177] Notably, specialty addiction consultation in the general hospital setting has been associated with increased initiation of medication for alcohol use disorder relapse prevention, with subsequent reduction in 30-day readmissions.[178] Further, psychosocial interventions aimed at referrals to ongoing treatment, including specialty programs to treat alcohol use disorder and peer based support groups, have evidence supporting improvement in outcomes (box 3).[179 180]

Drugs for prevention of alcohol relapse

Current treatment guidelines for alcohol use disorder recommend initiation of drugs to prevent a relapse, including naltrexone or acamprosate, which have been approved by the FDA.[164] These drugs are evidence based, with a number needed to treat of 9-12 for return to any drinking across pooled studies.[181 182] Suggested alternatives for individuals not responding to the preferred drugs include topiramate, gabapentin, or (in carefully selected cases) disulfiram. Benzodiazepine drugs are not recommended outside of acute withdrawal management, because these have been associated with increased risk of relapse.[154 164]

For individuals who have not responded to the preferred drugs or suggested alternatives, or who have medical contraindications, baclofen could be considered. Baclofen is a selective GABA-B agonist approved for the treatment of muscle spasticity that has also been studied in the prevention of alcohol use relapse. A recent meta-analysis showed greater abstinence compared with were no differences in other outcomes related to alcohol use such as reduction in heavy drinking or craving.[183] In individuals with alcohol use disorder and comorbid hepatic cirrhosis, baclofen could be considered if other treatment options have failed or are contraindicated, as there is some evidence for efficacy in this population.[104]

Emerging treatments

Ketamine is an emerging treatment for alcohol withdrawal and alcohol relapse prevention in the general hospital. Ketamine is an NMDA-receptor antagonist which has been approved by the FDA

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for anesthesia and analgesia. The s-enantiomer has been approved in an intranasal pharmaceutical form for the treatment of depression. Early studies of adjunctive ketamine for severe alcohol withdrawal syndromes in ICU settings suggest possible benefit for delirium management, lower benzodiazepine requirement, and shorter stays in hospital.[187-189] Intravenous ketamine in combination with structured psychotherapy has also shown benefit for alcohol use disorder relapse prevention in two randomized trials.[190 191] Ketamine increased abstinence rates in the following weeks and prolonged the time to relapse compared with those receiving midazolam or placebo control. Additionally, a pragmatic feasibility trial conducted in a general hospital setting that compared intramuscular naltrexone, intravenous ketamine, and referral to services, found fewer readmissions in the naltrexone and ketamine groups.[192] More research is needed before ketamine can be recommended for adjunctive severe alcohol withdrawal syndromes treatment in the ICU or for the prevention of alcohol use relapse, though its potential future utility might be greatest in the general hospital setting.

Research priorities

Comparisons of symptom triggered, fixed schedule, and loading dose treatment strategies with benzodiazepine drugs are needed in the general hospital setting, as current evidence for symptom triggered approaches have low generalizability to inpatient populations with higher risk of severe alcohol withdrawal syndromes.[106 184] The use of phenobarbital as an alternative to benzodiazepine drugs for severe alcohol withdrawal syndromes is an emerging strategy in the general hospital, including ICU and emergency department settings, as discussed above and outlined in the results of the literature review for drugs targeting alcohol withdrawal in the web appendix.

An important question for future research is identifying subpopulations of patients who most benefit from phenobarbital, including those individuals demonstrating alcohol withdrawal syndromes that are resistant to benzodiazepine drugs, as well as populations in the ICU with communication barriers which limit assessment of symptoms. Further characterization of subpopulations who benefit from specific adjunctive treatments, including adrenergic agents (dexmedetomidine, clonidine, and/or β-blockers), antiseizure medications, and antipsychotics, is needed.[184] Particularly, benzodiazepine-sparing protocols for alcohol withdrawal syndromes prophylaxis require further study, with attention to the risks of the resulting polypharmacy and utility in individuals at elevated risk for severe alcohol withdrawal syndromes.[165] Additional areas of further study identified in the literature include a need to create objective severity scoring systems for acutely ill patients with severe alcohol withdrawal syndromes (where CIWA-Ar is often invalid) and a need to accelerate implementation of emerging effective treatments into practice.[184]

