The ASAM

CLINICAL PRACTICE GUIDELINE ON

Alcohol Withdrawal Management

ASAM American Society *of* Addiction Medicine

The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management

Guideline Committee Members *(alpha order):*
Anika Alvanzo, MD, MS, DFASAM, FACP
Kurt Kleinschmidt, MD, FASAM
Julie A. Kmiec, DO, FASAM
George Kolodner, MD, DLFAPA, FASAM
Gerald E. Marti, MD, PhD
William F. Murphy, DO, MS, DFASAM
Carlos F. Tirado, MD, FASAM
Corey Waller, MD, MS, DFASAM, FACEP
Lewis S. Nelson, MD, FASAM, FACEP, FACMT *(Chair)*

Clinical Champions *(alpha order):*
Stephen Holt, MD, MS, FACP
Darius Rastegar, MD, FASAM
Richard Saitz, MD, MPH, FACP, DFASAM
Michael F. Weaver, MD, DFASAM

ASAM Quality Improvement Council* *(alpha order):*
John Femino, MD, DFASAM
Kenneth Freedman, MD, DFASAM *(Chair)*
R. Jeffrey Goldsmith, MD, DLFAPA, DFASAM
Barbara Herbert, MD, DFASAM *(Past- Chair)*
Margaret Jarvis, MD, DFASAM
Margaret M. Kotz, DO, DFASAM
P. Stephen Novack, DO
David R. Pating, MD
Sandrine Pirard, MD, PhD, MPH, FAPA, FASAM

ASAM Staff:
Maureen Boyle, PhD, Chief Quality and Science Officer
Leah White, MPH, Director of Quality Improvement
Taleen Safarian, Manager of Science and Dissemination

Institute for Research Education and Training in Addictions (IRETA) Team Members:
Dawn Lindsay, PhD, Project Director
Jessica Williams, MPH, Assistant Project Director
Piper Lincoln, MS, Senior Research Associate
Jackie Jones, MS, Research Associate
Rachael Vargo, BA, Research Associate
Peter F. Luongo, PhD, Executive Director

ASAM is honored that this clinical practice guideline has been endorsed by:
American College of Preventive Medicine
American Osteopathic Academy of Addiction Medicine
Federation of State Physician Health Programs
National Association of Addiction Treatment Providers
National Association of Clinical Nurse Specialists
National Commission on Correctional Health Care

Table of Contents

• Adopted by the ASAM Board of Directors January 23, 2020

GLOSSARY OF TERMS

Below are terms that are used throughout the guideline. Note that some terms listed below are used to convey a specific meaning for the purposes of this guideline (e.g., ''clinicians'').

Abstinence: Intentional and consistent restraint from the pathological pursuit of reward and/or relief that involves the use of substances and other behaviors. These behaviors may involve, but are not necessarily limited to substance use, gambling, video gaming, or compulsive sexual behaviors. Use of FDA approved medications for the treatment of substance use disorder is consistent with abstinence.

Addiction Specialist Physician: Addiction specialist physicians include addiction medicine physicians and addiction psychiatrists who hold either a subspecialty board certification in addiction medicine by the American Board of Preventative Medicine, a board certification in addiction medicine from the American Board of Addiction Medicine, a subspecialty board certification in addiction psychiatry from the American Board of Psychiatry and Neurology, a subspecialty board certification in addiction medicine from the American Osteopathic Association, or certification in addiction medicine from the American Society of Addiction Medicine.

Adjunct therapy (see also monotherapy): A pharmaceutical drug used together with a primary pharmaceutical drug whose purpose is to assist the primary treatment.[1]

Alcohol Hallucinosis/Alcohol-induced Psychotic Disorder: See Special Terms on page 16.

ASAM Criteria dimensions: *The ASAM Criteria* use six dimensions to define a holistic biopsychosocial assessment of an individual to be used for service and treatment planning including acute intoxication or withdrawal potential; biomedical conditions and complications; emotional, behavioral, or cognitive conditions or complications; readiness for change; continued use or continued problem potential; and recovery/living environment.

CIWA-Ar: The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised, is a reliable, valid, and reproducible severity of alcohol withdrawal in communicative patients once a diagnosis has been made.[2]

Complicated alcohol withdrawal: See Special Terms on page 16.

Clinicians (Healthcare providers): Used throughout the guideline, this term is intentionally broad. It encompasses anyone who participates in providing care to patients with substance use disorders, including staff at specialty addiction treatment centers or other healthcare settings that provide substance use disorder treatment.[3]

Fixed-dosing: See Special Terms on page 16.

Front loading: See Special Terms on page 16.

GABAergic agents: Drugs that affect the neurotransmitter GABA or its receptors. These include agonists, antagonists, modulators, reuptake inhibitors and enzymes. Examples include benzodiazepines, phenobarbital, and carbamazepine.

Inpatient Withdrawal Management: See Special Terms on page 16.

Kindling: The relationship between repeated episodes of alcohol withdrawal which become progressively more severe is referred to as the kindling effect or process.[4] The effect is theorized to be the result of increased neuronal excitability and sensitivity with repeated episodes of withdrawal and has been demonstrated to result in increased craving for alcohol and decreased responsiveness to treatment with benzodiazepines.[5–7]

Level of Care: See Special Terms on page 16.

Monotherapy (see also adjunct therapy): The use of a single drug to treat a disorder or disease.

Patients: Used throughout the guideline, this term is intentionally broad. It encompasses anyone who receives care for a Substance Use Disorder (SUD) in a specialty SUD treatment center or other healthcare setting.[3]

Pharmacotherapy: Therapy (medical treatment) using pharmaceutical drugs.

Recovery capital: The breadth and depth of internal and external resources that can be drawn upon to initiate and sustain recovery from alcohol and other drug problems. It can be found at the personal, social, community and cultural levels. Examples of recovery capital include physical health, financial assets, supportive social relationships, visible local recovery role models, and accessible/affordable community resources.[8]

Substance use: Used instead of ''drug use'' or ''drug and alcohol use,'' this term refers to the use of psychotropic substances, which may include illegal drugs, medications or alcohol. This does not refer to nicotine.[3]

Substance Use Disorder (SUD): Substance use disorder is marked by a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues to use alcohol, nicotine, and/or other drugs despite significant related problems. Diagnostic criteria are given in the DSM-5. Substance use disorder is the new nomenclature for what was included as substance dependence and substance abuse in the DSM-4.

Supportive care: Treatment given to prevent, control, or relieve complications and side effects and to improve the patient's comfort, quality of life and safety. This can include reassurance, orientation, general nursing care, and adherence to safety measures and protocols (e.g., risk for fall/syncope).

Symptom-triggered dosing: See Special Terms on page 16.

Therapeutic window: Range of drug dose amount needed to maintain therapeutic effect yet avoid adverse events. A drug with a narrower therapeutic window requires greater precision to be dosed correctly and safely compared to a drug with a broader therapeutic window. A drug's therapeutic window is taken into account when modifying dose amount due to patient variability and exposure to other substances including adjunt medications.[9]

Treatment plan: A therapeutic strategy that may incorporate patient education, drug therapy, and the participation of health professionals. Treatment plans are especially important in the optimal management of complex or chronic illnesses such as SUDs.[3]

Unhealthy alcohol use: Includes the following patterns of alcohol use: 1) Binge drinking (defined as consuming 4 or more alcoholic beverages per occasion for women or 5 or more drinks per occasion for men); 2) Heavy drinking (defined as consuming 8 or more alcoholic beverages per week for women or 15 or more alcoholic beverages per week for men); 3) Any drinking by pregnant women or those younger than age 21.[10]

Withdrawal Management: This term has replaced the formerly used ''detoxification.'' Withdrawal management refers to the medical and psychological care of patients who are experiencing withdrawal symptoms as a result of ceasing or reducing their substance use.[11] The process of withdrawal management includes not only attenuation of the physiological and psychological features of withdrawal, but also interrupting the momentum of habitual compulsive use in persons with SUD.[12]

ABBREVIATIONS AND ACRONYMS

A2AA	Alpha-2 adrenergic agonists
ALT	Alanine aminotransferase
AUDIT-PC	Alcohol Use Disorders Identification Test-(Piccinelli) Consumption
ASAM	American Society of Addiction Medicine
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AST	Aspartate aminotransferase
AUD	Alcohol Use Disorder
BAC	Blood Alcohol Concentration (or Content)
BAWS	Brief Alcohol Withdrawal Scale
CCU	Cardiac (or Coronary) Care Unit
CIWA-Ar	Clinical Institute Withdrawal Assessment for Alcohol, Revised
CNS	Central Nervous System
DSM-5	Diagnostic and Statistical Manual, 5th Edition
ED	Emergency Department
EEG	Electroencephalogram
FAS	Fetal Alcohol Syndrome
FASD	Fetal Alcohol Spectrum Disorders
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid, or γ-aminobutyric acid
GAD-7	Generalized Anxiety Disorder Test – 7
GGT	Gamma-glutamyl transferase
ICU	Intensive Care Unit
IM	Intramuscular
IPRAS	Interpercentile Range Adjusted for Symmetry
IV	Intravenous
LARS	Luebeck Alcohol-Withdrawal Risk Scale
MCV	Mean corpuscular volume
PAWSS	Prediction of Alcohol Withdrawal Severity Scale
PHQ-9	Patient Health Questionnaire – 9
PO	Per os, by mouth
RAM	RAND/UCLA Appropriateness Method
SAMHSA	Substance Abuse and Mental Health Services Administration
SAWS	Short Alcohol Withdrawal Scale
SUD	Substance Use Disorder
WHO	World Health Organization
WM	Withdrawal Management

EXECUTIVE SUMMARY

Purpose

The American Society of Addiction Medicine (ASAM) developed this *Guideline on Alcohol Withdrawal Management* to provide updated information on evidence-based strategies (hereafter referred to as the Practice Guideline) and standards of care for alcohol withdrawal management in both ambulatory and inpatient settings.

Background

In June 2017, the American Society of Addiction Medicine's (ASAM) Quality Improvement Council (QIC) elected to update ASAM's clinical guidelines on alcohol withdrawal management based on several factors. First, ASAM conducted an Educational Needs Assessment in 2016 that showed a strong interest and need for education on withdrawal management. Second, updated QIC policies recommend that all ASAM guidelines should be updated every five years. ASAM's previous guidelines on the topic of alcohol withdrawal management were published in 1997 and 2004. The first guideline, ''Pharmacological Management of Alcohol Withdrawal''[13] was published in JAMA, followed five years later with the most recent guideline entitled ''Management of Alcohol Withdrawal Delirium''[14] in JAMA Internal Medicine, formerly Archives of Internal Medicine. Subsequent guidelines have not been written since the 2004 guidelines thus an update was due. Third, the American Psychiatric Association (APA) released a practice guideline in 2018 on the appropriate use of medications in the treatment of alcohol use disorder that is not inclusive of alcohol withdrawal management.[15] An ASAM guideline on alcohol withdrawal should complement APA's guideline to provide clinicians with guidance on treatment and management approaches across a continuum of care. Fourth, outreach to other organizations indicated that other organizations are not planning on creating a guideline on alcohol withdrawal management.

The updated clinical guideline is intended to address current practice concerns and provide clear guidance that will lead to more consistent treatment practices in the field.

Scope of Guideline

While the current clinical guideline focuses primarily on alcohol withdrawal management, it is important to underscore that alcohol withdrawal management alone is not an effective treatment for alcohol use disorder. Withdrawal management should not be conceptualized as a discrete clinical service, but rather as a component of the process of initiating and engaging patients in treatment for alcohol use disorder.

Intended Audience

The intended audience of this guideline is clinicians, mainly physicians, nurse practitioners, physician assistants, and pharmacists who provide alcohol withdrawal management in specialty and non-specialty addiction treatment settings (including primary care and intensive care and surgery units in hospitals). The guideline will also have utility for administrators, insurers, and policymakers.

Qualifying Statement

This ASAM Alcohol Withdrawal Management Guideline is intended to aid clinicians in their clinical decision making and patient management. The Guideline strives to identify and define clinical decision making junctures that meet the needs of most patients in most circumstances. Clinical decision making should involve consideration of the quality and availability of expertise and services in the community wherein care is provided. In circumstances in which the Guideline is being used as the basis for regulatory or payer decisions, improvement in quality of care should be the goal. Finally, courses of treatment contained in recommendations in this Guideline are effective only if the recommendations, as outlined, are followed. Because lack of patient understanding and adherence may adversely affect outcomes, clinicians should make every effort to promote the patient's understanding of and adherence to recommended treatments. Patients should be informed of the risks, benefits, and alternatives to a particular treatment, and should be an active party in shared decision making whenever feasible. Recommendations in this Practice Guideline do not supersede any federal or state regulations.

Overview of Methodology

In order to develop a comprehensive practice guideline focused on alcohol withdrawal management, we utilized a hybrid of established methodologies. In order to develop the scope of the guideline and draft the guideline statements, we followed the Veterans Health Administration and Department of Defense (VA/DoD) Guideline for Guidelines. To rate and refine the draft guidelines, we used the RAND/UCLA Appropriateness Method (RAM), which is a specific process for combining the available scientific evidence with the clinical judgment of experts. Quality of the literature reviewed was rated using standardized rating scales and methodology. The external review process was informed by the VA/DoD method.

SUMMARY OF RECOMMENDATIONS

I. Identification and Diagnosis of Alcohol Withdrawal

A. Identification

Recommendation I.1: Incorporate universal screening for unhealthy alcohol use into medical settings using a validated scale to help identify patients with or at risk for alcohol use disorder and alcohol withdrawal.

Recommendation I.2: For patients known to be using alcohol recently, regularly, and heavily, assess their risk of developing alcohol withdrawal even in the absence of signs and symptoms (see II. Initial Assessment for risk factors and risk assessment scale).

Recommendation I.3: For patients who have signs and symptoms suggestive of alcohol withdrawal, assess the quantity, frequency, and time of day when alcohol was last consumed to determine whether the patient is experiencing or is at risk for developing alcohol withdrawal. For this assessment, it may be helpful to:

- Use a scale that screens for unhealthy alcohol use (e.g., Alcohol Use Disorders Identification Test-Piccinelli Consumption [AUDIT-PC])
- Use information from collateral sources (i.e., family and friends)
- Conduct a laboratory test that provides some measure of hepatic function

Recommendation I.4: A biological test (blood, breath, or urine) for alcohol use may be helpful for identifying recent alcohol use, particularly in patients unable to communicate or otherwise give an alcohol use history. When conducting a biological test, consider the range of time (window of detection) in which the test can detect alcohol use. Do not rule out the risk of developing alcohol withdrawal if the result of a test is negative.

B. Diagnosis

Recommendation I.5: To diagnose alcohol withdrawal and alcohol withdrawal delirium, use diagnostic criteria such as those provided by the Diagnostic and Statistical Manual 5 (DSM-5). To diagnose alcohol use disorder, use diagnostic criteria such as those provided by the DSM-5.

Recommendation I.6: Alcohol withdrawal severity assessment scales (including the Clinical Instrument Withdrawal Assessment for Alcohol, Revised [CIWA-Ar]) should **not** be used as a diagnostic tool because scores can be influenced by conditions other than alcohol withdrawal.

Recommendation I.7: Do not rule in or rule out the presence of alcohol withdrawal for patients who have a positive blood alcohol concentration.

C. Differential Diagnosis

Recommendation I.8: As part of differential diagnosis, assess the patient's signs, symptoms, and history. Rule out other serious illnesses that can mimic the signs and symptoms

of alcohol withdrawal. Determine if patients take medications that can mask the signs and symptoms of alcohol withdrawal.

Recommendation I.9: Do not rule in or rule out a co-occurring disease, co-occurring mental health disorder, co-occurring substance use disorder, or simultaneous withdrawal from other substances even in the presence of alcohol withdrawal.

Recommendation I.10: Conduct a neurological exam in patients presenting with a seizure to determine etiology. A seizure should only be attributed to alcohol withdrawal if there was a recent cessation of (or reduction in) alcohol consumption. For patients experiencing new onset seizures or for patients with a known history of alcohol withdrawal seizures showing a new pattern, an electroencephalogram and/or neuroimaging is recommended. For patients with a known history of withdrawal seizure who present with a seizure that can be attributed to alcohol withdrawal, additional neurological testing and a neurology consult may not be necessary. This includes if the seizure was generalized and without focal elements, if a careful neurological examination reveals no evidence of focal deficits, and if there is no suspicion of meningitis or other etiology.

Recommendation I.11: For patients presenting with delirium, conduct a detailed neurological and medical examination with appropriate testing to rule out other common causes of delirium regardless of the apparent etiology. Attempt to distinguish between hallucinations associated with alcohol withdrawal delirium and alcohol hallucinosis/alcohol-induced psychotic disorder.

II. Initial Assessment of Alcohol Withdrawal

A. General Approach

Recommendation II.1: First, determine whether a patient is at risk of developing severe and/or complicated alcohol withdrawal, or complications from alcohol withdrawal. In addition to current signs and symptoms, a validated risk assessment scale and an assessment of individual risk factors should be utilized (See Table 1. Alcohol Withdrawal Severity).

Recommendation II.2: A history and physical examination should be included as part of the comprehensive assessment process. Clinicians should conduct this examination themselves or ensure that a current physical examination is contained within the patient's medical record.

Recommendation II.3: Additional information about risk factors can be gleaned by interviewing family, friends, and caregivers about a patient's history of alcohol withdrawal, seizures, and delirium, as appropriate. Whenever possible in non-emergent situations, obtain written or verbal consent from the patient before speaking with or consulting with collateral sources.

Recommendation II.4: Clinicians should seek information about the time elapsed since the patient's cessation of (or reduction in) alcohol use. The timeline of symptom onset and severity helps determine the risk window for developing severe or complicated withdrawal.

B. Risk Factors for Severe or Complicated Withdrawal

Recommendation II.5: Assess for the following factors associated with increased patient risk for complicated withdrawal or complications of withdrawal:

- History of alcohol withdrawal delirium or alcohol withdrawal seizure
- Numerous prior withdrawal episodes in the patient's lifetime
- Comorbid medical or surgical illness (especially traumatic brain injury)
- Increased age (>65)
- Long duration of heavy and regular alcohol consumption
- Seizure(s) during the current withdrawal episode
- Marked autonomic hyperactivity on presentation
- Physiological dependence on GABAergic agents such as benzodiazepines or barbiturates

Recommendation II.6: The following individual factors *may* increase a patient's risk for complicated withdrawal or complications of withdrawal:

- Concomitant use of other addictive substances
- Positive blood alcohol concentration in the presence of signs and symptoms of withdrawal
- Signs or symptoms of a co-occurring psychiatric disorder are active and reflect a moderate level of severity

Recommendation II.7: Patients' risk for complicated withdrawal or complications of withdrawal is increased by the presence of multiple risk factors.

Recommendation II.8: In general, clinicians may consider patients at risk of severe or complicated withdrawal if

TABLE 1. Alcohol Withdrawal Severity.

Severity Category	Associated CIWA-Ar Range*	Symptom Description
Mild	CIWA-Ar < 10	Mild or moderate anxiety, sweating and insomnia, but no tremor
Moderate	CIWA-Ar 10-18	Moderate anxiety, sweating, insomnia, and mild tremor
Severe	CIWA-Ar ≥19	Severe anxiety and moderate to severe tremor, but not confusion, hallucinations, or seizure
Complicated	CIWA-Ar ≥19	Seizure or signs and symptoms indicative of delirium – such as an inability to fully comprehend instructions, clouding of the sensorium or confusion – or new onset of hallucinations

*Throughout this document, we provide examples for withdrawal severity using the CIWA-Ar, although other scales can be used. Regardless of the instrument used, there is a wide variety in the literature and in practice as to which scores best delineate mild, moderate and severe withdrawal. Classification of withdrawal severity is ultimately up to the judgment of clinicians and the choice of reference range may be based on their particular patient population or capabilities.

they are experiencing at least moderate alcohol withdrawal on presentation (e.g., CIWA-Ar score $\geq$10).

C. Risk Assessment Tools

Recommendation II.9: Clinicians can consider the use of a tool such as *The ASAM Criteria* Risk Assessment Matrix to assess a patient's risk of severe or complicated alcohol withdrawal as well as potential complications of withdrawal.

Recommendation II.10: The following scales can be helpful for assessing for the risk of severe alcohol withdrawal:

- Prediction of Alcohol Withdrawal Severity Scale (PAWSS)
- Luebeck Alcohol-Withdrawal Risk Scale (LARS)

D. Symptom Assessment Scales

Recommendation II.11: A validated scale should be used to assess alcohol withdrawal severity.

Recommendation II.12: Assess the risk for scores on an alcohol withdrawal severity assessment scale to be confounded by causes other than alcohol withdrawal. If risk factors are present, interpret the results of scales with caution. Use a scale that relies more on objective signs of withdrawal (autonomic activity) if a patient has difficulty communicating about their symptoms. See Appendix III for the features of different scales.

Recommendation II.13: A validated withdrawal severity assessment scale can be used as part of risk assessment. A high initial score can indicate risk of developing severe or complicated withdrawal, although scores should not be the only information used to predict patient risk.

E. Identify Concurrent Conditions

Recommendation II.14: When assessing for concurrent medical conditions, screen patients for medical conditions that could affect the course of alcohol withdrawal or treatment of alcohol withdrawal, as well as common chronic conditions that are associated with alcohol use disorders.

Recommendation II.15: A pregnancy test should be obtained for women of childbearing potential. For managing pregnant patients, see VII.F: Patients who are Pregnant.

Recommendation II.16: In settings with access to laboratory testing, clinicians should conduct and/or arrange for a comprehensive metabolic profile (CMP) or basic metabolic profile (BMP), a hepatic panel, and a complete blood count with differential to assess a patient's electrolytes, liver functioning, renal functioning, and immune functioning. In a setting with limited access to laboratory testing, clinicians should obtain results when practical to assist with treatment planning decisions. Address any nutritional deficiencies detected.

Initial screening may also include laboratory tests for:

- Hepatitis
- Human Immunodeficiency Virus (HIV) (with consent)
- Tuberculosis

Recommendation II.17: Assess patients for polysubstance use and be prepared to treat other potential withdrawal syndromes. To assess a patient's other substance use, it may be helpful to:

- Use a validated scale that addresses other substance use, such as the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)
- Conduct a urine or other toxicology test to detect other substance use
- Utilize information from collateral sources when possible (i.e., family and friends)

Recommendation II.18: Do not delay the initiation of treatment if alcohol withdrawal is suspected but laboratory test results are not available at the treatment setting or the results are pending.

Recommendation II.19: Assess patients for concurrent mental health conditions, including a review of their mental health history, to determine their mental health treatment needs. Consult with any mental health professionals caring for such patients. Obtain written or verbal consent before consultation whenever possible in non-emergent situations. The Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder (GAD-7) scales can be helpful to screen for mental health disorders. Be cautious when diagnosing a new primary mental health disorder during acute withdrawal, as it can be difficult to differentiate between substance-induced signs and symptoms and primary psychiatric disorders.

Recommendation II.20: Evaluate active suicide risk as part of the initial patient assessment.

III. Level of Care Determination

A. General Approach

Recommendation III.1: Level of care determination should be based on a patient's current signs and symptoms; level of risk for developing severe or complicated withdrawal or complications of withdrawal; and other dimensions such as recovery capital and environment. Alcohol withdrawal can typically be safely managed in an ambulatory setting for those patients with limited or mitigated risk factors. Patients with low levels of psychosocial support or an unsafe environment may benefit from a more intensive level of care than is otherwise indicated.

Recommendation III.2: Patients with active risk of suicide should be treated in a setting equipped to manage patients at risk of suicide, which often necessitates admission to an inpatient psychiatric setting that also provides withdrawal management services.

B. Level of Care Determination Tools

Recommendation III.3: *The ASAM Criteria* Risk Assessment Matrix and withdrawal severity scales can be helpful for determining the appropriate level of care for managing patients in alcohol withdrawal. Most withdrawal severity scales reflect current signs and symptoms and should not be used alone to determine level of care.

C. Considerations for Ambulatory vs Inpatient Management

Recommendation III.4: See Table 2. Ambulatory (Level 1-WM and Level 2-WM) and Inpatient Placement Considerations on p. 30.

IV. Ambulatory Management of Alcohol Withdrawal

Recommendations that are appropriate for both Ambulatory and Inpatient Management are repeated in both sections.

A. Monitoring

Recommendation IV.1: In ambulatory settings, arrange for patients to check in with a qualified health provider (e.g., medical assistant, nurse) daily for up to five days following cessation of (or reduction in) alcohol use. For some patients who are unable to attend daily in-person check-ins, alternating in-person visits with remote check-ins via phone or video call is an appropriate alternative.

Recommendation IV.2: Re-assessments should focus on the patient's health since the last checkup. Clinicians should assess general physical condition, vital signs, hydration, orientation, sleep and emotional status including suicidal thoughts at each visit. Ask about alcohol and other substance use and, if available, measure blood alcohol content (BAC) with a breathalyzer to detect recent alcohol use.

Recommendation IV.3: Alcohol withdrawal severity should be monitored with a validated instrument (see Appendix III for a summary of scales and their associated features). Patients who are able to monitor their own signs and symptoms may use an instrument designed for self-administration such as the Short Alcohol Withdrawal Scale (SAWS).

Recommendation IV.4: In ambulatory settings, patients with a current or past benzodiazepine use disorder need additional monitoring.

Recommendation IV.5: For patients managed in an ambulatory setting, the following indications would necessitate transfer to a more intensive level of care such as Level 2-WM (if in a Level 1-WM setting) or an inpatient setting:

- Agitation or severe tremor has not resolved despite having received multiple doses of medication, and the patient will not be continually monitored (e.g., treatment setting is closing)
- More severe signs or symptoms develop such as persistent vomiting, marked agitation, hallucinations, confusion, or seizure
- Existing medical or psychiatric condition worsens
- Patient appears over-sedated
- Patient returns to alcohol use
- Syncope, unstable vital signs (low/high blood pressure, low/high heart rate)

B. Supportive Care

Recommendation IV.6: Supportive care is a critical component of alcohol withdrawal management. Providers should ensure patients are educated about what to expect over the course of withdrawal, including common signs and symptoms and how they will be treated.

Recommendation IV.7: When treating patients in ambulatory settings, providers should ensure patients/caregivers are educated about monitoring for the development of more severe withdrawal and instructed to create a low-stimulation, reassuring environment at home to promote an effective outcome.

Recommendation IV.8: Patients should be advised to drink non-caffeinated fluids and that a daily multivitamin may be beneficial.

Recommendation IV.9: Patients can be offered oral thiamine. Typical dosing is 100 mg PO per day for 3–5 days.

Recommendation IV.10: Clinicians must explain the importance of taking medications as prescribed and confirm the patient's understanding.

Recommendation IV.11: Communicate that safe alcohol withdrawal management may necessitate a transfer to a more intensive level of care including to an inpatient setting and secure the patient's agreement to transfer if there are indications that management in the ambulatory setting is not safe or effective. See Recommendation IV.5 for indications for transfer to a more intensive level of care.

C. AUD Treatment Initiation and Engagement

Recommendation IV.12: When feasible, alcohol use disorder (AUD) treatment should be initiated concurrently with alcohol withdrawal management as cognitive status permits. If appropriate, clinicians should offer to initiate pharmacotherapy for AUD as cognitive status permits. If not initiating AUD treatment themselves, clinicians should explain the range of evidence-based treatment services available in the community, and engage patients with these options. In addition, clinicians may offer information about local recovery support groups, including 12-step groups.

D. Pharmacotherapy

(1) Prophylaxis

Recommendation IV.13: Patients at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal may be treated in ambulatory settings at the discretion of providers with extensive experience in management of alcohol withdrawal. Such patients should be provided with preventative pharmacotherapy. Benzodiazepines are first-line treatment because of their well-documented effectiveness in reducing the signs and symptoms of withdrawal including the incidence of seizure and delirium. Phenobarbital is an appropriate alternative in a Level 2-WM setting for providers experienced with its use. For patients with a contraindication for benzodiazepine use, phenobarbital (in Level 2-WM settings by providers experienced with its use) or transfer to a more intensive level of care are appropriate options.

Recommendation IV.14: A front loading regimen is recommended for patients at high risk of severe withdrawal syndrome. Providing at least a single dose of preventative medication is appropriate for patients at lower levels of risk who have:

- A history of severe or complicated withdrawal
- An acute medical, psychiatric, or surgical illness
- Severe coronary artery disease
- Displaying signs or symptoms of withdrawal concurrent with a positive blood alcohol content

Recommendation IV.15: Patients at risk of developing new or worsening signs or symptoms of withdrawal while away from the ambulatory treatment setting should be provided with pharmacotherapy. Some indications of risk include a history of withdrawal episodes of at least moderate severity and being within the window for the development of symptoms in the time course of withdrawal. Benzodiazepines, carbamazepine, or gabapentin are all appropriate options for monotherapy. Providing at least a single dose of benzodiazepine followed by ongoing treatment according to symptom severity is also appropriate. If the risk of developing worse withdrawal is unknown, patients should be reassessed frequently over the next 24 hours to monitor their need for withdrawal medication.

(2) Withdrawal symptoms

Recommendation IV.16: Patients experiencing mild alcohol withdrawal (e.g., CIWA-Ar score < 10) who are at minimal risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal may be provided pharmacotherapy or supportive care alone. If providing medication, carbamazepine or gabapentin are appropriate options. For patients who are at risk of developing new or worsening withdrawal while away from the treatment setting, benzodiazepines, carbamazepine, or gabapentin are appropriate.

Recommendation IV.17: Patients experiencing moderate alcohol withdrawal (e.g., CIWA-Ar scores 10–18) should receive pharmacotherapy. Benzodiazepines are first-line treatment. Carbamazepine or gabapentin are appropriate alternatives. For patients with a contraindication for benzodiazepine use, carbamazepine, gabapentin, or phenobarbital (in Level 2-WM settings for providers experienced with its use) are appropriate. Carbamazepine, gabapentin, or valproic acid (if no liver disease or childbearing potential) may be used as an adjunct to benzodiazepines.

Recommendation IV.18: Patients experiencing severe, but not complicated, alcohol withdrawal (e.g., CIWA-Ar $\geq$ 19) may be treated in ambulatory Level 2-WM settings at the discretion of providers with extensive experience in management of alcohol withdrawal. Such patients should receive pharmacotherapy. Benzodiazepines are first-line treatment. Phenobarbital is an appropriate alternative for providers experienced with its use. For patients with a contraindication for benzodiazepine use, phenobarbital, carbamazepine, or gabapentin are appropriate. The use of adjunct medications is also appropriate.

Recommendation IV.19: If a patient is taking medication as prescribed and symptoms are not controlled as expected:

- First, consider increasing the dose

If over-sedation or inadequate monitoring is a concern:

- Reassess for appropriate level of care
- Consider switching medications
- If using benzodiazepines, consider adding an adjunct medication

(3) Benzodiazepine use

Recommendation IV.20: While no particular benzodiazepine agent is more effective than another, longer-acting benzodiazepines are the preferred agents due to the clinical benefits of their longer duration of action.

Recommendation IV.21: If waiting for lab test results or if the test(s) are unavailable, if a patient has signs of significant liver disease, use a benzodiazepine with less hepatic metabolization.

Recommendation IV.22: Clinicians should monitor patients taking benzodiazepines for signs of over-sedation and respiratory depression.

Recommendation IV.23: A benzodiazepine prescription to treat alcohol withdrawal should be discontinued following treatment.

Recommendation IV.24: Clinicians can manage benzodiazepine misuse or diversion risk in ambulatory settings by dispensing or prescribing the minimum amount necessary given patients' level of stability and timing of their next in-person clinic visit. Alternative medications can also be considered such as carbamazepine or gabapentin.

Recommendation IV.25: In ambulatory settings, benzodiazepines should not be prescribed to patients with a history of even mild adverse events with benzodiazepine use because rapid intervention is not typically available. Benzodiazepines can be used with caution in patients with a high risk of benzodiazepine diversion including patients with a current or past benzodiazepine use disorder for the short period of acute alcohol withdrawal. Risk can be managed by dispensing or prescribing a small number of doses.

Recommendation IV.26: Patients who are taking benzodiazepines, and their caregivers, should be educated regarding:

- The danger of drug-drug interactions between benzodiazepines and other CNS depressants (impairment and respiratory depression)
- The risks associated with combining alcohol and benzodiazepines and importance of abstinence from alcohol
- The risks associated with driving or use of heavy machinery for the first few days of benzodiazepine administration
- Instructions to reduce their benzodiazepine dose if drowsiness occurs

(4) Benzodiazepine dosing regimens

Recommendation IV.27: At short-term observational settings with continuous monitoring (e.g. Level 2-WM), symptom-triggered treatment conducted by trained staff is the preferred benzodiazepine dosing method. Front loading while under clinical supervision or fixed dosing with additional as-needed medication are also appropriate.

Recommendation IV.28: At settings without extended on-site monitoring (Level 1-WM), symptom-triggered dosing is appropriate if patients or a caregiver can reliably monitor signs and symptoms with a withdrawal severity scale and follow dosing guidance. Otherwise, front loading while under

clinical supervision or fixed dosing with additional as-needed medication is appropriate.

Recommendation IV.29: Front loading is recommended for patients experiencing severe alcohol withdrawal (e.g., CIWA-Ar $\geq$ 19). Diazepam and chlordiazepoxide are preferred agents for front loading.

Recommendation IV.30: When using a fixed-dose schedule, patients' signs and symptoms should still be monitored. A few additional take-home doses can be provided to take as needed. When initiating a fixed-dose regimen, arrange for the patient to be follow up with the following day to modify the dose if needed.

Recommendation IV.31: If prescribing a shorter-acting benzodiazepine, using a fixed-dose regimen with a gradual taper may be appropriate to reduce the likelihood of breakthrough and rebound signs and symptoms.

(5) Carbamazepine, gabapentin, valproic acid

Recommendation IV.32: Gabapentin is a favorable choice for treating alcohol withdrawal when a clinician also plans to use it for a patient's ongoing treatment of alcohol use disorder.

Recommendation IV.33: If benzodiazepines are contraindicated, carbamazepine or gabapentin are appropriate alternatives.

Recommendation IV.34: Carbamazepine, gabapentin, or valproic acid may be used as an adjunct to benzodiazepine therapy to help control alcohol withdrawal. Before using as an adjunct, clinicians should ensure that an adequate dose of benzodiazepine has been administered.

Recommendation IV.35: Valproic acid should not be used in patients who have liver disease or women of childbearing potential.

Recommendation IV.36: There is insufficient evidence to support the use of valproic acid as monotherapy for the treatment of alcohol withdrawal.

(6) Phenobarbital

Recommendation IV.37: Phenobarbital can be used for some patients in Level 2-WM ambulatory settings; however, it should only be used by clinicians experienced with its use given its narrow therapeutic window and side effects.

Recommendation IV.38: In a Level 2-WM ambulatory setting (e.g., with extensive monitoring), phenobarbital monotherapy (managed by a clinician experienced with its use) is an appropriate alternative to benzodiazepines for patients who are experiencing severe alcohol withdrawal or who are at risk of developing severe or complicated alcohol withdrawal or complication of alcohol withdrawal.

Recommendation IV.39: In a Level 2-WM ambulatory setting (e.g., with extensive monitoring), phenobarbital monotherapy (managed by a clinician experienced with its use) is appropriate for patients with a contraindication for benzodiazepine use who are experiencing moderate or severe alcohol withdrawal or who are at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal.

(7) A2AAs and beta-blockers

Recommendation IV.40: Alpha2-adrenergic agonists (A2AAs) such as clonidine can be used as an adjunct to benzodiazepine therapy to control autonomic hyperactivity and anxiety when symptoms are not controlled by benzodiazepines alone. They should not be used alone to prevent or treat withdrawal-related seizures or delirium.

Recommendation IV.41: Beta-adrenergic antagonists (beta-blockers) can be used as an adjunct to benzodiazepines in select patients for control of persistent hypertension or tachycardia when these signs are not controlled by benzodiazepines alone. They should not be used to prevent or treat alcohol withdrawal seizures.

(8) Inappropriate medications

Recommendation IV.42: Oral or intravenous alcohol should not be used for the prevention or treatment of alcohol withdrawal.

Recommendation IV.43: There is insufficient evidence to support the use of baclofen for the treatment of alcohol withdrawal.

Recommendation IV.44: Providing magnesium as a prophylaxis or treatment for alcohol withdrawal management has no supporting evidence.

V. Inpatient Management of Alcohol Withdrawal

Recommendations that are appropriate for both Ambulatory and Inpatient Management are repeated in both sections.

A. Monitoring

Recommendation V.1: The following monitoring schedule is appropriate:

- In patients with moderate to severe withdrawal or those requiring pharmacotherapy, re-assess every 1–4 hours for 24 hours, as clinically indicated. Once stabilized (e.g., CIWA-Ar score $<$ 10 for 24 hours), monitoring can be extended to every 4–8 hours for 24 hours, as clinically indicated.
- Patients with mild withdrawal and low risk of complicated withdrawal may be observed for up to 36 hours, after which more severe withdrawal is unlikely to develop.

Recommendation V.2: Monitor patients' vital signs, hydration, orientation, sleep, and emotional status including suicidal thoughts.

Recommendation V.3: Monitor patients receiving pharmacotherapy for alcohol withdrawal for signs of oversedation and respiratory depression.

Recommendation V.4: Signs and symptoms of alcohol withdrawal should be monitored during withdrawal management with a validated assessment scale (see Appendix III for a summary of scales and their associated features).

B. Supportive Care

Recommendation V.5: Supportive care is a critical component of alcohol withdrawal management. Frequent reassurance, re-orientation to time and place, and nursing care are recommended non-pharmacological interventions. Providers should ensure patients are educated about what to expect over the course of withdrawal, including common signs and symptoms and how they will be treated. Patients with severe alcohol withdrawal should be cared for in an

evenly lit, quiet room. Patients should be offered hope and the expectation of recovery.

Recommendation V.6: Supportive care for alcohol withdrawal patients includes adherence to safety measures and protocols (e.g., assess risk for fall/syncope). If available and applicable, existing institutional/hospital-associated delirium protocols can be used for supportive care of patients with severe alcohol withdrawal.

Recommendation V.7: Thiamine should be provided to prevent Wernicke encephalopathy.

- Intravenous (IV) or intramuscular (IM) administration of thiamine is preferred, in particular for patients with poor nutritional status, malabsorption, or who are known to have severe complications of alcohol withdrawal.
- Typical dosing is 100 mg IV/IM per day for 3–5 days. Oral thiamine also can also be offered.
- Patients also receiving glucose can be administered thiamine and glucose in any order or concurrently.

Recommendation V.8: Clinicians should administer thiamine to patients admitted to the Intensive Care Unit (ICU) to treat alcohol withdrawal.

Recommendation V.9: For patients with hypomagnesemia, cardiac arrhythmias, electrolyte disturbances, or a previous history of alcohol withdrawal seizures, magnesium should be administered.

Recommendation V.10: If phosphorus is < 1 mg/dL, supplementation should be provided. Otherwise, in the case of moderate hypophosphatemia (1-2 mg/dL), correction through proper nutrition is recommended.

Recommendation V.11: In patients who are critically ill, folate supplementation may be considered, since chronic alcohol use is associated with hyperhomocysteinemia.

C. AUD Treatment Initiation and Engagement

Recommendation V.12: The period of alcohol withdrawal management should be used to engage patients with an alcohol use disorder (AUD) with comprehensive treatment. When feasible, AUD treatment should be initiated concurrently with alcohol withdrawal management as cognitive status permits. If appropriate, clinicians should also offer to initiate pharmacotherapy for AUD as cognitive status permits. Clinicians should explain the range of evidence-based treatment services available at the current site and in the community. Finally, clinicians should proactively connect patients to treatment services as seamlessly as possible, including initiating a warm handoff to treatment providers.

D. Pharmacotherapy

(1) Prophylaxis

Recommendation V.13: For patients at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal, preventative pharmacotherapy should be provided. Benzodiazepines are first-line treatment because of their well-documented effectiveness in reducing the signs and symptoms of withdrawal including the incidence of seizure and delirium. For patients with a contraindication for benzodiazepine use, phenobarbital can be used by providers experienced with its use. In settings with close monitoring, phenobarbital adjunct to benzodiazepines is also appropriate.

Recommendation V.14: A front loading regimen is recommended for patients at high risk of severe withdrawal syndrome. Providing at least a single dose of preventative medication is appropriate for patients at lower levels of risk not experiencing significant signs or symptoms but have:

- A history of severe or complicated withdrawal
- An acute medical, psychiatric, or surgical illness
- Severe coronary artery disease
- Displaying signs or symptoms of withdrawal concurrent with a positive blood alcohol content

(2) Withdrawal symptoms

Recommendation V.15: For patients experiencing mild alcohol withdrawal (e.g., CIWA-Ar score <10) who are at minimal risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal, pharmacotherapy or supportive care alone may be provided. If providing medication, benzodiazepines, carbamazepine, or gabapentin are appropriate. For patients with a contraindication for benzodiazepine use, carbamazepine, gabapentin, or phenobarbital (for providers experienced with its use) are appropriate. Carbamazepine, gabapentin, or valproic acid (if no liver disease or childbearing potential) may be used as an adjunct to benzodiazepines.

Recommendation V.16: Patients experiencing moderate alcohol withdrawal (e.g., CIWA-Ar scores 10–18) should receive pharmacotherapy. Benzodiazepines are first-line treatment. Carbamazepine or gabapentin are appropriate alternatives. For patients with a contraindication for benzodiazepine use, carbamazepine, gabapentin, or phenobarbital (for providers experienced with its use) are appropriate. Carbamazepine, gabapentin, or valproic acid (if no liver disease or childbearing potential) may be used as an adjunct to benzodiazepines.

Recommendation V.17: Patients experiencing severe alcohol withdrawal (e.g., CIWA-Ar scores $\geq$19) should receive pharmacotherapy. Benzodiazepines are first-line treatment. For patients with a contraindication for benzodiazepine use, phenobarbital is appropriate for providers experienced with its use. If close monitoring is available, phenobarbital can be used as an adjunct to benzodiazepines. Other adjunct medications can be considered after a clinician ensures that an adequate dose of benzodiazepines has been administered.

Recommendation V.18: If a patient's symptoms are not controlled as expected:

- First consider increasing the dose

If over-sedation or inadequate monitoring is a concern:

- Reassess for appropriate level of care
- Consider switching medication
- If using benzodiazepines, consider adding an adjunct medication

(3) Benzodiazepine use

Recommendation V.19: While no particular benzodiazepine agent is more effective than another, longer-acting benzodiazepines are the preferred agents due to clinical benefits of their longer duration of action.

Recommendation V.20: If waiting for lab test results or if the test(s) are unavailable, if a patient has signs of significant liver disease, use a benzodiazepine with less hepatic metabolization.

Recommendation V.21: Clinicians should monitor patients taking benzodiazepines for signs of over-sedation and respiratory depression.

Recommendation V.22: A benzodiazepine prescription to treat alcohol withdrawal should be discontinued following treatment.

