TERMINOLOGY

CLINICAL CLARIFICATION

- Alcohol withdrawal may occur after cessation or reduction of heavy and prolonged alcohol use; manifestations are characterized by autonomic hyperactivity and central nervous system excitation [1, 2]
- Severe symptom manifestations (eg, seizures, delirium tremens) may develop in up to 5% of patients [3]

CLASSIFICATION

- Based on severity
  - Minor alcohol withdrawal syndrome [4, 5]
    - Manifestations occur early, within the first 48 hours after last drink or decrease in consumption [6]
      - Manifestations develop about 6 hours after last drink or decrease in consumption and usually peak about 24 to 36 hours; resolution occurs in 2 to 7 days [7] if withdrawal does not progress to major alcohol withdrawal syndrome [4]
    - Characterized by mild autonomic hyperactivity (eg, tachycardia, hypertension, diaphoresis, hyperreflexia), mild tremor, anxiety, irritability, sleep disturbances (eg, insomnia, vivid dreams), gastrointestinal symptoms (eg, anorexia, nausea, vomiting), headache, and craving alcohol [4]
  - Major alcohol withdrawal syndrome [5, 4]
    - Progression and worsening of withdrawal manifestations, usually after about 24 hours from the onset of initial manifestations [4]
      - Manifestations often peak around 50 hours before gradual resolution or may continue to progress to severe (complicated) withdrawal, particularly without treatment [4]
    - Characterized by moderate to severe autonomic hyperactivity (eg, tachycardia, hypertension, diaphoresis, hyperreflexia, fever); marked tremor; pronounced anxiety, insomnia, or irritability; anorexia; decreased seizure threshold; hallucinations; and delirium [4]
  - Complicated or severe alcohol withdrawal
    - Rigorous definition is lacking [8]
    - Many experts define based on presence of any of the following:
      - Withdrawal seizures [3, 8]
      - Delirium tremens
      - Clinical Institute Withdrawal Assessment for Alcohol (Revised) score greater than 20 [9]
      - Major alcohol withdrawal syndrome manifestations refractory to high-dose benzodiazepines [8]
    - May occur in up to 5% of patients [3, 10]
- Based on progressive stages [5]
  - Stage 1
    - Minor symptoms not usually associated with significantly abnormal vital signs [9]
  - Stage 2
    - Mild to moderate symptoms associated with abnormal vital signs and possibly alcoholic hallucinosis [9]
  - Stage 3
    - Mild to moderate symptoms associated with abnormal vital signs and development of seizures
  - Stage 4
    - Moderate to severe symptoms associated with abnormal vital signs, possibly seizures, and development of delirium [9]

DIAGNOSIS

CLINICAL PRESENTATION

- Characteristic withdrawal syndrome develops within hours to days after cessation or reduction of heavy and prolonged alcohol use [1]
  - Probability of developing withdrawal rises with increasing quantity and frequency of alcohol consumption [1]
    - Most affected patients are drinking daily for multiple days and consuming large amounts (ie, more than 8 drinks/day for multiple days) [8, 1]
  - Symptoms typically begin after sharp decline in blood alcohol concentration [1]
  - Reduction or cessation in alcohol use may not always be intentional [5, 11]
    - Inability to acquire or pay for alcohol
    - Gastrointestinal illness characterized by decreased oral intake
    - Hospital admission for another medical issue [12]
      - Up to 8% of patients admitted to hospitals with non–alcohol-related diagnoses exhibit signs of withdrawal