The low representation of women in clinical studies of alcohol withdrawal syndromes (12.5% across identified studies in a recent scoping review) and the potential for sex-specific differences in the risk for severe alcohol withdrawal syndromes, likelihood of receiving benzodiazepine therapy, and mortality rate suggests a need for further study.[185] One study also noted a racial disparity in the use of CIWA-Ar monitoring for patients in ICU, with Black patients being less likely to receive monitoring.[96] Additional studies are needed to assess for disparities in access to appropriate withdrawal treatment in inpatient settings.

After the acute alcohol withdrawal syndromes treatment period, post-acute withdrawal symptoms (PAWS) could persist for some patients and contribute to the risk of relapse, with anxiety, depression, irritability, cognitive dysfunction, sleep disruption, fatigue, and dysautonomia persisting for 4-6 months or longer.[186] PAWS is not yet formally recognized in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) or the International Classification of Diseases (ICD-11), although it is recognized by the American Society of Addiction Medicine's *Clinical Practice Guideline on Alcohol Withdrawal Management*.[103] The current strength of evidence of drugs targeting PAWS symptoms has been reported as low in a recent scoping review, with the authors suggesting that gabapentinoid drugs, carbamazepine, and oxcarbazepine have some supporting evidence–and also note small positive trials for trazodone, mirtazapine, and acamprosate.[186] There have been no adequate studies of non-pharmacologic therapies for PAWS.

Conclusion

and assessment. Symptom triggered alcohol withdrawal management with benzodiazepine drugs is common across general hospital settings, though this treatment approach might be inadequate for the subset of individuals at greatest risk for severe alcohol withdrawal syndromes. This group might require fixed dose benzodiazepine drug loading or escalation to phenobarbital treatment to address resistance to benzodiazepine drugs. Adjunctive α-2 agonists could be added to withdrawal management strategies to address persistent dysautonomia. The role of (non-phenobarbital) antiseizure medications remains uncertain, although some specific drugs might have benefit in ambulatory treatment of patients at lower risk of severe alcohol withdrawal syndromes. Careful attention to nutritional deficiencies is also needed, especially in choosing aggressive empiric treatment of thiamine deficiency with high dose parenteral repletion to prevent progression to encephalopathy or neurocognitive disorder. Following the treatment of alcohol withdrawal syndromes, initiation of drugs to prevent relapse and referral to ongoing treatment

QUESTIONS FOR FUTURE RESEARCH

- Are there factors that may identify patients in hospital who will benefit from non-benzodiazepine drugs (eg, phenobarbital, antiseizure medications, adrenergic drugs) for alcohol withdrawal syndromes?
- What risk stratification strategies will allow early identification of hospitalized individuals at lowest and highest risk for severe alcohol withdrawal syndromes, which can be used to guide individualized treatments?
- Are there subpopulation differences in response to symptom triggered and fixed schedule loading protocols for alcohol withdrawal syndromes?
- How do gender and racial minority differences in alcohol withdrawal syndrome prevalence and treatment response require adjustments in clinical care?[185]
- What clinical measures should be included in future objective symptom severity scales for

PATIENT INVOLVEMENT

Two peer recovery specialists with lived experience of alcohol and other substance use disorders reviewed this manuscript and provided feedback about its
content, the presentation of the article, and the use of language. The authors are grateful for their input, which has ensured that patient centered language has been used throughout the manuscript.

is imperative to address the underlying alcohol use disorder because management of withdrawal alone will not address the process driving the risk for relapse and readmission.

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Web appendix: Results of literature review for drugs targeting alcohol withdrawal syndromes and Comparison of alcohol withdrawal syndromes guidelines