(4) Benzodiazepine dosing regimens

Recommendation V.23: Symptom-triggered treatment is the preferred benzodiazepine dosing method. Fixed dosing according to a scheduled taper may be appropriate if symptom-triggered treatment cannot be used.

Recommendation V.24: Front loading is recommended for patients experiencing severe alcohol withdrawal (e.g., CIWA-Ar scores $\geq$19). Diazepam or chlordiazepoxide are preferred agents for front loading.

Recommendation V.25: When using a fixed-dose schedule, patients' signs and symptoms should still be monitored, and additional doses of medication provided as needed.

Recommendation V.26: If prescribing a shorter-acting benzodiazepine, using a fixed-dose regimen with a gradual taper may be appropriate to reduce the likelihood of breakthrough and rebound signs and symptoms.

(5) Carbamazepine, gabapentin, valproic acid

Recommendation V.27: Gabapentin is a favorable choice for treating alcohol withdrawal when a clinician also plans to use it for a patient's ongoing treatment of alcohol use disorder.

Recommendation V.28: If benzodiazepines are contraindicated, carbamazepine or gabapentin are appropriate alternatives for patients in mild or moderate withdrawal.

Recommendation V.29: Carbamazepine, gabapentin, or valproic acid may be used as an adjunct to benzodiazepine therapy to help control alcohol withdrawal. Before using as an adjunct, clinicians should ensure that an adequate dose of benzodiazepine has been administered.

Recommendation V.30: Valproic acid should not be used in patients who have liver disease or women of childbearing potential.

Recommendation V.31: There is insufficient evidence to support the use of valproic acid as monotherapy for the treatment of alcohol withdrawal.

(6) Phenobarbital

Recommendation V.32: Phenobarbital can be used for some patients in inpatient settings; however, it should only be used by clinicians experienced with its use given its narrow therapeutic window and side effects.

Recommendation V.32: In an inpatient setting, phenobarbital monotherapy (managed by a clinician experienced with its use) is appropriate for patients with a contraindication for benzodiazepine use who are experiencing mild, moderate, or severe alcohol withdrawal or who are at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal.

Recommendation V.34: In an inpatient setting, if close monitoring is available, phenobarbital (managed by a clinician experienced with its use) as an adjunct to benzodiazepines is an option for patients experiencing severe alcohol withdrawal or who are at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal.

Recommendation V.35: Parenteral phenobarbital should only be used in highly supervised settings (e.g., ICU, CCU) because of risk of over-sedation and respiratory depression.

(7) A2AAs and beta-blockers

Recommendation V.36: Alpha2-adrenergic agonists (AA2 s) such as clonidine and dexmedetomidine can be used as an adjunct to benzodiazepine therapy to control autonomic hyperactivity and anxiety when these signs are not controlled by benzodiazepines alone. They should not be used alone to prevent or treat withdrawal-related seizures or delirium.

Recommendation V.37: Beta-adrenergic antagonists (beta-blockers) can be used as an adjunct to benzodiazepines in select patients for control of persistent hypertension or tachycardia when these signs are not controlled by benzodiazepines alone. They should not be used to prevent or treat alcohol withdrawal seizures.

(8) Inappropriate medications

Recommendation V.38: Oral or intravenous alcohol should not be used for the prevention or treatment of alcohol withdrawal.

Recommendation V.39: There is insufficient evidence to support the use of baclofen for the treatment of alcohol withdrawal.

Recommendation V.40: Providing magnesium as a prophylaxis or treatment for alcohol withdrawal management has no supporting evidence.

VI. Addressing Complicated Alcohol Withdrawal

A. Alcohol Withdrawal Seizure

(1) Monitoring

Recommendation VI.1: Patients should be monitored for alcohol withdrawal seizures even in the absence of other clinically prominent alcohol withdrawal signs or symptoms.

Recommendation VI.2: Following an alcohol withdrawal seizure, patients should be admitted to a setting with close monitoring available, and should be re-assessed every 1-2 hours for 6–24 hours. Patients should be closely monitored for delirium and the need to receive intravenous (IV) fluids, due to potential electrolyte imbalances.

(2) Supportive care

Recommendation VI.3: If available and applicable, existing institutional/hospital-associated delirium protocols can be used for supportive care of patients with an alcohol withdrawal seizure.

(3) Pharmacotherapy

Recommendation VI.4: Following a withdrawal seizure, patients should be immediately treated with a medication effective at preventing another seizure. Benzodiazepines are first-line treatment, and a fast-acting agent such as lorazepam or diazepam is preferred. Phenobarbital is also an option but is less preferred to benzodiazepines.

Recommendation VI.5: Following a withdrawal seizure, parenteral administration of medications is preferred. If available, IV administration is preferred to intramuscular (IM), but IM administration is also effective. Parenteral phenobarbital should only be used in highly supervised settings (e.g., Intensive Care Unit [ICU], CCU) because of risk of over-sedation and respiratory depression.

Recommendation VI.6: It is not recommended to use alpha2-adrenergic agonists or beta-adrenergic antagonists to prevent or treat alcohol withdrawal seizures because they are ineffective for this purpose. Beta-adrenergic antagonists also can lower the seizure threshold. Phenytoin should not be used unless treating a concomitant underlying seizure disorder.

B. Alcohol Withdrawal Delirium

(1) Monitoring

Recommendation VI.7: Patients with alcohol withdrawal delirium should be provided close nursing observation and supportive care, which often necessitates admission to an intensive or critical care unit. Agitated and disoriented patients should have continuous, one-to-one observation and monitoring.

Recommendation VI.8: Patients with alcohol withdrawal delirium should have their vital signs, oximetry and cardiac status monitored as frequently as required. Resuscitative equipment should be readily available when patients require high doses of benzodiazepines, when continuous infusion of medication is used, or when patients have significant concurrent medical conditions.

Recommendation VI.9: To monitor signs and symptoms of alcohol withdrawal delirium, use a structured assessment scale such as the Confusion Assessment Method for ICU Patients (CAM-ICU), Delirium Detection Score (DDS), Richmond Agitation-Sedation Scale (RASS), or Minnesota Detoxification Scale (MINDS). It is not recommended to use the CIWA-Ar in patients with delirium because it relies on patient-reported symptoms.

(2) Supportive care

Recommendation VI.10: Provide immediate intravenous access for administration of drugs and fluids to patients experiencing alcohol withdrawal delirium.

Recommendation VI.11: If available and applicable, existing institutional/hospital-associated delirium protocols can be used for supportive care of patients with alcohol withdrawal delirium.

Recommendation VI.12: Restraints should only be used when required to prevent injuries due to agitation or violence, and in compliance with state laws.

(3) Pharmacotherapy

Recommendation VI.13: Patients with alcohol withdrawal delirium should be sedated to achieve and maintain a light somnolence. Benzodiazepines are recommended as the first-line agents for managing alcohol withdrawal delirium.

Recommendation VI.14: When available, medication should be administered intravenously. The use of intermittent IV administration of long- and short-acting medications is acceptable and effective. Continuous IV infusion is considerably more expensive and there is no evidence of therapeutic superiority.

Recommendation VI.15: Patients receiving repeated high intravenous doses of lorazepam or diazepam should be monitored closely for signs of hyponatremia and metabolic acidosis.

Recommendation VI.16: When treating alcohol withdrawal delirium, use an established dosing protocol as a guide, but individualize dosing regimens based on patient's signs and symptoms. It is appropriate for patients with alcohol withdrawal delirium to receive intravenous symptom-triggered or fixed-dose front loading. Once light somnolence is achieved and patients are calm and cooperative, if on IV medication, shifting to oral symptom-triggered treatment is recommended.

Recommendation VI.17: Very large doses of benzodiazepines may be needed to control agitation in alcohol withdrawal delirium, including doses that are much higher than typically seen in other patient populations. Clinicians should not hesitate to provide such large doses to patients to control agitation but should keep in mind the possible risk of over-sedation and respiratory depression. Moreover, when large doses are used, there is risk of accumulation of long-acting benzodiazepine metabolites, especially in patients with impaired hepatic function or the elderly, and patients should be monitored closely.

Recommendation VI.18: For patients who have been delirious longer than 72 hours, assess for drug-induced delirium and withdrawal from another GABAergic agent (such as gabapentin or carisoprodol). When necessary, adjust the benzodiazepine dose.

Recommendation VI.19: Barbiturates can be considered an alternative option to benzodiazepines for the treatment of alcohol withdrawal delirium, but they are not preferred to benzodiazepines. Phenobarbital can be used as an adjunct to benzodiazepines in settings with close monitoring when alcohol withdrawal delirium is not adequately controlled by benzodiazepine therapy alone.

Recommendation VI.20: Antipsychotic agents can be used as an adjunct to benzodiazepines when alcohol withdrawal delirium and hallucinations are not adequately controlled by benzodiazepine therapy alone. They are not recommended as monotherapy for alcohol withdrawal delirium.

Recommendation VI.21: Alpha2-adrenergic agonists, beta-adrenergic antagonists and paraldehyde should not be used to treat alcohol withdrawal delirium.

C. Alcohol-Induced Psychotic Disorder

Recommendation VI.22: If available and applicable, existing institutional/hospital-associated delirium protocols can be used for supportive care of patients with an alcohol-induced psychotic disorder.

Recommendation VI.23: The treatment of alcohol-induced psychotic disorder may require consultation with a psychiatrist.

Recommendation VI.24: The treatment of alcohol-induced psychotic disorder may require addition of antipsychotics.

Recommendation VI.25: For patients experiencing hallucinations, diazepam may be considered a treatment option.

D. Resistant Alcohol Withdrawal

Recommendation VI.26: If available and applicable, existing institutional/hospital-associated delirium protocols can be used for supportive care of patients with resistant alcohol withdrawal.

Recommendation VI.27: Phenobarbital may be used as an adjunct to benzodiazepines to control resistant alcohol withdrawal syndrome in settings with close monitoring.

Recommendation VI.28: Propofol may be used with patients in the ICU experiencing resistant alcohol withdrawal who already require mechanical ventilation.

Recommendation VI.29: Dexmedetomidine may be used with patients in the ICU experiencing resistant alcohol withdrawal.

VII. Specific Settings and Populations

A. Primary Care

Recommendation VII.1: If patients are experiencing severe withdrawal (e.g., CIWA-Ar scores $\geq$19), refer them directly to the nearest Emergency Department.

Recommendation VII.2: If withdrawal is mild (e.g., CIWA-Ar $<$10), patients presenting to primary care can be prescribed a few doses of benzodiazepine. Whenever possible, medication can be supervised by a caregiver at home or staff at a nonmedical withdrawal management center. Do not prescribe medication to patients for ambulatory management of alcohol withdrawal without performing an adequate assessment or to patients without adequate support.

Recommendation VII.3: If withdrawal does not resolve (e.g., fall below a CIWA-Ar score of 10) after an adequate dose of medication (e.g., 80 mg diazepam), or patients appears sedated, transfer to an Emergency Department or other inpatient withdrawal management setting.

Recommendation VII.4: For patients treated in primary care settings, regular follow-up visits, at least monthly for one year, could increase the likelihood of sustained recovery.

B. Emergency Departments

Recommendation VII.5: If patients are experiencing severe alcohol withdrawal (e.g., CIWA-Ar $\geq$19), or are at risk of complicated withdrawal, administer medication immediately to treat withdrawal and reduce the risk of seizures and delirium.

Recommendation VII.6: Patients presenting with alcohol withdrawal syndrome in the Emergency Department should be evaluated for delirium as well as other conditions that mimic and/or accompany withdrawal. Patients presenting with delirium should be assessed for all potential etiologies including alcohol withdrawal.

Recommendation VII.7: Patients in the Emergency Department should receive a complete blood count and complete metabolic panel including liver enzyme and magnesium tests; alcohol withdrawal treatment should not be delayed while waiting for results.

Recommendation VII.8: The following indicators should be present for discharge to an ambulatory alcohol withdrawal management setting from the Emergency Department:

- Mild alcohol withdrawal (e.g., CIWA-Ar score $<$10).
- Moderate alcohol withdrawal (e.g., CIWA-Ar score 10–18) with no other complicating factors
- Not currently intoxicated (including alcohol or other drugs)
- No history of complicated alcohol withdrawal (seizures, delirium)
- No significant medical or psychiatric comorbidities that would complicate withdrawal management
- Able to comply with ambulatory visits and therapy

Recommendation VII.9: Patients with controlled withdrawal syndrome being discharged from the Emergency Department may be offered a short term (e.g., 1-2 day) prescription for appropriate alcohol withdrawal medication to last until follow-up with their healthcare provider.

C. Hospitalized Patients

(1) Identification

Recommendation VII.10: All patients admitted to the hospital should be screened for risk of alcohol withdrawal. Among hospitalized patients, the Alcohol Use Disorders Identification Test (AUDIT) and Alcohol Use Disorders Identification Test-Piccinelli Consumption (AUDIT-PC) can indicate risk of developing alcohol withdrawal.

Recommendation VII.11: Patients undergoing elective surgery should be screened for unhealthy alcohol use and the need to undergo alcohol withdrawal management before proceeding with surgery. Patients undergoing elective surgery who are at risk of alcohol withdrawal should undergo medically managed withdrawal before proceeding with surgery

(2) Assessment

Recommendation VII.12: Among hospitalized patients, the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) can be used for predicting risk of developing severe or complicated alcohol withdrawal in the medically ill.

Recommendation VII.13: Patients for whom alcohol withdrawal is suspected and for whom a complete medical history is not available, (i.e., are admitted from the Emergency Department or trauma unit, are in Intensive Care Unit [ICU]), or who are known to be at high risk of complicated alcohol withdrawal, medical decisions should be oriented toward a more aggressive treatment of alcohol withdrawal regardless of presenting signs and symptoms.

Recommendation VII.14: For patients who require more than standard amounts of medication to manage alcohol withdrawal, individualized assessment by clinicians experienced in the management of withdrawal is recommended. The medication and protocol used for treating other conditions and/or alcohol withdrawal syndrome may need to be modified.

(3) Monitoring

Recommendation VII.15: In patients who are hospitalized, monitor their vital signs. Fluid intake and output and serum electrolytes should be monitored as clinically indicated.

Recommendation VII.16: Signs and symptoms of alcohol withdrawal should be monitored during the course of withdrawal with a validated symptom assessment scale. Assess the risk for scores on a symptom assessment scale to be confounded by the use of certain medications, the presence of certain medical conditions (e.g. fever from infection), or a patient's difficulty communicating. Among general medical/surgical patients, low withdrawal scores can typically be interpreted with confidence, while high scores should be interpreted with caution. The use of alternative scales with patients with difficulty communicating is appropriate.

Recommendation VII.17: Patients with a reduced level of consciousness who are at risk for the development of alcohol withdrawal should be monitored for the appearance of alcohol withdrawal signs. If a co-occurring clinical condition worsens, do not assume it is related to alcohol withdrawal among alcohol withdrawal patients. However, immediate treatment is required if alcohol withdrawal develops after surgery or trauma.

(4) Supportive care

Recommendation VII.18: Clinicians should administer thiamine to ICU patients with signs or symptoms that mimic or mask Wernicke encephalopathy.

(5) Pharmacotherapy

Recommendation VII.19: Prophylactic treatment of alcohol withdrawal should be provided in the ICU to patients who are suspected to be physiologically dependent on alcohol.

Recommendation VII.20: Implementing an alcohol withdrawal management protocol in the ICU is appropriate. When using a symptom-triggered dosing protocol, use a validated scale to monitor signs and symptoms. For patients being treated in ICU settings for alcohol withdrawal, existing scales that are appropriate to use for monitoring withdrawal include the Richmond Agitation-Sedation Scale (RASS). Administration of medications via the intravenous route is preferred because of the rapid onset of action and more predictable bioavailability.

D. Patients With Medical Conditions

Recommendation VII.21: For patients with medical comorbidities, modify the medication and/or protocol used for treating alcohol withdrawal syndrome as necessary in consultation with other specialists.

Recommendation VII.22: For patients with medical conditions that prevent the use of oral medication, provide intravenous or intramuscular medications as necessary.

Recommendation VII.23: Aggressive withdrawal treatment is indicated for patients with cardiovascular disorders due to risk of harm associated with autonomic hyperactivity.

Recommendation VII.24: For patients with a medical condition associated with impaired hepatic function, adjust medication dose or use medications with less dependence on hepatic metabolism.

E. Patients who Take Opioids

Recommendation VII.25: Patients who are on chronic opioid medication (opioid agonist therapy for opioid use disorder or pain) should be monitored closely when benzodiazepines are prescribed, due to the increased risk of respiratory depression. Similarly, patients taking sedative-hypnotic medications exhibit tolerance to benzodiazepines and should be monitored closely for appropriate dose.

Recommendation VII.26: For patients with concomitant alcohol withdrawal and opioid use disorder, stabilize opioid use disorder (e.g., with methadone or buprenorphine) concomitantly with treating alcohol withdrawal.

F. Patients who are Pregnant

(1) Level of care and monitoring

Recommendation VII.27: Inpatient treatment should be considered for all pregnant patients with alcohol use disorder who require withdrawal management. Inpatient treatment should be offered to pregnant patients with at least moderate alcohol withdrawal (i.e., CIWA-Ar scores $\geq$ 10).

Recommendation VII.28: The CIWA-Ar is an appropriate symptom assessment scale to use with pregnant patients. Clinicians should consider signs and symptoms such as nausea, headache, anxiety, and insomnia to be connected to alcohol withdrawal rather than pregnancy that will abate once the alcohol withdrawal has been effectively treated.

Recommendation VII.29: During withdrawal management, consult with an obstetrician.

(2) AUD treatment initiation and engagement

Recommendation VII.30: Engagement in treatment for AUD is particularly important for pregnant patients with alcohol withdrawal given the risk of Fetal Alcohol Spectrum Disorder (FASD) including Fetal Alcohol Syndrome (FAS).)

(3) Pharmacotherapy

Recommendation VII.31: Before giving any medications to pregnant patients, ensure that patients understand the risks and benefits of the medication, both for the patient and the developing fetus.

Recommendation VII.32: Benzodiazepines and barbiturates are the medications of choice in treatment of pregnant patients with alcohol withdrawal. While there is a risk of teratogenicity during the first trimester, the risks appear small, and they are balanced in view of the risk for fetal alcohol spectrum disorder and consequences to mother and fetus should severe maternal alcohol withdrawal develop.

Recommendation VII.33: Due to the high teratogenic risk, valproic acid is not recommended for pregnant patients.

Recommendation VII.34: For patients at risk for preterm delivery or in the late third trimester, use of a short-acting benzodiazepine is recommended. This minimizes the risk for neonatal benzodiazepine intoxication given shorter onset and duration of action.

(4) Newborn considerations

Recommendation VII.35: In cases of alcohol withdrawal treated close to delivery, assess the newborn for benzodiazepine intoxication, sedative withdrawal, and Spectrum Disorder (FASD) including Fetal Alcohol Syndrome (FAS).

Recommendation VII.36: Inform pregnant patients of all wraparound services that will assist them in addressing newborn needs, including food, shelter, pediatric clinics for inoculations, as well as programs that will help with developmental or physical issues that the newborn may experience as a result of in-utero substance exposure.

Recommendation VII.37: Licensed clinical staff have an obligation to understand and follow their state laws regarding definitions of child abuse and neglect, reporting requirements, and plans of safe care for newborns with in-utero alcohol exposure.

INTRODUCTION

I. Purpose

The American Society of Addiction Medicine (ASAM) developed this *Guideline on Alcohol Withdrawal Management* to provide updated information on evidence-based strategies and standards of care for alcohol withdrawal management in both ambulatory and inpatient settings.

II. Background

Alcohol is responsible for a multitude of health conditions, including Alcohol Use Disorder (AUD) and alcohol withdrawal. Individuals physically dependent on alcohol may experience signs and symptoms of alcohol withdrawal upon cessation of (or reduction in) alcohol use, due to the sudden reversal of depressant effects on brain function. Signs and symptoms of alcohol withdrawal include anxiety, sleep disturbance, headache, nausea, hallucinations, delirium, and seizures. Clinical signs include sweating, elevated blood pressure, tachycardia, hyperthermia, and hyperactive reflexes. Hallucinations can range from mild perceptual distortions to frank hallucinations with a lack of insight. The most severe consequences of alcohol withdrawal include seizure, delirium, and death.

Patients with alcohol withdrawal frequently present in specialty addiction treatment settings and general medical settings. Patients experiencing or at risk for developing alcohol withdrawal also present in hospitals, emergency departments, and primary care settings. An estimated 2–7% of patients with heavy alcohol use admitted to the hospital will develop moderate to severe alcohol withdrawal.[16] Additionally, an estimated 32% of emergency department visits are alcohol related.[17] Many of these patients will develop alcohol withdrawal during their emergency department stay.

There is an extensive body of research on the management of alcohol withdrawal, much of which has focused on pharmacotherapy. However, due to the evolution of research evidence and clinical practice, questions continue to emerge about the appropriate management of patients with alcohol withdrawal. For example, although benzodiazepines have long been considered the mainstay of alcohol withdrawal treatment, research on other agents such as anticonvulsants have raised clinical questions about alternatives or adjuncts to benzodiazepines. Similarly, although the Clinical Instrument Withdrawal Assessment for Alcohol, Revised (CIWA-Ar) has long been considered the standard assessment scale for patients with alcohol withdrawal, several other instruments have been developed, raising questions about the value of a given instrument as compared to the others. Finally, although researchers have primarily focused on alcohol withdrawal management in inpatient settings, clinical practice has evolved and treatment in outpatient settings has become increasingly common. Therefore, numerous clinical questions have emerged about which patients are appropriate for ambulatory alcohol withdrawal management as well as how to tailor treatment interventions to specific settings.

A. Need for a New Guideline

In June 2017, the American Society of Addiction Medicine's (ASAM) Quality Improvement Council (QIC) elected to update ASAM's clinical guidelines on alcohol withdrawal management based on several factors. First, ASAM conducted an Educational Needs Assessment in 2016 that showed a strong interest and need for education on withdrawal management. Second, updated QIC policies recommend that all ASAM guidelines should be updated every five years. ASAM's previous guidelines on the topic of alcohol withdrawal management were published in 1997 and 2004. The first guideline, "Pharmacological Management of Alcohol Withdrawal"[13] was published in JAMA, followed five years later with the most recent guideline entitled "Management of Alcohol Withdrawal Delirium"[14] in JAMA, formerly Archives of Internal Medicine. Subsequent guidelines have not been written since the 2004 guidelines thus an update was due. Third, the American Psychiatric Association (APA) released a guideline on medications to treat alcohol use disorder that does not cover withdrawal management.[15] An ASAM guideline on alcohol withdrawal should complement APA's guideline. Fourth, outreach to other organizations indicated that other organizations are not planning to create a guideline on alcohol withdrawal.

Although alcohol withdrawal has been recognized for centuries and effective treatment strategies have been researched for decades, questions remain about effective approaches to treatment in specialty and non-specialty settings. At the outset of the guideline development process, ASAM identified several practice concerns related to alcohol withdrawal treatment:

1. Uncertainty about the CIWA-Ar, which is the most widespread symptom monitoring instrument but may not fit all patient populations and settings
2. Excessive caution about the use of benzodiazepines to treat alcohol withdrawal, which have been shown to prevent seizures and delirium
3. The use of barbiturates, which have a much narrower therapeutic window than benzodiazepines
4. Inconsistent treatment practices in non-specialty settings

The new clinical guideline is intended to address some of these current practice concerns and provide clear guidance that will lead to more consistent treatment practices in the field.

B. Previous ASAM Guidelines

This clinical practice guideline will replace the two previous ASAM guidelines related to alcohol withdrawal management, "Pharmacological Management of Alcohol Withdrawal"[13] in 1997 and "Management of Alcohol Withdrawal Delirium"[14] in 2004.

The 1997 guideline was based on a literature review conducted in 1995 and was primarily focused on pharmacotherapy,

with minimal attention to psychosocial treatment and considerations for various settings and levels of care. The 2004 guideline focuses specifically on Alcohol Withdrawal Delirium. This included a review and meta-analysis of nine prospective controlled trials published through 2001.

C. Additional ASAM Guidelines and Standards

ASAM has produced several other documents that provide guidance on the management of alcohol withdrawal, the most relevant of which are *The ASAM Criteria*,[12] *Principles of Addiction Medicine*,[18] and the ASAM *Standards of Care*.[19]

The ASAM Criteria provides comprehensive guidance on withdrawal management, specifically addressing alcohol withdrawal, including clear instruction for assessing and determining the patient's level of risk, matching patients to the appropriate level of care, and the service characteristics that should be present each level of care for withdrawal management.

Principles of Addiction Medicine contains a chapter titled ''Management of Alcohol Intoxication and Withdrawal,'' which reviews the clinical presentation and management of alcohol intoxication and withdrawal.

The *ASAM Standards of Care* provides a list of principles for Addiction Specialist Physicians to follow in order to support quality improvement activities and improve patient outcomes. The *Standards* ''outline a minimum standard of physician performance and should not be construed as describing the totality of care that a person with addiction might require.''[19(p 5)] The *Standards* help physicians identify their clinical and administrative roles to improve overall functioning and well-being of patients, while integrating addiction treatment into the larger healthcare system. Standards are organized by six performance measure domains. One of the six domains includes withdrawal management.

III. Scope of Guideline

While the current clinical guideline focuses primarily on alcohol withdrawal management, it is important to underscore that alcohol withdrawal management alone is not an effective treatment for alcohol use disorder. Withdrawal management should not be conceptualized as a discrete clinical service, but rather as a component in the process of initiating and engaging patients in treatment for alcohol use disorder.

IV. Intended Audience

The intended audience of this guideline is clinicians, mainly physicians, nurse practitioners, and physician assistants, who provide alcohol withdrawal management in specialty and non-specialty addiction treatment settings (including primary care and emergency departments, intensive care and surgery units in hospitals). The guideline will also have utility for administrators, insurers, and policymakers.

V. Qualifying Statement

This ASAM Alcohol Withdrawal Management Guideline is intended to aid clinicians in their clinical decision making and patient management. The Guideline strives to identify and define clinical decision making junctures that meet the needs of most patients in most circumstances. Clinical decision making should involve consideration of the quality and availability of expertise and services in the community wherein care is provided. In circumstances in which the Guideline is being used as the basis for regulatory or payer decisions, improvement in quality of care should be the goal. Finally, courses of treatment contained in recommendations in this Guideline are effective only if the recommendations, as outlined, are followed. Because lack of patient understanding and adherence may adversely affect outcomes, clinicians should make every effort to promote the patient's understanding of, and adherence to, prescribed and recommended treatments. Patients should be informed of the risks, benefits, and alternatives to a particular treatment, and should be an active party in shared decision making whenever feasible. Recommendations in this Practice Guideline do not supersede any federal or state regulations.

VI. Special Terms

Different terms have been used to describe various aspects and management methods of acohol withdrawal. Below are terms that are used throughout the guideline used to convey a specific meaning for the purposes of this guideline.

Alcohol Hallucinosis/Alcohol-induced Psychotic Disorder: Hallucinations that are not associated with alcohol withdrawal delirium and which can occur in the absence of other clinically prominent withdrawal signs and symptoms. Hallucinosis is characterized primarily by auditory hallucinations, paranoid symptoms and fear. Hallucinations occur in clear consciousness, are generally third person auditory hallucinations, and often derogatory. There may be secondary delusions or perseveration as well.[20] It is unclear if alcohol hallucinosis is part of alcohol withdrawal or if the hallucinations are a complication of chronic alcohol use unrelated to withdrawal. Currently, alcohol hallucinosis is diagnosed as alcohol-induced psychotic disorder in the Diagnostic and Statistical Manual 5 (DSM-5).

Ambulatory Withdrawal Management: Withdrawal management that occurs in outpatient settings, including primary care and intensive outpatient/day hospital settings. Level of clinical expertise and frequency of monitoring vary widely within various ambulatory withdrawal management settings.

Delirium and seizure: Unless otherwise specified, in this document these refer to alcohol withdrawal-related seizure or alcohol withdrawal delirium. Alcohol withdrawal delirium has replaced the formerly used ''delirium tremens.''

Dosing regimens: Different terms have been used to describe the many variations in dosing regimens used in alcohol withdrawal management. This document focuses on the following regimen types (see Appendix V for specific examples):

- *Symptom-triggered dosing:* An approach whereby patients are monitored through the use of a structured assessment scale and given medication only when symptoms cross a

threshold of severity (e.g., 25–100 mg chlordiazepoxide if CIWA-Ar score ≥10). Symptom-triggered dosing can be further refined by giving a different dose amount depending on the individual's score (e.g., 15 mg oxazepam for CIWA-Ar scores 8–15, 30 mg oxazepam for CIWA-Ar >15). The score can also determine the frequency of reassessment and further dosing.

- *Fixed dosing:* In a fixed-dose regimen, a predetermined dose is administered at fixed intervals according to a schedule. Doses usually decrease in a gradual taper over several days. A fixed-dose schedule can be refined by choosing an initial dose according to withdrawal severity as assessed by a withdrawal symptom severity scale.[21] When fixed-doses are given, allowances should be made to provide additional medication if the fixed-dose should prove inadequate to control symptoms.
- *Front loading:* An approach to dosing wherein moderate-to-high doses of a long-acting agent (e.g., 20 mg of diazepam) are given frequently at the outset of treatment to achieve rapid control of withdrawal signs and symptoms. The medication level is allowed to taper through metabolism. Front loading can be driven by a symptom assessment scale (e.g., 20 mg of diazepam every hour until CIWA-Ar scores <10) or a fixed-dosing schedule (e.g., 20 mg of diazepam every hour for 1-2 hours or until patient is sedated).

Inpatient Withdrawal Management: Alcohol withdrawal management that occurs in inpatient settings, including hospitals. The defining feature of inpatient settings for the purposes of this document is that patients are on site 24/7. Level of clinical expertise and frequency of monitoring vary widely within various inpatient withdrawal management settings. For the purposes of this document, residential facilities without continual medical monitoring are considered inpatient settings.

Level of care (LOC): Used in this guideline to describe different settings for the management of alcohol withdrawal, based on the definitions laid out in *The ASAM Criteria.*[12] *The ASAM Criteria* defines specific levels of care for alcohol withdrawal management as follows:

- *Level 1-WM:* Ambulatory withdrawal management without extended on-site monitoring
- *Level 2-WM:* Ambulatory withdrawal management with extended on-site monitoring
- *Level 3.2-WM:* Clinically managed residential withdrawal management
- *Level 3.7-WM:* Medically monitored inpatient withdrawal management
- *Level 4-WM:* Medically managed intensive inpatient withdrawal management

However, this guideline also uses two broad categories to describe settings where the management of alcohol withdrawal may take place. The first is an ambulatory level of care, which encompasses Level 1-WM and Level 2-WM. The second is an inpatient level of care, which encompasses Level 3-WM and Level 4-WM. Inpatient care also includes hospital settings. There is considerable variation in the staffing and resource availability within these two broad categories, which clinicians should consider when applying this guideline to their specific treatment setting.

Resistant alcohol withdrawal (RAW): Used in this guideline to describe patients experiencing severe or complicated alcohol withdrawal signs and symptoms despite having received high doses of benzodiazepines. There is not yet agreement in the field regarding the precise amount of benzodiazepines required before considering a patient to be in RAW, but various studies have used the cutoff of 200 mg diazepam in 4 hours,[22] ≥ 40 mg intravenous diazepam in 1 hour,[22] or ≥ 50 mg intravenous diazepam in 1 hour.[23] This phenomenon is also referred to as Refractory Alcohol Withdrawal, Benzodiazepine-Resistant Alcohol Withdrawal and Treatment-Resistant Alcohol Withdrawal in other sources.

Severe or complicated alcohol withdrawal or complications of alcohol withdrawal: These terms are used independently or jointly in this guideline to describe certain signs and symptoms and/or risks associated with alcohol withdrawal that are most harmful to patients. They are defined as:

- *Complicated alcohol withdrawal:* The development of alcohol withdrawal-related seizures or alcohol withdrawal delirium
- *Severe alcohol withdrawal:* Severe but not complicated signs and symptoms of alcohol
- *Complications of alcohol withdrawal:* Alcohol withdrawal signs and symptoms' potentially life-threatening exacerbation of existing medical or psychiatric conditions

Withdrawal severity: In this guideline, withdrawal severity is categorized in Table 1.

APPROACH AND METHODOLOGY

I. Overview of Approach

In order to develop a comprehensive practice guideline focused on alcohol withdrawal management, we utilized a hybrid of established methodologies. In order to develop the scope of the guideline and draft the guideline statements, we followed the Veterans Health Administration and Department of Defense (VA/DoD) Guideline for Guidelines. To rate and refine the draft guidelines, we used the RAND/UCLA Appropriateness Method (RAM), which is a specific process for combining the available scientific evidence with the clinical judgment of experts. Quality of the literature reviewed was rated using standardized rating scales and methodology. The external review process was informed by the VA/DoD method.

ASAM's Quality Improvement Council (QIC) was the oversight committee during the development of the alcohol withdrawal management guideline. The QIC originally chose two Clinical Champions to have a key role in accordance with the VA/DoD model of clinical practice guideline development. An additional two Clinical Champions were added to the project to represent ambulatory settings. The Clinical Champions have a deep knowledge of alcohol withdrawal management and a familiarity with the clinical language and decision making processes involved in this procedure. Additionally, the QIC chose a nine-member Guideline Committee to rate guideline statements. Panel members were selected to

represent a diverse spectrum of clinical practitioners who manage alcohol withdrawal. The QIC also recruited a Guideline Committee Moderator to act as a liaison between the Guideline Committee members and the project team and to lead the discussion during an in-person meeting of the Guideline Committee.

In selecting the panel members, the QIC made every effort to avoid actual, potential, or perceived conflicts of interest that might arise as a result of relationships with industry and other entities among members of the project personnel. All QIC members, Guideline Committee members, and external reviewers of the document were required to disclose all current related relationships, which are summarized in Appendix VII, http://links.lww.com/JAM/A194.

II. Develop the Scope and Key Questions

The QIC was responsible for identifying the guideline scope and intended audience. The Clinical Champions refined the scope by identifying the key clinical questions of greatest importance to the management of alcohol withdrawal. The key questions followed the Population, Intervention, Comparison, Outcome, Time and Setting (PICOTS) framework established by the AHRQ.[24] Indicators of interest in the PICOTS model are listed below:

- Population – The target population was adults 18 years or older with a diagnosis of alcohol withdrawal with or without other health conditions. The management of these other conditions, outside of identification and routine prophylaxis in the context of alcohol withdrawal, were not included, such as alcoholic liver disease and Wernicke encephalopathy.
- Intervention – Pharmacological and non-pharmacological interventions were included. Pharmacotherapies that are not widely available in the United States were excluded (e.g., sodium oxybate [GHB], cannabinoids, chlomethiazole). Off-label medications for alcohol withdrawal management were included. Non-pharmacological interventions included supportive care, nutritional correction, and symptom monitoring and assessment frequency.
- Comparison – All comparative interventions were included if they met criteria for an included intervention.
- Outcome – Outcomes of interest were those clinical outcomes most consequential and immediate to withdrawal including severity of withdrawal syndrome; treatment completion; transfer to more intensive level of care; incidence of seizure, delirium, death and adverse events; and linkage to long-term AUD treatment.
- Time – The duration of time of interest was 5 days from the start of withdrawal. Post-acute prolonged withdrawal or protracted withdrawal was not included. The Clinical Champions identified protracted withdrawal and benzodiazepine-resistant withdrawal as an area that should be included in the future.
- Setting – All clinical settings were included except for home management of withdrawal unless it took place in the United States.

After a face-to-face meeting of the Guideline Committee, feedback indicated that settings and levels of care had not been adequately delineated in the initial set of draft statements. This was largely due to the sparse literature specific to ambulatory settings and the focus of our Clinical Champions on the more moderate-severe end of the spectrum of alcohol withdrawal. Therefore, after the initial Guideline Committee Meeting, the project was expanded to place additional focus on considerations specific to alcohol withdrawal management in ambulatory settings. The expanded literature review and drafting of additional statements particular to ambulatory settings are described below.

III. Conduct a Literature Review

A systematic literature review including the indicators identified by the Clinical Champions was conducted. The literature review included all levels of published research literature, including studies with non-random assignment and case studies. A targeted internet search of gray literature was also conducted, including published and unpublished clinical guidelines on alcohol withdrawal management.

Procedures for review of the academic literature followed PRISMA guidelines for systematic reviews.[25] Articles were identified through searches conducted in four bibliographic databases using pre-defined search terms and selection criteria. Additional articles were identified through forward and reverse citation search of key articles. All databases were searched uniquely.

Searches were conducted for the time-period January 2012 to October 2017 using the following key terms: ''alcohol withdrawal'' or ''delirium tremens'' or ''alcohol-induced hallucinosis'' or ''alcohol-induced psychotic disorder.'' These terms also captured studies on alcohol withdrawal delirium and alcohol withdrawal seizure. Because clinical management encompasses topics from diagnosis to treatment, we did not include search terms for management and instead relied on the screening process to parse useful from peripheral sources. The databases searched were EBSCOhost Medline, Embase, Web of Science Core Collection, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Searches targeted all text fields and were restricted to availability in English and to human participants where available (Medline and Embase). If an article contained a secondary analysis of data from a relevant study, the primary source was included. 2,038 unique records were found. Results of the key term search are documented in Appendix II.

In addition to the systematic search, targeted title and abstract searches were conducted without a time-period limitation on key clinical questions identified by the Clinical Champions. These topics included: withdrawal symptom severity rating scales, comparison of benzodiazepine dose regimens, comparisons among benzodiazepines, comparison of benzodiazepines to anticonvulsants and barbiturates. An additional 70 records were identified. This method was also used to conduct a targeted search of ambulatory management of alcohol withdrawal.

In addition to the scientific literature search, we conducted an internet search for published clinical guidelines or appropriateness statements on alcohol withdrawal management across settings following the IOM process for searching gray literature. The following websites were searched using the on-site search engines with the search terms ''alcohol''

and ''substance abuse'': SAMHSA, VA, WHO, AHRQ, Michigan Quality Improvement Consortium. This search was not time-limited, but where recommending bodies had published updates of guidelines, only the most recent was included. The search yielded 115 records, 11 of which were screened for inclusion. The full search procedure is documented in Appendix II.

Two independent reviewers screened article abstracts and the full text of articles for inclusion. Articles were included if they were about the clinical management of patients with or at immediate risk for developing alcohol withdrawal syndrome. Reasons for exclusion are documented in Appendix II.

The quality of the evidence represented by each research article was rated by two independent reviewers; systematic reviews and other qualitative articles were rated by one reviewer. Comparative trials were evaluated using the Cochrane Risk of Bias tool. Systematic reviews were rated using the AMSTAR-2. Other qualitative articles were evaluated using the AACODS Checklist for Grey Literature. Study methods and results were extracted by two independent reviewers. A document summarizing the findings of the literature review and the quality of sources used was prepared for the Guideline Committee Members to refer to during the statement rating process. Sources were included in the summary document if they were randomized controlled trials (RCT)s, systematic reviews of RCTs, or guidelines based on systematic reviews. In the absence of such evidence, lower quality evidence sources were included.

IV. Develop Draft Guideline Statements

In order to develop the draft statements, a meeting was held with the project team, Clinical Champions, and ASAM/QIC representatives. The list of statements identified the different combinations of clinical indicators in various clinical situations seen in alcohol withdrawal management. A list of definitions for terms used in the statements was also developed.

V. Conduct Panel Ratings

The RAM method involves multiple rounds of rating and a face-to-face meeting between the project team and Guideline Committee. The first round of ratings was conducted remotely. Members of the committee received rating instructions, background material, and the list of potential guideline statements in electronic form. Committee members were asked to consider the appropriateness of each statement individually on a 1–9 scale using the literature review and evidence tables as well as their own best clinical judgment.

Shortly after members of the Guideline Committee received rating materials, the Guideline Committee Moderator contacted each member individually to gather feedback about the guideline which could not be well captured within the rating form. This opportunity was to seek comments on the general structure and organization of the guideline as well as suggested modifications.

Returned Guideline Committee ratings were aggregated and analyzed by IRETA staff. The RAM offers specific guidance for the analysis and classification of guideline statements: a statement is deemed appropriate if the median rating is in the 7–9 range, and no more than one-third of the experts rate the statement outside that range. A statement is deemed inappropriate if the median rating is in the 1–3 range and no more than one-third of the committee rate outside this range. All other statements (those with a median rating of 4–6 or with at least one-third of the experts rating the statement outside the median range) are labeled uncertain.

A two-day in-person Guideline Committee meeting took place in the D.C. area. Prior to this meeting, committee members received the list of guideline statements with the Round 1 rating results indicated for each statement; their own rating, the group median rating, and the frequency of each rating response. Discussion was led by the Guideline Committee Moderator and focused on statements labeled uncertain. The discussion aimed to identify whether the rating results reflected true uncertainty or disagreement in the field versus confusion about the statement's meaning. Qualitative feedback from the Round 1 ratings and individual feedback from IRETA's personal contacts also informed the Guideline Committee meeting discussion, in accordance with the RAM. Statements could be rewritten if the uncertainty was found to be due to confusion. New statements could also be drafted if any important clinical aspects were found to be missing by the Guideline Committee.

The second round of ratings was conducted remotely soon after the meeting. The list of uncertain statements, with the addition of new statements suggested during the meeting, were delivered in electronic form to the committee members. The committee members rated the guideline statements using the same criteria as the first round, considering the appropriateness of each statement. This second round of ratings were then aggregated and analyzed by IRETA staff.

One Guideline Committee member dropped out of participating after the Guideline Committee meeting. This necessitated finding a new method of identifying agreement that does not rely on group sizes that are multiples of three. The RAM manual recommends alternatives, and the Interpercentile Range Adjusted for Symmetry (IPRAS) method was used for the remainder of the project.

At this point, the project expansion took place. The other parts of the project were paused, while the project team conducted an expanded literature review focused on ambulatory considerations in alcohol withdrawal management. An additional two Clinical Champions representing ambulatory settings were recruited and new statements were drafted and rated in two rounds. A second meeting of the Guideline Committee was held remotely via webinar. The project expansion started in August 2018, and by May 2019, we were able to return to the original (although modified) timeline.

In a third round of ratings, committee members rated the agreed-upon appropriate statements from Rounds 1 and 2 on a 1–9 scale using the more stringent criterion of necessity. Appropriateness refers to procedures where the health benefits sufficiently outweigh potential harms such that the procedure is worth doing. Necessity refers to procedures that must be offered to patients fitting a particular clinical description, where it would be improper not to offer the procedure given the magnitude and likelihood of the expected benefit to

the patient. A statement is deemed necessary if the median rating is in the 7–9 range with agreement according to IPRAS. Statements that do not meet these criteria are deemed appropriate but not necessary. The full statement rating table can be found in Appendix VI, http://links.lww.com/JAM/A193.

VI. Drafting the Guideline Document

Recommendations were drafted by the project team by combining the statements identified as clinically appropriate by the Guideline Committee. Recommendations are accompanied by a brief discussion of the evidence or rationale for the statement. ASAM's two prior alcohol withdrawal guidelines were used as an initial framework for the guideline. This first draft of the guideline was reviewed by the Clinical Champions, Guideline Committee Moderator and Guideline Committee Members to ensure content clarity and logical flow of the guideline. A second draft was produced based on this feedback.