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- Earlier medical history may be significant for:[5]
  - Alcohol use disorder
    - 50% to 80% of patients with alcohol use disorder develop some form of central nervous system stimulation and adrenergic hyperactivity with reduction or discontinuation of alcohol consumption[6,10]
    - Suspect alcohol dependence in female patients who:[9]
      - Consume more than 1 drink daily or more than 7 weekly
      - Have had more than 4 drinks on a single occasion in the past year (generally within 2 hours)[13]
    - Suspect alcohol dependence in male patients who:[9]
      - Consume more than 2 drinks daily or more than 14 drinks weekly
      - Have had more than 5 drinks on a single occasion in the past year (generally within 2 hours)[13]
  - History of prior withdrawal
    - Course of prior alcohol withdrawal episodes is the most reliable predictor of subsequent episodes[14]
- Psychiatric history
  - Alcohol may cause several psychiatric conditions such as alcohol-induced mood, anxiety, or psychotic disorder[5]
  - Underlying psychiatric disorders (eg, antisocial personality disorder, schizophrenia, major anxiety disorders, bipolar disorder) or other drug use disorder and dependence may be present
- Factors that may modify withdrawal symptoms or course
  - Relief of symptoms can occur by administration of alcohol or benzodiazepines[1]
  - Concurrent use of medication for other underlying disorders (eg, β-blockers, α_2-adrenergic agonists) may blunt typical abnormalities noted in vital signs at presentation[3]
- Presence of comorbidity
  - Patients with underlying psychiatric disorders may use alcohol to alleviate psychiatric symptoms such as anxiety and depression[5]
  - Acute medical or surgical disorder may precipitate withdrawal[5]
  - Poorly controlled medical comorbidity may precipitate withdrawal[5]
- Acute withdrawal may progress in stages ranging in severity from mild to severe[15]
  - Manifestations during stages may overlap and may not progress in a precise sequential pattern[5]
  - Early withdrawal: symptoms of central nervous system stimulation typically occurring within 48 hours of drinking cessation[6]
    - Stage 1 (hangover stage)
      - Initial broad withdrawal manifestations begin 6 to 8 hours after last drink and may include:[3]
        - Sympathomimetic symptoms (eg, diaphoresis, palpitations)
        - Mild tremor
        - Insomnia and anxiety
        - Gastrointestinal (eg, nausea, vomiting)
        - Headache
      - If withdrawal does not progress, these manifestations may resolve within 24 to 48 hours[3]
    - Stage 2 (alcoholic hallucinosis stage)
      - Develops approximately 24 to 48 hours after last drink; may be up to 8 days[5]
      - Worsening sympathomimetic symptoms (eg, diaphoresis, fever), marked tremors, worsening hyperactivity, and insomnia
      - Sensorium is lucid but nightmares or illusions are not uncommon
      - Hallucinations may develop
        - Most commonly occur 12 to 24 hours after last drink[3]
        - Occur in 7% to 8% of untreated patients with withdrawal[3]
        - Can be visual, auditory, or tactile[3]
          - Isolated visual hallucinations are most common[16,9]
        - May occur in isolation without other broad withdrawal manifestations
        - Sensorium is normal (ie, delirium is absent; patient is aware that hallucinations are not real)[6]
    - Stage 3 (tonic-clonic seizure stage)
      - Similar to stage 2 with development of tonic-clonic seizures[5]
      - Withdrawal seizures (rum fits)
        - Commonly occur 12 to 48 hours after last drink[3]
        - May occur in up to 10% of patients[2]
          - Alcohol withdrawal represents 1 of the most common causes of adult-onset seizures[4]
        - Commonly consist of isolated, short-duration, generalized tonic-clonic seizures with short or absent postictal period[2]
          - May occur in clusters[17,5] and may be recurrent in a minority of patients[5,6]

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- Prolonged seizures and status epilepticus are relatively uncommon [5]
- Seizures impart increased risk for complications (eg, aspiration pneumonia, rhabdomyolysis) [5]
- About one-third of patients who develop seizures progress to delirium tremens without treatment

- Late withdrawal: symptoms typically occurring later than 48 hours after drinking cessation [6]
  - Stage 4 (delirium tremens stage)
    - High likelihood that a concurrent, clinically relevant medical condition exists when delirium develops [1]
      - May include liver failure, pneumonia, gastrointestinal bleeding, head trauma, hypoglycemia, electrolyte imbalance, and postoperative state
    - Delirium tremens
      - Consists of severe autonomic hyperactivity and ongoing agitation plus rapid-onset delirium (ie, fluctuating disturbance of attention and cognition)
        - Manifestations fluctuate in severity throughout the day and may include: [8]
          - Lack of attention and awareness
          - Memory loss and disorientation
          - Hallucinations
          - Agitation [6]
      - Usually begins 2 to 3 days after initial withdrawal symptoms appear and lasts for 1 to 8 days; may be delayed up to 12 days [5, 3]
        - Rarely, may develop as early as 8 hours after last drink [3]
      - Often associated with cardiovascular, respiratory, and metabolic abnormalities [5]
      - Occurs in 1% to 5% of hospitalized patients with withdrawal [3, 5]
      - Risk is significantly increased in patients with concurrent acute medical illness [5]