During an external review process, ASAM requested feedback on the second draft guideline via email to the ASAM listserv and also posted the draft for public comment on the ASAM website. At the end of the review period, ASAM aggregated the feedback, identified key issues raised, and tracked proposed changes. A two-day in-person meeting including ASAM staff, QIC representatives, the Guideline Committee Chair IRETA took place in Pittsburgh, PA to discuss all of the external review feedback and proposed edits. Feedback was incorporated as appropriate in discussion with those in attendance and in accordance with the evidence. IRETA then produced the Final Guideline Document.

RECOMMENDATIONS

I. Identification and Diagnosis of Alcohol Withdrawal

A. Identification

Recommendation I.1: Incorporate universal screening for unhealthy alcohol use into medical settings using a validated scale to help identify patients with or at risk for alcohol use disorder and alcohol withdrawal.

Recommendation I.2: For patients known to be using alcohol recently, regularly, and heavily, assess their risk of developing alcohol withdrawal even in the absence of signs and symptoms (see II. Initial Assessment for risk factors and risk assessment scales).

Recommendation I.3: For patients who have signs and symptoms suggestive of alcohol withdrawal, assess the quantity, frequency, and time of day when alcohol was last consumed to determine whether the patient is experiencing or is at risk for developing alcohol withdrawal. For this assessment, it may be helpful to:

- Use a scale that screens for unhealthy alcohol use (e.g., Alcohol Use Disorders Identification Test-(Piccinelli) Consumption [AUDIT-PC])
- Use information from collateral sources (i.e., family and friends)
- Conduct a laboratory test that provides some measure of hepatic function

Recommendation I.4: A biological test (blood, breath, or urine) for alcohol use may be helpful for identifying recent alcohol use, particularly in patients unable to communicate or otherwise give an alcohol use history. When conducting a biological test, consider the range of time (window of detection) in which the test can detect alcohol use. Do not rule out the risk of developing alcohol withdrawal if the result of a test is negative.

Discussion. Identifying the presence of or risk for alcohol withdrawal may begin with discovering that a patient has been consuming alcohol recently, heavily and regularly. This recognition can be aided by implementing universal screening for unhealthy alcohol use. Universal screening for unhealthy alcohol use is a recommended primary prevention practice that identifies patients with unhealthy alcohol use and increases early intervention in the development of alcohol-related health conditions and complications, including alcohol withdrawal. This practice has been endorsed by the U.S. Preventive Services Task Force (USPSTF) and is supported by an extensive evidence base.[4,26–29] Unfortunately, universal screening for unhealthy alcohol use has not been widely implemented in medical settings. As of the release of the USPSTF recommendation statement in 2018, it was estimated that only 1 out of 6 patients have ever discussed alcohol use with their physician.[30]

Screening begins with administering a brief, standard assessment to identify patients' unhealthy alcohol use, usually by assessing the amount and frequency of their recent consumption. Based on the results, patients may be identified as at-risk for developing alcohol withdrawal syndrome if they have recently (or plan to) stopped or significantly reduced their alcohol consumption. Standard assessments for unhealthy alcohol use that have been used as an initial screen to identify patients at risk of alcohol withdrawal include the Alcohol Use Disorders Identification Test (AUDIT),[31] CAGE,[32] and Alcohol Use Disorders Identification Test-Piccinelli Consumption (AUDIT-PC).[29,33] For example, in a retrospective case-control study of over 400 hospitalized patients, an initial AUDIT-PC score ≥ 4 identified patients who developed alcohol withdrawal during their stay with 91% sensitivity and 90% specificity.[29]

For patients who present with signs and symptoms suggestive of alcohol withdrawal, these screening instruments can also be helpful in assessing the amount and frequency of recent alcohol consumption. Screening for unhealthy alcohol use also is relevant for identification of and treatment planning for AUD. Clinicians may also gain additional information about a patient's recent alcohol use from other sources including friends and family.[4]

Laboratory tests that measure impairment of hepatic functioning such as the liver enzymes gamma-glutamyl transferase (GGT) and alanine aminotransferase (ALT) can identify recent heavy alcohol use and hence risk for alcohol withdrawal. When using a urine test, GGT is recommended as the marker of heavy alcohol consumption.[34] Clinicians should be aware that laboratory tests provide only partial

information relevant to alcohol withdrawal risk. For example, if a test with a narrow window of detection is negative, the sensitivity of the test to detect risk for alcohol withdrawal will be compromised. However, the inclusion of certain measures of hepatic function have been found to be beneficial in risk determination.[4] For example, the predictive ability of the AUDIT to recognize patients likely to develop alcohol withdrawal is increased when combined with biological markers for unhealthy alcohol use including ALT, GGT, mean corpuscular volume (MCV) and aspartate aminotransferase (AST).[35]

A biological test for alcohol use (blood, breath, or urine) can identify if a patient recently used alcohol, and may be particularly helpful for those who are unable to communicate or otherwise give an alcohol use history. Sometimes, patients may not be sure of the answer, or might be embarrassed to say that they drank very recently. When conducting a biological test, consider the range of time (window of detection) in which the test can detect alcohol use. For example, a breathalyzer can detect alcohol use at an approximate rate of 1 standard drink per hour. In addition, high tolerance to heavy consumption can lead to increased rates of alchol metabolism and clearance rates outside of expected ranges. This means patients can have a negative breathalyzer test result and be at risk for alcohol withdrawal.

Blood alcohol concentration (BAC) combined with clinical signs can indicate risk for withdrawal. Patients with elevated BAC who are not clinically intoxicated should be considered at risk for alcohol withdrawal, as this suggests tolerance to regular heavy use of alcohol.[2,7,36] Clinical guidance has differed regarding the specific BAC that might indicate heightened risk, but estimates include 100 mg/DL,[2] 150 mg/DL,[36] and 200 mg/DL.[7]

A diagnostic assessment for alcohol withdrawal or assessment of risk for developing alcohol withdrawal following cessation of (or reduction in) alcohol consumption is indicated if the clinician is aware that the patient's alcohol use patterns constitute a risk of alcohol withdrawal or if they are displaying signs or symptoms of alcohol withdrawal. See Appendix IV.A., http://links.lww.com/JAM/A192 for a flowchart on the full protocol for identification, diagnosis, initial assessment, level of care determination, and management of Alcohol Withdrawal Scale.

B. Diagnosis

Recommendation I.5: To diagnose alcohol withdrawal and alcohol withdrawal delirium, use diagnostic criteria such as those provided by the Diagnostic and Statistical Manual, 5th Edition (DSM-5). To diagnose alcohol use disorder, use diagnostic criteria such as those provided by the DSM-5.

Recommendation I.6: Alcohol withdrawal severity assessment scales (including the Clinical Instrument Withdrawal Assessment for Alcohol, Revised [CIWA-Ar]) should **not** be used as a diagnostic tool because scores can be influenced by conditions other than alcohol withdrawal.

Recommendation I.7: Do not rule in or rule out the presence of alcohol withdrawal for patients who have a positive blood alcohol concentration.

Discussion. Whenever a clinician is making a diagnosis such as those relevant to this guideline (Alcohol Withdrawal Syndrome, Alcohol Withdrawal Delirium, and Alcohol Use Disorder), they should use standard diagnostic criteria such as The Diagnostic and Statistical Manual-5 (DSM-5; see Boxes 2, 3, and 4). While withdrawal severity assessment scales such as the Clinical Instrument Withdrawal Assessment for Alcohol, Revised (CIWA-Ar) score many of the signs and symptoms listed in the DSM-5 Criteria, these scales are nonspecific regarding the etiology of signs and symptoms and high scores may be the result of the presence of other conditions (e.g., dehydration, fever from infection, Graves' Disease).[2,13,36] Alcohol withdrawal severity assessment scales are designed to assess the signs and symptoms of withdrawal only once a diagnosis has been established.[37]

As a primary criterion for the diagnosis of alcohol withdrawal, asking patients about the timing of a recent cessation of (or reduction in) alcohol use is essential. Sometimes, patients may not be sure of the answer, or might be embarrassed to say that they drank very recently. A biological test for alcohol use can be helpful in this case. Although alcohol withdrawal is associated with the sudden absence of alcohol in the system, it should be noted that minor signs and symptoms can be seen after a significant reduction in alcohol intake if the reduction changes the equilibrium of excitatory vs inhibitory neurochemical signaling (see Box 1) reached during a period of heavy, consistent and prolonged alcohol use.[38] This means patients can have a positive blood alcohol concentration and experience alcohol withdrawal signs and symptoms.

According to DSM-5, alcohol withdrawal delirium should be diagnosed when the primary symptoms of delirium predominate over other withdrawal symptoms.

Given that alcohol withdrawal is itself a diagnostic criterion for alcohol use disorder, patients presenting with alcohol withdrawal symptoms almost certainly also have an alcohol use disorder. It is still recommended that diagnostic criteria such as the DSM-5 should be used to establish such a diagnosis.

C. Differential Diagnosis

Recommendation I.8: As part of differential diagnosis, assess the patient's signs, symptoms, and history. Rule out other serious illnesses that can mimic the signs and symptoms of alcohol withdrawal. Determine if patients take medications that can mask the signs and symptoms of alcohol withdrawal.

Recommendation I.9: Do not rule in or rule out a co-occurring disease, co-occurring mental health disorder, co-occurring substance use disorder, or simultaneous withdrawal from other substances even in the presence of alcohol withdrawal.

Recommendation I.10: Conduct a neurological exam in patients presenting with a seizure to determine etiology. A seizure should only be attributed to alcohol withdrawal if there was a recent cessation of (or reduction in) a patient's alcohol consumption. For patients experiencing new onset seizures or for patients with a known history of alcohol withdrawal seizures showing a new pattern, an electroencephalogram and/or neuroimaging is recommended. For patients with a known history of withdrawal seizure who present with a seizure that can be attributed to alcohol withdrawal, additional

neurological testing and a neurology consult may not be necessary. This includes if the seizure was generalized and without focal elements, if a careful neurological examination reveals no evidence of focal deficits, and if there is no suspicion of meningitis or other etiology.

Recommendation I.11: For patients presenting with delirium, conduct a detailed neurological and medical examination with appropriate testing to rule out other common causes of delirium regardless of the apparent etiology. Attempt to distinguish between hallucinations associated with alcohol withdrawal delirium and alcohol hallucinosis/alcohol-induced psychotic disorder.

Discussion. As with any diagnosis, it is essential to rule out other possible explanations for the constellation of signs and symptoms presented. Because the syndrome can quickly progress in severity, clinicians suspecting alcohol withdrawal should gather information about recent alcohol use history, especially recent cessation of (or reduction in) alcohol use. For example, the DSM-5 notes that medical conditions including hypoglycemia and diabetic ketoacidosis both can mimic alcohol withdrawal, and an essential tremor may mimic tremors associated with alcohol withdrawal. Additionally, signs and symptoms of sedative, hypnotic, or anxiolytic withdrawal are similar to those of alcohol withdrawal, underscoring the importance of assessing for recent alcohol and other substance use. If recent alcohol use and cessation/reduction suggests possible withdrawal, but the patients is not exhibiting any signs or symptoms of withdrawal, clinicians should consider whether the patient is taking any medications that can mask these symptoms, such as beta-adrenergic antagonists (beta-blockers).

While making appropriate differential diagnosis is critical, it should be noted that alcohol withdrawal is often seen in conjunction with other health conditions, including mental health disorders, substance-related disorders, or simultaneous withdrawal from other substances besides alcohol. Therefore, clinicians should not discount the possibility of co-occurring conditions once a diagnosis of alcohol withdrawal has been made.

Patients presenting with seizure(s) should be provided a neurological exam and medical evaluation to determine seizure etiology.[2,36,41] The exam and evaluation should include a patient's history of marked cessation of (or reduction in) alcohol use. An alcohol withdrawal-related seizure should only be diagnosed if there has been a clear history of marked cessation of (or reduction in) alcohol use in the 24 to 48 hours prior to the seizure.[2]

Patients presenting with a new onset seizure should be provided a full neurologic examination including brain imaging with possible lumbar puncture and electroencephalogram (EEG). A thorough neurological examination and EEG should also be provided to patients with a new pattern of alcohol withdrawal related seizures.[2,42] However, if a patient has a known history of alcohol-withdrawal related seizures that are clearly attributed to alcohol withdrawal, it may not be necessary to do additional neurological testing. If a patient's alcohol use history and time course of the seizure are inconsistent with an alcohol withdrawal seizure or if the neurological examination identifies focal neurological deficits, meningitis, fever, status epilepticus, recent head trauma, or other possible causes of seizure, further testing should be completed to determine etiology.

Patients presenting with delirium should be provided a neurological exam and medical evaluation to determine etiology. The history and examination should provide a clear understanding of the relationship between cessation or reduction of alcohol intake and the onset of withdrawal signs and symptoms to eliminate other reasons for delirium.[2] The onset of alcohol withdrawal delirium typically occurs 24–48 hours after cessation of (or reduction in) alcohol use but can develop as many as 3–5 days later. If a patient's alcohol use history and the time course of delirium are inconsistent with alcohol withdrawal delirium or if there is not suspicion of substance-induced psychotic disorder, hypoglycemia, diabetic ketoacidosis, or other possible causes of delirium further testing should be completed to determine etiology.[43]

Patients may present with hallucinosis, which is hallucinations that occur in the absence of other clinically prominent withdrawal signs and symptoms such as clear delirium. Hallucinosis consist of primarily auditory hallucinations but may include visual hallucinations and delusions.[44] It is unclear if alcohol hallucinosis is part of alcohol withdrawal syndrome or if the hallucinations are a complication of chronic alcohol use unrelated to withdrawal. Alcohol hallucinosis is currently diagnosed as Alcohol-Induced Psychotic Disorder in the DSM-5. Clinicians should attempt to

Box 1: Neuroscience of Alcohol Withdrawal

The ingestion of ethanol does several things to the human body. But the most important in relation to the development of alcohol withdrawal is the effect of its binding to the ϒ-aminobutyric acid receptor A(GABA-A). At low levels of ethanol, we see the predicable GABA-A effects of decreased anxiety, decreased inhibition and an altering of the motor centers. However, if ethanol is used for an extended time, and at higher levels, we begin to see alterations in the signaling of the extended amygdala. In particular, prolonged alcohol use causes an upregulation of N-methyl-D-Aspartate receptors (NMDAr) and a downregulation of GABA-A. The ultimate result is that if the ethanol is abruptly stopped, there is an imbalance of excitatory vs inhibitory signals. With a high glutaminergic (excitatory) state and a low GABAergic (inhibitory) state, we see the typical signs of alcohol withdrawal; tremor, seizures, nausea and delirium. The major excitatory signal caused by excess glutamate and norepinephrine and the lower GABA-A signaling resulting from both a decrease in gamma-aminobutyric acid and a change in the GABA-A receptor binding characteristics. While the above explains (in very condensed form) the reasons for the clinical features of alcohol withdrawal, we can also glean why certain interventions may be helpful in abating the symptoms. For example, the use of benzodiazepines and certain anti-seizure medications with GABAergic activity (carbamazepine and valproic acid) can be used to abate the symptoms of alcohol withdrawal by reversing the GABA-A deficiency. When these are not sufficient, we can use adjuvants (alpha2-adrenergic agonists [A2AAs]) that can decrease the over activity of the excitatory molecule glutamate or one with both mechanisms of action (phenobarbital). Given the complexity of an individual's genetics, epigenetics, and patterns of use, we are left with a variable response to any single medication. This is why we have discussed many evidence-based options for the treatment of such a complex syndrome.

Box 2: DSM-5 Criteria for Alcohol Withdrawal

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B. Two (or more) of the following, developing within several hours to a few days after the cessation of (or reduction in) alcohol use described in Criterion A:
1. Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 bpm)
2. Increased hand tremor
3. Insomnia
4. Nausea or vomiting
5. Transient visual, tactile, or auditory hallucinations or illusions
6. Psychomotor agitation
7. Anxiety
8. Generalized tonic-clonic seizures
C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupation, or other important areas of functioning.
D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

distinguish between hallucinosis and alcohol withdrawal delirium when making a diagnosis, although this may not always be possible during the early stages of withdrawal.[2] If hallucinations persist beyond 72 hours of onset, the more likely diagnosis is alcohol-related psychotic disorder. While alcohol-induced disorders are not a focus of this Guideline, some general guidance is offered in the section VI.C: Alcohol-Induced Psychotic Disorder.

Box 3: DSM-5 Criteria for Alcohol Withdrawal Delirium (generic criteria for delirium in the presence of heavy and prolonged alcohol use)

A. A disturbance in attention (i.e., reduced ability to focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
B. Disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
D. The disturbances in Criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.
Specify:
Substance withdrawal delirium
a. This diagnosis should be made instead of substance withdrawal when the symptoms in Criteria A and C predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

Box 4: DSM-5 Criteria for Alcohol Use Disorder

A. A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects
4. Craving, or a strong desire or urge to use alcohol
5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol
7. Important social, occupations, or recreational activities are given up or reduced because of alcohol use
8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol
10. Tolerance, as defined by either of the following:
i. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect
ii. A markedly diminished effect with continued use of the same amount of alcohol
11. Withdrawal, as manifested by either of the following:
i. The characteristic withdrawal syndrome for alcohol
ii. Alcohol (or closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

II. Initial Assessment of Alcohol Withdrawal

A. General Approach

Recommendation II.1: First, determine whether a patient is at risk of developing severe and/or complicated alcohol withdrawal or complications from alcohol withdrawal. In addition to current signs and symptoms, a validated risk assessment scale and an assessment of individual risk factors should be utilized. (See Table 1. Alcohol Withdrawal Severity).

Recommendation II.2: A history and physical examination should be included as part of the comprehensive assessment process. Clinicians should conduct this examination themselves or ensure that a current physical examination is contained within the patient's medical record.

Recommendation II.3: Additional information about risk factors can be gleaned by interviewing family, friends, and caregivers about a patient's history of alcohol withdrawal, seizures, and delirium, as appropriate. Whenever possible in non-emergent situations, obtain written or verbal consent from the patient before speaking with or consulting with collateral sources.

Recommendation II.4: Clinicians should seek information about the time elapsed since the patient's cessation of (or reduction in) alcohol use. The timeline of symptom onset

and severity helps determine the risk window for developing severe or complicated withdrawal.

Discussion. It is common for recommendations about the initial assessment for managing alcohol withdrawal to focus on evaluating current signs and symptoms rather than the risk of developing serious forms of the syndrome. However, signs and symptoms can escalate quickly and the trajectory of alcohol withdrawal can vary considerably among patients. As the most severe presentations of alcohol withdrawal are life threatening, orienting the initial assessment toward evaluating risk as opposed to current presentation is recommended. In considering patient risk, clinicians should assess their risk of *severe* withdrawal, *complicated* withdrawal (used in this guideline to describe withdrawal-related seizures or alcohol withdrawal delirium), or *complications of* withdrawal, which refers to a potentially life-threatening exacerbation of existing medical or psychiatric conditions.

A detailed history and physical exam should be conducted as part of the initial assessment of alcohol withdrawal and can be an extension of the process of differential diagnosis. The history and physical exam should identify current withdrawal severity, risk factors for developing life-threatening symptoms and potentially complicating conditions. In the event a patient cannot provide a clear history, interviewing family, friends, and caregivers about risk factors is appropriate. Providers should follow their setting/state rules on obtaining written or verbal consent or release of information prior to consulting with collateral sources. Individual risk factors are described in the following section. Also discussed in the following section are the use of questionnaires developed to assess risk of severe or complicated withdrawal and to assess current signs and symptoms of withdrawal.

When evaluating risk, clinicians should consider the time elapsed since the patient's cessation of (or reduction in) alcohol use.[45] Signs and symptoms of alcohol withdrawal typically begin 6–24 hours after cessation of (or reduction in) alcohol use.[2] Early identification and medication management can reduce the risk of progression to severe or complicated alcohol withdrawal syndromes.[46] Early withdrawal signs and symptoms may include anxiety, sleep disturbances, anorexia, vivid dreams, headache, nausea, tachycardia, hyperactive reflexes, sweating, elevated blood pressure and hyperthermia.[2] Seizures may begin as early as 8 hours after cessation of (or reduction in) alcohol use and can continue for up to 48 hours with peak activity occurring around 24 hours.[2] Hallucinations develop within 12–24 hours following cessation of (or reduction in) alcohol use and typically resolve within 24–48 hours if other signs indicative of withdrawal delirium do not emerge. The onset of alcohol withdrawal delirium appears between 72 and 96 hours after a patient's last drink and can last as short as a few hours, but usually for 2–3 days.[2]

Not all patients progress through these stages sequentially. For example, a seizure may occur in the absence of other clinically prominent alcohol withdrawal signs or symptoms. In particular, elderly patients may have a different timeline of development.[2] Concomitant use of alcohol and other sedative hypnotics can also change the presentation of withdrawal signs and symptoms.[38] See Appendix IV.A., http://links.lww.com/JAM/A192 for a flowchart on the full protocol for identification, diagnosis, initial assessment, level of care determination, and management of Alcohol Withdrawal Scale.

B. Risk Factors for Severe or Complicated Withdrawal

Recommendation II.5: Assess for the following factors associated with increased patient risk for complicated withdrawal or complications of withdrawal:

- History of alcohol withdrawal delirium or alcohol withdrawal seizure
- Numerous prior withdrawal episodes in the patient's lifetime
- Comorbid medical or surgical illness (especially traumatic brain injury)
- Increased age (>65)
- Long duration of heavy and regular alcohol consumption
- Seizure(s) during the current withdrawal episode
- Marked autonomic hyperactivity on presentation
- Physiological dependence on GABAergic agents such as benzodiazepines or barbiturates

Recommendation II.6: The following individual factors *may* increase a patient's risk for complicated withdrawal or complications of withdrawal:

- Concomitant use of other addictive substances
- Positive blood alcohol concentration in the presence of signs and symptoms of withdrawal
- Signs or symptoms of a co-occurring psychiatric disorder are active and reflect a moderate level of severity

Recommendation II.7: Patients' risk for complicated withdrawal or complications of withdrawal is increased by the presence of multiple risk factors.

Recommendation II.8: In general, clinicians may consider patients at risk of severe or complicated withdrawal if they are experiencing at least moderate alcohol withdrawal on presentation (e.g., CIWA-Ar score $\geq$10).

Discussion. Several individual risk factors were deemed meaningful by the Guideline Committee based on an analysis of the existing empirical literature combined with their clinical experience. There is strong empirical and clinical support for a history of alcohol-related seizures or delirium as predictive of future incidences of severe withdrawal.[28,47] A systematic review and meta-analysis of 15 studies of predictors of severe alcohol withdrawal concluded that prior alcohol withdrawal delirium, prior withdrawal-related seizure, prior severe alcohol withdrawal, lower platelet count, and higher alanine aminotransferase (ALT) were associated with a significantly higher incidence of alcohol withdrawal-related seizure or alcohol withdrawal delirium.[48]

Consistent with the results of the 2014 systematic review, the idea that prior incidences of alcohol withdrawal delirium and seizure should be considered important risk factors for severe alcohol withdrawal has been echoed in numerous clinical guidelines and review articles.[12,36,49–51]

Repeated episodes of alcohol withdrawal syndrome also become progressively more severe as the result of increased neuronal excitability and sensitivity, a phenomenon known as the kindling effect.[4]

There is a lack of consensus about additional individual risk factors that contribute to severe alcohol withdrawal. Although the previously mentioned systematic review failed to find an association between other individual risk factors and risk of severe alcohol withdrawal, the review's primary finding was that ''prediction of severe alcohol withdrawal is highly variable, and that few demographic, clinical, or biochemical parameters are consistently predictive''.[48 (p2674)]

The presence of a severe medical illness has been reported to precipitate severe alcohol withdrawal and to increase the risk of withdrawal seizures and delirium.[4,7] SAMHSA's Treatment Improvement Protocol (TIP) 45 on withdrawal management,[4] as well as a number of other published guidelines,[2,7,36] recommend that comorbid medical or surgical illness be considered a significant risk factor for complicated withdrawal or complications of alcohol withdrawal.

Older age may heighten a patient's risk of severe alcohol withdrawal, although advanced age may simply be correlated with the presence of complex comorbid health conditions.[4,7]

The value of assessing a patient's alcohol use pattern or amount has been contested in the literature. Some note the duration of heavy drinking has not been useful in triaging patients,[2] others have argued the opposite.[36,44,49] As with advanced age, a longer duration of alcohol use may simply be correlated with more significant comorbid health issues, which can lead to complications of alcohol withdrawal.

Patients who have experienced a seizure as part of the current withdrawal episode, but prior to the clinical assessment, should be considered at high risk of complicated withdrawal. Following an alcohol withdrawal seizure, a patient is at increased risk for another seizure and progression to alcohol withdrawal delirium.[2,4,51,52]

Although heart rate and rhythm are often signs measured to assess alcohol withdrawal, there is disagreement about the predictive value of heart rate for identifying risk of withdrawal. Some of the literature suggests clinicians consider marked autonomic hyperactivity (measured by heart rate) to be an indication of severe withdrawal,[2] while others argue that an elevated heart rate does not identify the risk of severe withdrawal.[42]

Concomitant physiological dependence on central nervous system depressants such as benzodiazepines and barbiturates has also been suggested as a risk factor for complicated alcohol withdrawal.[7,36,51] Medication management may also be complicated as individuals taking sedative-hypnotic medications exhibit tolerance to benzodiazepines and should be monitored closely for appropriate dose if prescribed benzodiazepines for withdrawal (see IV.A: Monitoring).[53]

Additional individual risk factors were deemed *potentially* meaningful by the Guideline Committee based on an analysis of the existing empirical literature combined with their clinical experience. In terms of the value of concomitant substance use as a predicator of complicated withdrawal or complications of alcohol withdrawal, the Guideline Committee emphasized that the risk varies significantly based on the type of substance used, as well as patterns of use. However, concomitant substance use may play a role in the development of life-threatening presentations of the syndrome.[7,51]

An indication of risk for severe or complicated alcohol withdrawal is the presence of alcohol withdrawal signs and symptoms while having a positive blood alcohol concentration (BAC).[4] Although alcohol withdrawal is associated with the sudden absence of alcohol in the system, minor signs and symptoms can be seen after a significant reduction in alcohol intake if the reduction alters the equilibrium of excitatory vs inhibitory neurochemical signaling (see Box 1) reached during a period of heavy, consistent and prolonged alcohol use.[38] When using a breathalyzer, clinicians may wish to repeat their measurement serially to follow the level and course of intoxication.[39,40]

Withdrawal can complicate the treatment of an underlying mental health disorder. A patient whose co-occurring psychiatric disorder symptoms are active may need specialist treatment.

Moderate to severe withdrawal at baseline (e.g., CIWA-Ar $\geq$ 10) has been identified as a risk factor for developing more severe withdrawal in inpatient settings.[54] The Guideline Committee also agreed that risk for complicated withdrawal or complications of withdrawal is increased when multiple risk factors are present.

C. Risk Assessment Tools

Recommendation II.9: Clinicians can consider the use of a tool such as *The ASAM Criteria* Risk Assessment Matrix to assess a patient's risk of severe or complicated alcohol withdrawal as well as potential complications of withdrawal.

Recommendation II.10: The following scales can be helpful for assessing for the risk of severe alcohol withdrawal:

- Prediction of Alcohol Withdrawal Severity Scale (PAWSS)
- Luebeck Alcohol-Withdrawal Risk Scale (LARS)

Discussion. The Risk Assessment Matrix is described in *The ASAM Criteria*[12] and offers a multidimensional risk assessment for patients with or at risk for developing alcohol withdrawal. It classifies patient risk on a scale of 0–4 across six dimensions and provides decision rules to recommend appropriate treatment interventions for patients at each level.

Scales have been developed to identify patients at risk of developing severe or complicated alcohol withdrawal, including the Luebeck Alcohol Withdrawal Risk Scale (LARS)[55] and Prediction of Alcohol Withdrawal Severity Scale (PAWSS).[28] The LARS was specifically designed to predict severe alcohol withdrawal among patients without significant comorbid medical illness. A prospective study of 100 patients in a hospital psychiatric ward showed that a LARS score $\geq$17 significantly differentiated patients with severe withdrawal from patients with mild to moderate withdrawal with a sensitivity of 100% and a specificity of 88%.[55] The PAWSS is a severity scale designed specifically for predicting risk of developing complicated alcohol withdrawal (defined as a

CIWA-Ar score ≥15) in the medically ill, validated by prospective studies comparing the PAWSS with retrospective chart review and with the CIWA-Ar.[28,47] The PAWSS includes an initial screener question (''Have you consumed any amount of alcohol within the last 30 days'' or ''did the patient have a positive BAL upon admission'') and can be used with patients who are not currently exhibiting signs of withdrawal. The authors identified a threshold score which identified patients who later scored ≥15 on the CIWA-Ar during their hospital stay with 93.1% sensitivity and 99.5% specificity.[47]

These scales and their associated features and evidence base are summarized in Appendix III.

D. Symptom Assessment Scales

Recommendation II.11: A validated instrument should be used to assess alcohol withdrawal severity.

Recommendation II.12: Assess the risk for scores on a withdrawal severity assessment scale to be confounded with causes other than alcohol withdrawal. If risk factors are present, interpret the results of scales with caution. Use a scale that relies more on objective signs of withdrawal (autonomic activity) if a patient has difficulty communicating about their symptoms. See Appendix III for the features of different scales.

Recommendation II.13: A validated withdrawal severity assessment instrument can be used as part of risk assessment. A high initial score can indicate risk of developing severe or complicated withdrawal, although scores should not be the only information used to predict patient risk.

Discussion. A patient's current withdrawal symptom severity should be assessed using a structured withdrawal assessment scale. Scores on a symptom assessment scale can be confounded with causes other than alcohol withdrawal. For example, scores can be falsely elevated due to comorbid conditions (e.g. fever from infection, concurrent withdrawal from another substance) and falsely suppressed due to the use of certain medications (e.g., beta-blockers and other sympatholytic drugs).[2] If risk factors are present, interpret the results of symptom assessment scales with caution. Some scales require self-report from patients about their symptoms and cannot be administered to patients with a communication difficulty, those who are experiencing symptoms of delirium, or those who are critically ill. In these instances, use a withdrawal symptom assessment scale that relies more on objective signs of withdrawal (autonomic activity). These scales and their associated features and evidence base are summarized in Appendix III.

Currently, there is insufficient evidence to prefer one scale to another; the choice instead depends on clinician preference. The most commonly discussed and utilized scale is the CIWA-Ar.[12,38,56,57] The CIWA-Ar was designed to measure the severity of alcohol withdrawal for research studies.[37] It is a 10-item standardized scale with demonstrated validity and interrater reliability. The CIWA-Ar itself does not offer score ranges categorizing symptom severity. The developers of the CIWA-Ar suggested different interventions for scores of <10, 10–20, and > 20, but these were based on the clinical experience of the authors and not empirical data.[37] Numerous guidelines and review articles offer guidance about the appropriate intervention for different ranges of CIWA-Ar scores.[4,41,58]

Throughout this document, we provide examples for withdrawal severity using the CIWA-Ar, although other scales can be used. Regardless of the instrument used, there is a wide variety in the literature and in practice as to which scores best delineate mild, moderate and severe withdrawal. Classification of withdrawal severity is ultimately up to the judgment of clinicians and clinical programs might choose reference ranges based on their particular patient population or capabilities.

See Table 1. Alcohol Withdrawal Severity for the categorization of withdrawal severity used in this guideline.

Despite its widespread use, clinicians should be aware of the limitations of the CIWA-Ar. It requires clinician training for reliable administration and is criticized for the time it takes to administer.[57,59] It also requires patients to self-report about symptoms including nausea/vomiting, anxiety, tactile and auditory disturbances, and headache and can be difficult, if not impossible, to administer to patients experiencing severe or complicated withdrawal or those who are critically ill.

While the CIWA-Ar is the most well-known and widely adopted alcohol withdrawal severity scale, modifications and alternative scales have been developed and evidence of their validity and reliability is emerging. The Newcastle Alcohol Withdrawal Scale is a modified version of the CIWA-Ar which relies more on objective signs of withdrawal.[60] The Brief Alcohol Withdrawal Scale (BAWS) was developed as a shorter and more objective method to assess alcohol withdrawal signs and symptoms and early evidence has demonstrated favorable sensitivity and specificity compared with the CIWA-Ar.[59] The Short Alcohol Withdrawal Scale (SAWS), a 10-item instrument designed to be self-administered by patients, has been validated in ambulatory settings.[61]

The CIWA-Ar and similar scales are not designed to assess the risk for developing severe withdrawal, but they are commonly called upon for this task. The Guideline Committee noted that withdrawal assessment scales can provide some indication of risk in that a patient's current signs and symptoms can provide valuable (although partial) information about their risk of severe or complicated withdrawal. However, it should be stressed that symptom assessment scales cannot indicate alcohol withdrawal risk if the patient is not currently experiencing signs or symptoms of withdrawal.[58] One observational study using the Newcastle Alcohol Withdrawal Scale to guide treatment found that hospital patients scoring >15 at baseline were at higher risk of severe withdrawal if they did not receive medication.[60]

Although these scales have generally not been found to be superior to the CIWA-Ar at identifying the potential risk of developing severe or complicated withdrawal, they may be more feasible to administer than the CIWA-Ar in some inpatient settings. The Guideline Committee considered each scale to be an acceptable option for assessing hospitalized patients after diagnosis of alcohol withdrawal.

E. Identify Concurrent Conditions

Recommendation II.14: When assessing for concurrent medical conditions, screen patients for medical conditions that could affect the course of alcohol withdrawal or treatment of alcohol withdrawal, as well as common chronic conditions that are associated with alcohol use disorders.

Recommendation II.15: A pregnancy test should be obtained for women of childbearing potential. For information on managing pregnant patients, see section VII.F: Patients who are Pregnant.

Recommendation II.16: In settings with access to laboratory testing, clinicians should conduct and/or arrange for a comprehensive metabolic profile (CMP) or basic metabolic profile (BMP), a hepatic panel, and a complete blood count with differential to assess a patient's electrolytes, liver functioning, renal functioning and immune functioning. In a setting with limited access to laboratory testing, clinicians should obtain results when practical to assist with treatment planning decisions. Address any nutritional deficiencies detected.

Initial screening may also include laboratory tests for:

- Hepatitis
- Human Immunodeficiency Virus (HIV) (with consent)
- Tuberculosis

Recommendation II.17: Assess patients for polysubstance use and be prepared to treat other potential withdrawal syndromes. To assess a patient's other substance use, it may be helpful to:

- Use a validated scale that addresses other substance use, such as the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)
- Conduct a urine or other toxicology test to detect other substance use
- Utilize information from collateral sources when possible (i.e., family and friends)

Recommendation II.18: Do not delay the initiation of treatment if alcohol withdrawal is suspected but laboratory test results are not available at the treatment setting or the results are pending.

Recommendation II.19: Assess patients for concurrent mental health conditions, including a review of their mental health history, to determine their mental health treatment needs. Consult with any mental health professionals caring for such patients. Obtain written or verbal consent before consultation whenever possible in non-emergent situations. The Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder (GAD-7) scales can be helpful to screen for mental health disorders. Be cautious when diagnosing a new primary mental health disorder during acute withdrawal, as it can be difficult to differentiate between substance-induced signs and symptoms and primary psychiatric disorders.

Recommendation II.20: Evaluate active suicide risk as part of the initial patient assessment.

Discussion. Clinicians should thoroughly assess patients for concurrent physical and mental health conditions that may a) complicate the course of alcohol withdrawal and/or b) necessitate their own treatment interventions. There is not a standard medical evaluation process for patients with, or at risk for, alcohol withdrawal, but it should include a history and physical examination and an assessment for concurrent mental health conditions. The Guideline Committee recommends that clinicians be knowledgeable about common chronic conditions associated with alcohol use disorders in order to screen for likely concurrent medical conditions. Common chronic conditions associated with alcohol use disorders include high blood pressure, heart disease, liver disease and digestive problems.

Conditions that may be exacerbated by the increased autonomic hyperactivity associated with withdrawal, such as cardiac illness, should be identified early for aggressive autonomic symptom prevention. It should also be identified whether patients take medications that may suppress autonomic symptoms and therefore mask withdrawal severity, such as beta-adrenergic antagonists. Conditions associated with impaired liver functioning should also be identified as they may influence medication choice and/or dosing amounts. Medical conditions that prevent the use of oral medication should also be identified, as parenteral administration of medication is not available in all treatment settings.

Because pregnancy influences alcohol withdrawal management decisions and pregnancy tests are typically available at most settings with rapid results, the Guideline Committee recommended that clinicians conduct a pregnancy test for patients of childbearing potential with suspected alcohol withdrawal. However, it should be noted that if a patient is presenting with signs and symptoms of alcohol withdrawal and pregnancy status is unknown and a test is not immediately available, alcohol withdrawal management should not be delayed.

To aid in the identification of concurrent medical conditions, laboratory testing may be helpful. The decision to conduct routine laboratory testing and what to test for should be informed by the patient's signs and symptoms, known concurrent medical conditions, and availability. At a minimum, the Guideline Committee recommended clinicians conduct and/or arrange for a comprehensive metabolic profile (CMP) or basic metabolic profile (BMP), a hepatic panel, and a complete blood count with differential to assess a patient's electrolytes, liver functioning, renal functioning, and immune functioning. In addition, laboratory tests for hepatitis, Human Immunodeficiency Virus (HIV), and tuberculosis may be considered if indicated. In addition to identifying medical conditions with a high rate of co-occurrence with alcohol withdrawal, the results of some tests, primarily for liver functioning, might guide the choice of medication for alcohol withdrawal as discussed in later sections on pharmacotherapy.

Hospitalized patients are a unique population because clinicians have greater access to laboratory tests and rapid results. In an ambulatory setting, clinicians may have less access to laboratory tests and be less able to obtain rapid results.[62] Therefore, in ambulatory settings, the Guideline Committee recommends that in general, laboratory testing should be done when practical. However, clinicians should not

delay treatment if testing is unavailable or if test results are pending.

As discussed previously, concomitant substance use may play a role in the development of life-threatening presentations of alcohol withdrawal syndrome.[7,51] Of particular concern is concurrent physiological dependence or withdrawal from other sedative hypnotics as it can affect symptom presentation and response to commonly used withdrawal medications. Clinicians can use a screening questionnaire to begin the identification process. Numerous validated scales are available for assessing a patient's substance use patterns. A recommended option is The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), developed by the World Health Organization.[63,64] While the ASSIST takes longer to complete than many available scales, it is more comprehensive in the identification of polysubstance use while many others scales focus on a substance use broadly.

Also discussed previously are the complications that can be caused by alcohol withdrawal for managing a patient's underlying mental health problem and vice versa. A mental health condition is not thought to increase risk for severe, complicated, or complications of withdrawal. However, given the shared symptomology of even mild forms of withdrawal, such as anxiety, agitation and sleep problems, with common mental health disorders, determining the etiology of symptoms and judging appropriate response to medication for alcohol withdrawal may be complicated.[4] A review of the patient's medical record can reveal primary diagnoses and if the patient is currently under the care of a mental health professional, that individual should be consulted. Providers should follow their setting/state rules on obtaining written or verbal consent or release of information prior to consultation.

Clinicians can also consider the use of a standardized screening instrument for depression and anxiety, but they should not diagnose a new primary mental health disorder during the acute withdrawal period.[46,47] Both the Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder (GAD-7) questionnaires ask a patient to assess their symptoms over the prior two weeks and recall can be affected by current symptom state. Clinicians should also evaluate active suicide risk as part of the initial patient assessment.

III. Level of Care Determination

A. General Approach

Recommendation III.1: Level of care determination should be based on a patient's current signs and symptoms; level of risk for developing severe or complicated withdrawal or complications of withdrawal; and other dimensions such as recovery capital and environment. Alcohol withdrawal can typically be safely managed in an ambulatory setting for those patients with limited or mitigated risk factors. Patients with low levels of psychosocial support or an unsafe environment may benefit from a more intensive level of care than is otherwise indicated.

Recommendation III.2: Patients with active risk of suicide should be treated in a setting equipped to manage patients at risk of suicide, which often necessitates admission to an inpatient psychiatric setting that also provides withdrawal management services.

Discussion. The ASAM Criteria provides comprehensive guidance on determining the appropriate level of care for patients in need of withdrawal management. Level of care determinations are based on an evaluation of the expected risks and benefits of treatment within each setting. A central tenet of *The ASAM Criteria* is that patients should be matched with the least intensive level of care in which they can be safely and effectively treated. In the absence of indications for inpatient treatment, which will be described in following sections, most patients with alcohol withdrawal can be safely and effectively managed in ambulatory settings.[65–67] One 1995 estimate found that approximately 10% of patients with alcohol withdrawal syndrome require inpatient treatment.[68] In general, patients benefit from being treated in less restrictive settings that minimize disruptions to family life, housing and employment, and reduce costs. One RCT found that patients with mild-to-moderate alcohol withdrawal assigned to outpatient treatment had faster resolution of withdrawal compared to inpatient treatment.[66] Ambulatory withdrawal management should be preferred in the absence of any indications for inpatient treatment.[51]

Inpatient management is indicated for some patients. Lack of 24-hour monitoring and distance to life saving medical intervention means that some patients with or at risk for developing severe or complicated withdrawal or complications of alcohol withdrawal could experience great harm if treated in an ambulatory setting. Ambulatory treatment is most appropriate for patients who have a low risk of developing severe or complicated withdrawal,[69,70] which may include patients with mild or moderate withdrawal syndrome.[71] Some low-risk patients may benefit from treatment in an inpatient setting. For example, patients with an absence of or unreliable support network may benefit from a more intensive level of care.[21,49] See Appendix IV.A., http://links.lww.com/JAM/A192 for a flowchart on the full protocol for identification, diagnosis, initial assessment, level of care determination, and management of Alcohol Withdrawal Scale.

B. Level of Care Determination Tools

Recommendation III.3: *The ASAM Criteria* Risk Assessment Matrix and withdrawal severity scales can be helpful for determining the appropriate level of care for managing patients in alcohol withdrawal. Most withdrawal severity scales reflect current signs and symptoms and should not be used alone to determine level of care.

Discussion. The ASAM Criteria provide a guide for clinicians treating patients experiencing alcohol withdrawal or seeking alcohol withdrawal management services. It accounts for current signs and symptoms and identifies potential risks for complicated withdrawal. This framework allows clinicians the ability to make level of care determinations based on the most appropriate needs for each patient. *The ASAM Criteria* encourages the use of symptom assessment scales such as the CIWA-Ar score in the decision making process; however, it

also emphasizes that symptom severity should not be used alone to make level of care determinations.

The ASAM Criteria measures a patient's risk of developing severe or complicated withdrawal or complications of alcohol withdrawal by utilizing a multidimensional assessment that determines a patient's risks and strengths based on six dimensions. These dimensions include: (1) acute intoxication and/or withdrawal potential, (2) biomedical conditions and complications, (3) emotional, behavioral, or cognitive conditions and complications, (4) readiness to change, (5) relapse, continued use, or continued problem potential, and (6) recovery/living environment. Using the multidimensional assessment, clinicians provide a risk rating for each dimension and an overall rating that allow them to identify the patient's treatment needs and level of care most appropriate to meet those needs.

The ASAM Criteria provides a comprehensive set of criteria for appropriate placement in one of five levels of care:

- Level 1-WM: Ambulatory withdrawal management without extended on-site monitoring
- Level 2-WM: Ambulatory withdrawal management with extended on-site monitoring
- Level 3.2-WM: Clinically managed residential withdrawal management
- Level 3.7-WM: Medically monitored inpatient withdrawal management
- Level 4-WM: Medically managed intensive inpatient withdrawal management

See *The ASAM Criteria* for a detailed description of services available in each level of care.

C. Considerations for Ambulatory vs Inpatient Management

While there are five distinct levels of care for withdrawal management defined by *The ASAM Criteria*, much of the research on patient placement evaluates factors indicating (or contraindicating) placement in an ambulatory or inpatient treatment setting. These settings align with the following ASAM levels of care:

- Ambulatory
  - Level 1-WM: Ambulatory withdrawal management without extended on-site monitoring
  - Level 2-WM: Ambulatory withdrawal management with extended on-site monitoring.
- Inpatient
  - Level 3.2-WM: Clinically managed residential withdrawal management
  - Level 3.7-WM: Medically monitored inpatient withdrawal management
  - Level 4-WM: Medically managed intensive inpatient withdrawal management

So as not to duplicate *The ASAM Criteria*, and in the interest of identifying consensus and strength of evidence where it exists, this Guideline will largely focus on determining appropriate placement criteria in these two categories of withdrawal setting: ambulatory and inpatient. However, due to increasing interest in office-based alcohol withdrawal management by specialty and non-specialty clinicians, the significant difference in monitoring levels afforded by the two ambulatory settings, and at the request of the Guideline Committee, the Guideline will distinguish between considerations for Level 1-WM and Level 2-WM settings in this section.

Level 1-WM is ambulatory withdrawal management without extended on-site monitoring. It can be carried out in a physician's office, by a home health care agency, or addiction treatment facility. Level 2-WM is ambulatory withdrawal management with extended on-site monitoring. It can be carried out in structured outpatient settings such as a day hospital setting, a general health care or mental health facility, or an addiction treatment facility. Level 2-WM is an organized service with the capacity to provide regular medical assessments and monitor alcohol withdrawal syndrome progression. They may also have access to psychological or psychiatric treatment (see *The ASAM Criteria* for additional details).

Level of care determination is organized around risk-benefit principles, where an appropriate level of care is one in which the expected benefits of treating a patient at a particular level of care are outweighed by the risks. More intensive levels of care are appropriate for patients at increased risk of harm. This means that if Level 1-WM is not appropriate for a particular patient, Level 2-WM may still be appropriate. However, if Level 2-WM is not appropriate, then Level 1-WM is also not appropriate. This patient should be treated in an inpatient setting. The guideline does not currently make recommendations regarding placement within the three levels of inpatient settings: Level 3.2-WM, Level 3.7-WM, and Level 4-WM.

It should be noted that a patient's refusal or inability to attend a recommended level of care should not delay or preclude treatment at a level of care they are able to attend.[12]

Recommendation III.4:

Discussion

Withdrawal severity

Patients experiencing signs and symptoms of mild alcohol withdrawal such as mild or moderate anxiety, sweating and insomnia, but no tremor (generally associated with a CIWA-Ar <10) can be managed in Level 1-WM or Level 2-WM settings.[2,39,62,72] While providing withdrawal management is within the scope of practice for many clinicians including primary care physicians, an addiction specialist can be consulted, if needed.[72]

Patients experiencing signs and symptoms of moderate alcohol withdrawal such as moderate anxiety, sweating, insomnia, and mild tremor (generally associated with a CIWA-Ar 10–18) can be managed in Level 2-WM settings. Moderate withdrawal is not a reason to exclude patients from Level 1-WM settings, but the risk for such patients should be carefully considered. It should only be undertaken by experienced clinicians.

Patients experiencing signs and symptoms of severe withdrawal such as severe anxiety and moderate to severe tremor, but *not* confusion, hallucinations, or seizure (generally associated with a CIWA-Ar ≥ 19) should not be managed in Level 1-WM settings.[58] Severe uncomplicated withdrawal is not a reason to exclude patients from Level 2-WM settings. The risk for such patients should be carefully considered.

TABLE 2. Ambulatory (Level 1-WM and Level 2-WM) and Inpatient Placement Considerations

	Level 1-WM			Level 2-WM		
	Appropriate	**Neutral/Uncertain**	**Inappropriate**	**Appropriate**	**Neutral/Uncertain**	**Inappropriate**
Withdrawal severity	Mild (e.g., CIWA-Ar <10).	Moderate (e.g., CIWA-Ar 10–18).	Severe or complicated (e.g., CIWA-Ar ≥ 19).	Mild or moderate (e.g., CIWA-Ar <18).	Severe but not complicated (e.g., CIWA-Ar ≥ 19).	Complicated (e.g., CIWA-Ar ≥ 19).
Concurrent withdrawal or physiological dependence		Withdrawing from other substance(s). Physiological dependence on opioids or OUD.	Physiological dependence on BZDs or BZD use disorder.	Physiological dependence on opioids or OUD.	Withdrawing from other substance(s). Physiological dependence on BZDs or BZD use disorder.	
Recent alcohol consumption		Consumes > 8 standard drinks per day.			Consumes > 8 standard drinks per day.	
Alcohol withdrawal history		Previous severe withdrawal episode. Complicated withdrawal > 1 year ago.	Recent complicated withdrawal episode.	Severe withdrawal > 1 year ago.	Previous complicated withdrawal episode. Recent severe withdrawal episode.	
Treatment history		Previous failure to benefit from ambulatory-WM.			Previous failure to benefit from ambulatory-WM.	
Other inpatient need			Medical or psychiatric condition that needs inpatient treatment.			Medical or psychiatric condition that needs inpatient treatment.
Biomedical conditions and complications		Older age. History of epilepsy. History of non-alcohol related seizure. Clinically significant abnormal lab results.	Moderate, active, and potentially destabilizing medical problem. Moderate to severe active and potentially destabilizing medical problem, including unstable chronic condition. Suspected head injury. Unable to take oral medications.	Older age. History of epilepsy.	Moderate, active, and potentially destabilizing medical problem. History of non-alcohol related seizure. Clinically significant abnormal lab results. Suspected head injury.	Moderate to severe active and potentially destabilizing medical problem including unstable chronic condition. Unable to take oral medications.
Emotional, behavioral, or cognitive conditions and complications	Mild/stable psychiatric symptoms.	Active psychiatric symptoms. Mild cognitive impairment.	Moderate or severe psychiatric symptoms. Moderate or severe cognitive impairment.	Mild/stable psychiatric sypmtoms.	Active or moderate psychiatric symptoms. Mild or moderate cognitive impairment.	Severe psychiatric symptoms. Severe cognitive impairment.
Symptom monitoring		Absence of reliable caregiver. Communication barrier (e.g., language, hearing, speech).			Absence of reliable caregiver. Communication barrier (e.g., language, hearing, speech).	
Recovery/ living environment		Absence of reliable support network. Unable to come to treatment setting daily.	Unable to obtain transportation or housing. Family/friends not supportive of WM process.		Absence of reliable support network. Unable to come to treatment setting daily. Family/friends not supportive of WM process.	Unable to obtain transportation or housing.
Risk of harm			Commitment not high, cooperation and reliability questionable. Imminent risk of harm – not cooperative or reliable. Significant risk of imminent relapse.		Commitment not high, cooperation and reliability questionable. Significant risk of imminent relapse.	Imminent risk of harm – not cooperative or reliable.

The Guideline Committee rated each placement consideration on a benefit-to-harm ratio, comparing the potential harm that might result from the factor bing considered to the expected benefit to the patient of being managed in a less restrictive setting. The rating was made in terms of the average patient in an average setting for both Level 1-WM and Level 2-WM. A consideration is *Inappropriate* for a given setting when the potential harm outweighs the expected benefit. A consideration is *Appropriate* for a given setting if the expected benefit outweighs the potential harm. *Neutral/Uncertain* considerations are ones where the harms and benefits are about equal or cannot be determined or where the Guideline Committee disagreed. If a consideration that is inappropriate for Level-2-WM is present, the patient should be managed in an inpatient setting.

BZD, Benzodiazepine; CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, Revised; OUD, Opioid Use Disorder; WM, Withdrawal Manageemnt.

Some Level 2-WM settings have intensive monitoring capabilities and experienced clinicians can safely manage patients in severe withdrawal as long as they are not experiencing complicated symptoms.

Patients experiencing complicated withdrawal syndrome including seizure or signs indicative of delirium – such as an inability to fully comprehend instructions, clouding of the sensorium or confusion – or new onset of hallucinations, or has experienced a seizure during the current episode (generally associated with a CIWA-Ar $\geq$19) should be managed in inpatient settings.[4,21,51,62,65]

Concurrent withdrawal and/or physiological dependence

Concurrent withdrawal from or physiological dependence on another substance is a risk factor for developing complicated alcohol withdrawal.[21,58,62] The literature supports the management of these patients in a level of care setting with increased monitoring and aggressive treatment.[62]

Concurrent withdrawal from other substance(s) is not an exclusionary factor for either level of ambulatory care. The risk for such patients should be carefully considered. Managing alcohol withdrawal and withdrawal from another sedative hypnotic[58] is more complicated clinically than withdrawal from a substance with different pharmacologic effects, such as a stimulant. Patients should be placed in the level of care appropriate to their most acute problem, which may be withdrawal from the other substance.[12] Withdrawal from benzodiazepines produces more autonomic nervous system signs than does withdrawal from alcohol.[73]

Patients with a physiological dependence on benzodiazepines or a co-occurring benzodiazepine use disorder should not be treated in a Level 1-WM setting, but are not excluded from management in a Level 2-WM setting. The risk for such patients should be carefully considered. If deemed appropriate, patients may be treated with cautious use of benzodiazepines (see IV.D(3): Benzodiazepine use) or an alternative medication depending on the clinician's judgment and with careful monitoring

Patients with a physiological dependence on opioids or a concurrent opioid use disorder can be managed in a Level 2-WM setting and are not excluded from management in a Level 1-WM setting. The risk for such patients should be carefully considered. Clinicians should have experience with co-managing opioid use disorder and/or physiological dependence including initiating evidence-based medications for opioid use disorder[74] and with identifying emergent opioid withdrawal syndrome in addition to alcohol withdrawal.

Recent high levels of consumption

Recent high levels of alcohol consumption has been cited as a consideration for level of care determination.[38,44] While most sources did not provide specific threshold amounts, the NICE guideline[21] suggested that inpatient management be considered for patients who consume over 30 U.K. standard units of alcohol per day, which is equivalent to 17 U.S. standard drinks per day. Inpatient treatment was recommended for patients consuming over 7 U.S. standard drinks per day.[36] The Guideline Committee considered a cutoff of 8 U.S. standard drinks per day. Consumption of more than 8 U.S. standard drinks per day is not an exclusionary factor for either ambulatory withdrawal managent setting.

Alcohol withdrawal history

A history of severe and/or complicated alcohol withdrawal is a risk factor for alcohol withdrawal seizure and delirium[48] (see section II.B: Risk Factors for Severe or Complicated Withdrawal) and is frequently cited as an indication for treatment in an inpatient setting.[21,51,58,65] The number and recency of prior withdrawal episodes may also be a factor when determining appropriate level of care.[49] An increasing number of withdrawal episodes is associated with increasing severity through the kindling process.

With one exception, the Guideline Committee determined that a history of severe or complicated alcohol withdrawal does not exclude patients from management in ambulatory settings. However, patients with a recent (within the prior year) episode of complicated alcohol withdrawal should not be managed in Level 1-WM settings. Also, patients with a prior episode of severe alcohol withdrawal which occurred more than one year ago can be managed in Level 2-WM settings.

Treatment history

While multiple prior failed attempts to complete alcohol withdrawal treatment has been cited as a contraindication for ambulatory care,[56,58,65] previous unsuccessful attempts at ambulatory withdrawal management does not exclude patients from management in ambulatory settings. The risk for such patients should be carefully considered. Circumstances that led to unsuccessful treatment or a return to problem alcohol use in the past may have changed and should be assessed by the clinician in making a determination of the appropriate level of care.

Other inpatient needs

Patients with medical or psychiatric conditions may receive alcohol withdrawal management at all levels of care; however, if patients have a co-morbid condition which requires inpatient treatment or hospitalization, patients should not be treated in an ambulatory setting.[12,56] *The ASAM Criteria* states that "for management provided in conjunction with treatment for co-occurring conditions identified in the comprehensive biopsychosocial screening assessment, *The ASAM Criteria* calls for the patient to be placed in the level of care appropriate to the most acute problem."[12(p131)] Therefore, patients with a psychiatric or medical condition that requires services that are provided exclusively in an inpatient setting should not be managed in ambulatory settings.

Biomedical conditions and complications

Comorbid illness

Comorbid illness is a risk factor for complicated/complications of alcohol withdrawal (see II.B: Risk Factors for Severe or Complicated Withdrawal), but the severity of illness and its likelihood of complicating alcohol withdrawal management is a factor for level of care determination.[4,58] Patients with a moderate to severe active and potentially destabilizing medical problem should be managed in inpatient settings. This includes unstable, severe chronic conditions such as cardiovascular disease, liver disease, COPD, or renal impairment.[21,65] Patients with a moderate, active, and potentially destabilizing medical problem should not be managed in

a Level 1-WM setting. Such patients are not excluded from management in a Level 2-WM setting. Some clinicians or programs may have greater experience or access to resources allowing them to manage less severe comorbid illnesses in an ambulatory setting.

Clinically significant laboratory values

Clinically significant abnormal laboratory values indicate the presence of a potentially destabilizing medical problem. Abnormal lab results are not an exclusionary factor for managing patients in ambulatory levels of care. Some abnormal values can be corrected in ambulatory setting, while some may signal the presence of medical conditions that should be managed in inpatient settings.[62]

Suspected head injury

Patients with a suspected head injury should not be managed in Level 1-WM settings. A suspected head injury does not exclude management in Level 2-WM settings, but the risk for such patients should be carefully considered. Some Level 2-WM settings have the capability to intensively monitor patients for complications which may develop.

History of epilepsy and generalized seizure

A history of epilepsy and generalized seizure has been cited as an indication for inpatient treatment.[21,51,75] Managing patients with a history of epilepsy is appropriage in Level 2-WM settings and is not a reason for exclusion from Level 1-WM settings. A history of non-alcohol withdrawal related seizures is not an exclusionary factor for ambulatory settings. Uncertainty about risk may be the result of limited scientific research and evidence regarding the impact of non-alcohol withdrawal seizures and current withdrawal management. Use clinical experience in the level of care determination.

Older age

Older age has been identified as a risk factor for complicated/complications of alcohol withdrawal (see II.B: Risk Factors for Severe or Complicated Withdrawal), possibly by heightening the severity of signs or symptoms of withdrawal or due to correlation with other health problems. ''Older age'' has been left undefined in other guidelines[4,21] but was designated as age 65 and older by the Guideline Committee. It is appropriate to manage older patients in a Level 2-WM setting. Older age is not a reason to exclude older patients from Level 1-WM settings, but the risk for such patients should be carefully considered. Some older patients may be otherwise relatively healthy.

Tolerance of oral medications

Patients who are unable to tolerate oral medication should not be treated in an ambulatory setting.[58,62] Parenteral administration of medication is required in patients who are unable to take medication orally, which is not always available in the average ambulatory setting.

Pregnancy

Pregnancy has been described as one of the ''medical conditions that could make ambulatory withdrawal management problematic,''[58(p57)] and other guidelines have cited pregnancy as an indication for inpatient treatment.[62,65] See VII.F: Patients who are Pregnant for more information.

Emotional, behavioral, or cognitive conditions and complications

While the presence of a co-occurring psychiatric condition is frequently cited as a contraindication for ambulatory care,[4,62] the type/severity and stability of psychiatric disorders is an important distinction in determining appropriate level of care. Some patients' mental health problems are well-controlled and some ambulatory programs have onsite psychological or psychiatric staff. As withdrawal progresses in severity, the average ambulatory clinic is less likely to have the resources needed to manage patients safely and effectively and inpatient management with specialty psychiatric resources may be more appropriate.

Patients whose co-ocurring psychiatric disorder signs and symptoms are mild, reflecting a low level of severity or stability as the result of treatment, can be managed in Level 1-WM or Level 2-WM settings. Active psychiatric disorder signs and symptoms, reflecting a level of severity that may complicate withdrawal management, are not a reason to exclude patients from ambulatory care, but the risk for such patients should be carefully considered. Management may be appropriate if appropriate psychiatric treatment resources are accessed. Patients whose psychiatric disorder signs and symptoms are moderate should not be treated in Level 1-WM settings, but are not excluded from management in Level 2-WM settings. Patients whose co-ocurring psychiatric disorder signs and symptoms are severe or unstable should be managed in inpatient settings.[21,44,58,65]

Cognitive impairment is allso cited as a contraindication for ambulatory care.[58,62,65] However, patients may have access to stable support services and ambulatory clinics may have the staff or resources necessary to manage a patient's withdrawal safely and effectively. Mild cognitive impairment is not an exclusionary factor for ambulatory care. Patients with a moderate cognitive impairment should not be managed in Level 1-WM settings, but moderate cognitive imparment is not a reason to exclude patients from Level 2-WM settings. Patients with severe cognitive impairment should be managed in inpatient settings.[21,58] The appropriateness of managing patients with moderate or mild cognitive impairment in any setting depends on the availability of support services and experience of the treating clinicians.

Symptom monitoring

Even if not using a validated symptom severity scale, the ability of a patient to communicate with clinicians or a caretaker about their symptoms is critical to the safe and effective management of alcohol withdrawal, particularly in the early stages when symptoms continue to develop. A communication difficulty due to a language barrier, a hearing or speech difficulty, or other non-withdrawal symptom related cause is not a reason to exclude patients from ambulatory settings. The appropriateness of treating patients with these difficulties will depend on staff capabilities and available accommodation services.

Because patients are not on-site for the whole day, the absence of a reliable caregiver such as family or friends willing to monitor signs and symptoms at home has been cited as a contraindication for ambulatory withdrawal management.[65,73] However, the absence of a reliable caregiver to monitor withdrawal at home is not a reason to exclude patients from ambulatory management. The appropriateness will

depend on the need to monitor signs and symptoms and other factors that influence treatment adherence and maintenance.

Recovery/living environment

A patient's recovery and living environment is a consideration when determining level of care. These considerations fall into three categories: the presence of social support, access to safe housing and transportation, and ability to visit the clinic frequently during withdrawal management (which may be complicated by available transportation, but also employment, childcare, etc.). The absence of a social support network is commonly cited as an indication for inpatient treatment.[62] However, the absence of a reliable social support network is not a reason to exclude patients from ambulatory management, and appropriateness will depend on a patient's access to other resources. Patients with family or friends who are not supportive of or oppose the withdrawal management process should not be managed in a Level 1-WM setting. The assumption is that patients have contact with those family or friends and their opposition will be detrimental to the withdrawal process. Having family or friends who are not supportive of or oppose the withdrawal management process is not a reason to exclude patietns from Level 2-WM settings. Increased hours of clinic attendance will reduce contact with oppositional family and friends. Patients in Level 2-WM settings also have greater access to AUD treatment services, which can help patients address interpersonal problems and teach coping mechanisms.

It is not appropriate to manage alcohol withdrawal in an ambulatory setting if patients are unable to access or arrange for safe housing.[21,58,65] It is also not appropriate to manage alcohol withdrawal in an ambulatory setting if patients are unable to access or arrange for transportation to the treatment setting. The inability to come to the treatment setting daily is not a reason to exclude patients from ambulatory settings. An alternative to daily visits for these patients may involve alternating in-person clinic visits with consultations with a qualified clinician every other day via phone or video conference (see IV.A: Monitoring).

Risk of harm and use

A patient's likelihood of completing ambulatory withdrawal treatment and of refraining from alcohol use has been cited as a factor for determining level of care in prior guidelines.[12,58,62] Patients being treated in ambulatory settings have greater access to and are at greater risk for using alcohol and other drugs during alcohol withdrawal management compared to patients in an inpatient withdrawal treatment setting. When alcohol is combined with medications such as benzodiazepines, which are used to treat alcohol withdrawal symptoms, it can be particularly dangerous to patients. *The ASAM Criteria*[12] uses the concept of imminent danger (gravity of consequences to self/others) to categorize the proximity and likelihood of consequences and need for structured services and continuous monitoring. Ambulatory withdrawal management is not appropriate for uncooperative or unreliable patients who are at imminent risk of harm. Patients with an uncertain level of cooperation or reliability, with a low level of commitment to the withdrawal process, or who are at significant risk of imminent return to alcohol use should not be managed in Level 1-WM settings. Such patients are not excluded from management in evel 2-WM settings, but their risk should be carefully considered. Level 2-WM settings can provide a structured, monitored environment for such patients.

IV. Ambulatory Management of Alcohol Withdrawal

This guideline divides recommendations on the management of alcohol withdrawal into two broad categories where withdrawal management services are provided: ambulatory and inpatient settings. While there are many differences in the services provided within these categories, and services should not ideally be tied to a specific setting, this organization follows a reasonable structure that seems to match how providers currently think about their practice context. The goal is that practitioners can reference one management section or the other. There are many shared service practices across categories, however, which creates a great deal of repetition across sections. This organization was intentional. As most readers do not read through an entire guideline, the goal was to ensure that each section stands on its own.

Within each section, differences between levels of care are highlighted. In ambulatory settings, *Level 1-WM* is ambulatory withdrawal management without extended on-site monitoring. This service can be carried out in a physician's office, by a home health care agency, or an addiction treatment facility. *Level 2-WM* is ambulatory withdrawal management with extended on-site monitoring. It can be carried out in structured outpatient settings such as a day hospital setting, a general health care or mental health facility, or an addiction treatment facility. Level 2-WM is an organized service with the capacity to provide regular medical assessments and monitor alcohol withdrawal progression. Level 2-WM settings may also provide access to psychological or psychiatric treatment (see *The ASAM Criteria* for additional details). (See Appendix IV.C., http://links.lww.com/JAM/A192 for a summary of ambulatory management protocols).

The following recommendations apply to both Level 1-WM and Level 2-WM settings unless otherwise specified. Additional recommendations specific to Primary Care settings are included in the section VII.A: Primary Care.

A. Monitoring

Recommendation IV.1: In ambulatory settings, arrange for patients to check in with a qualified health provider (e.g., medical assistant, nurse) daily for up to five days following cessation of (or reduction in) alcohol use. For some patients who are unable to attend daily in-person check-ins, alternating in-person visits with remote check-ins via phone or video call is an appropriate alternative.

Recommendation IV.2: Re-assessments should focus on the patient's health since the last checkup. Clinicians should assess general physical condition, vital signs, hydration, orientation, sleep and emotional status including suicidal thoughts at each visit. Ask about alcohol and other substance use and, if available, measure Blood Alcohol Contend (BAC) with a breathalyzer to detect recent alcohol use.

Recommendation IV.3: Alcohol withdrawal severity should be monitored with a validated instrument (see

Appendix III for a summary of scales and their associated features). Patients who are able to monitor their own signs and symptoms may use an instrument designed for self-administration such as the Short Alcohol Withdrawal Scale (SAWS).

Recommendation IV.4: In ambulatory settings, patients with a current or past benzodiazepine use disorder need additional monitoring.

Recommendation IV.5: For patients managed in an ambulatory setting, the following indications would necessitate transfer to a more intensive level of care such as Level 2-WM (if in a Level 1-WM setting) or an inpatient setting:

- Agitation or severe tremor has not resolved despite having received multiple doses of medication, and the patient will not be continually monitored (e.g., treatment setting is closing)
- More severe signs or symptoms develop such as persistent vomiting, marked agitation, hallucinations, confusion, or seizure
- Existing medical or psychiatric condition worsens
- Patient appears over-sedated
- Patient returns to alcohol use
- Syncope, unstable vital signs (low/high blood pressure, low/high heart rate)

Discussion. One of the key differences between the Level 1-WM and Level 2-WM levels of care is the frequency and intensity of monitoring they provide. Optimal monitoring frequency is a balance between clinical need and feasibility. While broad ranges of recommended optimal monitoring frequency were found in the literature, the modal recommendation seemed to be daily.[62,75,76] Face-to-face check-ins with a qualified healthcare provider are preferred. Patients who are unable to come to the treatment setting on a daily basis can be assessed on alternate days via phone or video conference if assessment using that method would not increase the risk of unsafe withdrawal.[62] This practice might be reserved for patients in mild withdrawal or who are nearing completion of withdrawal and for patients who have demonstrated commitment to the withdrawal management process. The decision to monitor a patient's progress remotely is at the discretion of the clinician.

Monitoring a patient in alcohol withdrawal should include multiple indicators of withdrawal progress and patient health. This includes the patient's general physical and mental health including vital signs, emotional status and sleep quality.[76] Clinicians should ensure that the patient is following directions regarding hydration and nutrition (see IV.B: Supportive Care for instructions). The worsening of medical or mental health conditions or circumstances that interfere with a patient's ability to correct fluid, electrolyte, or nutritional deficiencies indicates the need to reinforce self-care instructions and reassess a patient's treatment plan and/or level of care. If not included in the withdrawal symptom monitoring scale, orientation should be assessed as an indication of withdrawal severity, possible alcohol or other substance use, and oversedation from prescribed withdrawal medication.

The patient should be asked about alcohol and other drug use at each follow up appointment. If feasible, a breathalyzer should be used to verify that the patient has not been using alcohol recently.[71] A breath alcohol test can detect use for approximately 1 hour per standard unit of alcohol consumed, so a negative result does not guarantee the patient has not consumed alcohol since their last appointment.[3] A positive result, if the test is properly administered, does indicate that the patient has alcohol in their system. This is particularly important to know if prescribing medication that is dangerous to use in combination with alcohol (i.e., benzodiazepines or phenobarbital). Alcohol use may indicate that the patient is not receiving an adequate dose of medication to ease discomfort from withdrawal and/or reduce cravings. It also indicates a clinician should choose a medication for withdrawal with a tolerable safety profile when used in combination with alcohol. It may also indicate that there are circumstances in the patient's environment that make it difficult to avoid alcohol and that an inpatient setting is more likely to lead to successful withdrawal management. In this case, it is important that alcohol use not lead to ejection from treatment, but rather transfer to a more intensive level of care. The Guideline Committee added that patients with current or past benzodiazepine use disorder will need more intensive monitoring during alcohol withdrawal management.

The severity of alcohol withdrawal should be monitored using a validated withdrawal scale.[37,38,56,57,62] The same instrument should ideally be used to track signs and symptoms throughout the course of withdrawal.[71] Clinicians should ensure that signs and symptoms are not worsening, that patients are responding as expected to medication if provided, and that signs and symptoms are not persisting beyond the expected timeline of withdrawal. Any of these indicate the need to reassess a patient's treatment plan and/or level of care.

As discussed in section II.D: Symptom Assessment Scales, various symptom assessment and monitoring scales have been developed to address circumstances such as a confounding illness or symptom self-reporting barriers (see Appendix III Random I a summary of scales and their associated features). Of most relevance to scale choice in ambulatory settings is clinician- vs. self-administration. While the CIWA-Ar was designed to be administered by a clinician, it can be used by patients or caregivers if given adequate instructions. The SAWS, a 10-item instrument designed to be self-administered, can be used as a supplement while the patient is away from the treatment setting. It has been used and validated in ambulatory settings.[61,77,78] Unlike the CIWA-Ar, which is designed to measure in-the-moment signs and symptoms, the SAWS is an up-to-the-moment measure of symptoms in the prior few hours. It was originally written to measure symptoms during the 24 hours prior to patients returning for a daily clinic appointment, although the developers state that the assessment period can be adjusted to whatever is needed, for example, tracking nighttime symptoms while away from the more extensive monitoring of a Level 2-WM setting.[61]

While most patients with alcohol withdrawal can be successfully managed in an ambulatory setting, it is important to recognize signs that a more intensive level of care is needed. Patients and caregivers should be informed of warning signs to look for while away from the treatment setting,

and that safe alcohol withdrawal management may necessitate transfer to a more intensive level of care if certain indications emerge (see the following section, IV.B: Supportive Care for patient and caregiver instructions). In settings with less frequent monitoring such as primary care, the threshold for transfer to a more intensive level of care is lower than in settings with more frequent monitoring. If signs or symptoms such as persistent vomiting, agitation, hallucinations, or confusion develop, patients should be transferred to an inpatient setting as they can presage the onset of electrolyte disturbance, withdrawal seizures, alcohol withdrawal delirium, or Wernicke encephalopathy.[79,80] If an existing medical or psychiatric condition worsens despite adequate control of withdrawal symptoms, patients should be transferred to a setting with the resources to manage the condition.[73,80] If significant signs or symptoms such as agitation are present despite having received multiple doses of medication or if the patient appears over-sedated at the close of the day, transfer to a setting where the patient can continue to be observed, such as the Emergency Department (ED) or a specialized withdrawal management setting, is warranted.[72] Signs of over-sedation include respiratory depression, ataxia, confusion, memory impairment, and delirium. If the patient experiences a loss of consciousness or has unstable vital signs that cannot be attributed to and controlled for by the prescribed treatment regimen, patients should be transferred to a level of care capable of providing the patient with a thorough assessment to properly identify etiology of signs and symptoms as well as provide continuous observation and care.

B. Supportive Care

Recommendation IV.6: Supportive care is a critical component of alcohol withdrawal management. Providers should ensure patients are educated about what to expect over the course of withdrawal, including common signs and symptoms and how they will be treated.

Recommendation IV.7: When treating patients in ambulatory settings, providers should ensure patients/caregivers are educated about monitoring for the development of more severe withdrawal and instructed to create a low-stimulation, reassuring environment at home to promote an effective outcome.

Recommendation IV.8: Patients should be advised to drink non-caffeinated fluids and that a daily multivitamin may be beneficial.

Recommendation IV.9: Patients can be offered oral thiamine. Typical dosing is 100 mg PO per day for 3–5 days.

Recommendation IV.10: Clinicians must explain the importance of taking medications as prescribed and confirm the patient's understanding.

Recommendation IV.11: Communicate that safe alcohol withdrawal management may necessitate a transfer to a more intensive level of care including to an inpatient setting and secure the patient's agreement to transfer if there are indications that management in the ambulatory setting is not safe or effective. See Recommendation IV.5 for indications for transfer to a more intensive level of care.

Discussion. Supportive non-pharmacologic care is a critical component of alcohol withdrawal management. Informing patients of what to expect over the course of treatment, offering reassurance, providing a quiet environment and ensuring adequate hydration and nutrition are important aspects of supportive care in all settings. The importance of supportive family members and/or other caregivers is most relevant to the discussion of ambulatory alcohol withdrawal management as patients will spend a portion of their time at home. Several reviews of ambulatory withdrawal management highlight the role of these individuals as not only one of monitoring signs and symptoms and medication intake, but of offering encouragement and reassurance.

Patients and caregivers should be instructed on how to monitor for worsening signs and symptoms including worsening anxiety, insomnia and suicidal thoughts. If using a withdrawal severity scale, patients and caregivers should be instructed on how it should be completed.[81,82] Important information to convey is the precise meaning of clinical or other terms used in the scale, for example, what constitutes sleep disturbance. It should also be made clear how to score the severity of items, for example, what the meaningful difference is between scoring a 1 (Mild) and a 2 (Moderate) on the restlessness item of the SAWS. The instruction period is also an opportunity to evaluate circumstances that may interfere with scale self-administration, for example through literacy problems or confusion about item severity scores.[61]

Patients and caregivers should be instructed to create a low stimulation, reassuring environment, since environment is a critical component of success in alcohol withdrawal management and ultimately recovery.[83] As volume depletion is a common condition for patients with alcohol withdrawal and intravenous fluids are not provided in ambulatory settings, encouraging consumption of non-caffeinated fluids is important.[36,65,76] Nutritional support is also a consideration in ambulatory alcohol withdrawal management. Some patients may benefit from a daily multivitamin and thiamine supplement. Typical dosing of oral thiamine is 100 mg PO daily for three to five days.[65] However, oral thiamine is not well absorbed, and thiamine deficiencies can typically be corrected through diet. If Wernicke encephalopathy is suspected, the patient should be transferred to an inpatient setting and receive immediate parenteral administration of thiamine. See Box 5 for more information on Wernicke Encephalopathy and Wernicke-Korsakoff Syndrome.

In an early review of ambulatory alcohol withdrawal management, it was explicitly recommended that medications should be administered in the treatment setting rather than at home when possible.[39] However, this recommendation has not been repeated in more recent work, and concerns can be addressed by providing only a few take-home doses at a time and ensuring patients understand how to self-administer medications properly. Instructions on warnings for specific medications will be addressed in a later section. Most importantly, patients should be advised about the risk of impairment or overdose if certain medications are combined with alcohol or other substances.[7,36]

Finally, it is important to explain to patients and caregivers the circumstances under which a transfer to a more

Box 5: Wernicke Encephalopathy and Wernicke-Korsakoff Syndrome[84,85]

Wernicke encephalopathy is a severe complication resulting from insufficient thiamine in the body. It is characterized by an often reversible acute confusional state. Patients consuming large volumes of alcohol are at an increased risk of developing Wernicke encephalopathy due to inadequate nutrition as well as biological interactions between cellular functioning and alcohol. Thiamine is required for carbohydrate metabolism and plays a key role in normal body functioning. Thiamine deficiency can lead to an increase in pyruvic acid, impaired oxygen uptake, and cerebral tissue damage. Because the body does not synthesize thiamine, daily ingestion through food or supplements is required to maintain adequate metabolic functioning. Thiamine must be converted to different forms to function properly, and alcohol can also impact this conversion by inhibiting key enzymes. Patients with thiamine deficiency often present with signs and symptoms such as confusion, abnormal gaze patterns or nystagmus, ataxia, and possibly delirium. Patients who experience alcohol withdrawal syndrome are at risk of developing Wernicke encephalopathy. Thus, routine practice includes providing patients with thiamine supplements as a preventative measure. If left untreated, Wernicke encephalopathy can progress to chronic Korsakoff syndrome. While Wernicke encephalopathy is a reversible confusional state, if left untreated it can progress to an irreversible syndrome that includes dementia and gait abnormalities. The prevalence of this syndrome ranges between 0–2% worldwide and is not connected to alcohol consumption per capita. Effects of the thiamine deficiency can be found throughout the brain. The damage associated with Wernicke-Korsakoff syndrome seems to occur in a combination of areas including the mammillary bodies, the cerebellum, the frontal lobe, the periaqueductal gray, the thalamus, the walls of the third ventricle, and the floor of the fourth ventricle. Damage to these structures yields the defining features found in the clinical exam consisting of ocular disturbances, mental status changes, gait abnormalities, agitation, and confabulations. Unfortunately, once Wernicke-Korsakoff syndrome occurs, the effects are not reversible and are often progressive.

intensive level of care may be necessary, for example if signs and symptoms continue to increase in severity despite taking medication as prescribed. See Recommendation IV.5 for indications for transfer to a more intensive level of care. Explaining this at the beginning of the withdrawal management process is optimal to ensure a smooth transition if necessary.

C. AUD Treatment Initiation and Engagement

Recommendation IV.12: When feasible, alcohol use disorder (AUD) treatment should be initiated concurrently with alcohol withdrawal management as cognitive status permits. If appropriate, clinicians should offer to initiate pharmacotherapy for AUD as cognitive status permits. If not initiating AUD treatment themselves, clinicians should explain the range of evidence-based treatment services available in the community, and engage patients with these options. In addition, clinicians may offer information about local recovery support groups, including 12-step groups.

Discussion. To the fullest extent possible, patients undergoing alcohol withdrawal management should be engaged, if not initiated, in treatment for alcohol use disorder (AUD) as soon as cognitive status permits. This engagement should be considered part of the withdrawal management process and should not be delayed until withdrawal management is complete. There are currently no evidence-based practices for addressing AUD as part of alcohol withdrawal management.

In early discussions of ambulatory alcohol withdrawal management, it was recognized that AUD outreach and case management is important for patients.[39] In a now-classic study comparing inpatient and outpatient alcohol withdrawal management, it was noted that patients benefit from receiving treatment for AUD in the same outpatient facility at which they complete alcohol withdrawal management.[86] As patients in ambulatory settings typically have less severe withdrawal syndromes, treatment initiation and engagement can begin closer to initiating withdrawal management. When discussing AUD, emphasize patient engagement, and offer a variety of treatment and support options, even if the current goal is not abstinence from alcohol. Patients undergoing ambulatory alcohol withdrawal management in a setting such as primary care represent a less ''captive'' audience, and therefore more commitment may be needed from clinicians to engage patients in continuing treatment. Motivational interviewing or enhancement, delivered in primary care settings, has been demonstrated to reduce alcohol and other drug use and to help engage patients in AUD treatment.[87,88] Regular follow-up visits at least monthly for a year in Level 1-WM settings may increase the chances of continued recovery, although the Guideline Committee acknowledged that this may not always be realistic.

D. Pharmacotherapy

(1) Prophylaxis

Recommendation IV.13: Patients at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal may be treated in ambulatory settings at the discretion of providers with extensive experience in management of alcohol withdrawal. Such patients should be provided with preventative pharmacotherapy. Benzodiazepines are first-line treatment because of their well-documented effectiveness in reducing the signs and symptoms of withdrawal including the incidence of seizure and delirium. Phenobarbital is an appropriate alternative in Level 2-WM setting for providers experienced with its use. For patients with a contraindication for benzodiazepine use, phenobarbital (in Level 2-WM settings by providers experienced with its use) or transfer to a more intensive level of care are appropriate options.

Recommendation IV.14: A front loading regimen is recommended for patients at high risk of severe withdrawal syndrome. Providing at least a single dose of preventative medication is appropriate for patients at lower levels of risk who have:

- A history of severe or complicated withdrawal
- An acute medical, psychiatric, or surgical illness
- Severe coronary artery disease
- Displaying signs or symptoms of withdrawal concurrent with a positive blood alcohol content

Recommendation IV.15: Patients at risk of developing new or worsening signs or symptoms of withdrawal while away from the ambulatory treatment setting should be

provided with pharmacotherapy. Some indications of risk include a history of withdrawal episodes of at least moderate severity and being within the window for the development of symptoms in the time course of withdrawal. Benzodiazepines, carbamazepine, or gabapentin are all appropriate options for monotherapy. Providing at least a single dose of benzodiazepine followed by ongoing treatment according to symptom severity is also appropriate. If the risk of developing worse withdrawal is unknown, patients should be reassessed frequently over the next 24 hours to monitor their need for withdrawal medication.

Discussion. Determining risk of developing severe or complicated withdrawal or complications of withdrawal is addressed in section II: Initial Assessment of Alcohol Withdrawal. As discussed in section III: Level of Care Determination, if there is a risk that patients will develop severe or complicated withdrawal or complications of withdrawal, it should first be determined if ambulatory care is the appropriate level of care. Some providers with extensive experience in managing alcohol withdrawal may decide to treat at-risk patients in ambulatory settings.

Patients at risk of developing severe or complicated withdrawal or complications of withdrawal should receive pharmacotherapy as soon as possible to prevent these signs and symptoms.[4,13,89] Benzodiazepines are recommended as the primary medication to prevent the development of severe, complicated or complications of withdrawal. There is clear evidence that benzodiazepines reduce the incidence of alcohol withdrawal seizures and alcohol withdrawal delirium.[2,13,44,51,90] Phenobarbital can be used as an alternative in Level 2-WM settings, particularly for patients with a contraindication for benzodiazepine use. However, given its narrow therapeutic window and extended half-life, it should only be used by clinicians experienced with its use, particularly in ambulatory settings where patients have greater access to alcohol.

For patients at high risk of severe withdrawal, front loading with a benzodiazepine is recommended to rapidly achieve therapeutic levels of medication. Front loading has been shown to reduce the duration of treatment and incidence of withdrawal seizure and duration of delirium.[2,13,91] Patients should be closely observed for over-sedation and respiratory depression following the administration of a front loading dose.

For patients at lower levels of risk, providing at least a single or a few doses of benzodiazepine is appropriate and can be followed by a medication chosen according to symptom severity (see IV.D(2): Withdrawal symptoms). If a clinician determines that a patient is no longer at risk, for example, because risk has been sufficiently mitigated by administration of medication or because the course of withdrawal has passed the period of acute risk, ongoing pharmacotherapy for alcohol withdrawal can be determined according to the severity of a patient's withdrawal at that time. Some situations which have been called out as appropriate for administering at least a single dose of benzodiazepines include: a history of severe or complicated withdrawal; risk for complications of significant medical, surgical, or psychiatric illness (particularly cardiovascular disease including coronary artery disease);[4] and displaying signs or symptoms of withdrawal concurrent with a positive blood alcohol content (an indication of risk for developing severe withdrawal syndrome).

A concern in ambulatory withdrawal management is the lack of continuous observation of patients to identify worsening withdrawal syndrome and provide medication to address symptoms if needed. Patients experiencing mild alcohol withdrawal (e.g., CIWA-Ar score <10) who are at low risk of developing severe, complicated, or complications of withdrawal can be managed with supportive non-pharmacotherapy in both ambulatory and inpatient settings (see Recommendations IV.16 and V.15). In the ambulatory setting, clinicians may want to use medication to prevent the emergence of mild or worsening to moderate withdrawal while patients are away from the clinic, meaning the severity threshold for prescribing medication is lower in ambulatory settings than inpatient settings, particularly if there is an indication of risk for symptom development. The recommendation that patients with even very mild withdrawal who cannot be monitored be provided medication has been supported in prior guidelines.[51]

Risk of developing more severe withdrawal is determined, in part, by the severity of previous withdrawal episodes as well as timing (within the 6–36 hour window) of the emergence, peak, and resolution of withdrawal signs and symptoms after cessation of (or reduction in) alcohol consumption.[2] While withdrawal tends to worsen with each episode, patients with repeated bouts of mild alcohol withdrawal have reported similar signs and symptoms for each episode.[46]

Sometimes the risk of withdrawal progression is unknown, for example, if patients have not had prior withdrawal episodes or do not know the exact timing of their last drink. It is appropriate to either provide medication or reassess the patient frequently over the next 24 hours, after which more serious withdrawal is unlikely to develop.[62] Reassessment can be done in person or over the phone or video chat.

Benzodiazepines, carbamazepine, or gabapentin are appropriate options for managing patients at risk of developing mild or moderate withdrawal. These medications are also appropriate for patients already experiencing mild and moderate withdrawal as seen in the next section. As in the case of risk of developing severe, complicated, or complications of withdrawal, a dose or doses of a benzodiazepine followed by ongoing treatment according to symptom severity is also appropriate. (See Appendix IV.B., http://links.lww.com/JAM/A192 for a flowchart on pharmacotherapy considerations).