- Physical examination
  - Common findings [5, 2]
    - Autonomic hyperactivity with sympathomimetic signs
      - Tachycardia
      - Hypertension
      - Diaphoresis
      - Fever
      - Mydriasis
      - Tachypnea
    - Central nervous system hyperstimulation
      - Coarse tremor
        - Often most easily found in the hands or tongue
      - Hyperreflexia
      - Hallucinations
      - Seizures
      - Delirium
  - Findings concerning for concurrent Wernicke encephalopathy
    - Nystagmus or oculomotor abnormalities
    - Ataxia or gait disturbance

CAUSES AND RISK FACTORS

- Causes
  - Underlying cause of alcohol withdrawal syndrome is multifactorial; undetermined genetic factors likely play a role
    - Long-term alcohol use causes a depressant effect on the central nervous system, leading to adaptive changes in neurotransmitter and receptor physiology [5]
      - Central nervous system depression occurs with long-term alcohol use
        - Enhanced inhibitory tone occurs through GABA receptor modulation (affecting several proteins involved in γ-aminobutyric acid pathways) [3]
        - Inhibited excitatory tone occurs through NMDA receptor modulation (affecting several proteins involved in *N*-methyl-D-aspartate pathways) [3]
      - Alcohol administration increases catecholamine levels affecting central α- and β-adrenergic receptors [5, 4]
      - Alterations of balance in other neurochemical systems (eg, serotonin, endogenous opioid, nicotinic cholinergic, dopamine), electrolytes (eg, hypomagnesemia), and vitamin deficiencies (eg, thiamine) occur with long-term alcohol intake
    - Functional adaptations result in development of tolerance phenomenon in patients with alcohol use disorder

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  - Kindling phenomenon
    - Refers to development of neuronal networks that may result in worsening episodes of withdrawal on subsequent episodes
  - Discontinuation or dramatic reduction in alcohol consumption
  - Central nervous system hyperstimulation results from loss of GABA receptor inhibition and potentiation of NMDA receptor excitation[3]
  - Dopaminergic dysregulation may also play a role in agitation, hallucinations, and delirium[6]
  - Gradual increase in adrenergic activity results from an excess glutamate activity on excitatory NMDA receptors and excess catecholamine effects on central α- and β-adrenergic receptors[5,4]
  - Abnormalities in the balance of other neurochemical systems, electrolytes, and vitamins may also contribute to development of withdrawal
- Risk factors and/or associations
  - Age
  - Risk of withdrawal increases with age[1]
    - Most commonly in middle-aged adults[5]
    - Relatively rare in patients younger than 30 years[1]
  - Older patients are at increased risk for morbidity and mortality[12]
  - Sex
  - Most patients admitted to hospitals with alcohol withdrawal syndrome are male[5]
  - Other risk factors/associations
  - Risk factors for withdrawal
    - Risk increases linearly with quantity and frequency of alcohol intake[8]
    - Concurrent medical condition that precludes alcohol intake[1]
    - Family history of alcohol withdrawal[1]
    - Personal history of alcohol withdrawal[1]
    - Concurrent long-term use and then discontinuation of sedative, hypnotic, or anxiolytic drugs[1]
    - Patients with tolerance phenomenon[6]
  - Risk factors for severe withdrawal course are inconsistently reported in literature but may include:
    - Prior episode of withdrawal, especially severe withdrawal[17]
    - Drinking patterns that include:[5]
      - Greater maximum dose of daily alcohol
      - Greater number of drinking days per month
      - Need for alcoholic drink in the early morning
    - Older age, especially 60 years or older[1,18]
    - Acute and chronic comorbid medical problems (eg, alcoholic liver disease, cointoxications, trauma, infections, sepsis, history of structural brain lesion[19])[5]
    - Nonmedical use of sedative hypnotics[5]
    - Detectable blood alcohol level on admission with withdrawal manifestations[5]
    - Severe symptoms early in withdrawal course[6]
    - Grade 2 severity or higher on presentation (initial Clinical Institute Withdrawal Assessment for Alcohol [Revised] score greater than 10)[5]
    - Abnormal liver function (serum AST activity above 80 units/L)[5]
    - Presence of significant dehydration or electrolyte abnormalities at presentation[15]
    - Low initial platelet count and/or serum potassium level[14,19]
    - Male sex[5]
  - Risk factors for delirium tremens are inconsistently reported in literature but may include:
    - Concurrent medical illness (eg, pneumonia, active ischemia)[6]
    - History of delirium tremens[10]
    - Withdrawal seizures, specifically if left untreated or recurrent[6,10]
    - Clinical Institute Withdrawal Assessment for Alcohol (Revised) score of 15 or higher[10]
    - Sustained drinking history[3]
    - Systolic blood pressure above 150 mm Hg and/or heart rate above 100 beats per minute[10]
    - Last alcohol intake greater than 2 days[3]
    - Age older than 30 years[3]
    - Recent misuse of other depressants (eg, benzodiazepines)[10]

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DIAGNOSTIC PROCEDURES

- Primary diagnostic tools
  - Withdrawal is a clinical diagnosis and a diagnosis of exclusion[3]
    - *DSM-5* diagnostic criteria define the diagnosis
    - Exclude alternate diagnoses that mimic withdrawal
    - Consider presence of concomitant condition (eg, comorbidities, complications of alcohol use disorder) that may have contributed to the withdrawal state by forcing abstinence
    - Consider risk of progression to severe withdrawal[15]
  - Measure severity of withdrawal with applicable severity assessment tool
    - Several scales are available; most commonly used include:
      - Short Alcohol Withdrawal Scale[9]
        - 10-item scale requiring patient participation; most common tool used for outpatients
      - Clinical Institute Withdrawal Assessment for Alcohol (Revised) scale[5,20]
        - 10-item scale requiring patient cooperation; most common tool used for inpatients
      - Richmond Agitation-Sedation Scale[5,21]
        - Reliable scale for patients requiring ICU care
    - Scales are ***not*** diagnostic tools; rather, scales objectively measure degree of withdrawal in a patient with clinical diagnosis of withdrawal[3,15]
  - Evaluate for other disease that may have contributed to precipitation of withdrawal[3]
    - Consider presence of concomitant condition or complication of long-term alcohol use, especially in the presence of severe withdrawal (eg, delirium)[1]
      - Withdrawal is often precipitated in patients with comorbid medical or surgical conditions during periods of abstinence when illness or surgery prevents alcohol intake[5]
      - Investigations may be necessary to exclude conditions such as pneumonia, sepsis, meningitis or encephalitis, pancreatitis, liver failure, gastrointestinal bleeding, head trauma, intracerebral hemorrhage, acute coronary syndrome, drug overdose, hypoglycemia, and electrolyte abnormalities
      - Guide additional diagnostic testing and work-up based on individual clinical presentation
    - Wernicke encephalopathy may present in association with withdrawal and triad of altered mental status, ophthalmoplegia, and ataxia
      - Full triad is present in only about one-third of patients and diagnosis is missed in up to 80% of cases[3]
  - Obtain baseline admission studies for patients with moderate to severe alcohol withdrawal syndrome based on individual presentation (routine laboratory testing is ***not*** necessary for most patients with mild withdrawal)[9,5]
    - Obtain finger stick glucose measurement for all patients with altered mental status or seizures[17]
    - Most experts order the following:
      - Metabolic panel with serum electrolyte, magnesium, phosphate, and glucose levels, plus renal function testing[17]
      - CBC[17]
      - Liver function tests, including INR and serum AST, ALT, bilirubin, and ammonia[17]
    - Consider the following:
      - Head CT or other brain imaging for patients with seizures[15]
      - Blood alcohol concentration and urine drug screen
      - Serum calcium, phosphate, lipase, and creatinine kinase levels
      - Chest radiograph
      - ECG, cardiac biomarkers, and echocardiogram
      - Urinalysis
      - Arterial blood gas analysis
      - Blood, urine, and sputum cultures
      - Lumbar puncture with studies to assess for central nervous system infection in patients presenting with fever and mental status changes
      - Pregnancy test for premenopausal women
  - Refer to regionally specified protocols to guide evaluation strategy[22]
- Laboratory
  - Serum blood alcohol concentration
    - Serum blood alcohol concentration may assist in determining likelihood of withdrawal
      - High likelihood of withdrawal exists after prolonged heavy alcohol consumption when early manifestations (eg, autonomic hyperactivity) appear in the context of a moderately high but falling alcohol level[1]
      - Anticipate worsening of withdrawal manifestations as ethanol concentration falls in patients presenting with alcohol withdrawal and an elevated ethanol concentration[3]