(2) Withdrawal symptoms

Recommendation IV.16: Patients experiencing mild alcohol withdrawal (e.g., CIWA-Ar score <10) who are at minimal risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal may be provided pharmacotherapy or supportive care alone. If providing medication, carbamazepine or gabapentin are appropriate options. For patients who are at risk of developing new or worsening withdrawal while away from the treatment setting, benzodiazepines, carbamazepine, or gabapentin are appropriate.

Recommendation IV.17: Patients experiencing moderate alcohol withdrawal (e.g., CIWA-Ar scores 10–18) should receive pharmacotherapy. Benzodiazepines are first-line treatment. Carbamazepine or gabapentin are appropriate alternatives. For patients with a contraindication for benzodiazepine use, carbamazepine, gabapentin, or phenobarbital (in Level 2-WM settings for providers experienced with its use) are appropriate. Carbamazepine, gabapentin, or valproic acid (if no liver disease or childbearing potential) may be used as an adjunct to benzodiazepines.

Recommendation IV.18: Patients experiencing severe, but not complicated, alcohol withdrawal (e.g., CIWA-Ar $\geq$ 19), may be treated in ambulatory Level 2-WM settings at the discretion of providers with extensive experience in management of alcohol withdrawal. Such patients should receive pharmacotherapy. Benzodiazepines are first-line treatment. Phenobarbital is an appropriate alternative for providers experienced with its use. For patients with a contraindication for benzodiazepine use, phenobarbital, carbamazepine, or gabapentin are appropriate. The use of adjunct medications is also appropriate.

Recommendation IV.19: If a patient is taking medication as prescribed and symptoms are not controlled as expected:

- First, consider increasing the dose

  If over-sedation or inadequate monitoring is a concern:
- Reassess for appropriate level of care
- Consider switching medications
- If using benzodiazepines, consider adding an adjunct medication

Discussion. Appropriate pharmacotherapy for alcohol withdrawal managed in an ambulatory setting is a balance of alleviating symptoms enough to minimize the likelihood that patients will return to alcohol use and the possibility they will experience negative side effects or other negative outcomes due to medication use. Patients experiencing mild withdrawal (e.g., CIWA-Ar score <10) can be treated with pharmacotherapy or supportive therapy alone if they are not at risk of symptom progression. Patients experiencing moderate or severe withdrawal (e.g., CIWA-Ar scores $\geq$ 10) should receive pharmacotherapy.

Carbamazepine or gabapentin are appropriate for managing mild and moderate alcohol withdrawal in patients who are at minimal risk of developing severe or complicated alcohol withdrawal.[92–94] There is evidence that carbamazepine and gabapentin are as effective as benzodiazepines as monotherapy for low-risk patients[44,94–96] and they have characteristics which increase their favorability compared to benzodiazepines and phenobarbital in ambulatory settings. They have lower risk for drug-alcohol toxicity and are less sedating.[58,62,73,92] Carbamazepine and gabapentin have been shown to decrease craving for alcohol and reduce alcohol consumption after the withdrawal period.[92] This may make them particularly beneficial for patients treated in ambulatory settings where the opportunity for exposure to alcohol is greater.

As symptom severity or risk of developing severe symptoms increases, medications with well-established effectiveness in preventing the incidence of severe and complicated withdrawal are preferred.[54] Benzodiazepines are first-line agents for treating moderate[58,65,81] and severe alcohol withdrawal[13,58] due to their known effectiveness in preventing seizures and delirium.[13,90,94] Carbamazepine, gabapentin and phenobarbital can be used for patients with a contraindication for benzodiazepine use.[58,65,81,92] However, given its narrow therapeutic window and extended half-life, phenobarbital should only be used in Level 2-WM settings by clinicians experienced with its use, particularly in ambulatory settings where patients have greater likelihood of exposure to alcohol.

As discussed in section III: Level of Care Determination, if patients are experiencing severe withdrawal (e.g., CIWA-Ar $\geq$ 19), it should first be determined if ambulatory treatment is the appropriate level of care. Some ambulatory providers with extensive experience in managing alcohol withdrawal may decide to treat patients experiencing severe withdrawal in the absence of confusion or hallucinations indicative of delirium or seizure during the current withdrawal episode in a Level 2-WM ambulatory setting. Benzodiazepines are first-line treatment, but phenobarbital is an appropriate alternative for providers experienced with its use, even if benzodiazepine use is not contraindicated.

Patients receiving pharmacotherapy should be monitored for signs of response to medication. If patients do not respond as expected, a number of actions can be considered. First, consider increasing the dose. The amount of medication required to control symptoms is variable and ultimately determined by clinical judgment. Patients with more severe withdrawal may require larger doses than are typically seen in other patient populations, particularly during early withdrawal. Providing large doses of benzodiazepine can lead to over-sedation and respiratory depression and patients should be monitored closely.

Second, patients should be reassessed for appropriate level of care. Failure to respond may reflect the presence of more severe withdrawal than expected and significant risk of major complications.[13] A more intensive level of care may be needed to monitor and manage major complications if they occur.[82]

Third, consider switching to a different medication. Failure to respond to benzodiazepine may reflect benzodiazepine resistance due to kindling (see VI.D: Resistant Alcohol Withdrawal). Higher numbers of previous alcohol withdrawal episodes is associated with decreased responsiveness to benzodiazepines.[4] Failure to respond may also be due to withdrawal from another GABAergic agent such as gabapentin. In these cases, switching to an alternative medication should be considered.

Fourth, if using benzodiazepines, consider adding an adjunct medication. Some patients benefit from the addition of an adjunct medication to control signs and symptoms of withdrawal and their use can be considered as part of the treatment plan. The use of carbamazepine, gabapentin, or valproic acid as an adjunct medication to benzodiazepines is also appropriate for patients experiencing moderate or severe withdrawal. Valproic acid should not be used in patients who

have liver disease, with women of childbearing potential, or as monotherapy for withdrawal. Alpha2-adrenergic agonists (A2AAs) and beta-adrenergic antagonist (beta-blockers) can be used in conjunction with benzodiazepines to manage persistent hypertension or tachycardia.[44,97]

(3) Benzodiazepine use

Recommendation IV.20: While no particular benzodiazepine agent is more effective than another, longer-acting benzodiazepines are the preferred agents due to the clinical benefits of their longer duration of action.

Recommendation IV.21: If waiting for lab test results or if the test(s) are unavailable, if a patient has signs of significant liver disease, use a benzodiazepine with less hepatic metabolization.

Recommendation IV.22: Clinicians should monitor patients taking benzodiazepines for signs of over-sedation and respiratory depression.

Recommendation IV.23: A benzodiazepine prescription to treat alcohol withdrawal should be discontinued following treatment.

Recommendation IV.24: Clinicians can manage benzodiazepine misuse or diversion risk in ambulatory settings by dispensing or prescribing the minimum amount necessary given the patient's level of stability and timing of their next in-person clinic visit. Alternative medications can also be considered such as carbamazepine or gabapentin.

Recommendation IV.25: In ambulatory settings, benzodiazepines should not be prescribed to patients with a history of even mild adverse events with benzodiazepine use because rapid intervention is not typically available. Benzodiazepines can be used with caution in patients with a high risk of benzodiazepine diversion including patients with a current or past benzodiazepine use disorder for the short period of acute alcohol withdrawal. Risk can be managed by dispensing or prescribing a small number of doses.

Recommendation IV.26: Patients who are taking benzodiazepines, and their caregivers, should be educated regarding:

- The danger of drug-drug interactions between benzodiazepines and other CNS depressants (impairment and respiratory depression)
- The risks associated with combining alcohol and benzodiazepines and importance of abstinence from alcohol
- The risks associated with driving or use of heavy machinery for the first few days of benzodiazepine administration
- Instructions to reduce their benzodiazepine dose if drowsiness occurs

Discussion. Benzodiazepines are commonly recommended as first-line agents for managing most forms of alcohol withdrawal.[13,90] Diazepam, lorazepam, and chlordiazepoxide are the most frequently used in treating alcohol withdrawal. While there is no evidence showing superiority of effectiveness among benzodiazepine agents,[13,90] longer-acting agents are preferred by many clinicians.[2,51,81] A long duration of action contributes to a smoother course of withdrawal and greater control of breakthrough and rebound signs or symptoms. This provides greater coverage for preventing alcohol withdrawal seizures and delirium.[90,98] For this reason, patients prescribed a shorter-acting agent should have a more gradual taper and be reassessed more frequently (see IV.D(4): Benzodiazepine dosing regimens).

Longer-acting agents can accumulate and lead to over-sedation and respiratory depression, particularly in older patients or those with compromised health. Other signs of over-sedation include ataxia, confusion, memory impairment, and delirium, which may be difficult to differentiate from alcohol withdrawal-related delirium.[2] Benzodiazepine associated delirium has been diagnosed by the administration of flumazenil, a GABA-A receptor antagonist, but this protocol was not reviewed by the Guideline Committee.[99] A reduction in the benzodiazepine dose and the addition of a neuroleptic agent to control for agitation and/or confusion can be considered if patients are not at an elevated risk of seizure (i.e., they are outside of the acute risk window).[2] Some neuroleptic agents have been shown to reduce the seizure threshold.

Benzodiazepine accumulation is more likely in patients with impaired hepatic function. Medication dose can be reduced or a benzodiazepine with less dependence on hepatic metabolism can be used (see section VII.D: Patients with Medical Conditions). Laboratory testing recommended in section II.E: Identify Concurrent Conditions can indicate the need to adjust the treatment plan, but as treatment should not be delayed while waiting for lab test(s) results or if the test(s) are unavailable at the treatment setting, if a patient has signs of significant liver disease, reduce the dose or use a benzodiazepine with less hepatic metabolization.

Signs of significant liver disease include:

- Skin and eyes that appear yellowish (jaundice)
- Swelling in the legs and ankles (edema)
- Itchy skin
- Dark urine color
- Pale stool color, or bloody or tar-colored stool
- Confusion
- Chronic fatigue
- Nausea or vomiting

Benzodiazepines prescribed for alcohol withdrawal should be discontinued after withdrawal is complete. Patients are at risk of developing a physiological dependence on benzodiazepines, developing a benzodiazepine use disorder, or experiencing benzodiazepine withdrawal. The decision process for determining appropriate duration of treatment is affected by the amount of benzodiazepine used during the acute withdrawal period, particularly when seizure or delirium has occurred, and any associated physiological dependence that may have developed.[51] Managing the phenomenon of protracted withdrawal, where subacute symptoms of irritability, anxiety and sleep disturbances can persist for weeks, is beyond the scope of the current guideline.

In ambulatory settings, benzodiazepine use has liabilities not present in inpatient settings. Risk can be managed by dispensing or prescribing a very small number of doses, with some suggesting providing only enough medication for one day.[38,39,72,100,101] The Clinical Champions determined that recommending daily prescriptions might be too restrictive and

giving enough medication until a patient's next appointment (e.g., 1–3 three days) is reasonable. They noted that these considerations are relevant primarily for benzodiazepine prescriptions due to the risk involved and that they would be comfortable giving several days' worth of carbamazepine or gabapentin due to lower risk for diversion and/or drug-drug interactions.

There are some situations where the risks of benzodiazepine use outweigh the benefits in an ambulatory management setting. In these cases, patients can be offered an alternative medication rather than transfer to inpatient treatment. Patients with a history of even mild adverse events with benzodiazepine use should not be prescribed benzodiazepines for ambulatory withdrawal because of the lack of continuous monitoring.

Benzodiazepines should be prescribed with extra caution to some patients if managed by dispensing or prescribing a very small number of doses and more frequent monitoring. Patients with a high risk of benzodiazepine misuse or diversion (history of previous misuse or diversion or another household member with a history of misuse or diversion of benzodiazepines) and patients with a current or past benzodiazepine use disorder can be prescribed benzodiazepines if managed cautiously. The potential for misuse is limited during the short period of supervised alcohol withdrawal.[62]

It is critical that patients who are prescribed benzodiazepines and their caregivers understand the danger of drug-drug interactions with this medication.[71,100] As respiratory depression and death can result from the combination of alcohol or opioids with benzodiazepines, clinicians should emphasize the importance of not using alcohol or other drugs during withdrawal management.[71,100] Patients should also be warned about the risk of drowsiness and advised not to drive or use heavy machinery for the first few days of taking benzodiazepines.[75] Patients should be advised to reduce the dose if drowsiness occurs.[41]

(4) Benzodiazepine dosing regimens

Recommendation IV.27: At short-term observational settings with continuous monitoring (e.g. Level 2-WM), symptom-triggered treatment conducted by trained staff is the preferred benzodiazepine dosing method. Front loading while under clinical supervision or fixed dosing with additional as-needed medication are also appropriate.

Recommendation IV.28: At settings without extended on-site monitoring (Level 1-WM), symptom-triggered dosing is appropriate if patients or a caregiver can reliably monitor signs and symptoms with a withdrawal severity scale and follow dosing guidance. Otherwise, front loading while under clinical supervision or fixed dosing with additional as-needed medication is appropriate.

Recommendation IV.29: Front loading is recommended for patients experiencing severe alcohol withdrawal (e.g., CIWA-Ar $\geq$ 19). Diazepam and chlordiazepoxide are preferred agents for front loading.

Recommendation IV.30: When using a fixed-dose schedule, patients' signs and symptoms should still be monitored. A few additional additional take-home doses can be provided to take as needed. When initiating a fixed-dose regimen, arrange for the patients to be followed up with the following day to modify the dose if needed.

Recommendation IV.31: If prescribing a shorter-acting benzodiazepine, using a fixed-dose regimen with a gradual taper may be appropriate to reduce the likelihood of breakthrough and rebound signs and symptoms.

Discussion. Examples for these dosing regimens can be found in Appendix V.

Multiple dosing strategies have been used to administer benzodiazepines during alcohol withdrawal. In general, symptom-triggered treatment is the preferred dosing method,[4,36] but there is disagreement regarding its appropriateness for ambulatory settings. In this regimen, medication is administered only when patients are experiencing significant withdrawal symptoms according to a severity scale. This allows dosing to be individualized according to symptom severity and reduces the risk of under- and over-treating by assessing and dosing according to real-time symptom severity. It is possible that very large doses of medication will be needed rapidly, and reduced as symptoms resolve.[2,13] Symptom-triggered dosing has been shown to reduce the duration of treatment and inpatient length of stay compared to a fixed-dose schedule.[2,21,44,51]

The disagreement regarding its appropriateness for ambulatory settings generally hinges on how signs and symptoms will be assessed and by whom. Symptom-triggered treatment is appropriate when conducted by healthcare professionals in Level 2-WM settings.[2,13,21] In Level 1-WM settings, where symptoms would be assessed by caregivers or patients themselves, most prior guidelines have only considered the use of the CIWA-Ar, which requires training in order to score reliably. Other symptom assessment instruments such as the Short Alcohol Withdrawal Scale (SAWS) are designed to be self-administered and used in ambulatory settings.[81] Symptom-triggered treatment using the SAWS has been shown to be as safe and effective as a fixed-dose scheduled taper in an open-label RCT of outpatients.[78] Other sources, including the Guideline Committee, argue that the CIWA-Ar can be administered by patients or caregivers for symptom-triggered treatment if given sufficient instruction.[82] If patients meet criteria for treatment in a Level 1-WM setting and they or a caregiver can reliably assess signs and symptoms and follow guidance to determine whether a dose is needed, symptom triggered treatment is an appropriate option.

Fixed dosing is also appropriate in ambulatory settings. In a fixed-dose regimen, set amounts of medication are administered at regular intervals, and the dose amount, dosing frequency, or both are gradually tapered according to a set schedule. While fixed dosing is easy to administer, over- or underestimating the amount of benzodiazepine needed may lead to insufficient symptom control and over-sedation.[26] With fixed dosing, additional take home doses should be provided in the event symptoms are not adequately controlled.[58] Fixed-dose regimens do not eliminate the need for frequent monitoring and dose adjustment.[7,42] When initiating a fixed-dose regimen in an ambulatory setting, patients should be reassessed the next day to modify the dose, if needed.

Front loading conducted by trained staff is also appropriate in ambulatory settings and is preferred for patients at

risk for or experiencing severe alcohol withdrawal (e.g., CIWA-Ar scores $\geq$19).[45,70] Front loading describes when a moderate to high dose of a long-acting benzodiazepine is administered to achieve rapid control of withdrawal signs and symptoms and is allowed to taper through metabolism. Diazepam and chlordiazepoxide are the preferred agents for front loading. This regimen is typically used when rapid administration of a benzodiazepine is required, either because the patient is experiencing significant symptoms or is at risk of developing them. Front loading has been shown to reduce the duration of treatment, incidence of withdrawal seizure, and duration of delirium.[102] This effect is usually attributed to the rapid administration of large amounts of benzodiazepines early in the withdrawal period.[2,13] A front-loading regimen can be driven by a withdrawal severity scale (e.g., 10 mg diazepam PO every hour if CIWA-Ar score $\geq$ 10) or according to a fixed schedule (e.g., 20 mg diazepam PO every 2 hours for 3 doses). Symptom-triggered front loading has been shown to reduce symptom duration and the amount of benzodiazepine used,[70,103–106] the incidence of withdrawal seizures, and the duration of delirium for patients being treated in the Intensive Care Unit (ICU).[102] Fixed-dose front loading can be used with patients for whom it would be difficult to obtain an accurate score on a withdrawal severity scale.

Clinicians should monitor patients closely before and after providing a front loading dose for signs of over-sedation and respiratory depression as doses are more frequent with this regimen.[7,42] The need to observe patients does not necessarily preclude front loading in a Level 1-WM setting, as symptoms can often resolve in as few as 2-3 doses.

Because of their shorter duration of action, short-acting benzodiazepine concentrations can diminish rapidly, increasing the chance for rebound and breakthrough symptoms and signs including seizure. For this reason, a fixed-dose schedule with a long taper may be more feasible than a symptom-triggered dosing regimen requiring very frequent reassessment. Shorter-acting benzodiazepines should be tapered carefully even after withdrawal resolves to prevent the development of rebound or breakthrough signs and symptoms. If the CIWA-Ar is used in conjunction with short acting benzodiazepines, the assessments should be done promptly in order to prevent seizures due to protocol errors.[98]

(5) Carbamazepine, gabapentin, valproic acid

Recommendation IV.32: Gabapentin is a favorable choice for treating alcohol withdrawal when a clinician also plans to use it for a patient's ongoing treatment of alcohol use disorder.

Recommendation IV.33: If benzodiazepines are contraindicated, carbamazepine or gabapentin are appropriate alternatives.

Recommendation IV.34: Carbamazepine, gabapentin, or valproic acid may be used as an adjunct to benzodiazepine therapy to help control alcohol withdrawal. Before using as an adjunct, clinicians should ensure that an adequate dose of benzodiazepine has been administered.

Recommendation IV.35: Valproic acid should not be used in patients who have liver disease or women of childbearing potential.

Recommendation IV.36: There is insufficient evidence to support the use of valproic acid as monotherapy for the treatment of alcohol withdrawal.

Discussion. Evidence suggests that anticonvulsants, particularly carbamazepine, are effective at preventing alcohol withdrawal progression, seizures and delirium.[4] At this time, there is insufficient evidence to support their use over benzodiazepines for patients at increased risk of severe withdrawal, seizures, or delirium. [2,13,38,92,107] As the efficacy of benzodiazepines is well-established, there have been ethical concerns with running placebo-controlled or treatment-as-usual-controlled (i.e., compared to benzodiazepines) studies in at-risk populations.[2,92]

Carbamazepine or gabapentin are appropriate medications for treating low risk patients. They are also appropriate alternatives for patients with a benzodiazepine contraindication. Gabapentin may provide an effective bridge therapy from alcohol withdrawal treatment to long-term alcohol use disorder treatment.[92,93] It has been found to improve rates of abstinence and reduce heavy drinking days compared with placebo during the maintenance phase of alcohol use disorder treatment.[62] See Box 6 for caution regarding gabapentin misuse and diversion.

Some patients benefit from the addition of an adjunct medication to control signs and symptoms of withdrawal. Use of carbamazepine, gabapentin, or valproic acid as an adjunct to benzodiazepines may be appropriate. For patients in severe withdrawal, other medications can be used to manage signs and symptoms if benzodiazepines are already being given.[36] Before using an adjunct medication, clinicians should ensure that an adequate dose of benzodiazepine has been administered since large doses of benzodiazepine are sometimes needed to control withdrawal.

While valproic acid has been found to be promising for the treatment of alcohol withdrawal, more evidence is needed before it can be recommended as monotherapy.[62,109] Its use as

Box 6: Gabapentin misuse, abuse, and diversion[108]

The FDA approved the use of gabapentin for the treatment of epilepsy and post-herpetic neuralgia. However, gabapentin has commonly been used off-label for the treatment of various other conditions, including alcohol use disorder or chronic pain. When the development process for this guideline began, gabapentin was largely perceived as safe and having limited potential for misuse or abuse and was not classified as a controlled substance in most of the country. However, with the increased use of gabapentin in the treatment of other conditions, some states have identified the potential risk for misuse, abuse, and diversion and have reclassified gabapentin as a Schedule–V medication. A systematic review examining gabapentin's misuse, abuse and diversion potential found evidence to support the risk associated with prescribing gabapentin. Although gabapentin was only misused by 1% of the general population, 40–65% of individuals prescribed gabapentin have misused or abused the medication. Similarly, patients with a substance use disorder were more likely to misuse gabapentin. Given this recent evidence, the recommendations made in this guideline pertaining to the risk of misuse, abuse, or diversion of gabapentin should be interpreted cautiously.

an adjunct to benzodiazepines is supported.[2,13,44,58] However, valproic acid should not be used in patients with hematological or hepatic disorders including acute liver impairment[44] or in women of childbearing potential because of teratogenic risk.[110]

(6) Phenobarbital

Recommendation IV.37: Phenobarbital can be used for some patients in Level 2-WM ambulatory settings; however, it should only be used by clinicians experienced with its use given its narrow therapeutic window and side effects.

Recommendation IV.38: In a Level 2-WM ambulatory setting, phenobarbital monotherapy, managed by a clinician experienced with its use, is an appropriate alternative to benzodiazepines for patients who are experiencing severe alcohol withdrawal or who are at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal.

Recommendation IV.39: In a Level 2-WM ambulatory setting, phenobarbital monotherapy, managed by a clinician experienced with its use, is appropriate for patients with a contraindication for benzodiazepine use who are experiencing moderate or severe alcohol withdrawal or who are at risk of developing severe or complicated alcohol withdrawal or complication of alcohol withdrawal.

Discussion. There is disagreement in the literature regarding the appropriateness of phenobarbital in ambulatory settings, due to the risk of toxicity when used in combination with alcohol or in high doses.[13,97,111] In general, phenobarbital should only be used by clinicians experienced with its use in settings that offer close monitoring. Phenobarbital may cause respiratory depression and over-sedation and its narrow therapeutic window makes it challenging to dose correctly compared to other medications used to treat alcohol withdrawal. As with benzodiazepines, effects on the central nervous system are exacerbated when other CNS depressants such as alcohol are also used.

Phenobarbital may be appropriate in Level 2-WM ambulatory settings (e.g., ambulatory settings with extended onsite monitoring) as an alternative to benzodiazepines when benzodiazepine use is contraindicated. Phenobarbital is appropriate for such patients experiencing moderate or severe withdrawal or who are at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal. Phenobarbital is also an appropriate benzodiazepine alternative outright for patients experiencing or who are at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal.

See Box 7 for more information on phenobarbital.

Box 7: History of phenobarbital use in the treatment of alcohol withdrawal[128–130]

Phenobarbital is the first medication to be used successfully to treat alcohol withdrawal in a predictable way. It has been used for this purpose since the 1920's after first being introduced in 1912 for the treatment of seizures. It exerts its effects on the GABA-A receptor by increasing the duration of channel opening when bound to GABA, which increases the hyperpolarization of the neuron, thus indirectly increasing the sedative effects of the "GABA system." It also has direct blockade effects on excitatory glutamate signaling. Given these two mechanisms, it seems to be a perfect fit for the treatment of alcohol withdrawal, which creates an imbalance in these two systems. And, in experienced hands, it can be very effective.

However, phenobarbital has a number of side effects including bradycardia, bradypnea, hypothermia, hypotension, pulmonary edema, acute renal failure and Steven-Johnson syndrome. It has a half-life of up to seven days, is primarily metabolized by the liver and induces many isoenzymes of the P450 system. This coupled, with a relatively narrow therapeutic window, caused it to fall out of favor in the 1960's as chlordiazepoxide and oxazepam were shown to be as effective, but harbor a much lower risk. Now we have solid data that supports the use of GABA sensitive antiepileptiform medications that are as effective, require less training, and have a much lower side effect profile than phenobarbital or benzodiazepines. While, there is a current reemergence of interest in phenobarbital as a standalone therapy for alcohol withdrawal, these guidelines have taken into account history and comparative safety when developing the evidence-based recommendations for its use in the population as a whole.

(7) A2AAs and beta-blockers

Recommendation IV.40: Alpha2-adrenergic agonists (A2AAs) such as clonidine can be used as an adjunct to benzodiazepine therapy to control autonomic hyperactivity and anxiety when symptoms are not controlled by benzodiazepines alone. They should not be used alone to prevent or treat withdrawal-related seizures or delirium.

Recommendation IV.41: Beta-adrenergic antagonists (beta-blockers) can be used as an adjunct to benzodiazepines in select patients for control of persistent hypertension or tachycardia when these signs are not controlled by benzodiazepines alone. They should not be used to prevent or treat alcohol withdrawal seizures.

Discussion. No existing guidance or evidence was found regarding the use of alpha2-adrenergic agonists (A2AAs) and beta-adrenergic antagonists (beta-blockers) in ambulatory settings.

Many patients in alcohol withdrawal experience cardiac or adrenergic symptoms such as hypertension and tachycardia. These symptoms can be addressed by treating medical problems commonly seen in patients with alcohol withdrawal syndrome, such as dehydration and electrolyte imbalances or through use of benzodiazepines. A2AAs and beta-blockers can be used in conjunction with benzodiazepines to manage persistent hypertension or tachycardia.[44,97] While these medications reduce the signs of sympathetic activation, they do not treat the underlying pathophysiology, which may mask the hyperadrenergic state and lead to a false perception that these signs are properly treated. They also do not prevent withdrawal-related seizures or delirium and should not be used alone in the treatment of alcohol withdrawal.

See Box 8 for more information on A2AAs and beta-blockers.

(8) Inappropriate medications

Recommendation IV.42: Oral or intravenous alcohol should not be used for the prevention or treatment of alcohol withdrawal.

Recommendation IV.43: There is insufficient evidence to support the use of baclofen for the treatment of alcohol withdrawal.

Box 8: Alpha2-adrenergic agonists and beta-adrenergic antagonists

Alpha2-adrenergic agonists (A2AAs) and beta-adrenergic antagonists (beta-blockers) can be used in conjunction with benzodiazepines to manage persistent hypertension or tachycardia. A2AAs bind to receptors inhibiting the release of norepinephrine from the presynaptic neuron. The release of norepinephrine would cause an increase in activity of the sympathetic pathway leading to increased heart rate and blood pressure. Therefore, A2AAs reduce cardiac output and reduce tachycardia and hypertension.

Beta-blockers have a different mechanism of action. Normally norepinephrine released from sympathetic nerves binds to beta-adrenoceptors resulting in activation of the sympathetic pathway causing an increase in heart rate and blood pressure. However, beta-blockers compete with norepinephrine and epinephrine for the same binding site. Thus norepinephrine is unable to bind to the site, which reduces the signs of sympathetic activity including heart rate and blood pressure. Unlike A2AAs, beta-blockers do not reduce sympathetic activity but rather mask signs and symptoms associated with sympathetic activation such as tachycardia and hypertension.

These medications do not treat the underlying pathophysiology, but reduce signs, which may mask the hyperadrenergic state and lead to a false perception that these signs are properly treated. Although not explicitly rated by the Guideline Committee, persistent hypertension or tachycardia may be reasons to transfer patients to an inpatient setting.

Recommendation IV.44: Providing magnesium as a prophylaxis or treatment for alcohol withdrawal management has no supporting evidence.

Discussion. While ethyl alcohol administration has been used to manage withdrawal, it is not recommended.[2,13,58] Administration of oral or intravenous alcohol has no proven efficacy, no accepted protocols, and known toxicity.[13]

A recent Cochrane review of three RCTs on the use of baclofen for alcohol withdrawal treatment drew no conclusions about efficacy or safety of baclofen due to insufficient and low quality evidence.[112,113]

ASAM's 2004 guideline, ''Management of Alcohol Withdrawal Delirium'', suggested that magnesium may reduce neuromuscular activity in patients experiencing alcohol withdrawal delirium. However, a recent Cochrane review[114] concluded that there is not enough evidence to determine the benefit of magnesium in alcohol withdrawal prevention or management, which is in agreement with the ASAM's 1997 guideline on alcohol withdrawal management.[13]

V. Inpatient Management of Alcohol Withdrawal

This guideline divides recommendations on the management of alcohol withdrawal into two broad categories where withdrawal management services are provided: ambulatory and inpatient settings. While there are many differences in the services provided within these categories, and services should not ideally be tied to a specific setting, this organization follows a reasonable structure that seems to match how providers currently think about their practice context. The goal is that practitioners can reference one management section or the other. There are many shared service practices across categories, however, which creates a great deal of repetition across sections. This organization was intentional. As most readers do not read through an entire guideline, the goal was to ensure that each section stands on its own.

The section applies to inpatient settings where withdrawal management is provided. This includes two Level 3 settings and one Level 4 setting as defined in *The ASAM Criteria.* These levels of care are primarily differentiated by the intensity of clinical services and medical training of staff. *Level 3.2-WM* clinically managed residential withdrawal management is a residential service providing 24-hour structure and support by trained, non-medical staff. They may have concurrent medical services equivalent to primary care, but medical care is not provided 24/7. In some programs, staff supervise patients as they self-administer medications. *Level 3.7-WM* medically monitored inpatient withdrawal management is a residential service providing 24-hour structure and support by medical and nursing staff. They may be located in a specialty addiction treatment or mental health setting with addiction treatment services. *Level 4-WM* medically managed intensive inpatient withdrawal management is a medical or psychiatric hospital service with an addiction specialist physician (see *The ASAM Criteria* for additional details). (See Appendix IV.D., http://links.lww.com/JAM/A192 for a summary inpatient management protocol).

This section is primarily informed by the extensive body of research conducted in hospital settings. However, they should apply to all inpatient settings unless otherwise specified (e.g., treatment in Intensive Care Unit [ICU] or Cardiac/Coronary Care Unit [CCU]). Additional recommendations specific to hospitalized patients or patients that are hospitalized primarily for a reason other than alcohol withdrawal are included in the section VII: Specific Settings and Populations.

A. Monitoring

Recommendation V.1: The following monitoring schedule is appropriate:

- In patients with moderate to severe withdrawal or those requiring pharmacotherapy, re-assess every 1–4 hours for 24 hours, as clinically indicated. Once stabilized (e.g., CIWA-Ar score < 10 for 24 hours), monitoring can be extended to every 4–8 hours for 24 hours, as clinically indicated.
- Patients with mild withdrawal and low risk of complicated withdrawal may be observed for up to 36 hours, after which more severe withdrawal is unlikely to develop.

Recommendation V.2: Monitor patients' vital signs, hydration, orientation, sleep, and emotional status including suicidal thoughts.

Recommendation V.3: Monitor patients receiving pharmacotherapy for alcohol withdrawal for signs of oversedation and respiratory depression.

Recommendation V.4: Signs and symptoms of alcohol withdrawal should be monitored during withdrawal management with a validated assessment scale (see Appendix III for a summary of scales and their associated features).

Discussion. Optimal monitoring frequency is a balance between clinical need and feasibility. Many sources, including *The ASAM Criteria*, designate appropriate thresholds for

frequency of monitoring. In a review of studies comparing inpatient with outpatient alcohol withdrawal management, monitoring intervals ranged from 30 minutes to 8 hours.[42,45] Monitoring of patients experiencing moderate and severe withdrawal or patients experiencing mild withdrawal who are at increased risk for developing severe, complicated, or complications of withdrawal should initially be conducted every 1–4 hours or as clinically indicated.[7] Monitoring frequency can be reduced to every 4–8 hours or as clinically indicated for stabilized patients, usually defined as having controlled symptoms (e.g., CIWA-Ar score < 10) for 24 hours.[45]

Patients experiencing mild withdrawal who are at minimal risk for developing severe, complicated, or complications of withdrawal can be observed for a shorter duration of up to 36 hours, after which more severe withdrawal is unlikely to develop.[41] Optimal frequency of monitoring for patients in mild withdrawal was not established by the Guideline Committee, and they determined that frequency would be driven more by the complicating factor(s) that led a patient in mild withdrawal to be treated in an inpatient setting.

Signs and symptoms of alcohol withdrawal should be monitored using a validated withdrawal severity scale.[13,45] As discussed in section II.D: Symptom Assessment Scales, various symptom assessment scales have been developed to address circumstances such as a confounding illness or symptom self-reporting barriers (see Appendix III for a summary of scales and their associated features). Clinicians should ensure that signs and symptoms are not worsening, that patients are responding as expected to medication if provided, and that signs and symptoms are not persisting beyond the expected timeline of withdrawal. Any of these indicate the need to reassess a patient's treatment plan and/or level of care.

Monitoring should consist of assessing a patient's vital signs, hydration, orientation, sleep, and emotional status including suicidal thoughts.[36,115] Fluid intake and output can be tracked in hospital settings, but they can be monitored by patient report and observing for signs of dehydration in other inpatient settings.[36] Orientation, sleep quality and emotional status including suicidality should be monitored. Orientation and anxiety are included in many withdrawal severity scales. Poor orientation can also indicate over-sedation from prescribed withdrawal medication. Patients receiving pharmacotherapy for alcohol withdrawal should be monitored for other signs of over-sedation and respiratory depression including ataxia, confusion, memory impairment, and delirium.

B. Supportive Care

Recommendation V.5: Supportive care is a critical component of alcohol withdrawal management. Frequent reassurance, re-orientation to time and place, and nursing care are recommended non-pharmacological interventions. Providers should ensure patients are educated about what to expect over the course of withdrawal, including common signs and symptoms and how they will be treated. Patients with severe alcohol withdrawal should be cared for in an evenly lit, quiet room. Patients should be offered hope and the expectation of recovery.

Recommendation V.6: Supportive care for alcohol withdrawal patients includes adherence to safety measures and protocols (e.g., assess risk for fall/syncope). If available and applicable, existing institutional/hospital-associated delirium protocols can be used for supportive care of patients with severe alcohol withdrawal.

Recommendation V.7: Thiamine should be provided to prevent Wernicke encephalopathy.

- Intravenous (IV) or intramuscular (IM) administration of thiamine is preferred, in particular for patients with poor nutritional status, malabsorption, or who are known to have severe complications of alcohol withdrawal.
- Typical dosing is 100 mg IV/IM per day for 3–5 days. Oral thiamine also can also be offered.
- Patients also receiving glucose can be administered thiamine and glucose in any order or concurrently.

Recommendation V.8: Clinicians should administer thiamine to patients admitted to the ICU to treat alcohol withdrawal.

Recommendation V.9: For patients with hypomagnesemia, cardiac arrhythmias, electrolyte disturbances, or a previous history of alcohol withdrawal seizures, magnesium should be administered.

Recommendation V.10: If phosphorus is <1 mg/dL, supplementation should be provided. Otherwise, in the case of moderate hypophosphatemia (1–2 mg/dL), correction through proper nutrition is recommended.

Recommendation V.11: In patients who are critically ill, folate supplementation may be considered, since chronic alcohol use is associated with hyperhomocysteinemia.

Discussion. Supportive non-pharmacologic care is a critical component of alcohol withdrawal management. While empirical research on many of the components of supportive care is not available, existing reviews and guidelines support interventions such as informing patients of what to expect over the course of treatment and providing frequent reassurance,[4] reality orientation, and general nursing care during treatment.[2,7,36,70,115] Also emphasized was providing care in a quiet, evenly-lit room.[2,7,14,36,70,116]

Non-pharmacological supportive care also includes following standard care protocols and safety protocols. Safety measures such as fall precautions and routine nurse check-ins and assistance with activities of daily living (ADLs) ensures patient safety and provides autonomy. For facilities with a hospital-associated delirium protocol, clinicians should implement the protocol to prevent and reduce the incidence and duration of acute delirium among patients with severe alcohol withdrawal. Studies have shown standardized protocols to be effective at reducing the incidence, duration, and frequency of delirium among hospitalized patients.[117]

Determining risk for Wernicke is not standardized. For example, the NICE guideline recommends parenteral administration of thiamine to any hospitalized patient who is a harmful or dependent drinker.[21] At least one Wernicke encephalopathy risk assessment scale for patients withdrawing from alcohol has been developed.[118] The presence of risk factors for Wernicke encephalopathy (malnutrition or poor

diet, weight loss, vomiting, confusion, or other neurological symptoms) is scored depending on severity and results indicate whether enteral or parenteral thiamine should be administered.

Previous guidelines, including the previous ASAM alcohol withdrawal management guideline, have recommended that IV thiamine be given prior to intravenous glucose.[14,36,44,115] The reasoning was that thiamine is necessary for carbohydrate metabolism and thiamine deficiency can lead to decreased absorption of glucose, perhaps precipitating acute Wernicke encephalopathy. However, there is a lack of clinical evidence to support this theory and it is important that glucose delivery not be delayed in patients who are nutritionally compromised. The Guideline Committee concluded that it is not necessary to administer thiamine prior to glucose, that these could be provided in any order or concurrently in order to not delay treatment.

Other common deficiencies seen in patients with alcohol withdrawal include low folate, magnesium, phosphorous and potassium. While early work recommended an aggressive approach to correcting nutritional deficiencies, more recent thinking is that levels self-correct rapidly with improved diet. The Guideline Committee supported a conservative stance of selectively correcting hypomagnesemia, hypokalemia, and acute severe hypophosphatemia (serum phosphate $<$ 1 mg/dL) when they are detected through laboratory testing.[115] Magnesium can also be routinely supplemented in patients with cardiac arrhythmias or a previous history of alcohol withdrawal seizures.[7] Folate supplementation with 1 mg daily can also be considered for patients who are critically ill because folate is not included in the recommended routine laboratory tests and chronic alcohol use is associated with hyperhomocysteinemia resulting from folate deficiency.[26,45,115]

C. AUD Treatment Initiation and Engagement

Recommendation V.12: The period of alcohol withdrawal management should be used to engage patients with an alcohol use disorder (AUD) with comprehensive treatment. When feasible, AUD treatment should be initiated concurrently with alcohol withdrawal management as cognitive status permits. If appropriate, clinicians should also offer to initiate pharmacotherapy for AUD as cognitive status permits. Clinicians should explain the range of evidence-based treatment services available at the current site and in the community. Finally, clinicians should proactively connect patients to treatment services as seamlessly as possible, including initiating a warm handoff to treatment providers.

Discussion. One important function of supportive care is to connect with patients to help facilitate continuing treatment.[2]

It is widely recognized that alcohol withdrawal management alone is not a treatment for alcohol use disorder (AUD). The need for alcohol withdrawal management services almost universally signifies the presence of an alcohol use disorder and need for treatment. The Guideline Committee agreed that it should be explicitly communicated to alcohol withdrawal patients if they have an alcohol use disorder and engaged with treatment for that disorder.

Several leading clinical guidelines conclude that the success of an alcohol withdrawal management episode is defined not only by the acute management of withdrawal signs and symptoms, but by the engagement in continued treatment for alcohol use disorder by patients.[4,12,80] Whenever possible, AUD treatment should be initiated concurrent with alcohol withdrawal management as cognitive status permits.[12] At a minimum, clinicians should proactively connect patients to AUD treatment services and transition patients as seamlessly as possible through a warm handoff to treatment providers.

Despite the clear and frequently stated importance of the transition between withdrawal management and long-term AUD treatment, research on optimal strategies is extremely sparse. More recently, studies are including follow-up measures such as entry into AUD treatment following withdrawal completion, but this is rarely a primary outcome of interest. One RCT conducted in the United States[119] found that participants who received three Motivational Interviewing sessions during inpatient withdrawal treatment were more likely to attend self-help groups two months after discharge compared to control participants, but were not more likely to be abstinent or engage in formal AUD treatment.

Another method of improving AUD treatment initiation may result from changes in health care system integrations and payment structures. Successfully transitioning patients from alcohol withdrawal management to alcohol use disorder treatment will result in fewer repeat alcohol withdrawal management episodes, and therefore better outcomes and lower cost. Initiating AUD treatment after alcohol withdrawal can be used as a performance measure or integrated into reimbursement contracts as "to not include facilitation of treatment entry would be considered inadequate and incomplete treatment."[4 (p7)] Levels of care that are part of "integrated systems of care which are accountable (financially and otherwise) for health outcomes will be highly motivated to use the withdrawal management encounter as an opportunity to identify cases of addiction that need to be treated and otherwise may have escaped identification."[12 (p129)]

D. Pharmacotherapy

(1) Prophylaxis

Recommendation V.13: For patients at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal, preventative pharmacotherapy should be provided. Benzodiazepines are first-line treatment because of their well-documented effectiveness in reducing the signs and symptoms of withdrawal including the incidence of seizure and delirium. For patients with a contraindication for benzodiazepine use, phenobarbital can be used by providers experienced with its use. In settings with close monitoring, phenobarbital adjunct to benzodiazepines is also appropriate.

Recommendation V.14: A front loading regimen is recommended for patients at high risk of severe withdrawal syndrome. Providing at least a single dose of preventative medication is appropriate for patients at lower levels of risk who have:

- A history of severe or complicated withdrawal
- An acute medical, psychiatric, or surgical illness
- Severe coronary artery disease
- Displaying signs or symptoms of withdrawal concurrent with a positive blood alcohol content

Discussion. Determining risk of developing severe or complicated withdrawal or complications of withdrawal is addressed in section II: Initial Assessment of Alcohol Withdrawal. Patients at risk of developing severe or complicated alcohol withdrawal or complications from alcohol withdrawal should receive pharmacotherapy as soon as possible to prevent these signs and symptoms.[4,13,89] Benzodiazepines are recommended as the primary medication to prevent the development of severe, complicated, or complications of withdrawal. There is clear evidence that benzodiazepines reduce the incidence of alcohol withdrawal seizures and alcohol withdrawal delirium. Phenobarbital can be used for patients with a contraindication for benzodiazepine use. However, given its narrow therapeutic window, it should only be used by clinicians experienced with its use.

For patients at high risk of severe withdrawal, front loading with a benzodiazepine is recommended to rapidly achieve therapeutic levels of medication. Front loading has been shown to reduce the duration of treatment, incidence of withdrawal seizure, and duration of delirium.[2,13,102] Patients should be closely observed for over-sedation and respiratory depression following the administration of a loading dose.