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- Metabolic panel with serum electrolyte (including magnesium) and glucose levels[23]
  - Abnormal findings are common in long-term alcohol use and may include:[24]
    - Hypoglycemia
    - Hypokalemia
    - Hypomagnesemia
    - Hypophosphatemia
- Renal function tests (BUN, creatinine)
  - Renal insufficiency can guide choice of doses in treatment[25]
- Liver function testing
  - Evaluation of hepatic transaminases and synthetic liver function (eg, prothrombin time, INR) may help guide medication choice and assess for alcohol-related hepatic injury[25]

- Imaging
  - Head CT
    - May be indicated to exclude alternate causes of manifestations or with concern for trauma
  - Chest radiograph
    - May be indicated to assess for acute pneumonia or other concurrent pulmonary disease
- Other diagnostic tools
  - *DSM-5* clinical diagnostic criteria
    - Alcohol withdrawal syndrome[1]
      - A: cessation of (or reduction in) alcohol use that has been heavy and prolonged
      - B: 2 (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:
        - Autonomic hyperactivity (eg, sweating, pulse greater than 100 beats per minute)
        - Increased hand tremor
        - Insomnia
        - Transient visual, tactile, or auditory hallucinations or illusions
        - Psychomotor agitation
        - Anxiety
        - Generalized tonic-clonic seizures
      - C: the signs and symptoms in criterion B cause clinically significant distress or impairment in social, occupational, 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
    - Substance withdrawal delirium[26]
      - Substance withdrawal delirium diagnosis should be made instead of substance withdrawal when symptoms in criteria A and C predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention
      - Delirium criteria
        - A: disturbance in attention (ie, reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)
        - B: disturbance develops over a short period (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during course of day
        - C: additional disturbance in cognition (eg, memory deficit, disorientation, language, visuospatial ability, or perception)
        - D: the disturbance in A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of reduced level of arousal (eg, 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 (ie, due to drug use disorder or medication), or exposure to a toxin, or is due to multiple causes
  - Short Alcohol Withdrawal Scale
    - Validated for use in outpatient setting[9]
      - Symptoms that are scored include anxiety, confusion, restlessness, feeling miserable, memory issues, tremors (shakes), nausea, heart pounding, sleep disturbance, and sweating in the past 24 hours
      - Score is based on presence and severity of each symptom
        - None: 0 points
        - Mild: 1 point
        - Moderate: 2 points
        - Severe: 3 points

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- Mild withdrawal: score less than 12 points
- Moderate to severe: score of 12 points or higher

- Clinical Institute Withdrawal Assessment for Alcohol (Revised) [20]
  - Objectively measures severity of withdrawal and determines likelihood of progressing alcohol withdrawal syndrome; clinical uses may include: [5]
    - Determination of need for medically supervised withdrawal management
      - An initial score of greater than 10 is correlated with risk of developing severe withdrawal; requires further evaluation and development of admission goals of therapy [5]
    - Monitor course of withdrawal and guide symptom-triggered treatment when alcohol use history is known
      - Patients with score less than 10 do not usually need additional medication [9]
      - Patients requiring treatment with scores of 15 or less likely respond to moderate benzodiazepine doses [10]
      - Patients with scores higher than 15 require close monitoring and aggressive treatment to avoid seizures and alcohol withdrawal delirium [10]
  - Score is based on symptoms including nausea/vomiting, tremors, paroxysmal sweating, anxiety, agitation, tactile disturbances, auditory disturbances, visual disturbances, headache/head fullness, and orientation/clouding of sensorium [3]
  - Scores are altered by pain, other medical and surgical issues, and administration of sedation agents [5]
  - Scoring-based severity is variably reported and not rigorously standardized; refer to regional protocol to guide symptom-triggered treatment based on specific score
    - One source suggests the following: [9]
      - Absent or very mild withdrawal: score of 8 or lower
      - Mild withdrawal: score of 9 to 14
      - Moderate withdrawal: score of 15 to 20
      - Severe withdrawal: score of 21 to 67
    - Other sources suggest the following levels of severity based on score
      - Absent, minimal, or mild: 9 or less, [27] less than 8, [10] 0 to 8 [15]
      - Moderate: 10 to 18, [27] 8 to 15, [10] 9 to 15 [15]
      - Severe: 19 or higher, [27] higher than 15, [10] 16 or higher [15]
- Richmond Agitation-Sedation Scale [21, 5]
  - Use to assess effectiveness of sedation in patients who lack the ability to cooperate (eg, heavily sedated, intubated, combative)
  - Score is based on overall patient responsiveness and general level of sedation
    - +4: patient is combative; immediate danger to staff
    - +3: patient is very agitated; aggressive toward staff, removes catheters/tubes
    - +2: patient is agitated; patient-ventilator dyssynchrony, persistent nonpurposeful movement
    - +1: patient is restless; movements are not aggressive or vigorous, anxious or apprehensive mood
    - 0: patient is calm and alert
    - −1: patient is drowsy; awakening to voice, with eye contact, for periods of 10 seconds or more
    - −2: patient is lightly sedated; awakens to voice, with eye contact, for brief periods (less than 10 seconds)
    - −3: patient is moderately sedated; movement in response to voice, without eye contact
    - −4: patient is deeply sedated; movement in response to physical stimulation, but does not respond to voice
    - −5: patient is unarousable; does not respond to physical stimulation or voice
  - Goal is score of 0 to −2 (patient is in a calm, arousable state) [3]

DIFFERENTIAL DIAGNOSIS

- Most common
  - Sedative-hypnotic medication withdrawal [28, 29]
    - Withdrawal from chronically used sedative-hypnotic medications, including benzodiazepines, barbiturates, baclofen, or γ-hydroxybutyrate (GHB) [30, 31]
    - May present with symptoms similar to those of alcohol withdrawal syndrome such as anxiety, restlessness, tremor, tachycardia, delirium, hallucinations, and seizures
    - Sedative-hypnotic medication withdrawal and alcohol withdrawal are virtually indistinguishable from a clinical standpoint
    - History of long-term alcohol use may point toward a diagnosis of alcohol withdrawal or mixed withdrawal syndrome
    - Laboratory testing for potential drug use and blood alcohol concentration may help narrow specific cause of manifestations; review of state prescription drug database may reveal fulfillment of benzodiazepine prescriptions