For patients at lower levels of risk, providing at least a single or a few doses of benzodiazepine is appropriate and can be followed by a medication chosen according to symptom severity (see V.D(2): Withdrawal symptoms).[2,4] If a clinician determines that a patient is no longer at risk, for example, because risk is sufficiently mitigated by administration of medication or because the course of withdrawal has passed the period of acute risk, ongoing pharmacotherapy for alcohol withdrawal can be determined according to the severity of a patient's withdrawal at that time. Some situations which have been called out as appropriate for administering at least a single dose of benzodiazepines include: a history of severe or complicated withdrawal; risk for complications of significant medical, surgical, or psychiatric illness (particularly cardiovascular disease including coronary artery disease);[4] and displaying signs or symptoms of withdrawal concurrent with a positive blood alcohol content (an indication of risk for developing severe withdrawal syndrome). (See Appendix IV.B., http://links.lww.com/JAM/A192 for a flowchart on pharmacotherapy considerations).

(2) Withdrawal symptoms

Recommendation V.15: For patients experiencing mild alcohol withdrawal (e.g., CIWA-Ar score <10) who are at minimal risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal, pharmacotherapy or supportive care alone may be provided. If providing medication, benzodiazepines, carbamazepine, or gabapentin are appropriate. For patients with a contraindication for benzodiazepine use, carbamazepine, gabapentin, or phenobarbital (for providers experienced with its use) are appropriate. Carbamazepine, gabapentin, or valproic acid (if no liver disease or childbearing potential) may be used as an adjunct to benzodiazepines.

Recommendation V.16: Patients experiencing moderate alcohol withdrawal (e.g., CIWA-Ar scores 10–18) should receive pharmacotherapy. Benzodiazepines are first-line treatment. Carbamazepine or gabapentin are appropriate alternatives. For patients with a contraindication for benzodiazepine use, carbamazepine, gabapentin, or phenobarbital (for providers experienced with its use) are appropriate. Carbamazepine, gabapentin, or valproic acid (if no liver disease or childbearing potential) may be used as an adjunct to benzodiazepines.

Recommendation V.17: Patients experiencing severe alcohol withdrawal (e.g., CIWA-Ar scores ≥19) should receive pharmacotherapy. Benzodiazepines are first-line treatment. For patients with a contraindication for benzodiazepine use, phenobarbital is appropriate for providers experienced with its use. If close monitoring is available, phenobarbital can be used as an adjunct to benzodiazepines. Other adjunct medications can be considered after a clinician ensures that an adequate dose of benzodiazepines has been administered.

Recommendation V.18: If a patient's symptoms are not controlled as expected:

- First consider increasing the dose

If over-sedation or inadequate monitoring is a concern:

- Reassess for appropriate level of care
- Consider switching medication
- If using benzodiazepines, consider adding an adjunct medication

Discussion. For patients experiencing mild alcohol withdrawal (e.g., CIWA-Ar score <10) who are at minimal risk of developing severe, complicated, or complications of alcohol withdrawal, the decision to provide medication to alleviate symptoms of withdrawal is at the discretion of clinicians. Previous guidelines and reviews have indicated that patients experiencing mild alcohol withdrawal (e.g., CIWA-Ar score <10) who are at minimal risk of worsening symptoms can be safely treated with monitored supportive care alone.[13,51] Early evidence for the safety of non-pharmacological treatment of alcohol withdrawal draws from studies of ''social detoxification'' settings.[120–122] Research has demonstrated that patients who never reach a CIWA-Ar score ≥ 10 and thus do not receive medication in accordance with a symptom-triggered protocol are not at higher risk of adverse events than patients who received medication through a fixed-dose protocol. In addition, patients receiving medications through a symptom triggered protocol require less medication overall and experience a shorter duration of treatment.[123–126] Others have argued that any withdrawal signs and symptoms are harmful to patient health[4] and that untreated withdrawal contributes to the kindling process, whereby repeated episodes of alcohol withdrawal syndrome become progressively severe through increased neuronal excitability and sensitivity.[7] Patients experiencing moderate or severe withdrawal (e.g., CIWA-Ar scores ≥ 10) should receive pharmacotherapy. Moderate to severe withdrawal at treatment baseline has been identified as a risk factor for developing more severe withdrawal during the course of treatment.[54]

Carbamazepine and gabapentin are appropriate for managing mild and moderate alcohol withdrawal in patients who are at minimal risk of developing severe or complicated alcohol withdrawal.[92–94] As symptom severity or risk of developing severe symptoms increases, medications with well-established effectiveness in preventing the incidence of severe and complicated withdrawal are preferred.[54] Benzodiazepines are first-line agents for treating moderate[58,65,81] and severe alcohol withdrawal[13,58] due to their known effectiveness in preventing seizures and delirium.[13,90,94] Benzodiazepines are also appropriate for patients experiencing mild withdrawal in inpatient settings due to the reduced risks associated with use in settings with more intensive monitoring. Carbamazepine, gabapentin, or phenobarbital can be used for patients experiencing mild or moderate withdrawal who have a contraindication for benzodiazepine use.[58,65,81,92] Phenobarbital is the preferred alternative for patients experiencing severe withdrawal. However, given its narrow therapeutic window, phenobarbital should only be used by clinicians experienced with its use.

Patients receiving pharmacotherapy should be monitored for signs of response to medication. If the patient does not respond as expected, a number of actions can be considered. First, consider increasing the dose. The amount of medication required to control symptoms is variable and ultimately determined by clinical judgment. Patients with more severe withdrawal may require larger doses than are typically seen in other patient populations, particularly during early withdrawal (see Appendix V for typical doses). Providing large doses of benzodiazepine can lead to over-sedation and respiratory depression and patients should be monitored closely.

Second, patients should be reassessed for appropriate level of care. Failure to respond may reflect the presence of more severe withdrawal than expected and significant risk of major complications.[13] A more intensive level of care may be needed to monitor and manage major complications if they occur.[82]

Third, consider switching to a different medication. Failure to respond to benzodiazepine may reflect benzodiazepine resistance due to kindling (see section VI.D: Resistant Alcohol Withdrawal). A greater number of previous alcohol withdrawal episodes can be associated with decreased responsiveness to benzodiazepines.[4] Failure to respond may also be due to withdrawal from another GABAergic agent. In these cases, switching to an alternative medication should be considered.

Fourth, if using benzodiazepines, consider adding an adjunct medication. Some patients benefit from the addition of an adjunct medication to control signs and symptoms of withdrawal and their use can be considered as part of the treatment plan. The use of carbamazepine, gabapentin, or valproic acid as an adjunct medication may be appropriate for patients experiencing moderate or severe withdrawal. Valproic acid should not be used in patients who have acute liver impairment or women of childbearing potential (see V.D: Carbamazepine, gabapentin, valproic acid). Adjunct phenobarbital can be used in patients with severe withdrawal in settings with close monitoring. Phenobarbital and benzodiazepines act on the same receptors, which leads to additive clinical effects in controlling alcohol withdrawal syndrome (see Box 7).[111] Alpha2-adrenergic agonists and beta-adrenergic antagonist can be used in conjunction with benzodiazepines to manage persistent hypertension or tachycardia (see V.D: A2AAs and beta-blockers).[44,97]

(3) Benzodiazepine use

Recommendation V.19: While no particular benzodiazepine agent is more effective than another, longer-acting benzodiazepines are the preferred agents due to clinical benefits of their longer duration of action.

Recommendation V.20: If waiting for lab test results or if the test are unavailable, if a patient has signs of significant liver disease, use a benzodiazepine with less hepatic metabolization.

Recommendation V.21: Clinicians should monitor patients taking benzodiazepines for signs of over-sedation and respiratory depression.

Recommendation V.22: A benzodiazepine prescription to treat alcohol withdrawal should be discontinued following treatment.

Discussion. Benzodiazepines are commonly recommended as first-line agents for managing most forms of alcohol withdrawal.[13,94] Diazepam, lorazepam, and chlordiazepoxide are the most frequently used in treating alcohol withdrawal. While there is no evidence showing superiority of effectiveness among benzodiazepine agents,[13,90] longer-acting agents are preferred by many clinicians.[2,51,81] A long duration of action contributes to a smoother course of withdrawal and greater control of breakthrough and rebound signs or symptoms. This provides greater coverage for preventing alcohol withdrawal seizures and delirium.[90] For this reason, patients prescribed a shorter-acting agent should have a more gradual taper and be reassessed more frequently (see V.D(4): Benzodiazepine dosing regimens).[98]

Longer-acting agents can accumulate and lead to over-sedation and respiratory depression, particularly in older patients or those with compromised health. Other signs of accumulation include ataxia, confusion, memory impairment, and delirium, which may be difficult to differentiate from alcohol withdrawal-related delirium.[2] Benzodiazepine associated delirium has been diagnosed by the administration of flumazenil, a GABA-A receptor antagonist, but this protocol was not reviewed by the Guideline Committee.[99] A reduction in the benzodiazepine dose and the addition of a neuroleptic agent to control for agitation and/or confusion can be considered if patients are not at an elevated risk of seizure (i.e., they are outside of the acute risk window).[2] Some neuroleptic agents have been shown to reduce the seizure threshold.

Benzodiazepine accumulation is more likely in patients with impaired hepatic function. Medication dose can be reduced or a benzodiazepine with less dependence on hepatic metabolism can be used (see VII.D: Patients with Medical Conditions). The laboratory tests recommended in section II.E: Identify Concurrent Conditions can indicate the need to adjust the treatment plan. However, as treatment should not be delayed while waiting for lab test results or if the test(s) are unavailable at the treatment setting, it is appropriate to

initially reduce the dose or use a benzodiazepine with less hepatic metabolization if a patient has signs of significant liver disease.

Signs of significant liver disease include:

- Skin and eyes that appear yellowish (jaundice)
- Swelling in the legs and ankles (edema)
- Itchy skin
- Dark urine color
- Pale stool color, or bloody or tar-colored stool
- Confusion
- Chronic fatigue
- Nausea or vomiting

(4) Benzodiazepine dosing regimens

Recommendation V.23: Symptom-triggered treatment is the preferred benzodiazepine dosing method. Fixed dosing according to a scheduled taper is appropriate if symptom-triggered treatment cannot be used.

Recommendation V.24: Front loading is recommended for patients experiencing severe alcohol withdrawal (e.g., CIWA-Ar scores $\geq$19). Diazepam or chlordiazepoxide are preferred agents for front loading.

Recommendation V.25: When using a fixed-dose schedule, patients' signs and symptoms should still be monitored, and additional doses of medication provided as needed.

Recommendation V.26: If prescribing a shorter-acting benzodiazepine, using a fixed-dose regimen with a gradual taper may be appropriate to reduce the likelihood of breakthrough and rebound signs and symptoms.

Discussion. Examples for these dosing regimens can be found in Appendix V.

Multiple dosing strategies have been used to administer benzodiazepines during alcohol withdrawal. In general, symptom-triggered treatment is the preferred dosing method. In this regimen, medication is administered only when patients are experiencing significant withdrawal symptoms according to a severity scale. This allows dosing to be individualized according to symptom severity and reduces the risk of under- and over-treating by assessing and dosing according to real-time symptom severity. Very large doses of medication may be needed rapidly, and reduced as symptoms resolve.[2,13] Symptom-triggered dosing has been shown to reduce the duration of treatment and inpatient length of stay compared to a fixed-dose schedule.[2,21,44,51]

Fixed dosing is appropriate when it is not practical to obtain a symptom severity score to conduct symptom-triggered treatment. In a fixed-dose regimen, set amounts of medication are administered at regular intervals, and the dose amount, dosing frequency, or both are gradually tapered according to a set schedule. While fixed dosing is easy to administer, over- or underestimating the amount of benzodiazepine needed may lead to insufficient symptom control or over-sedation.[26] Additional doses[58] and dose adjustment should be provided as needed.[7,42]

Front loading is preferred for patients at risk for or experiencing severe alcohol withdrawal (e.g., CIWA-Ar scores $\geq$19). Front loading describes when a moderate to high dose of a long-acting benzodiazepine is administered to achieve rapid control of withdrawal signs and symptoms and is allowed to taper through metabolism. Diazepam and chlordiazepoxide are the preferred agents for front loading. This regimen is typically used when rapid administration of a benzodiazepine is required, either because patients are experiencing significant symptoms or are at risk of developing them. Front loading has been shown to reduce the duration of treatment and incidence of withdrawal seizure and duration of delirium.[102] This effect is usually attributed to the rapid administration of large amounts of benzodiazepines early in the withdrawal period.[2,13] A front loading regimen can be driven by a withdrawal symptom severity scale (e.g., 10 mg diazepam PO every hour if CIWA-Ar score $\geq$10) or according to a fixed schedule (e.g., 20 mg diazepam PO every 2 hours for 3 doses). Symptom-triggered front loading has been shown to reduce symptom duration and the amount of benzodiazepine used,[70,103–106] the incidence of withdrawal seizures, and the duration of delirium for patients being treated in the ICU.[102] Fixed-dose front loading can be used in patients for whom it would be difficult to obtain an accurate score on a withdrawal severity scale.

While monitoring for signs of over-sedation and respiratory depression is important for any dosing regimen,[49] it is particularly important for patients on fixed-dose and front-loading regimens. Patients receiving fixed doses can become over-sedated if the wrong schedule is chosen and front-loading doses are rapidly administered.[7,42]

Because of their shorter duration of action, short-acting benzodiazepine concentrations can diminish rapidly, increasing the chance for rebound and breakthrough symptoms and signs including seizure. For this reason, a fixed-dose schedule with a long taper may be more feasible than a symptom-triggered dosing regimen requiring very frequent reassessment. Shorter-acting benzodiazepines should be tapered carefully even after withdrawal resolves to prevent the development of rebound or breakthrough signs and symptoms. If the CIWA-Ar is used in conjunction with short acting benzodiazepines, the assessments should be done promptly in order to prevent seizures due to protocol errors.[98]

(5) Carbamazepine, gabapentin, valproic acid

Recommendation V.27: Gabapentin is a favorable choice for treating alcohol withdrawal when a clinician also plans to use it for a patient's ongoing treatment of alcohol use disorder.

Recommendation V.28: If benzodiazepines are contraindicated, carbamazepine or gabapentin are appropriate alternatives for patients in mild or moderate withdrawal.

Recommendation V.29: Carbamazepine, gabapentin, or valproic acid may be used as an adjunct to benzodiazepine therapy to help control alcohol withdrawal. Before using as an adjunct, clinicians should ensure that an adequate dose of benzodiazepine has been administered.

Recommendation V.30: Valproic acid should not be used in patients who have liver disease or women of childbearing potential.

Recommendation V.31: There is insufficient evidence to support the use of valproic acid as monotherapy for the treatment of alcohol withdrawal.

Discussion. Evidence suggests that anticonvulsants, particularly carbamazepine, are effective at preventing alcohol withdrawal progression, seizures and delirium.[4] At this time, there is insufficient evidence to support their use over benzodiazepines for patients at increased risk of severe withdrawal, seizures, or delirium.[2,13,38,92,107] As the efficacy of benzodiazepines is well-established, there have been ethical concerns with running placebo-controlled or treatment-as-usual-controlled (i.e., compared to benzodiazepines) studies in at-risk populations.[2,92]

Carbamazepine or gabapentin are appropriate medications for treating low risk patients. They are also appropriate alternatives for patients with a benzodiazepine contraindication. Gabapentin may provide an effective bridge therapy from alcohol withdrawal treatment to long-term alcohol use disorder treatment.[92,93] It has been found to improve rates of abstinence and reduce heavy drinking days compared with placebo during the maintenance phase of alcohol use disorder treatment.[62]

Some patients benefit from the addition of an adjunct medication to control signs and symptoms of withdrawal. Use of carbamazepine, gabapentin, or valproic acid as an adjunct to benzodiazepines is an appropriate therapy for patients experiencing mild or moderate withdrawal. For patients in severe withdrawal, other medications can be used to manage signs and symptoms if benzodiazepines have already being given.[36] Before using as an adjunct medication, clinicians should ensure that an adequate dose of benzodiazepine has been administered since large doses of benzodiazepine are sometimes needed to control withdrawal.

While valproic acid has been found to be promising for the treatment of alcohol withdrawal, more evidence is needed before it can be recommended as monotherapy.[62,109] Its use as an adjunct to benzodiazepines is supported.[2,13,44,58] However, valproic acid should not be used in patients with hematological or hepatic disorders including acute liver impairment[44] or in women of childbearing potential because of teratogenic risk.[110]

(6) Phenobarbital

Recommendation V.32: Phenobarbital can be used for some patients in inpatient settings; however, it should only be used by clinicians experienced with its use given its narrow therapeutic window and side effects.

Recommendation V.33: In an inpatient setting, phenobarbital monotherapy (managed by a clinician experienced with its use) is appropriate for patients with a contraindication for benzodiazepine use who are experiencing mild, moderate, or severe withdrawal or who are at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal.

Recommendation V.34: In an inpatient setting, if close monitoring is available, phenobarbital (managed by a clinician experienced with its use) as an adjunct to benzodiazepines is an option for patients experiencing severe withdrawal or who are at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal.

Recommendation V.35: Parenteral phenobarbital should only be used in highly supervised settings (e.g., ICU, CCU) because of risk of over-sedation and respiratory depression.

Discussion. In general, phenobarbital should only be used by clinicians experienced with its use and should be used cautiously in settings that offer less monitoring. Phenobarbital may cause respiratory depression and over-sedation and its narrow therapeutic window makes it challenging to dose correctly compared to other medications used to treat alcohol withdrawal. Phenobarbital is more commonly used in an inpatient setting that is highly supervised such as the ICU or the Emergency Department (ED) for these reasons.

A primary indication for phenobarbital use is as an alternative to benzodiazepines when benzodiazepine use is contraindicated. This is appropriate for patients experiencing mild, moderate, or severe withdrawal or who are at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal.

Phenobarbital is also an effective adjunct to benzodiazepines and, if close monitoring is available, can be used for patients experiencing severe withdrawal or who are at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal. Providing a single dose of IV phenobarbital 10 mg/kg in 100 mL normal saline infused over 30 minutes in addition to lorazepam in the ED was shown to reduce the rate of ICU admissions without increasing the incidence of adverse events.[127] This strategy requires close monitoring in highly supervised settings as parenteral administration of phenobarbital is associated with increased overdose risk.

(7) A2AAs and beta-blockers

Recommendation V.36: Alpha2-adrenergic agonists (A2AAs) such as clonidine and dexmedetomidine can be used as an adjunct to benzodiazepine therapy to control autonomic hyperactivity and anxiety when these signs are not controlled by benzodiazepines alone. They should not be used alone to prevent or treat withdrawal-related seizures or delirium.

Recommendation V.37: Beta-adrenergic antagonists (beta-blockers) can be used as an adjunct to benzodiazepines in select patients for control of persistent hypertension or tachycardia when these signs are not controlled by benzodiazepines alone. They should not be used to prevent or treat alcohol withdrawal seizures.

Discussion. Many patients in alcohol withdrawal experience cardiac or adrenergic signs such as hypertension and tachycardia.[45] These signs can be addressed by treating medical problems commonly seen in patients with alcohol withdrawal syndrome, such as dehydration and electrolyte imbalances or through the use of benzodiazepines. Alpha2-adrenergic agonists (A2AAs) and beta-adrenergic antagonist (beta-blockers) can be used in conjunction with benzodiazepines to manage persistent hypertension or tachycardia.[44,97] While these medications reduce the signs of sympathetic activation, they do not treat the underlying pathophysiology, which may mask the hyperadrenergic state and lead to a false perception that these signs are properly treated. They also do not prevent

withdrawal-related seizures or delirium and should not be used alone in the treatment of alcohol withdrawal.

(8) Inappropriate medications

Recommendation V.38: Oral or intravenous alcohol should not be used for the prevention or treatment of alcohol withdrawal.

Recommendation V.39: There is insufficient evidence to support the use of baclofen for the treatment of alcohol withdrawal.

Recommendation V.40: Providing magnesium as a prophylaxis or treatment for alcohol withdrawal management has no supporting evidence.

Discussion. While ethyl alcohol administration has been used to manage withdrawal, it is not recommended.[2,13,58] Administration of oral or intravenous alcohol has no proven efficacy, no accepted protocols, and known toxicity.[13]

A recent Cochrane review of three RCTs on the use of baclofen for alcohol withdrawal treatment drew no conclusions about efficacy or safety of baclofen due to insufficient and low quality evidence.[112]

ASAM's 2004 guideline, ''Management of Alcohol Withdrawal Delirium,'' suggested that magnesium may reduce neuromuscular activity in patients experiencing alcohol withdrawal. However, a recent Cochrane review[114] concluded that there is not enough evidence to determine the benefit of magnesium in alcohol withdrawal prevention or management, which is in agreement with the ASAM's 1997 guideline.[13]

VI. Addressing Complicated Alcohol Withdrawal

In this section, we highlight special considerations for patients with or at risk for alcohol withdrawal seizure or alcohol withdrawal delirium, alcohol-induced psychotic disorder, or resistant alcohol withdrawal. Aspects of management that might need to be adjusted for these patients, including monitoring, supportive care, and pharmacotherapy are discussed. Guidelines pertaining to assessment and overall management can be found in the relevant sections above.

A. Alcohol Withdrawal Seizure

(1) Monitoring

Recommendation VI.1: Patients should be monitored for alcohol withdrawal seizures even in the absence of other clinically prominent alcohol withdrawal signs or symptoms.

Recommendation VI.2: Following an alcohol withdrawal seizure, patients should be admitted to a setting with close monitoring available, and should be re-assessed every 1-2 hours for 6–24 hours. Patients should be closely monitored for delirium and the need to receive intravenous (IV) fluids, due to potential electrolyte imbalances.

Discussion. Patients identified as at risk of experiencing an alcohol withdrawal seizure should be closely monitored.[20] Alcohol withdrawal seizures typically occur between 8–48 hours after cessation of (or reduction in) alcohol use with risk peaking around 24 hours.[20,22] Signs of an impending seizure can include tremors, increased blood pressure, overactive reflexes and high temperature and pulse.[15] However, clinicians should be aware that an alcohol withdrawal seizure can occur in the absence of other clinically prominent withdrawal signs or symptoms. Risk of seizure is typically bundled with risk of alcohol withdrawal delirium when evaluating predictive factors[12,36,48–51] (see section II.B: Risk Factors for Severe or Complicated Withdrawal).

Following an alcohol withdrawal seizure, a patient is at increased risk for another seizure and progression to alcohol withdrawal delirium.[2,4,52] Patients should be observed for at least 24 hours,[52] or if in a setting where continuous observation is not feasible, observed for a minimum of 6 hours before being discharged to a treatment setting with continuous monitoring. The Guideline Committee recommended that patients be re-assessed at least every 1–2 hours during the post-seizure monitoring period.

(2) Supportive care

Recommendation VI.3: If available and applicable, existing institutional/hospital-associated delirium protocols can be used for supportive care of patients with an alcohol withdrawal seizure.

Discussion. Non-pharmacological supportive care for patients with a recent alcohol withdrawal seizure includes safety measures as well as standard care protocols. Safety measures such as fall precautions and standard care protocols such as routine nurse check-ins and assistance with activities of daily living (ADLs) ensures patient safety as well as provides autonomy. Patients with a recent alcohol withdrawal seizure are at increased risk for developing delirium. For facilities with a hospital-associated delirium protocol, clinicians should implement the protocol to prevent and reduce the incidence and duration of acute delirium among patients with a recent alcohol withdrawal-related seizure. Studies have shown standardized protocols to be effective at reducing the incidence, duration, and frequency of delirium among hospitalized patients.[117] The Guideline Committee agreed with the use of institutional/hospital-associated delirium protocols, when available.

(3) Pharmacotherapy

Recommendation VI.4: Following a withdrawal seizure, patients should be immediately treated with a medication effective at preventing another seizure. Benzodiazepines are first-line treatment, and a fast-acting agent such as lorazepam or diazepam is preferred. Phenobarbital is also an option but is less preferred to benzodiazepines.

Recommendation VI.5: Following a withdrawal seizure, parenteral administration of medications is preferred. If available, IV administration is preferred to intramuscular (IM), but IM administration is also effective. Parenteral phenobarbital should only be used in highly supervised settings (e.g., Intensive Care Unit [ICU)] or Cardiac/Coronary Care Unit [CCU]) because of risk of over-sedation and respiratory depression.

Recommendation VI.6: It is not recommended to use alpha2-adrenergic agonists or beta-adrenergic antagonists to prevent or treat alcohol withdrawal seizures because they are ineffective for this purpose. Beta-adrenergic antagonists also can lower the seizure threshold. Phenytoin should not be used unless treating a concomitant underlying seizure disorder.

Discussion. Benzodiazepines are effective in the primary and secondary prevention of alcohol withdrawal seizures.[13,131] Intravenous (IV) administration of a fast-acting agent such as lorazepam or diazepam is recommended after a withdrawal-related seizure.[2,4,21,52] In a randomized, double-blind trial, patients admitted to the emergency department with an alcohol withdrawal-related seizure were provided either 2 mL of saline or 2 mL of lorazepam intravenously to prevent subsequent seizures. The use of intravenous lorazepam was shown to significantly reduce the risk of recurrent seizures.[131]

All patients presenting with an alcohol withdrawal seizure should have IV access established immediately, which can be used for fluids in the prevention of dehydration as well as the administration of medication.[132] IM is also an effective and acceptable route of administration.

A prospective study examining the effects of phenobarbital for the treatment of alcohol withdrawal and convulsions found that none of the 38 patients who presented with alcohol withdrawal seizures had a subsequent convulsion after the administration of IV phenobarbital.[133] A more recent small prospective, randomized trial comparing phenobarbital to benzodiazepines for the treatment of acute alcohol withdrawal found phenobarbital to be as effective in reducing patient CIWA-Ar scores from baseline to discharge in the emergency department as benzodiazepines.[134]

Phenobarbital is an appropriate option for the treatment of alcohol withdrawal symptoms and prevention of additional seizures. It should be noted that phenobarbital may cause respiratory depression and over-sedation because of its effects on the central nervous system and narrow therapeutic window. Phenobarbital is therefore more commonly used in an inpatient setting, such as the ICU or Emergency Department (ED) where there is continuous supervision. The Guideline Committee recommended caution when using in settings that offer less monitoring than the ICU and ED. Additionally, clinicians who are less familiar with the therapeutic window and have minimal experience with phenobarbital should use extra caution in case over-sedation or respiratory depression occurs.

While animal studies have shown that anticonvulsants can prevent seizures and delirium,[4] evidence of their efficacy in humans is mixed, and is insufficient to conclude their effects are superior to benzodiazepines.[2,38,107] Also, phenytoin has been shown to be ineffective in preventing the recurrence of seizure and is not recommended, unless the patient is being treated for a concomitant underlying seizure disorder.[14,52]

B. Alcohol Withdrawal Delirium

(1) Monitoring

Recommendation VI.7: Patients with alcohol withdrawal delirium should be provided close nursing observation and supportive care, which often necessitates admission to an intensive or critical care unit. Agitated and disoriented patients should have continuous, one-to-one observation and monitoring.

Recommendation VI.8: Patients with alcohol withdrawal delirium should have their vital signs, oximetry and cardiac status monitored as frequently as required. Resuscitative equipment should be readily available when patients require high doses of benzodiazepines, when continuous infusion of medication is used, or when patients have significant concurrent medical conditions.

Recommendation VI.9: To monitor signs and symptoms of alcohol withdrawal delirium, use a structured assessment scale such as the Confusion Assessment Method for ICU Patients (CAM-ICU), Delirium Detection Score (DDS), Richmond Agitation-Sedation Scale (RASS), or Minnesota Detoxification Scale (MINDS). It is not recommended to use the CIWA-Ar in patients with delirium because it relies on patient-reported symptoms.

Discussion. Patients experiencing alcohol withdrawal delirium should be provided supportive care in a quiet, well-lit room with continuous monitoring of vital signs by nursing staff.[2,13,116] For patients who are disoriented or agitated, one-to-one observation should be provided.[14] The appropriateness of additional monitoring tools and measures depends on (1) the dose and frequency of medication,[2,14] (2) concurrent medical conditions,[14] and (3) degree of abnormality of the vital signs. Hospital or institutional prevention and treatment protocols can be implemented to reduce the risk of delirium among patients. Studies have shown standardized protocols to be effective at reducing the incidence, duration, and frequency of delirium among hospitalized patients.[117]

Intravenous administration is commonly used when treating alcohol withdrawal delirium, but clinicians should be cautious because benzodiazepines, such as diazepam, have a rapid onset of response. Due to this, patients may be at greater risk of respiratory depression when these medications are administered intravenously.[2] A meta-analysis on the pharmacological management of alcohol withdrawal recommends having resuscitative equipment readily available when patients require high doses of benzodiazepines, when continuous infusion of medication is used, or when patients have significant concurrent medical conditions.[14]

While a structured assessment scale should be used to monitor alcohol withdrawal delirium, the use of the CIWA-Ar is problematic in patients experiencing delirium. Other scales are effective at identifying and monitoring delirium among patients who are unable to communicate clearly. The Confusion Assessment Method for ICU Patients (CAM-ICU),[135–137] is a reliable, rapid and valid instrument for diagnosing delirium among ICU patients and can be used for mechanically ventilated patients as well. The Delirium Detection Score (DDS)[138] is another valid and reliable assessment scale used in the ICU. The Richmond Agitation Sedation Scale (RASS)[139] has demonstrated reliability and validity in medical and surgical patients, including patients who are sedated and/or ventilated. Although not officially validated, the Minnesota Detoxification Scale (MINDS)[140] has been used to assess and monitor patients in the ICU setting. The scale takes less time to administer than the CIWA-Ar and has produced reliable scores that are reflective of the severity of alcohol withdrawal symptoms among patients.

(2) Supportive care

Recommendation VI.10: Provide immediate intravenous access for administration of drugs and fluids to patients experiencing alcohol withdrawal delirium.

Recommendation VI.11: If available and applicable, existing institutional/hospital-associated delirium protocols can be used for supportive care of patients with alcohol withdrawal delirium.

Recommendation VI.12: Restraints should only be used when required to prevent injuries due to agitation or violence, and in compliance with state laws.

Discussion. Patients experiencing alcohol withdrawal delirium should quickly be provided immediate intravenous access for administration of fluids and medication.[41] Intravenous benzodiazepines have been shown to provide more rapid control of signs and symptoms compared to oral administration,[2] which is ideal in treating alcohol withdrawal delirium. However, intravenous administration of benzodiazepines also increases the risk of respiratory depression in patients due the quick onset.[2] Patients should be monitored for signs of respiratory depression with resuscitative equipment readily available if needed.[14]

Delirium is an acute state of confusion with impaired cognition that often occurs during hospitalization, especially among elderly patients.[117,141,142] Delirium has been associated with increased morbidity, mortality, length of hospital stay, and increased health service utilization.[142,143] Early recognition as well as preventative measures are key for the management of the risk of delirium.[143,144] Hospital or institutional prevention and treatment protocols can be implemented to reduce the risk of delirium among patients. One study evaluated the effects of a multicomponent intervention on reducing the incidence of delirium among hospitalized patients as well as the duration and frequency of delirious episodes among 852 hospitalized patients.[117] The intervention utilized standardized protocols that measured six factors for delirium, which were: cognitive impairment, hearing impairment, sleep deprivation, immobility, visual impairment, and dehydration. Results from the study showed that implementation of standardized protocols were effective at preventing and reducing the risk of delirium, number of episodes and duration of episodes. Fifteen percent of patients who did not receive the intervention developed delirium compared to 9.9% who did receive the intervention. Additionally, patients who received the intervention had a shorter duration compared to those receiving usual care (105 vs 161 days). The number of episodes were also significantly less among the intervention group (62 vs 90).

Sedative medications, such as benzodiazepines and barbiturates are associated with an increased burden of delirium among patients.[144] Both medications are commonly used in the treatment of alcohol withdrawal including for patients with alcohol withdrawal delirium. Therefore, these patients should be monitored for early symptoms of delirium and interventions, such as hospital-associated delirium protocols, should be implemented in addition to routine monitoring. The Guideline Committee agreed with the use of institutional/hospital-associated delirium protocols, when available.

Patients experiencing severe alcohol withdrawal, particularly alcohol withdrawal delirium, are confused, agitated, and may try to remove peripheral lines.[145] Providing early pharmacological management may alleviate signs and symptoms of delirium that are likely to cause patients to attempt to remove peripheral lines, but it may be necessary to use restraints, in accordance with state laws, to ensure the safety of patients and staff.

(3) Pharmacotherapy

Recommendation VI.13: Patients with alcohol withdrawal delirium should be sedated to achieve and maintain a light somnolence. Benzodiazepines are recommended as the first-line agents for managing alcohol withdrawal delirium.

Recommendation VI.14: When available, medication should be administered intravenously. The use of intermittent IV administration of long- and short-acting medications is acceptable and effective. Continuous IV infusion is considerably more expensive and there is no evidence of therapeutic superiority.

Recommendation VI.15: Patients receiving repeated high intravenous doses of lorazepam or diazepam should be monitored closely for signs of hyponatremia and metabolic acidosis.

Recommendation VI.16: When treating alcohol withdrawal delirium, use an established dosing protocol as a guide, but individualize dosing regimens based on patient's signs and symptoms. It is appropriate for patients with alcohol withdrawal delirium to receive intravenous symptom-triggered or fixed-dose front loading. Once light somnolence is achieved and patients are calm and cooperative, if on IV medication, shifting to oral symptom-triggered treatment is recommended.

Recommendation VI.17: Very large doses of benzodiazepines may be needed to control agitation in alcohol withdrawal delirium, including doses that are much higher than typically seen in other patient populations. Clinicians should not hesitate to provide such large doses to patients to control agitation but should keep in mind the possible risk of over-sedation and respiratory depression. Moreover, when large doses are used, there is risk of accumulation of long-acting benzodiazepine metabolites, especially in patients with impaired hepatic function or the elderly, and patients should be monitored closely.

Recommendation VI.18: For patients who have been delirious longer than 72 hours, assess for drug-induced delirium and withdrawal from another GABAergic agent (such as gabapentin or carisoprodol). When necessary, adjust the benzodiazepine dose.

Recommendation VI.19: Barbiturates can be considered an alternative option to benzodiazepines for the treatment of alcohol withdrawal delirium, but they are not preferred to benzodiazepines. Phenobarbital can be used as an adjunct to benzodiazepines in settings with close monitoring when alcohol withdrawal delirium is not adequately controlled by benzodiazepine therapy alone.

Recommendation VI.20: Antipsychotic agents can be used as an adjunct to benzodiazepines when alcohol withdrawal delirium and hallucinations are not adequately controlled by benzodiazepine therapy alone. They are not recommended as monotherapy for alcohol withdrawal delirium.

Recommendation VI.21: Alpha2-adrenergic agonists, beta-adrenergic antagonists and paraldehyde should not be used to treat alcohol withdrawal delirium.

Discussion. Patients experiencing alcohol withdrawal delirium should be provided enough medication to achieve a light somnolence.[14,44,132] The goal or therapeutic endpoint of this recommendation is to help control agitation associated with delirium.[14,44] Patient should be in a level of sedation where they are awake, but have a tendency to fall asleep unless stimulated.

Benzodiazepines are the most commonly used medication to treat patients with delirium because of the favorable therapeutic window.[14] Intermittent IV administration of a long-acting medication or continuous IV infusion of short-acting medication are both effective treatments for alcohol withdrawal delirium.[14] Administering medication intravenously allows for rapid and accurate control over signs and symptoms such as fear, autonomic hyperactivity, and hallucinations.[116,146,147] Clinicians should be aware that very large doses of benzodiazepines may be required to control delirium and be ready to provide a sufficient amount of medication to effectively treat the symptoms.[2] Because intravenous lorazepam and diazepam are both stabilized with propylene glycol, hyponatremia and metabolic acidosis may occur.[2]

While dosing regimens should be individualized based on the patient's signs and symptoms, using an established dosing protocol as a guide for treatment has been shown to be a safe and effective means of managing alcohol withdrawal delirium.[22,148] Symptom-triggered front loading with diazepam has also been shown to reduce the duration of delirium.[149] Fixed-dose front loading is also appropriate during the early management of alcohol withdrawal delirium if a withdrawal scale cannot be completed.[41,132] Once patients have reached a calm state, patients can be shifted to a symptom-triggered approach.[70,132] See Appendix III for guidance on the use of scales to guide dosing in patients with communication difficulty.

Patients treated with repeated high doses of lorazepam or diazepam require close monitoring due to the rapid onset of action and the risk of accumulation of long-acting benzodiazepine metabolites.[2] This accumulation is especially common in patients with impaired hepatic function or among the elderly.[2] If a patient has been delirious longer than 72 hours and has been receiving high doses of benzodiazepines (in the thousands of milligrams), the patient may have developed benzodiazepine-induced delirium. Because the temporal window of alcohol withdrawal seizures has passed, clinicians should consider reducing the benzodiazepine dose and adding an antipsychotic agent to control agitation and/or confusion.[2]

Even if patients are at reduced risk of seizure, antipsychotics should not be used as monotherapy because they lower the seizure threshold. Second generation atypical antipsychotics, such as risperidone and quetiapine, are preferred because they have less of an effect on the seizure threshold compared to other antipsychotics.[2,44] Haloperidol, a first generation antipsychotic, is also an appropriate agent.[2,14,44] Antipsychotics may also be used in conjunction with benzodiazepines to control severe agitation and hallucinations associated with early alcohol withdrawal delirium.[2,14] Barbiturates are also an appropriate option for treating patients with alcohol withdrawal delirium. A retrospective cohort study found that patients treated with 100–200 mg of phenobarbital (PO or IV) had similar duration of symptoms and length of stay compared to patients who received 10–20 mg of diazepam IV hourly until sedated.[147] However, barbiturates are not preferred as monotherapy over benzodiazepines due to their narrow therapeutic window and risk of over-sedation and respiratory depression. Phenobarbital may be used in conjunction with benzodiazepines in settings with continuous monitoring available when delirium is not adequately controlled by benzodiazepines.

Due to difficulties in administration and titration of dose, paraldehyde is not recommended for the treatment of alcohol withdrawal delirium.[1414] Additionally, alpha2-adrenergic agonists and beta-adrenergic antagonists should not be used to treat alcohol withdrawal delirium.

C. Alcohol-Induced Psychotic Disorder

Recommendation VI.22: If available and applicable, existing institutional/hospital-associated delirium protocols can be used for supportive care of patients with an alcohol-induced psychotic disorder.

Recommendation VI.23: The treatment of alcohol-induced psychotic disorder may require consultation with a psychiatrist.

Recommendation VI.24: The treatment of alcohol-induced psychotic disorder may require addition of antipsychotics.

Recommendation VI.25: For patients experiencing hallucinations, diazepam may be considered a treatment option.

Discussion. Alcohol-induced psychosis may develop in patients withdrawing from alcohol. Symptoms of alcohol-induced psychosis consist of auditory hallucinations and possibly visual hallucinations and delusions.[44] Differentiating between alcohol-induced psychosis due to alcohol withdrawal and alcohol-induced hallucinations as a complication of chronic alcohol use can be difficult. The DSM-5 illustrates the distinctions between substance-induced psychotic disorders associated with intoxication as well as withdrawal and requires clinicians to document and code accordingly.[43] Currently, there is no established pharmacotherapy for the treatment of alcohol-induced psychosis, but a randomized controlled trial of 50 patients showed diazepam to be effective at reducing hallucinations compared to placebo.[150] The Guideline Committee rated diazepam as an appropriate medication for the treatment of alcohol-induced psychosis, but they also concluded that it may be necessary to treat these patients with an additional antipsychotic medications to alleviate the symptoms.

Patients experiencing alcohol-induced psychosis are at risk of developing acute delirium while in the inpatient setting and appropriate hospital-associated delirium protocols should be implemented, if available, to reduce the risk of delirium and associated health outcomes.

D. Resistant Alcohol Withdrawal

Recommendation VI.26: If available and applicable, existing institutional/hospital-associated delirium protocols can be used for supportive care of patients with resistant alcohol withdrawal.

Recommendation VI.27: Phenobarbital may be used as an adjunct to benzodiazepines to control resistant alcohol withdrawal syndrome in settings with close monitoring.

Recommendation VI.28: Propofol may be used with patients in the ICU experiencing resistant alcohol withdrawal who already require mechanical ventilation.

Recommendation VI.29: Dexmedetomidine may be used with patients in the ICU experiencing resistant alcohol withdrawal.

Discussion. Resistant Alcohol Withdrawal (RAW) is not well defined, but generally describes patients who experience severe or complicated withdrawal despite having received high doses of benzodiazepines.[97] Prior reviews have defined this as having uncontrolled symptoms despite having received doses of more than 150–200 mg diazepam or 30–40 mg lorazepam in the first 3–4 hours of treatment.[46,115,151] In such cases, patients may require the addition of an adjunct medication such as phenobarbital, propofol, or dexmedetomidine.[46,111,151,152] This phenomenon is also referred to as benzodiazepine-resistant alcohol withdrawal or refractory alcohol withdrawal.

There is evidence to support the use of phenobarbital as an adjunct to benzodiazepines in patients with severe withdrawal or RAW.[111] A strategy of symptom-triggered escalating doses of diazepam and/or phenobarbital has been shown to reduce the need for mechanical ventilation and showed trends toward reductions in ICU length of stay in patients admitted to the ICU for treatment of alcohol withdrawal syndrome.[22] ICU admission was called for if patients required either 200 mg diazepam in 4 hours or an individual dose greater than 40 mg IV diazepam to control agitation. The same strategy has been shown to be effective for patients admitted to the ICU for any reason who also experienced alcohol withdrawal. Patients treated with the protocol had a reduced ICU length of stay, need for mechanical ventilation and benzodiazepine requirements compared to a group of historical controls treated with physician determined dosing of benzodiazepines alone.[22,148].

Propofol is appropriate as a benzodiazepine adjunct in patients with RAW treated in the ICU.[7,97,115] One systematic review of observational studies evaluated the use of propofol as an adjunct for the treatment of patients with RAW.[97] The authors concluded that propofol was useful in reducing signs of alcohol withdrawal, but due to the risk of respiratory depression it is only appropriate for patients who already require mechanical ventilation "unless other adjuvant therapies and methods of BZD [benzodiazepine] administration have proved to be ineffective."[97 (p. 441)]

Dexmedetomidine is appropriate as a benzodiazepine adjunct in patients with RAW being treated in the ICU. Three systematic reviews of primarily observational studies on the use of dexmedetomidine in the ICU were found.[115,153,154] These authors concluded that dexmedetomidine is a useful adjunct for treating patients with RAW, although monitoring for bradycardia is required. Two randomized controlled trials were found on the use of dexmedetomidine as a benzodiazepine adjunct in ICU patients.[155,156] Both studies found that the use of dexmedetomidine increased sedation quality (reduced agitation) and decreased benzodiazepine requirements in the 24-hours after dexmedetomidine administration but also increased the incidence of bradycardia. A reduction in total benzodiazepine dose is thought to reduce the potential for prolonged delirium and sedation seen in these patients.[153]

One study compared the effectiveness of propofol to dexmedetomidine in treating ICU patients experiencing RAW and found that both agents were similarly effective in reducing signs and symptoms of withdrawal and benzodiazepine requirements.[97] However, propofol was associated with fewer instances of bradycardia but more instances of hypotension compared to dexmedetomidine.[97] This study and others have stressed the need to better define RAW and for further well-controlled, prospective trials to define the role of dexmedetomidine and propofol in the treatment of RAW.[97,153]

VII. Specific Settings and Populations

In this section, we highlight settings where non-addiction specialty clinicians are likely to encounter patients at risk for or experiencing alcohol withdrawal (primary care), settings with unique resources (Emergency Departments and hospitals), and patient populations who require treatment plan modifications (patients with medical conditions, patients who take opioids, and patients who are pregnant).

A. Primary Care

Primary care is a setting where generalist clinicians may be the first point of contact for patients at risk for or experiencing alcohol withdrawal. They may prescribe medication for alcohol withdrawal management. Crucially, they may be the best-placed practitioner to engage patients in long-term follow-up care following the acute withdrawal period. This section is not intended to provide a set of recommendations for primary care settings separate from ambulatory Level 1-WM settings. Primary care clinicians should follow recommendations outlined in sections I: Identification and Diagnosis, II: Initial Assessment, and III: Level of Care Determination before initiating alcohol withdrawal management. If providing alcohol withdrawal management, they should follow recommendations outlined in the section IV: Ambulatory Management of Alcohol Withdrawal.

Recommendation VII.1: If patients are experiencing severe withdrawal (e.g., CIWA-Ar scores $\geq$19), refer them directly to the nearest Emergency Department.

Recommendation VII.2: If withdrawal is mild (e.g., CIWA-Ar $<$10), patients presenting to primary care can be prescribed a few doses of benzodiazepine. Whenever possible, medication dispensing can be supervised by a caregiver at home or staff at a nonmedical withdrawal management center. Do not prescribe medication to patients for ambulatory management of alcohol withdrawal without performing an adequate assessment.

Recommendation VII.3: If withdrawal does not resolve (e.g., fall below a CIWA-Ar score of 10) after an adequate dose of medication (e.g., 80 mg diazepam), or patients appears sedated, transfer to an Emergency Department or other inpatient withdrawal management setting.

Recommendation VII.4: For patients treated in primary care settings, regular follow-up visits, at least monthly

for one year, could increase the likelihood of sustained recovery.

Discussion. During assessment, if patients are determined to be experiencing severe withdrawal (e.g., CIWA-Ar scores ≥19), they should be immediately transferred to the Emergency Department (ED) or other setting with the resources to manage complications that might arise.[72] When considering prescribing medication to a patient for alcohol withdrawal, clinicians should first assess the patient for risk factors of severe, complicated, or complications of withdrawal (see II. Initial Assessment of Alcohol Withdrawal). For patients with mild withdrawal (e.g., CIWA-Ar <10), clinicians may prescribe patients a few doses of medication.[72] Whenever possible, have a supportive caregiver or withdrawal management center staff dispense the medication.[157] If it is possible to dispense or observe medication administration on-site, if patients' withdrawal does not resolve (e.g., fall below a CIWA-Ar score of 10) after an adequate dose of medication, or if they show a worsening of symptoms, or appear sedated should be transferred to the ED or a specialized withdrawal management facility with 24-hour supervision.

Implementation of nonpharmacological support in the management of alcohol withdrawal among patients treated in a primary care setting may increase the likelihood of sustained recovery compared to patients who do not receive additional nonpharmacological support.[82] According to one outpatient withdrawal protocol, nonpharmacological support such as monthly, routine follow-up appointments for one year with a primary health care provider, offers support in the recovery process and can increase abstinence.

B. Emergency Departments

Emergency Departments (EDs) are unique medical settings that do not fit neatly into the categories of ambulatory or inpatient settings. They have the resources of a hospital and frequently see patients in moderate or severe withdrawal. While alcohol withdrawal can be managed in the ED until it resolves, most patients will be stabilized and leave with a referral for continuing withdrawal management and/or alcohol use disorder treatment.

Recommendation VII.5: If patients are experiencing severe alcohol withdrawal (e.g., CIWA-Ar ≥19) or are at risk of complicated withdrawal, administer medication immediately to treat withdrawal and reduce the risk of seizures and delirium.

Recommendation VII.6: Patients presenting with alcohol withdrawal syndrome in the Emergency Department should be evaluated for delirium as well as other conditions that mimic and/or accompany withdrawal. Patients presenting with delirium should be assessed for all potential etiologies including alcohol withdrawal.

Recommendation VII.7: Patients in the Emergency Department should receive a complete blood count and complete metabolic panel including liver enzyme and magnesium tests; alcohol withdrawal treatment should not be delayed while waiting for results.

Recommendation VII.8: The following indicators should be present for discharge to an ambulatory alcohol withdrawal management setting from the Emergency Department:

- Mild alcohol withdrawal (e.g., CIWA-Ar score <10).
- Moderate alcohol withdrawal (e.g. CIWA-Ar score 10–18) with no other complicating factors
- Not currently intoxicated (including alcohol or other drugs)
- No history of complicated alcohol withdrawal (seizures, delirium)
- No significant medical or psychiatric comorbidities that would complicate withdrawal management
- Able to comply with ambulatory visits and therapy

Recommendation VII.9: Patients with controlled withdrawal syndrome being discharged from the Emergency Department may be offered a short term (e.g., 1-2 day) prescription for appropriate alcohol withdrawal medication to last until follow-up with their healthcare provider.

Discussion. The Guideline Committee recommends that alcohol withdrawal management be initiated in the ED. This might include diagnosis and assessment, management of acute signs and symptoms, and referral to inpatient or ambulatory treatment. The signs and symptoms of alcohol withdrawal often mimic or mask a wide variety of other health conditions and it is recommended that all patients entering the ED with alcohol withdrawal be given a thorough evaluation.[152] The etiology of signs and symptoms and identification of coexisting illnesses that may precipitate alcohol withdrawal should be determined from the evaluation.[152] While assessing patients, clinicians should be aware that severe intoxication can mimic alcohol withdrawal and often leads to confusion, delirium, tachycardia and diaphoresis.[126] A serum ethanol level may be necessary to determine etiology if the patient history is inconclusive.[126] Clinicians can obtain a complete blood count and metabolic panel including liver enzymes and magnesium test to identify factors that may complicate alcohol withdrawal management.

As in any setting, patients experiencing severe withdrawal (e.g., CIWA-Ar score ≥ 19) or who are at risk of severe, complicated, or complications of withdrawal, should be provided medication immediately to treat withdrawal signs and symptoms and reduce the risk of developing more severe withdrawal.[73] Among patients with co-occurring illnesses, the likelihood of developing delirium is higher and they should be provided aggressive treatment of both conditions.[158]

Patients can be referred to an ambulatory setting and discharged once their symptoms have stabilized (e.g., CIWA-Ar score < 10). While patients experiencing moderate withdrawal (e.g., CIWA-Ar 10–18) may be eligible for ambulatory withdrawal management, the Guideline Committee emphasized that not all clinicians may be comfortable managing patients with moderate withdrawal in this setting and the decision to do so is at the discretion of the treating clinician. When discharging patients to an ambulatory setting, clinicians may provide patients with a short-term (e.g., 1-2 day) prescription for benzodiazepines.[159] The Guideline Committee does not recommend providing a short-term prescription to patients currently intoxicated (including alcohol

or other drugs) or discharging patients to an ambulatory setting if they have a history of complicated alcohol withdrawal and withdrawal has not fully resolved. A simple referral may not be adequate when patients are being discharged from the Emergency Department. Section III: Level of Care Determination provides guidance on determining an appropriate level of care to which to refer the patient. A warm hand-off should be used to ensure the patient made the transition to the next level of care. This may include arranging the appointment in the presence of the patient, arranging for transportation of the patient to the treatment setting, and following up to ensure effective engagement in care.

C. Hospitalized Patients

This section specifically pertains to patients who are hospitalized for a primary complaint other than alcohol withdrawal who then subsequently develop or are at risk of developing alcohol withdrawal during their hospitalization.

(1) Identification

Recommendation VII.10: All patients admitted to the hospital should be screened for risk of alcohol withdrawal. Among hospitalized patients, the Alcohol Use Disorders Identification Test (AUDIT) and Alcohol Use Disorders Identification Test-Piccinelli Consumption (AUDIT-PC) can indicate risk of developing alcohol withdrawal.

Recommendation VII.11: Patients undergoing elective surgery should be screened for unhealthy alcohol use and the need to undergo alcohol withdrawal management before proceeding with surgery. Patients undergoing elective surgery who are at risk of alcohol withdrawal should undergo medically managed withdrawal before proceeding with surgery

Discussion. The Guideline Committee recommends that all patients in the hospital setting be screened for unhealthy alcohol use and assessed for the risk of alcohol withdrawal, if appropriate. Screening and assessment should include the use of a validated scale, information from collateral sources such as friends or family members and medical clinicians, and laboratory tests. For patients undergoing elective surgery, an alcohol withdrawal risk assessment should be conducted prior to surgery, if necessary, because of the postoperative risks and complications associated with alcohol withdrawal.[2]

Unhealthy alcohol use screens with demonstrated ability to identify patients at risk of developing alcohol withdrawal in general hospital settings include the AUDIT and AUDIT-PC.[31] The AUDIT is a 10-item instrument developed to screen for likelihood of the respondent having an alcohol use disorder.[160] A large prospective study of patients admitted to an acute medical unit found that admission AUDIT score $\geq$ 8 identified patients who developed alcohol withdrawal with 100% sensitivity and 90.5% specificity.[35] While only 17.3% of patients who screened positive went on to develop alcohol withdrawal, no patients with an AUDIT score $<$ 8 experienced withdrawal. This makes clear the point that these instruments should be used as screens; patients who screen positive should be further assessed prior to a diagnosis and treatment of alcohol withdrawal syndrome.[35] The AUDIT-PC, a shortened version of the AUDIT, identified patients who experienced alcohol withdrawal syndrome in medical and surgical units with 91% sensitivity and 90% specificity using an admission AUDIT-PC score $\geq$ 4.[29]

(2) Assessment

Recommendation VII.12: Among hospitalized patients, the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) can be used for predicting risk of developing severe or complicated alcohol withdrawal in the medically ill.

Recommendation VII.13: Patients for whom alcohol withdrawal is suspected and for whom a complete medical history is not available, (i.e., are admitted from the Emergency Department, trauma unit, or are in Intensive Care Unit [ICU]) or who are known to be at high risk of complicated alcohol withdrawal, medical decisions should be oriented toward a more aggressive treatment of alcohol withdrawal regardless of presenting signs and symptoms.

Recommendation VII.14: For patients who require more than standard amounts of medication to manage alcohol withdrawal, individualized assessment by clinicians experienced in the management of withdrawal is recommended. The medication and protocol used for treating other conditions and/or alcohol withdrawal syndrome may need to be modified.

Discussion. Clinicians can use validated scales such as the Prediction of Alcohol Withdrawal Severity Scale (PAWSS)[29] to identify patients at risk of developing severe or complicated alcohol withdrawal in the hospital setting. The PAWSS is designed to asses patients who are medically ill and has been validated by prospective studies, which compared the PAWSS with retrospective chart review and the CIWA-Ar.[29,47] See section II.C: Risk Assessment Tools for more information on the PAWSS. Additional information on the scale and its features can be found in Appendix III.

When a patient's medical history is unavailable and it is unclear if the patient has a co-occurring medical condition or is at high risk of complicated alcohol withdrawal, clinicians should be prepared for such events and orient care towards more aggressive treatment regardless of current signs and symptoms. Patients with co-occurring medical diseases may be at risk of developing complications associated with withdrawal and clinicians should consult with appropriate medical professionals from different specialties (e.g. infectious diseases, cardiology, pulmonary medicine, hematology, neurology, and surgery) when necessary. Patients identified with underlying cardiac conditions should be provided aggressive withdrawal treatment due to the potential of alcohol withdrawal worsening cardiac symptoms.[4]

Patients with co-occurring medical conditions may require modifications to medication regimens and protocols in order to minimize potentially harmful effects related to exacerbation of these conditions.[4] However, if a patient experiences withdrawal signs and symptoms that are not easily controlled, consultation with an addiction specialist is warranted to ensure patient safety.[2]

(3) Monitoring

Recommendation VII.15: In patients who are hospitalized, monitor their vital signs. Fluid intake and output and serum electrolytes should be monitored as clinically indicated.

Recommendation VII.16: Signs and symptoms of alcohol withdrawal should be monitored during the course of withdrawal with a validated symptom assessment scale. Assess the risk for scores on a symptom assessment scale to be confounded by the use of certain medications, the presence of certain medical conditions (e.g. fever from infection), or a patient's difficulty communicating. Among general medical/surgical patients, low withdrawal scores can typically be interpreted with confidence, while high scores should be interpreted with caution. The use of alternative scales with patients with difficulty communicating is appropriate.

Recommendation VII.17: Patients with a reduced level of consciousness who are at risk for the development of alcohol withdrawal should be monitored for the appearance of alcohol withdrawal signs. If a co-occurring clinical condition worsens, do not assume it is related to alcohol withdrawal among alcohol withdrawal patients. However, immediate treatment is required if alcohol withdrawal develops after surgery or trauma.

Discussion. Although the use of validated scales is recommended in the hospital setting, clinicians should be particularly cognizant of the risk for scores to be affected by comorbid conditions and/or interventions for those conditions. Choose a withdrawal scale that can be administered to patients who are critically ill or have reduced consciousness (see Appendix III). Low withdrawal scores can typically be interpreted with confidence, although beta-adrenergic antagonists (beta-blockers) and other sympatholytic drugs may mask the signs and symptoms of withdrawal and lead to low scores.[2] However, high scores have alternative causes that are common in medical/surgical patients and must be interpreted with caution.

Patients who have a reduced level of consciousness due to trauma or general surgery should be monitored for the appearance of signs and symptoms of alcohol withdrawal to provide appropriate treatment.[7] Clinicians should not necessarily assume that worsening symptoms in patients in or at risk for alcohol withdrawal are related to alcohol withdrawal.[161] Patients in the ICU are at an increased risk of adverse changes due to their illness and worsening condition; however, these changes may be the result of another medical condition.

(4) Supportive care

Recommendation VII.18: Clinicians should administer thiamine to ICU patients with signs or symptoms that mimic or mask Wernicke encephalopathy.

Discussion. Due to the risks associated with thiamine deficiency among patients experiencing alcohol withdrawal, it is common practice to provide thiamine to prevent Wernicke encephalopathy[162–164] Patients in the ICU with a condition that may mask or mimic signs and symptoms associated with WE should receive thiamine.

Thiamine is required for basic cellular functioning and carbohydrate metabolism.[164] Because the body is unable to synthesize thiamine, daily ingestion is necessary for routine functioning and maintaining homeostasis. If there is insufficient thiamine in the body, a patient may develop a thiamine deficiency such as Wernicke encephalopathy.[163,165,166] Patients who consume large amounts of alcohol are particularly susceptible to thiamine deficiencies due to inadequate dietary intake as well as biological interactions between cellular enzymes and alcohol.[163,166] For example, alcohol inhibits thiamine pyrophosphokinase, an enzyme responsible for synthesizing thiamine diphosphate (TDP) from thiamine, while also increasing the activity of an enzyme that is responsible for the degradation of TDP.[166] The effects of alcohol on both of these enzymes results in a reduction of available TDP within the cell and ultimately inhibits cellular metabolism.

(5) Pharmacotherapy

Recommendation VII.19: Prophylactic treatment of alcohol withdrawal should be provided in the ICU to patients who are suspected to be physiologically dependent on alcohol.

Recommendation VII.20: Implementing an alcohol withdrawal management protocol in the ICU is appropriate. When using a symptom-triggered dosing protocol, use a validated scale to monitor signs and symptoms. For patients being treated in ICU settings for alcohol withdrawal, existing scales that are appropriate to use for monitoring withdrawal include the Richmond Agitation-Sedation Scale (RASS). Administration of medications via the intravenous route is preferred because of the rapid onset of action and more predictable bioavailability.

Discussion. Because alcohol withdrawal can cause significant morbidity among patients in the critical care setting, patients admitted to the ICU may receive prophylaxis to reduce the risk of developing alcohol withdrawal.[167] Additionally, patients should be monitored for worsening signs and symptoms and development of Wernicke encephalopathy. Typically, a multivitamin infusion or ''banana bag'' is given to patients in the ICU to prevent Wernicke encephalopathy. One study examined the effectiveness of the standard protocol commonly used in the ICU to prevent Wernicke encephalopathy when signs and symptoms are masked or mimicked by other illnesses.[168] The findings recommended abandoning the ''banana bag'' approach and provide patients with 200–500 mg IV thiamine every 8 hours, 64 mg/kg magnesium sulfate, and 400–1,000 mcg IV folate for patients with signs or symptoms that mimic or mask Wernicke encephalopathy. As mentioned, patients also receiving glucose can be administered thiamine and glucose in any order or concurrently.

Intravenous administration of benzodiazepines has been recommended for ICU patients due to the rapid onset of action.[161] The Guideline Committee recommends a standard protocol, such as symptom-triggered benzodiazepine therapy in the ICU. Systematic reviews show that symptom-triggered therapy is beneficial among critically ill patients[50,89] and showed a reduction in the need for mechanical ventilation.[50] A combination of symptom-triggered therapy with the use of a validated scale designed for dosing in patients that are unable to communicate or have comorbidities has been shown to be effective.[89] When using symptom-triggered dosing, using validated scales specific for ICU patients such as the Richmond Agitation-Sedation Scale,[7,115] the Confusion Assessment Method for ICU Patients,[161,167] or the Minnesota Detoxification Scale[115,140,161,167] is recommended.

D. Patients With Medical Conditions

This section is relevant to patients with comorbid medical conditions who are treated in any setting.

Recommendation VII.21: For patients with medical comorbidities, modify the medication and/or protocol used for treating alcohol withdrawal syndrome as necessary in consultation with other specialists.

Recommendation VII.22: For patients with medical conditions that prevent the use of oral medication, provide intravenous or intramuscular medications as necessary.

Recommendation VII.23: Aggressive withdrawal treatment is indicated for patients with cardiovascular disorders due to risk of harm associated with autonomic hyperactivity.

Recommendation VII.24: For patients with a medical condition associated with impaired hepatic function, adjust medication dose or use medications with less dependence on hepatic metabolism.

Discussion. The main differences in managing alcohol withdrawal in patients with co-occurring medical conditions arises from the need to modify medications used and protocols implemented. The presence of alcohol withdrawal can exacerbate other conditions and illnesses, particularly cardiovascular disease including coronary artery disease. For example, the autonomic arousal (e.g., elevated blood pressure, increased pulse) associated with even mild alcohol withdrawal can exacerbate an underlying cardiac condition.[4] Cardiac conditions should be identified early and aggressive treatment is warranted. Clinicians may want to provide at least a single dose of a benzodiazepine to prevent the development of even minor withdrawal symptoms. Other treatment plan modifications might be needed due to impaired liver functioning, medication interactions, or a medical condition that prevents administration of oral medication.[58] When treating patients with comorbidities, clinicians should consult with appropriate medical professionals from different specialties (e.g. infectious diseases, cardiology, pulmonary medicine, hematology, neurology, and surgery) when necessary.

E. Patients who Take Opioids

Recommendation VII.25: Patients who are on chronic opioid medication (opioid agonist therapy for opioid use disorder or pain) should be monitored closely when benzodiazepines are prescribed, due to the increased risk of respiratory depression. Similarly, patients taking sedative-hypnotic medications exhibit tolerance to benzodiazepines and should be monitored closely for appropriate dose.

Recommendation VII.26: For patients with concomitant alcohol withdrawal and opioid use disorder, stabilize opioid use disorder (e.g. with methadone or buprenorphine) concomitantly with treating alcohol withdrawal.

Discussion. Patients with concomitant substance use or patients who are currently receiving opioid therapy require special attention and monitoring. The Guideline Committee emphasized that patients with concomitant substance use, in general, are managed similarly to other patients, but special attention should be given to monitoring signs and symptoms. Benzodiazepines may be given but should be used with caution and only in facilities with close monitoring. Patients receiving opioid agonist therapy with concomitant alcohol withdrawal should be admitted and managed in a hospital setting or other setting with the resources to manage increased risk of respiratory depression and other complications.

Patients who are using sedative-hypnotic medication are at higher risk of major complications and may exhibit tolerance to benzodiazepines and require dose adjustment. These patients should be monitored closely.[13]

F. Patients who are Pregnant

(1) Level of care and monitoring

Recommendation VII.27: Inpatient treatment should be considered for all pregnant patients with alcohol use disorder who require withdrawal management. Inpatient treatment should be offered to pregnant patients with at least moderate alcohol withdrawal (i.e., CIWA-Ar scores $\geq$ 10).

Recommendation VII.28: The CIWA-Ar is an appropriate symptom assessment scale to use with pregnant patients. Pregnancy is not expected to bias scores on symptom assessment scales. Clinicians should consider signs and symptoms such as nausea, headache, anxiety, and insomnia to be connected to alcohol withdrawal rather than pregnancy and presume they will abate once the alcohol withdrawal has been effectively treated.

Recommendation VII.29: During withdrawal management, consult with an obstetrician.

Discussion. Inpatient treatment should be considered for all pregnant patients with alcohol withdrawal given the risk of fetal alcohol spectrum disorder including fetal alcohol syndrome and the risk of abruption, preterm delivery, and fetal distress or demise due to continued alcohol use during pregnancy.[169] While inpatient management is not more effective than ambulatory management for patients who are appropriately matched to level of care, it does limit exposure to alcohol. If patients are experiencing at least moderate alcohol withdrawal (i.e., CIWA-Ar $\geq$10) and are pregnant, the VA/DoD[58] recommend patients be treated at an inpatient facility that has medical withdrawal supervision.

Pregnancy is not expected to bias scores on symptom assessment scales when assessing withdrawal severity during the initial assessment and monitoring. Clinicians can consider signs and symptoms such as nausea, headache, anxiety, and insomnia to be connected to alcohol withdrawal. They can further presume these symptoms will abate once alcohol withdrawal has been effectively treated.

The Guideline Committee recommends consulting with an obstetrician when managing alcohol withdrawal in a pregnant patient. Fetal monitoring appropriate to the stage of pregnancy may be warranted due to risk of abruption, preterm delivery, and fetal distress or demise.[169]

(2) AUD treatment initiation and engagement

Recommendation VII.30: Engagement in treatment for AUD is particularly important for pregnant patients with alcohol withdrawal given the risk of Fetal Alcohol Spectrum Disorder (FASD) including Fetal Alcohol Syndrome (FAS).

Discussion. The Guideline Committee emphasized the importance of engaging pregnant patients in ongoing treatment for alcohol use disorder given the risk of fetal alcohol spectrum disorder including fetal alcohol syndrome and the risk of abruption, preterm delivery, and fetal distress or demise due to continued alcohol use during pregnancy.[169] As discussed in the ambulatory and withdrawal management sections, the presence of alcohol withdrawal almost universally signifies the presence of an alcohol use disorder and need for treatment. Alcohol withdrawal management alone is not an effective treatment for alcohol use disorder. The period of withdrawal management should include the process of initiating and engaging patients in treatment for alcohol use disorder.

(3) Pharmacotherapy

Recommendation VII.31: Before giving any medications to pregnant patients, ensure that patients understand the risks and benefits of the medication, both for the patient and the developing fetus.

Recommendation VII.32: Benzodiazepines and barbiturates are the medications of choice in treatment of pregnant patients with alcohol withdrawal. While there is a risk of teratogenicity during the first trimester, the risks appear small, and they are balanced in view of the risk for fetal alcohol spectrum disorder and consequences to mother and fetus should severe maternal alcohol withdrawal develop.

Recommendation VII.33: Due to the high teratogenic risk, valproic acid is not recommended for pregnant patients.

Recommendation VII.34: For patients at risk for preterm delivery or in the late third trimester, use of a short-acting benzodiazepine is recommended. This minimizes the risk for neonatal benzodiazepine intoxication given shorter onset and duration of action.

Discussion. In SAMHSA's TIP 45,[4] the importance of educating patients about the risks and benefits associated with alcohol withdrawal treatment medication is emphasized. Due to the potential risks imposed on both the patient and developing fetus during withdrawal, it is recommended that patients provide informed consent confirming they have received and understand the risks associated with treatment.[4]

For patients planning to take medication to treat withdrawal, the World Health Organization (WHO)[170] suggests clinicians use the CIWA-Ar to facilitate alcohol withdrawal management.

A systematic review found consensus regarding the use of benzodiazepines and barbiturates during pregnancy.[13] Although both medications are considered teratogenic and have been associated with adverse effects on the fetus, these risks appear small and must be weighed against the risk of harm to the patient and fetus should severe alcohol withdrawal or seizures develop in pregnant patients. The WHO's guidelines[170] also recommend short-term use of a long-acting benzodiazepine to treat pregnant patients who develop alcohol withdrawal. When using medication to treat alcohol withdrawal among pregnant patients, limit the amount of medication to only what is necessary to prevent major complications of withdrawal.[13] For patients at risk for pre-term delivery or in the late third trimester, use of a short-acting benzodiazepine is recommended. This minimizes the risk for neonatal benzodiazepine intoxication given shorter onset and duration of action. Valproic acid should not be used in pregnant patients because of teratogenic risk.[110]

(4) Newborn considerations

Recommendation VII.35: In cases of alcohol withdrawal treated close to delivery, assess the newborn for benzodiazepine intoxication, sedative withdrawal, and Fetal Alcohol Spectrum Disorder (FASD) including Fetal Alcohol Syndrome (FAS).

Recommendation VII.36: Inform pregnant patients of all wraparound services that will assist them in addressing newborn needs, including food, shelter, pediatric clinics for inoculations, as well as programs that will help with developmental or physical issues that the newborn may experience as a result of in-utero substance exposure.

Recommendation VII.37: Licensed clinical staff have an obligation to understand and follow their state laws regarding substance use during pregnancy which may include definitions of child abuse and neglect, reporting requirements, and plans of safe care for newborns with in-utero alcohol exposure.

Discussion. If a pregnant patient's alcohol withdrawal was treated close to delivery, newborns should be monitored for signs of FASD and sedative withdrawal and intoxication if withdrawal was managed with medication.

As recommended by SAMHSA, pregnant patients should be made aware of wraparound services that will help them with newborn concerns as well as programs that will help with developmental or physical issues that the neonate may experience as a result of in-utero alcohol exposure.[4] It is the clinician's responsibility to know state laws regarding drug use during pregnancy as well as the definitions of child abuse and neglect to reassure and encourage patients to enter treatment.[4] Clinicians should also know the reporting requirements for such cases[4] and should discuss them with patients.

AREAS FOR FURTHER RESEARCH

Identification and Diagnosis

Further research is warranted on evidence-based strategies to identify alcohol withdrawal in various settings including primary care, Emergency Departments, and medical/surgical units in hospitals. Research would include the appropriate use of validated screening instruments, testing to rule out alternative diagnoses, and laboratory tests for alcohol and other drug use.

Initial Assessment

Areas for further research in alcohol withdrawal assessment include the development and testing of scales to predict the risk of alcohol withdrawal (and the risk of severe withdrawal). Further research on assessing the risk of severe alcohol withdrawal would include the relative importance of predictors, as well as additional research on individual risk factors for complicated withdrawal/complications of withdrawal. Furthermore, for clinicians in ambulatory

settings, further research on triaging patients based on risk would help guide clinical practice.

Level of Care Determination

Further research on the role of *The ASAM Criteria* Risk Matrix in determining appropriate level of care for individuals with alcohol withdrawal would be welcome. In particular, evidence-based improvements in the assessment of the recovery environment and available social support networks would be helpful to determine appropriateness for ambulatory management.

Ambulatory Management

Further research on optimal monitoring intervals at various levels of care would be useful in guiding clinical practice. The literature revealed a wide variety of recommendations for monitoring frequency and intensity.

While the importance of supportive care is widely recognized, it is not well-researched. Additional research on individualizing nutritional supplementation and alternative interventions for symptom management (e.g., acupuncture, massage, etc.) would be helpful.

Finally, further research is needed on the design and implementation of effective strategies to transition patients from alcohol withdrawal management to AUD treatment initiation and engagement. Comparative effectiveness studies of various models and strategies for linkages to care would be particularly helpful, as would investigation into the moderating or mediating influence of patient and setting factors.

Inpatient Management

Several promising medications have not yet been well-researched. Hence, large, well-controlled studies of specific medications would be helpful in expanding the options for individualization of alcohol withdrawal management. Some examples of useful comparative trials include phenobarbital vs. or as adjunct to benzodiazepines, ketamine as adjunct to other medications, carbamazepine vs. gabapentin. Further research on managing resistant or refractory withdrawal is also needed.

Addressing Complicated Alcohol Withdrawal

There is a minimal literature on the management of alcohol-induced psychosis associated with alcohol withdrawal. Although the Guideline Committee agreed with the one study conducted by Sellers in 1983, there is insufficient evidence to support the use of other medications to control for alcohol-induced psychosis during withdrawal. Further research on differentiating between alcohol-induced intoxication and alcohol-induced withdrawal as well as the management for both is warranted.

Specific Settings and Populations

The literature and Guideline Committee agreed that clinically significant alcohol withdrawal is rare among adolescents, and this special population was beyond the scope of the current guideline. However, further research on potential modifications to alcohol withdrawal management protocols for adolescents would be useful. Other special populations in need of further research include the elderly and criminal justice populations.

Appendices

I. Cited References
II. Literature Search Methods
III. Alcohol Withdrawal Scales Table
IV. Flowcharts (Supplemental Digital Content, http://links.lww.com/JAM/A192)
V. Sample Medication Regimens
VI. Statement Rating Table (Supplemental Digital Content, http://links.lww.com/JAM/A193)
VII. ASAM Guideline Committee and QIC (ASAM) (Supplemental Digital Content, http://links.lww.com/JAM/A194)

I. Cited References

1. National Cancer Institute. Adjunctive Therapy. NCI Dictionary of Cancer Terms. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/adjunctive-therapy. Accessed December 19, 2019.
2. Wartenberg A. Management of Alcohol Intoxication and Withdrawal. In: Ries RK, Fiellin DA, Miller SC, Saitz R, eds. *The ASAM Principles of Addiction Medicine*. 5th ed., Lippincott Williams & Wilkins; 2014 :635–651.
3. Jarvis M, Williams J, Hurford M, et al. Appropriate Use of Drug Testing in Clinical Addiction Medicine. *J Addict Med*. 2017;11(3):163–173. doi:10.1097/ADM.0000000000000323.
4. Center for Substance Abuse Treatment (CSAT). Detoxification and Substance Abuse Treatment. Treatment Improvement Protocol (TIP) Series, No. 45. Rockville, MD; 2015.
5. Malcolm R, Herron JE, Anton RF, Roberts J, Moore J. Recurrent Detoxification May Elevate Alcohol Craving as Measured by the Obsessive Compulsive Drinking Scale. *Alcohol*. 2000;20(2):181–185. doi:10.1016/S0741-8329(99)00073-7.
6. Malcolm R, Roberts JS, Wang W, Myrick H, Anton RF. Multiple Previous Detoxifications are Associated with Less Responsive Treatment and Heavier Drinking During an Index Outpatient Detoxification. *Alcohol*. 2000;22(3):159–164.
7. Mirijello A, D'Angelo C, Ferrulli A, et al. Identification and Management of Alcohol Withdrawal Syndrome. *Drugs*. 2015;75(4):353–365. doi:10.1007/s40265-015-0358-1.
8. White WL, Cloud W. Recovery Capital: A Primer for Addictions Professionals. *Counselor*. 2008;9(5):22–27.
9. ScienceDirect. Therapeutic Window. Elsevier. https://www.sciencedirect.com/topics/medicine-and-dentistry/therapeutic-window. Published 2019. Accessed January 6, 2020.
10. CDC's National Center for Chronic Disease Prevention and Health Promotion. *Excessive Alcohol Use*. Atlanta, GA; 2019.
11. World Health Organization. *Clinical Guidelines for Withdrawal Management and Treatment of Drug Dependence in Closed Setting*. Geneva, Switzerland; 2009.
12. Mee-Lee D, Shulman GD, Fishman M, Gastfriend DR, Miller MM, Provence SM, eds. *The ASAM Criteria: Treatment for Addictive, Substance-Related, and Co-Occurring Conditions*. Lippincott Williams & Wilkins; 2013.
13. Mayo-Smith M. Pharmacological Management of Alcohol Withdrawal. *JAMA*. 1997;50(5):265–269.
14. Mayo-Smith MF, Beecher LH, Fischer TL, et al. Management of Alcohol Withdrawal Delirium: An Evidence-Based Practice Guideline. *Arch Intern Med*. 2004;164(13):1405–1412.
15. American Psychiatric Association (APA). *Practice Guideline for the Pharmacological Treatment of Patients with Alcohol Use Disorder*. American Psychiatric Association; 2018, doi:10.1176/appi.books.9781615371969.
16. Wood E, Albarqouni L, Tkachuk S, et al. Will This Hospitalized Patient Develop Severe Alcohol Withdrawal Syndrome? *JAMA*. 2018;320(8):825. doi:10.1001/jama.2018.10574.
17. MacLeod JBA, Hungerford DW. Injury. *Int J Care Injured*. 2001;42:922–926.
18. Ries RK, Fiellin DA, Miller SC, Saitz R, eds. *The ASAM Principles of Addiction Medicine*. 5th ed., Lippincott Williams & Wilkins; 2014.
19. American Society of Addiction Medicine (ASAM). *The ASAM Standards of Care for the Addiction Specialist Physician*. Rockville, MD: American Society of Addiction Medicine; 2014.
20. Wright P, Stern J, Phelan M, eds. *Core Psychiatry*. 3rd ed., Elsevier Health Sciences; 2012.
21. National Institute for Health and Care Excellence (NICE). *Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence*. Manchester, UK; 2011.
22. 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(3):724–730. doi:10.1097/01.CCM.0000256841. 28351.80.
23. Hack JB, Hoffmann RS, Nelson LS. Resistant alcohol withdrawal: does an unexpectedly large sedative requirement identify these patients early? *J Med Toxicol*. 2006;2(2):55–60. doi:10.1007/BF03161171.
24. Buckley DI, Ansari M, Butler M, Williams C, Chang C. *The Refinement of Topics for Systematic Reviews*. Rockville: Agency for Healthcare Research and Quality (US); 2013.
25. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *BMJ*. 2009;339:b2535. doi:10.1136/bmj. b2535.
26. Bialer PA, Miller AC. Management of Alcohol Withdrawal and Other Selected Substance Withdrawal Issues. In: Amos J, Robinson R, eds. *Psychosomatic Medicine: An Introduction to Consultation-Liaison Psychiatry*. Cambridge: Cambridge University Press (CUP); 2010 :193–201. doi:10.1017/CBO9780511776878.022.
27. Curry SJ, Krist AH, Owens DK, et al. Screening and Behavioral Counseling Interventions to Reduce Unhealthy Alcohol Use in Adolescents and Adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2018;320(18):1899–1909. doi:10.1001/jama. 2018. 16789.
28. Maldonado JR, Sher Y, Ashouri JF, et al. The "Prediction of Alcohol Withdrawal Severity Scale" (PAWSS): Systematic Literature Review and Pilot Study of a New Scale for the Prediction of Complicated Alcohol Withdrawal Syndrome. *Alcohol*. 2014;48(4):375–390. doi:10.1016/j.alcohol.2014.01.004.

29. Pecoraro A, Ewen E, Horton T, et al. Using the AUDIT-PC to Predict Alcohol Withdrawal in Hospitalized Patients. *J Gen Intern Med*. 2014;29(1):34–40. doi:10.1007/s11606-013-2551-9.
30. Bazzi A, Saitz R. Screening for Unhealthy Alcohol Use. *JAMA*. 2018;320(18):1869–1871. doi:10.1001/jama.2018.16069.
31. Reoux JP, Malte CA, Kivlahan DR, Saxon AJ. The Alcohol Use Disorders Identification Test (AUDIT) Predicts Alcohol Withdrawal Symptoms During Inpatient Detoxification. *J Addict Dis*. 2002;21(4):81–91. doi:10.1300/J069v21n04_08.
32. Lansford C, Guerriero C, Kocan M, et al. Improved Outcomes in Patients With Head and Neck Cancer Using a Standardized Care Protocol for Postoperative Alcohol Withdrawal. *Arch Otolaryngol Head Neck Surg*. 2008;134(8):865–872.
33. Melson J. Improving Alcohol Withdrawal Outcomes in Acute Care. *Perm J*. 2014;18(2):e141–e145. doi:10.7812/tpp/13-099.
34. Worner TM. New Strategies in Treating the Alcohol Withdrawal Syndrome. *Hosp Med*. 1995;54–67.
35. Dolman JM, Hawkes ND. Combining the AUDIT Questionnaire and Biochemical Markers to Assess Alcohol Use and Risk of Alcohol Withdrawal in Medical Inpatients. *Alcohol Alcohol*. 2005;40(6):515–519. doi:10.1093/alcalc/agh189.
36. Blondell R, Azadfard M. Hospital Management. In: Saitz R, editor. *Addressing Unhealthy Alcohol Use in Primary Care*. New York, NY: Springer-Verlag; 2013 :207–219. doi:10.1007/978-1-4614-4779-5_18.
37. 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(11):1353–1357.
38. Bayard M, McIntyre J, Hill K, Woodside J. Alcohol Withdrawal Syndrome. *Am Fam Pysician*. 2004;69(6):1443–1450.
39. Abbott PJ. Admission Criteria and Patient Placement Guidelines for Ambulatory Alcohol Medical Detoxification. *Alcohol Treat Q*. 1996;14(2):15–27. doi:10.1300/j020v14n02_02.
40. Smith I, Woolston C. Management of Alcohol Use Disorders in Primary Care. *Prescriber*. 2015;26(23–24):14–18.
41. Kattimani S, Bharadwaj B. Clinical Management of Alcohol Withdrawal: A Systematic Review. *Ind Psychiatry J*. 2013;22(2):100–108. doi:10.4103/0972-6748.132914.
42. Jesse S, Bråthen G, Ferrara M, et al. Alcohol Withdrawal Syndrome: Mechanisms, Manifestations, and Management. *Acta Neurol Scand*. 2016;135(1):4–16. doi:10.1111/ane.12671.
43. American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, D.C: American Psychiatric Association; 2013 doi:10.1176/appi.books.9780890425596.
44. Soyka M, Kranzler HR, Hesselbrock V, Kasper S, Mutschler J, Möller HJ. Guidelines for Biological Treatment of Substance Use and Related Disorders, Part 1: Alcoholism. *World J Biol Psychiatry*. 2017;18(2):86–119. doi:10.1080/15622975.2016.1246752.
45. Gortney JS, Raub JN, Patel P, Kokoska L, Hannawa M, Argyris A. Alcohol Withdrawal Syndrome in Medical Patients. *Cleve Clin J Med*. 2016;83(1):67–79. doi:10.3949/ccjm.83a.14061.
46. Perry EC. Inpatient Management of Acute Alcohol Withdrawal Syndrome. *CNS Drugs*. 2014;28(5):401–410. doi:10.1007/s40263-014-0163-5.
47. Maldonado JR, Sher Y, Das S, et al. Prospective Validation Study of the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) in Medically Ill Inpatients: A New Scale for the Prediction of Complicated Alcohol Withdrawal Syndrome. *Alcohol Alcohol*. 2015;50(5):509–518. doi:10.1093/alcalc/agv043.
48. Goodson CM, Clark BJ, Douglas IS. Predictors of Severe Alcohol Withdrawal Syndrome: A Systematic Review and Meta-Analysis. *Alcohol Clin Exp Res*. 2014;38(10):2664–2677. doi:10.1111/acer.12529.
49. Asplund CA, Aaronson JW, Aaronson HE. 3 Regimens for Alcohol Withdrawal and Detoxification. *J Fam Pract*. 2004;53(7):545–554.
50. Awissi DK, Lebrun G, Coursin DB, Riker RR, Skrobik Y. Alcohol Withdrawal and Delirium Tremens in the Critically Ill: A Systematic Review and Commentary. *Intensive Care Med*. 2013;39(1):16–30. doi:10.1007/s00134-012-2758-y.
51. Rolland B, Paille F, Gillet C, et al. Pharmacotherapy for Alcohol Dependence: The 2015 Recommendations of the French Alcohol Society, Issued in Partnership with the European Federation of Addiction Societies. *CNS Neurosci Ther*. 2016;22:25–37. doi:10.1111/cns.12489.
52. Task Force EFNS, Ben-Menachem E, Brodtkorb E, et al. EFNS Guideline on the Diagnosis and Management of Alcohol-Related Seizures. *Eur J Neurol*. 2005;12:575–581.
53. Martinez L, Vorspan F, Declèves X, et al. An Observational Study of Benzodiazepine Prescription During Inpatient Alcohol Detoxification for Patients with vs. without Chronic Pretreatment with High-Dosage Baclofen. *Fundam Clin Pharmacol*. 2018;32(2):200–205. doi:10.1111/fcp.12339.
54. Saitz R. Introduction to Alcohol Withdrawal. *Alcohol Heal Res World*. 1998;22(1):5–12.
55. Wetterling T, Weber B, Depenhart M, Schneider B, Junghanns K. Development of a Rating Scale to Predict the Severity of Alcohol Withdrawal Syndrome. *Alcohol Alcohol*. 2006;41(6):611–615. doi:10.1093/alcalc/agl068.
56. Fiellin DA, Reid MC, O'Connor PG. Outpatient Management of Patients with Alcohol Problems. *Ann Intern Med*. 2000;133(10):815–827. doi:10.7326/0003-4819-133-10-200011210-00015.
57. Foy A, McKay S, Ling S, Bertram M, Sadler C. Clinical Use of a Shortened Alcohol Withdrawal Scale in a General Hospital. *Intern Med J*. 2006;36(3):150–154. doi:10.1111/j.1445-5994.2006.01032.x.
58. Department of Veterans Affairs, Department of Defense. *VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders*. Washington, DC; 2015.
59. Rastegar DA, Applewhite D, Alvanzo AAH, Welsh C, Niessen T, Chen ES. Development and Implementation of an Alcohol Withdrawal Protocol Using a 5-Item Scale, the Brief Alcohol Withdrawal Scale (BAWS). *Subst Abus*. 2017;38(4):394–400. doi:10.1080/08897077.2017.1354119.
60. 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. *Alcohol Clin Exp Res*. 1988;12(3):360–364. doi:10.1111/j.1530-0277.1988.tb00208.x.
61. Gossop M, Keaney F, Stewart D, Jane Marshall E, Strang J. A Short Alcohol Withdrawal Scale (SAWS): Development and Psychometric Properties. *Addict Biol*. 2002;7(1):37–43. doi:10.1080/1355621 01200100571.
62. Holt S, Tetrault JM. Ambulatory Management of Alcohol Withdrawal. UpToDate. www.uptodate.com. Accessed January 8, 2018.
63. Humeniuk R, Ali R, Babor TF, et al. Validation of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). *Addiction*. 2008;103(6):1039–1047. doi:10.1111/j.1360-0443.2007.02114.x.

64. WHO ASSIST Working Group. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): Development, Reliability and Feasibility. *Addiction*. 2002;97:1183–1194.
65. BC Guidelines. *Problem Drinking Part 3 - Office Based Management of Alcohol Withdrawal and Prescribing Medications for Alcohol Dependence*. Province of British Columbia; 2013.
66. Hayashida M, Alterman A, McLellan T, et al. Comparative Effectiveness and Cost of Inpatient and Outpatient Detoxification of Patients with Mild-To-Moderate Alcohol Withdrawal Syndrome. *N Engl J Med*. 1989;320(6):358–365.
67. Stinnett J. Outpatient Detoxification of the Alcoholic. *Int J Addict*. 1982;17(6):1031–1046.
68. Abbott PJ, Quinn D, Knox L. Ambulatory Medical Detoxification for Alcohol. *Am J Drug Alcohol Abuse*. 1995;21(4):549–563. doi:10.3109/00952999509002715.
69. Foote E, Dukes CH. Acute Management of Substance-Related and Addictive Disorders: A Review. *Psychiatr Ann*. 2017;47(4):192–199. doi:10.3928/00485713-20170306-01.
70. Sachdeva A, Chandra M, Deshpande SN. A Comparative Study of Fixed Tapering Dose Regimen versus Symptom-Triggered Regimen of Lorazepam for Alcohol Detoxification. *Alcohol Alcohol*. 2014;49(3):287–291. doi:10.1093/alcalc/agt181.
71. Muncie HL, Yasinian Y, Oge' L. Outpatient Management of Alcohol Withdrawal Syndrome. *Am Fam Physician*. 2013;88(9):589–595.
72. Spithoff S, Kahan M. Primary Care Management of Alcohol Use Disorder and At-Risk Drinking: Part 1: Screening and Assessment. *Can Fam Physician*. 2015;61(6):509–514. doi:61/6/515 [pii].
73. Kosten TR, O'Connor PG. Management of Drug and Alcohol Withdrawal. *N Engl J Med*. 2003;348(18):1786–1795. doi:10.1056/NEJMra020617.
74. American Society of Addiction Medicine (ASAM). *National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use*. Chevy Chase, MD: American Society of Addiction Medicine; 2015.
75. Prescrire Editorial Staff. Alcohol Withdrawal Syndrome: How to Predict, Prevent, Diagnose and Treat it. *Prescrire Int*. 2007;16(87): 24–31.
76. Gershkovich P, Wasan KM, Ribeyre C, Ibrahim F, McNeill JH. Effect of Variations in Treatment Regimen and Liver Cirrhosis on Exposure to Benzodiazepines During Treatment of Alcohol Withdrawal Syndrome. *Drugs Context*. 2015;4. doi:10.7573/dic.212287.
77. Elholm B, Larsen K, Hornnes N, Zierau F, Becker U. A Psychometric Validation of the Short Alcohol Withdrawal Scale (SAWS). *Alcohol Alcohol*. 2010;45(4):361–365. doi:10.1093/alcalc/agq033.
78. Elholm B, Larsen K, Hornnes N, Zierau F, Becker U. Alcohol Withdrawal Syndrome: Symptom-Triggered versus Fixed-Schedule Treatment in an Outpatient Setting. *Alcohol Alcohol*. 2011;46(3):318–323. doi:10.1093/alcalc/agr020.
79. Bulmer DR. Treatment of Alcoholism in Family Practice. *Can Fam Physician*. 1980;26:563–570.
80. Prater CD, Miller KE, Zylstra RG. Outpatient Detoxification of the Addicted or Alcoholic Patient. *Am Fam Physician*. 1999;60(4):1175–1182.
81. Kaiser Permanente. *Unhealthy Drinking in Adults Screening and Intervention Guideline*. Seattle, WA; 2016.
82. Martin A. Protocol for Alcohol Outpatient Detoxification. *Lippincotts Prim Care Pract*. 2000;4(2):221–227.
83. Bischof GH, Richmond CJ, Case AR. Detoxification at Home: A Brief Solution-Oriented Family Systems Approach. *Contemp Fam Ther*. 2003;25(1):17–39. doi:10.1023/A:1022553920603.
84. Kril JJ, Harper CG. Neuroanatomy and neuropathology associated with Korsakoff's syndrome. *Neuropsychol Rev*. 2012;22(2):72–80. doi:10.1007/s11065-012-9195-0.
85. Akhouri S, Kuhn J, Newton EJ. Wernicke-Korsakoff Syndrome. *StatPearls*. 2019.
86. Hayashida M. An Overview of Outpatient and Inpatient Detoxification. *Alcohol Heal Res World*. 1998;22(1):44–46.
87. Vanbuskirk KA, Wetherell JL. Motivational interviewing with primary care populations: A systematic review and meta-analysis. *J Behav Med*. 2014;37(4):768–780. doi:10.1007/s10865-013-9527-4.
88. Carroll KM, Libby B, Sheehan J, Hyland N. Motivational Interviewing to Enhance Treatment Initiation in Substance Abusers: An Effectiveness Study. *Am J Addict*. 2001;10(4):335–339. doi:10.1111/j.1521-0391.2001.tb00523.x.
89. Ungur LA, Neuner B, John S, Wernecke K, Spies C. Prevention and Therapy of Alcohol Withdrawal on Intensive Care Units: Systematic Review of Controlled Trials. *Alcohol Clin Exp Res*. 2013;37(4):675–686. doi:10.1111/acer.12002.
90. Amato L, Minozzi S, Vechhi S, Davoli M. Benzodiazepines for Alcohol Withdrawal. *Am Fam Physician*. 2010;(7).
91. Muzyk AJ, Rogers RE, Dighe G, et al. Impact of an Alcohol Withdrawal Treatment Pathway on Hospital Length of Stay: A Retrospective Observational Study Comparing Pre and Post Pathway Implementation. *J Psychiatr Pract*. 2017;23(3):233–241. doi:10.1097/PRA.0000000000000229.
92. Hammond CJ, Niciu MJ, Drew S, Arias AJ. Anticonvulsants for the treatment of alcohol withdrawal syndrome and alcohol use disorders. *CNS Drugs*. 2015;29(4):293–311. doi:10.1007/s40263-015-0240-4.
93. Leung JG, Hall-Flavin D, Nelson S, Schmidt KA, Schak KM. Role of Gabapentin in the Management of Alcohol Withdrawal and Dependence. *Ann Pharmacother*. 2015;49(8):897–906. doi:10.1177/1060028015585849.
94. Minozzi S, Amato L, Vecchi S, Davoli M. Anticonvulsants for Alcohol Withdrawal (Review). *Cochrane Database Syst Rev*. 2010;(3). doi:10.1002/14651858.CD005064.pub3.www.cochranelibrary.com.
95. Amato L, Minozzi S, Davoli M. Efficacy and Safety of Pharmacological Interventions for the Treatment of the Alcohol Withdrawal Syndrome (Review). *Cochrane Database Syst Rev*. 2011;(6). doi:10.1002/14651858.CD008537.pub2.www.cochranelibrary.com.
96. Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-Analysis of Benzodiazepine Use in the Treatment of Insomnia. *CMAJ*. 1999;162(2): 225–233.
97. Brotherton AL, Hamilton EP, Kloss HG, Hammond DA. Propofol for Treatment of Refractory Alcohol Withdrawal Syndrome: A Review of the Literature. *Pharmacotherapy*. 2016;36(4):433–442. doi:10.1002/phar.1726.
98. Weaver MF, Hoffman HJ, Johnson RE, Mauck K. Alcohol Withdrawal Pharmacotherapy for Inpatients with Medical Comorbidity. *J Addict Dis*. 2006;25(2):17–24. doi:10.1300/j069v25n02_03.
99. Moore PW, Donovan JW, Burkhart KK, et al. Safety and Efficacy of Flumazenil for Reversal of Iatrogenic Benzodiazepine-Associated Delirium Toxicity During Treatment of Alcohol Withdrawal, a Retrospective Review at One Center. *J Med Toxicol*. 2014;10(2):126–132. doi:10.1007/s13181-014-0391-6.
100. Claassen CA, Adinoff B. Alcohol Withdrawal Syndrome: Guidelines for Management. *CNS Drugs*. 1999;12(4):279–291. doi:10.2165/00023210-199912040-00003.

101. Managing the Heavy Drinker in Primary Care. *Drug Ther Bull*. 2000; 38(8):60-64. doi:10.1136/dtb.2000.38860
102. Muzyk AJ, Kerns S, Brudney S, Gagliardi JP. Dexmedetomidine for the treatment of alcohol withdrawal syndrome: rationale and current status of research. *CNS Drugs*. 2013;27(11):913–920. doi:10.1007/s40263-013-0106-6.
103. Daeppen J-B, Gache P, Landry U, et al. Symptom-Triggered vs Fixed-Schedule Doses of Benzodiazepine for Alcohol Withdrawal. *Arch Intern Med*. 2002;162(10):1117–1121. doi:10.1001/archinte.162.10.1117.
104. Day E, Patel J, Georgiou G. Evaluation of a Symptom-Triggered Front-Loading Detoxification Technique for Alcohol Dependence: A Pilot Study. *Psychiatr Bull*. 2004;28(11):407–410. doi:10.1192/pb.28. 11.407.
105. Manikant S, Tripathi BM, Chavan BS. Loading Dose Diazepam Therapy for Alcohol Withdrawal State. *Indian J Med Res*. 1993;98:170–173.
106. 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(7): 519–523.
107. Barrons R, Roberts N. The Role of Carbamazepine and Oxcarbazepine in Alcohol Withdrawal Syndrome. *J Clin Pharm Ther*. 2010;35(2):153–167. doi:10.1111/j.1365-2710.2009.01098.x.
108. Smith RV, Havens JR, Walsh SL. Gabapentin misuse, abuse and diversion: a systematic review. *Addiction*. 2016;111(7):1160–1174. doi:10.1111/add.13324.
109. Malcolm R, Myrick H, Brady KT, Ballenger JC. Update on Anticonvulsants for the Treatment of Alcohol Withdrawal. *Am J Addict*. 2001;10:16–23. doi:10.1080/10550490190942489.
110. Prescriber's Digital Reference. Valproic Acid - Drug Summary. https://www.pdr.net/drug-summary/Depakene-valproic-acid-979.5705. Accessed September 3, 2019.
111. Hammond DA, Rowe JM, Wong A, Wiley TL, Lee KC, Kane-Gill SL. Patient Outcomes Associated With Phenobarbital Use with or Without Benzodiazepines for Alcohol Withdrawal Syndrome: A Systematic Review. *Hosp Pharm*. 2017;52(9):607–616. doi:10.1177/0018578717720310.
112. J.L., L.W. Baclofen for alcohol withdrawal. *Cochrane Database Syst Rev*. 2011;1:CD008502.
113. Liu J, Ln W. Baclofen for alcohol withdrawal (Review) SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. 2017;(8). doi:10.1002/14651858.CD008502.pub5.www.cochranelibrary.com
114. Sarai M, Tejani A, Chan A, Kuo I, Li J. Magnesium for Alcohol Withdrawal (Review). *Cochrane Database Syst Rev*. 2013;(6). doi:10.1002/14651858.CD008358.pub2.www.cochranelibrary.com.
115. Schmidt KJ, Doshi MR, Holzhausen JM, Natavio A, Cadiz M, Winegardner JE. Treatment of Severe Alcohol Withdrawal. *Ann Pharmacother*. 2016;50(5):389–401. doi:10.1177/1060028016629161.
116. Schuckit MA. Recognition and Management of Withdrawal Delirium (Delirium Tremens). *N Engl J Med*. 2014;371(22):2109–2113. doi:10.1056/NEJMra1407298.
117. Inouye SK, Bogardus ST, Charpentier PA, et al. A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients. *N Engl J Med*. 1999;340(9):669–676. doi:10.1056/NEJM199903043400901.
118. Green A, Parker R, Williams TM. A Novel Scoring System to Guide Risk Assessment of Wernicke's Encephalopathy. *Alcohol Clin Exp Res*. 2013;37(5):885–889. doi:10.1111/acer.12028.
119. Schilling RF, El-Bassel N, Finch JB, Roman RJ, Hanson M. Motivational Interviewing to Encourage Self-Help Participation Following Alcohol Detoxification. *Res Soc Work Pract*. 2002;12(6):711–730. doi:10.1177/104973102237469.
120. C.A.N., E.M. S., K.C. Nonpharmacologic intervention in acute alcohol withdrawal. *Clin Pharmacol Ther*. 1983;34(2):214–219.
121. Shaw JM, Kolesar GS, Sellers EM, Kaplan HL, Sandor P. Development of Optimal Treatment Tactics for Alcohol Withdrawal. I. Assessment and Effectiveness of Supportive Care. *J Clin Psychopharmacol*. 1981;1(6):382–389. doi:10.1097/00004714-198111000-00006.
122. Whitfield CL, Thompson G, Lamb A, Spencer V, Pfeifer M, Browning-Ferrando M. Detoxification of 1,024 alcoholic patients without psychoactive drugs. *JAMA*. 1978;239(14):1409–1410.
123. Sohraby R, Attridge RL, Hughes DW. Use of Propofol-Containing Versus Benzodiazepine Regimens for Alcohol Withdrawal Requiring Mechanical Ventilation. *Ann Pharmacother*. 2014;48(4):456–461. doi:10.1177/1060028013515846.
124. Weithmann G, Hoffmann M. A randomised clinical trial of in-patient versus combined day hospital treatment of alcoholism: primary and secondary outcome measures. *Eur Addict Res*. 2005;11(4):197–203. doi:10.1159/000086402.
125. Wilson A, Vulcano B. A Double-Blind, Placebo-Controlled Trial of Magnesium Sulfate in the Ethanol Withdrawal Syndrome. *Alcohol Clin Exp Res*. 1984;8(6):542–545. doi:10.1111/j.1530-0277.1984. tb05726.x.
126. Yanta J, Swartzentruber GS, Pizon AF. Alcohol Withdrawal Syndrome: Improving Outcomes Through Early Identification And Aggressive Treatment Strategies. *Emerg Med Pract*. 2015;17(6).
127. Rosenson J, Clements C, Simon B, et al. Phenobarbital for Acute Alcohol Withdrawal: A Prospective Randomized Double-Blind Placebo-Controlled Study. *J Emerg Med*. 2013;44(3):592–598. doi:10.1016/j.jemermed.2013.08.158.
128. Lewis CB, Adams N. Phenobarbital. *StatPearls*. 2019.
129. Suddock JT, Cain MD. Barbiturate Toxicity. *StatPearls*. 2019.
130. Nestler EJ, Hyman SE, Malenka RC. *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience*. McGraw-Hill Medical; 2001 .
131. D'Onofrio G, Rathlev N, Ulrich A, Fish S, Freedland E. Lorazepam for the Prevention of Recurrent Seizures Related to Alcohol. *N Engl J Med*. 1999;340(12):915–919.
132. Sachdeva A, Choudhary M, Chandra M. Alcohol Withdrawal Syndrome: Benzodiazepines and Beyond. *J Clin Diagnostic Res JCDR*. 2015;9(9):VE01–VE07. doi:10.7860/JCDR/2015/13407. 6538.
133. Young GP, Rores C, Murphy C, Dailey RH. Intravenous Phenobarbital for Alcohol Withdrawal and Convulsions. *Ann Emerg Med*. 1987;16(8):847–850. doi:10.1016/S0196-0644(87)80520-6.
134. Hendey GW, Dery RA, 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):382–385. doi:10.1016/j.ajem.2009.10.010.
135. Maldonado JR. Novel Algorithms for the Prophylaxis and Management of Alcohol Withdrawal Syndromes–Beyond Benzodiazepines. *Crit Care Clin*. 2017;33(3):559–599. doi:10.1016/j.ccc.2017.03.012.
136. Ely EW, Inouye SK, Bernard GR, et al. Delirium in Mechanically Ventilated Patients. *JAMA*. 2001;286(21):2703. doi:10.1001/jama. 286.21.2703.

137. Ely EW, Margolin R, Francis J, et al. Evaluation of Delirium in Critically Ill Patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med*. 2001;29(7):1370–1379. doi:10.1097/00003246-200107000-00012.
138. Otter H, Martin J, Bäsell K, et al. Validity and Reliability of the DDS for Severity of Delirium in the ICU. *Neurocrit Care*. 2005;2(2):150–158. doi:10.1385/NCC:2:2:150.
139. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;166(10):1338–1344. doi:10.1164/rccm.2107138.
140. DeCarolis DD, Rice KL, Ho L, Willenbring ML, Cassaro S. Symptom-Driven Lorazepam Protocol for Treatment of Severe Alcohol Withdrawal Delirium in the Intensive Care Unit. *Pharmacotherapy*. 2007;27(4):510–518. doi:10.1592/phco.27.4.510.
141. Inouye SK. Delirium in Hospitalized Older Patients: Recognition and Risk Factors. *J Geriatr Psychiatry Neurol*. 1998;11(3):118–125. doi:10.1177/089198879801100302.
142. Michaud L, Büla C, Berney A, et al. Delirium: Guidelines for general hospitals. *J Psychosom Res*. 2007;62(3):371–383. doi:10.1016/j.jpsychores.2006.10.004.
143. Inouye S. Delirium in Older Persons. *N Engl J Med*. 2006;354(11):1157–1165. doi:10.1001/jama.2017.12067.
144. Vasilevskis EE, Han JH, Hughes CG, Ely EW. Epidemiology and Risk Factors for Delirium Across Hospital Settings. *Best Pract Res Clin Anaesthesiol*. 2012;26(3):277–287. doi:10.1016/j.bpa.2012.07.003.
145. Rainier NC. Reducing physical restraint use in alcohol withdrawal patients: a literature review. *Dimens Crit Care Nurs*. 2014;33(4):201–206. doi:10.1097/DCC.0000000000000059.
146. Brown JH, Moggey DE, Shane FH. Delirium Tremens: A Comparison of Intravenous Treatment with Diazepam and Chlordiazepoxide. *Scott Med J*. 1972;17(1):9–12.
147. Michaelsen I, Anderson J, Fink-Jensen A, Allerup P, Ulrichsen J. Phenobarbital versus Diazepam for Delirium Tremens - A Retrospective Study. *Dan Med Bull*. 2010;57(8). doi:10.1136/jcp.43.9.787-d.
148. Duby JJ, Berry AJ, Ghayyem P, Wilson MD, Cocanour CS. Alcohol Withdrawal Syndrome in Critically Ill Patients: Protocolized versus Nonprotocolized Management. *J Trauma Acute Care Surg*. 2014;77(6):938–943. doi:10.1097/TA.0000000000000352.
149. Wasilewski D, Matsumoto H, Kur EWA, et al. Assessment of Diazepam Loading Dose Therapy of Delirium Tremens. *Alcohol Alcohol*. 1996;31(3):273–278.
150. Sellers EM, Sandor P, Giles HG, Shaw J. Diazepam loading: Simplified treatment of alcohol withdrawal. *Clin Investig Med*. 1981;4(2):822–826.
151. Mo Y, Thomas MC, Karras GE. Barbiturates for the Treatment of Alcohol Withdrawal Syndrome: A Systematic Review of Clinical Trials. *J Crit Care*. 2016;32:101–107. doi:10.1016/j.jcrc.2015. 11.022.
152. Long D, Long B, Koyfman A. The Emergency Medicine Management of Severe Alcohol Withdrawal. *Am J Emerg Med*. 2017;35(7):1005–1011. doi:10.1016/j.ajem.2017.02.002.
153. Albertson TE, Chenoweth J, Ford J, Owen K, Sutter ME. Is It Prime Time for Alpha2-Adrenocepter Agonists in the Treatment of Withdrawal Syndromes? *J Med Toxicol*. 2014;10(4):369–381. doi:10.1007/s13181-014-0430-3.
154. Linn DD, Loeser KC. Dexmedetomidine for Alcohol Withdrawal Syndrome. *Ann Pharmacother*. 2015;49(12):1336–1342. doi:10.1177/1060028015607038.
155. Mueller SW, Preslaski CR, Kiser TH, et al. A Randomized, Double-Blind, Placebo-Controlled Dose Range Study of Dexmedetomidine as Adjunctive Therapy for Alcohol Withdrawal. *Crit Care Med*. 2014;42(5):1131–1139. doi:10.1097/CCM.0000000000000141.
156. Bielka K, Kuchyn I, Glumcher F. Addition of Dexmedetomidine to Benzodiazepines for Patients with Alcohol Withdrawal Syndrome in the Intensive Care Unit: A Randomized Controlled Study. *Ann Intensive Care*. 2015;5(33):1–7. doi:10.1186/s13613-015-0075-7.
157. Day E, Copello A, Hull M. Assessment and Management of Alcohol Use Disorders. *Britsh Med J*. 2015;715:1–9. doi:10.1136/bmj.h715.
158. H.M., J.C., S.S., H.P. Diagnosis and treatment of co-occurring affective disorders and substance use disorders. *Psychiatr Clin North Am*. 2004;27(4):649–659. doi:10.1016/j.psc.2004.06.003.
159. Etherington JM. Emergency Management of Acute Alcohol Problems Part 1: Uncomplicated Withdrawal. *Can Fam Physician*. 1996;42: 2186–2190.
160. Saunders J, Aasland O, Babor T, De La Fuente J, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption-II. *Addiction*. 1993;88(6):791–804. doi:10.1111/j.1360-0443.1993.tb02093.x.
161. Sutton LJ, Jutel A. Alcohol Withdrawal Syndrome in Critically Ill Patients: Identification, Assessment, and Management. *Crit Care Nurse*. 2016;36(1):28–39. doi:10.4037/ccn2016420.
162. Thomson AD, Marshall EJ. The Natural History and Pathophysiology of Wernicke's Encephalopathy and Korsakoff's Psychosis. *Alcohol Alcohol*. 2006;41(2):151–158. doi:10.1093/alcalc/agh249.
163. Thomson AD, Guerrini I, Marshall EJ. The Evolution and Treatment of Korsakoff's Syndrome. *Neuropsychol Rev*. 2012;22(2):81–92. doi:10.1007/s11065-012-9196-z.
164. Latt N, Dore G. Thiamine in the Treatment of Wernicke Encephalopathy in Patients with Alcohol Use Disorders. *Intern Med J*. 2014;44(9):911–915. doi:10.1111/imj.12522.
165. Galvin R, Bråthen G, Ivashynka A, Hillbom M, Tanasescu R, Leone MA. EFNS Guidelines for Diagnosis, Therapy and Prevention of Wernicke Encephalopathy. *Eur J Neurol*. 2010;17(12):1408–1418. doi:10.1111/j.1468-1331.2010.03153.x.
166. Todd K, Hazell A, Butterworth R. Alcohol-Thiamine Interactions: An Update on the Pathogenesis of Wernick encephalopathy. *Addict Biol*. 1999;4:261–272.
167. Heymann A, Nachtigall I, Goldman A, Spies C. Alcohol Withdrawal in the Surgical Patient: Prevention and Treatment. In: *Surgical Intensive Care Medicine: Second Edition*.; 2010:659-666. doi:10.1007/978-0-387-77893-8
168. Flannery AH, Adkins DA, Cook AM. Unpeeling the Evidence for the Banana Bag: Evidence-Based Recommendations for the Management of Alcohol-Associated Vitamin and Electrolyte Deficiencies in the ICU. *Crit Care Med*. 2016;44(8):1545–1552. doi:10.1097/CCM.0000000000001659.
169. Bhat A, Hadley A. The Management of Alcohol Withdrawal in Pregnancy - Case Report, Literature Review and Preliminary Recommendations. *Gen Hosp Psychiatry*. 2015;37(3). 273.e1-273.e3. doi:10.1016/j.genhosppsych.2015.02.001.
170. World Health Organization. *Guidelines for Identification and Management of Substance Use and Substance Use Disorders in Pregnancy*. Geneva, Switzerland; 2014. doi:10.4324/9781315775425

II. Literature Search Methods

A. Empirical Literature Search Terms

Without date limiters (1/1/2013 - 11/6/2017)

Medline (EBSCOhost)

Search ID	Search Terms
1	TX "Alcohol withdrawal" OR TX "Delirium tremens" OR TX "Alcohol-induced hallucinosis" OR TX "Alcohol-induced psychotic disorder"
2	1 AND Limiters: Animals
3	1 AND Limiters: Human
4	2 AND 3
5	2 NOT 4
6	1 NOT 5
7	6 AND Limiters: English

CINAHL

Search ID	Search Terms
1	TX "Alcohol withdrawal" OR TX "Delirium tremens" OR TX "Alcohol-induced hallucinosis" OR TX "Alcohol-induced psychotic disorder"
2	1 AND Limiters: English

EMBASE

Search ID	Search Terms
1	'alcohol withdrawal' OR 'delirium tremens' OR 'alcohol-induced hallucinosis' OR 'alcohol-induced psychotic disorder'
2	1 AND [animals]/lim
3	1 AND [humans]/lim
4	2 AND 3
5	2 NOT 4
6	1 NOT 5
7	6 AND [english]/lim

Web of Science

Search ID	Search Terms
1	TOPIC: ("Alcohol withdrawal") OR TOPIC: ("Delirium tremens") OR TOPIC: ("Alcohol-induced hallucinosis") OR TOPIC: ("Alcohol-induced psychotic disorder")
2	1 AND Refined by: LANGUAGES: (ENGLISH)

B. Gray Literature Search

Source	Detail
National Technical Information Service (NTIS 1964–present)	Searched website; nothing pertaining to alcohol
New York Academy of Medicine	Searched website; nothing pertaining to alcohol
Guidelines International Network (GIN Database)	Searched current publications for "alcohol," which returned 38 results. Relevant publications: Substance misuse and alcohol use disorders. In: Evidence-based geriatric nursing protocols for best practice. Hartford Institute for Geriatric Nursing. (2012) https://consultgeri.org/geriatric-topics/substance-abuse Problem drinking. Medical Services Commission, British Columbia. NGC:009465 (2011) https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/problem-drinking#part3 EFNS guideline on the diagnosis and management of alcohol-related seizures: Report of an EFNS task force. European Federation of Neurological Societies. NGC: 005164 (2005) http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.463.3968&rep=rep1&type=pdf Alcohol-use disorders: physical complications. NICE. (CG100) (2010) https://www.nice.org.uk/guidance/cg100
National Institute for Health and Care Excellence (NICE)	Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence (NICE Guideline (UK), 2011) https://www.nice.org.uk/guidance/cg115
Scottish Intercollegiate Guidelines Network (SIGN)	Searched current guidelines: none pertaining to alcohol. There was an archived guideline regarding the management of alcohol use disorder in primary care, but it was withdrawn in 2015. There is a proposal for a new guideline on the management of harmful drinking, but guideline development has not yet begun.
New Zealand Guidelines Group (NZGG)	Searched current publications for "alcohol," which returned 70 results. None pertained to withdrawal management.

Guidelines Advisory Committee (GAC)	Searched current guidelines: none pertaining to alcohol.
America's Health Insurance Plans (AHIP)	Nothing related to alcohol withdrawal management
Blue Cross and Blue Shield Association, Technology Evaluation Center (BCBS TEC)	Website info merged with AHRQ
Kaiser Permanente	Unhealthy Drinking in Adults Screening and Intervention Guideline (revised 2016) https://wa.kaiserpermanente.org/static/pdf/public/guidelines/alcohol-adult.pdf
Kaiser Family Foundation (KFF)	Searched ''alcohol'' 10–30-17 with no result. KFF publications more likely to be fact sheets than clinical guidelines.
Robert Wood Johnson Foundation (RWJF)	Searched ''alcohol'' 10-30-17 and reviewed the following content types: Journal Articles, Reports, and Briefs. No result.
Substance Abuse and Mental Health Services Administration (SAMHSA)	SAMHSA's TIP 45: Detoxification and Substance Abuse Treatment (2015) https://www.store.samhsa.gov/product/TIP-45-Detoxification-and-Substance-Abuse-Treatment/SMA15-4131
Veterans Administration (VA)	VA/DOD Clinical Practice Guideline for the Management of SUDs (2015) https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf
World Health Organization (WHO)	Alcohol and injuries: Emergency department studies in an international perspective, 2009. http://www.who.int/substance_abuse/msbalcinuries.pdf?ua=1
Agency for Healthcare Research and Quality (AHRQ)	Searched website; no published guidelines pertaining to alcohol withdrawal management. Searched ''substance abuse'' category 10-30-17. Profile of model program: https://innovations.ahrq.gov/profiles/hospital-wide-inpatient-screening-alcohol-withdrawal-and-algorithm-driven-treatment-improve Searched ''guideline-related'' category 10-30-17. General Recommendations for the Care of Homeless Patients http://www.nhchc.org/wp-content/uploads/2011/09/GenRecsHomeless2010.pdf
Michigan Quality Improvement Consortium (MQIC)	Searched website; nothing pertaining to alcohol
Scopus	See Empirical Literature search

C. PRISMA Flow Diagram

# of records identified through database searching (n = 3,138)		# of studies included from targeted search (n = 70)	
→		←	
	# of records after duplicates removed (n = 2,107)		
	# of records screened (n = 2,107)	→	# of records excluded (n = 1,365)
	# of full-text articles assessed for eligibility (n = 742)	→	# of full-text articles excluded (n = 545) Abstract, protocol only = 219 Commentary / Editorial = 58 Excluded reviews = 88 Case study = 32 Wrong population = 43 Wrong condition/disorder = 23 Wrong intervention = 52 Wrong outcome = 21 Not English = 8
	# of studies included in quantitative synthesis (n = 134)		
	# of studies included in qualitative synthesis (n = 64)		

D. Reasons for Exclusion

Reason for Exclusion	Examples
Abstract, Brief report only	Conference abstracts Study protocols
Case Study	Case studies were excluded if controlled studies were included
Commentary/Editorial	Letters to the editor and editorials were read, but not included for extraction
More Recent Available	Systematic reviews (e.g. Cochrane Reviews) and guidelines were excluded if an updated version was available.
More Recent Review Available	Non-systematic reviews and gray literature were excluded if more recent quality reviews or systematic reviews were available
Not English	Full text not available in English
Original Research Included	Systematic and non-systematic reviews were excluded if all original research was included
Wrong Intervention	No intervention/ Not about management (e.g. Etiology and pathophysiology, Pharmacodynamics, Genetics and Epigenetics) Intervention not available in US (e.g. GHB, Chlormethiazole, Cannabinoids) Healthcare service capacity
Wrong Population	Animal study Neonatal abstinence syndrome
Wrong Condition/Disorder	Hangover Alcohol Use Disorder AUD-related disorders (e.g. Alcoholic Liver Disease, Pellagra) Non-alcohol withdrawal related seizure or delirium
Wrong Outcome	Attention, cue-reactivity to alcohol-related stimuli Provider education, training, level of knowledge
Wrong Timing	Management of the post-acute withdrawal period
Wrong Setting	Setting not available in US (Home-based withdrawal)

III. Alcohol Withdrawal Scales Table

Abbreviation	Scale Name	Brief Description	Primary Use	Appropriate setting	Summary of Evidence	Reference
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test	8 items Interview format	Alcohol use screen	Any	Results of a study in 7 countries indicate that the ASSIST provides a valid measure of risk for individual substances and for total substance involvement.	WHO, 2002
AUDIT	Alcohol Use Disorder Identification Test	10 items	Alcohol use screen, Risk of alcohol withdrawal	Any	AUDIT is a useful alcohol screen in general medical settings and that its ability to correctly predict which patients will experience alcohol withdrawal is increased when used in combination with biological markers.	Dolman et al., 2005; Saunders et al., 1993
AUDIT-PC	Alcohol Use Disorders Identification Test-(Piccinelli) Consumption	10 items Range 0-19	Alcohol use screen, Risk of alcohol withdrawal	Hospital	Admission AUDIT-PC score is an excellent discriminator of AWS (Sensitivity = 91%, Specificity = 98.7%)	Pecoraro et al., 2014
AWS	Alcohol Withdrawal Scale	11-items Based on CIWA-A In German	Risk of delirium	Hospital	AWS scale had good performance in predicting alcohol withdrawal delirium	Wetterling et al., 1997a
AWS - Newcastle	Alcohol Withdrawal Scale	10 items Based on CIWA	Withdrawal Severity	Hospital	Patients demonstrated shorter overall course of alcohol withdrawal using the AWS compared with WAS	Foy et al., 2006
BAWS	Brief Alcohol Withdrawal Scale	5 items Scored 0–3	Withdrawal severity	Hospital	BAWS patients received less diazepam and had fewer assessments, but both groups had similar lengths of stay, treatment completion rate, no incidence of seizure or delirium.	Rastegar et al., 2017

Alcohol Withdrawal Scales Table

Abbreviation	Scale Name	Brief Description	Primary Use	Appropriate setting	Summary of Evidence	Reference
CAM-ICU	Confusion Assessment Method	4 items	Confusion	ICU	Excellent reliability and validity in identifying patients with delirium in ICU	Ely et al., 2001
CIWA-Ar	Clinical Institute Withdrawal Assessment, Revised	10 items	Symptom Assessment Scale	Any	Well established reliability and validity	Sullivan et al., 1989
DDS	Delirium Detection Scale	8 items	Delirium	Hospital	Good reliability and validity specific to detection of delirium	Otter et al., 2005
GMAWS	Glasgow Modified Alcohol Withdrawal Scale	5 items Scored 0–2 with max score of 10	Withdrawal severity	Hospital	GMAWS score of >=1 predicted CIWA-A >=8, with a sensitivity of 100% and a specificity of 12%. GMAWS score of >=2 predicted CIWA-A >=8, with a sensitivity of 98% and a specificity of 39%.	Holzman et al., 2016b
LARS	Luebeck Alcohol-Withdrawal Risk Scale	11 items 10 items	Risk of severe withdrawal	Hospital	Predicted severe withdrawal among patients admitted for alcohol withdrawal management	Wetterling et al., 2006
MINDS	Minnesota Detoxification Scale	9 items	Symptom severity	Hospital; ICU	No formal validity study	DeCarolis et al., 2007
PAWSS	Prediction of Alcohol Withdrawal Severity Scale	10 items	Risk of severe withdrawal	Hospital; ICU	Predicted complicated alcohol withdrawal among medically ill, hospitalized patients	Maldonado et al., 2014; 2015
RASS	Richmond Agitation-Sedation Scale	One item Scored on a continuum with +4 (combative), 0 (alert and calm), and -5 (unarousable)	Sedation and agitation	Medical and surgical	Reliability and validity in medical and surgical patients, including patients who are sedated and/or ventilated.	Sessler et al., 2002
SAWS	Short Alcohol Withdrawal Scale	10-items Scored 0–3 Designed to be self-administered	Withdrawal severity	Ambulatory and Inpatient	High internal consistency, good construct and concurrent validity.	Gossop et al., 2002
SEWS	Severity of Ethanol Withdrawal Scale	7 items Scored 0–3.	Withdrawal severity	ICU	SEWS-driven protocol led to shorter treatment episodes, possibly driven by high administration of medication in first 24 hours of treatment	Beresford et al., 2017
SHOT	Sweating, Hallucinations, Orientation, and Tremor	4-items Range 0-10	Withdrawal severity	Emergency Department	Showed potential for measuring pretreatment alcohol withdrawal severity in the emergency department.	Gray et al., 2010
WAS	Withdrawal Assessment Scale	18 Items Based on CIWA	Withdrawal severity	Hospital	Use of a shortened 10-item CIWA led to similar complication rates but reduced symptom duration compared to 18-item CIWA.	Foy et al., 2006

IV. Flowcharts (Supplemental Digital Content, http://links.lww.com/JAM/A192)

V. Sample Medication Regimens

Medication	Regimen	Description, Examples
Benzodiazepines *(doses in Chlordiazepoxide)*	Typical single dose	Mild withdrawal (CIWA-Ar < 10): 25–50 mg PO Moderate withdrawal (CIWA-Ar 10–18): 50–100 mg PO Severe withdrawal (CIWA-Ar ≥19): 75–100 mg PO
	Symptom-triggered	25–100 mg PO q4–6h when CIWA-Ar ≥10. Additional doses PRN.
	Fixed-dose	Taper daily total dose by 25–50% per day over 3–5 days by reducing the dose amount and/or dose frequency. Additional doses PRN. Day 1: 25–100 mg PO q4–6h Day 2: 25–100 mg PO q6–8h Day 3: 25–100 mg PO q8–12h Day 4: 25–100 mg PO at bedtime (Optional) Day 5: 25 to 100 mg PO at bedtime
	Front loading	*Symptom-triggered:* 50–100 mg PO q1–2h until CIWA-Ar < 10. *Fixed-dose:* 50–100 mg PO q1-2h for 3 doses.
Phenobarbital	Typical single dose	10 mg/kg IV infused over 30 minutes or 60-260 mg PO/IM.
	Monotherapy	*Symptom-triggered in the ICU:* 130 mg IV q30m to target a RASS score of 0 to -1. *Fixed dose in the ED:* Loading dose 260 mg IV, then 130 mg IV q30m at physician's discretion. *Fixed dose in ambulatory management:* Loading dose 60–120 mg PO. Then 60 mg PO q4h until patient is stabilized. Then 30–60 mg PO q6h tapered over 3–7 days. Additional doses PRN.
	Adjunct therapy	*Single dose in the ED:* 10 mg/kg IV infused over 30 minutes. *Escalating dose in the ICU:* After maximum diazepam dose (120 mg), if RASS ≥1, escalating dose of 60 mg → 120 mg → 240 mg IV q30m to target RASS score of 0 to -2.
Carbamazepine (Tegretol)	Monotherapy	600–800 mg total per day tapered to 200–400 mg/d over 4–9 days.
	Adjunct therapy	200 mg q8h or 400 mg q12h.
Gabapentin (Neurontin)	Monotherapy	Loading dose 1200 mg, then 600 mg q6h on Day 1 or 1200 mg/d for 1–3 days, tapered to 300–600 mg/d up to 4–7 days. Additional doses PRN.
	Adjunct therapy	400 mg q6–8h.
Valproic acid (Depakene)	Monotherapy	1200 mg/d tapered to 600 mg/d over 4–7 days or 20 mg/kg/d.
	Adjunct therapy	300–500 mg q6–8h.

CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, Revised; ED, Emergency Department; h, hour(s); ICU, Intensive Care Unit; IM, intramuscularly; IV, intravenously; m, minute(s); mg, milligrams; PO, by mouth; PRN, as needed; q, every; RASS, Richmond Agitation Sedation Scale.

VI. Statement Rating Table (Supplemental Digital Content, http://links.lww.com/JAM/A193)

VII. Disclosures and Conflicts of Interest

A. 2020 Guideline Committee Member Relationships with Industry and Other Entities

Guideline Committee Member	Salary	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Institutional, Organizational or other financial benefit	Research
Anika Alvanzo, MD, MS, FACP, DFASAM	Johns Hopkins University School of Medicine	None	None	None	Nobils**	None
Kurt Kleinschmidt, MD, FASAM	UT Southwestern Medical Center	None	None	None	None	None
Julie A. Kmiec, DO, FASAM	University of Pittsburgh	None	None	None	None	None
George Kolodner, MD, DLFAPA, FASAM	Kolmac Outpatient Recovery Centers	None	None	Kolmac Outpatient Recovery Centers**	None	None
Gerald E. Marti, MD, PhD	National Institutes of Health	None	None	None	None	None

2020 Guideline Committee Member Relationships with Industry and Other Entities

Guideline Committee Member	Salary	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Institutional, Organizational or other financial benefit	Research
William M. Murphy, DO, MS, DFASAM, Med. Ed.	n/a	None	None	None	American Osteopathic Academy of Addiction	None
Lewis S. Nelson, MD, FASAM, FACEP, FACMT (Chair)	Rutgers New Jersey Medical School	None	None	None	None	None
Carlos F. Tirado, MD, FASAM	CARMAHealth	US World Meds**	Alkermes**	None	None	Spark Biomedical**
Corey Waller, MD, MS, DFASAM, FACEP	Health Management Associates	None	None	None	California Department of Health Services**	None

The above table presents relationships of the **Guideline Committee** during the past 12 months with industry and other entities that were determined to be relevant to this document. These relationships are current as of the completion of this document and may not necessarily reflect relationships at the time of this document's publication. A relationship or arrangement is considered to be *significant* if the individual receives compensation which includes cash, shares, and/or anything else of value including direct ownership of shares, stock, stock options or other interest of 5% more of an entity or valued at $10,000 or more (excluding mutual funds), whichever is greater. A relationship or arrangement is considered to be *modest* if it is less than significant under the preceding definition. A relationship or arrangement is considered to be *unpaid* if the individual does not receive monetary reimbursement. **Indicates significant relationship. *Indicates modest relationship.

B. 2020 ASAM Board of Directors Relationships with Industry and Other Entities (Supplemental Digital Content, http://links.lww.com/JAM/A194)

C. 2020 ASAM Quality Improvement Council (Oversight Committee) Relationships with Industry and Other Entities (Supplemental Digital Content, http://links.lww.com/JAM/A194)

D. 2020 Clinical Champions Relationships with Industry and Other Entities

Board Member	Salary	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Institutional, Organizational or other financial benefit	Research
Stephen Holt, MD, MS, FACP	Yale School of Medicine	None	None	None	None	None
Darius Rastegar, MD, FASAM	Johns Hopkins University School of Medicine	None	None	None	None	None
Richard Saitz, MD, MPH, FACP, DFASAM	Boston University	Check-Up and Choices American Medical Association** National Committee on Quality Assurance** Wolters Kluwer** Oxford University Press* Massachusetts Medical Society* American Society of Addiction Medicine* Kaiser Foundation Hospitals* Beth Israel Hospital* University of Oregon** Boston Medical Center* University of Southern California* Westwood High School* Harvard University* Yale University* Massachusetts Society of Addiction Medicine* Karolinska Institute* American Academy of Addiction Psychiatry* SMART Recovery/ Ebix*	None	None	National Institutes of Health** Boston Medical Center** Public Health Management Corporation**	Alkermes National Institutes of Health**
Michael F. Weaver, MD, DFASAM	University of Texas Health Science Center at Houston	Texas Children's Health Plan* Oakbend Medical Center*	None	None	National Institute on Drug Abuse	None

The above table presents relationships of the **Clinical Champions** during the past 12 months with industry and other entities that were determined to be relevant to this document. These relationships are current as of the completion of this document and may not necessarily reflect relationships at the time of this document's publication. A relationship or arrangement is considered to be *significant* if the individual receives compensation which includes cash, shares, and/or anything else of value including direct ownership of shares, stock, stock options or other interest of 5% more of an entity or valued at $10,000 or more (excluding mutual funds), whichever is greater. A relationship or arrangement is considered to be *modest* if it is less than significant under the preceding definition. A relationship or arrangement is considered to be *unpaid* if the individual does not receive monetary reimbursement. **Indicates significant relationship. *Indicates modest relationship.

E. 2020 External Reviewers Relationships with Industry and Other Entities (Supplemental Digital Content, http://links.lww.com/JAM/A194)

Approved by the ASAM Board of Directors January 23, 2020.

American Society of Addiction Medicine
11400 Rockville Pike, Suite #200
Rockville, MD 20852

Phone: (301) 656-3920 | Fax (301)-656-3815
Email: email@asam.org | www.ASAM.org