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- Stimulant intoxication [32]
  - Intoxication with substances such as cocaine, methamphetamine, amphetamine, and synthetic cathinones (eg, bath salts) can present similarly to alcohol withdrawal with agitation, tremor, sympathomimetic hyperactivity, and occasionally hallucinations and/or seizures
  - Clinical differentiation may be difficult; however, patients with stimulant intoxication characteristically exhibit stereotyped behaviors such as picking at objects (real or imagined) on the skin or bed sheets and paranoid behavior
  - Mydriasis is more consistently present and pronounced in patients with stimulant intoxication than with alcohol withdrawal
  - Laboratory testing for potential drug use and blood alcohol concentration may help narrow specific cause of manifestations; caveat: most synthetic cathinones are not detectable on standard drug testing
- Schizophrenia [33]
  - Chronic psychiatric disorder characterized by faulty perceptions and withdrawal from reality that may present similarly to alcohol withdrawal with delusions and hallucinations
  - Onset of schizophrenia is typically in adolescence or young adulthood and may be more gradual than onset of alcohol withdrawal syndrome
    - While substance use is common among schizophrenic patients, a history of long-term alcohol use would be present in patients with alcohol withdrawal syndrome
  - Delusions, movement disorders, and paranoia are common in patients with schizophrenia
  - Signs such as tremors and tachycardia may not be present in schizophrenia; sustained sympathomimetic findings should not be present in patients with schizophrenia
  - Schizophrenia is a clinical diagnosis based on *DSM-5* criteria [34]
- Encephalitis [35]
  - Rapid onset of inflammation of the brain usually caused by an infectious or autoimmune process
  - Presents similarly with hallucinations, delirium, tremors, and/or seizures
  - Signs of inflammation (eg, fever) are common
  - While historical features can usually be used to differentiate between encephalitis and alcohol withdrawal, objective testing may be necessary
  - MRI of the brain, lumbar puncture with cerebrospinal fluid analysis, and/or continuous EEG monitoring can aid in diagnosis
- Hepatic encephalopathy [5]
  - Encephalopathy associated with chronic liver dysfunction characterized by delirium and asterixis
  - May present similarly with seizures and altered sensorium
  - Other stigmata of chronic liver disease (eg, jaundice, scleral icterus, coagulopathy, caput medusa) may be present
  - In contrast to alcohol withdrawal syndrome, hepatic encephalopathy is typically associated with central nervous system depression and asterixis, as opposed to coarse tremor and central nervous system excitation
  - Elevated serum ammonia level can assist in differentiating from alcohol withdrawal syndrome
- Thyrotoxicosis [36]
  - Caused by exposure to excess circulating thyroid hormones
  - Similar manifestations include restlessness, tremors, palpitations, tachycardia, and hypertension
  - History of long-term alcohol use and recent cessation or reduction of alcohol use can differentiate alcohol withdrawal syndrome from thyrotoxicosis
  - Physical examination findings such as thyromegaly and/or exophthalmos are sometimes seen in hyperthyroidism but will be absent in alcohol withdrawal syndrome
  - Laboratory testing can be used if history is not sufficient to differentiate cause of patient's presentation
    - Low or nondetectable TSH level and elevated thyroid hormone levels will be present in thyrotoxicosis
- Epilepsy [37]
  - Often idiopathic or related to a previous medical cause, an underlying chronic seizure disorder may be mistaken for alcohol withdrawal syndrome
  - If seizures are generalized and tonic-clonic, they will appear similar to alcohol withdrawal seizures
  - History of recurrent seizures or long-term anticonvulsant use is more commonly associated with epilepsy
    - Status epilepticus may occur as part of alcohol withdrawal syndrome but is relatively uncommon
  - Thorough medication and alcohol use histories can differentiate these diagnoses
  - Diagnosis is clinical and usually based on occurrence of at least 2 unprovoked seizures occurring more than 24 hours apart; central nervous system imaging and EEG may aid in diagnosis
- Cranial trauma [38, 39]
  - Patients with cranial trauma may have confusion, altered mental status, and seizures; physical signs of trauma to the head and neck may be present
  - Patients with alcohol use disorder are at increased risk of trauma

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- Cranial trauma presentation usually does not include other signs seen in alcohol withdrawal syndrome (such as tremors)
- History of long-term alcohol use, as opposed to acute alcohol intoxication, can help differentiate between these entities
- If significant cranial trauma is suspected, obtain CT scan of brain (without contrast material) to evaluate for fractures or intracranial hemorrhage

- ICU delirium [40]
  - Delirium is a generic syndrome with many causes; delirium seen in the ICU setting is associated with critical illness and often respiratory failure
  - Both ICU delirium and delirium tremens present with alterations in sensorium and can occur after admission to ICU setting
  - ICU delirium will typically occur in older adults with critical illness and is associated with more adverse prognosis
  - While delirium tremens presents with a hyperactive delirium, ICU delirium will typically be of a mixed or hypoactive subtype [5]
  - Diagnosis of delirium is clinical and based on *DSM-5* diagnostic criteria [41]

TREATMENT

GOALS

- Monitor withdrawal course and provide symptomatic treatment with aim to normalize vital signs, relieve anxiety, and halt progression to severe withdrawal [2]
- Manage severe withdrawal (eg, seizures, delirium) and monitor for complications (eg, respiratory depression, pneumonia, rhabdomyolysis) [2]
- Address and manage other comorbid or concurrent medical, surgical, traumatic, toxicologic, or psychiatric issues [5]
- Arrange for substance use disorder treatment and encourage long-term abstinence [2]

DISPOSITION

- General criteria for outpatient management [9]
  - Mild to moderate withdrawal and:
    - No serious psychiatric problems (ie, suicidal ideation, psychosis), medical comorbidity, or acute illness
    - No significant laboratory abnormalities, when obtained
    - No concurrent substance use disorder
    - Low risk for development of delirium tremens
    - No history of significant alcohol withdrawal (eg, withdrawal seizure)
    - Patient ability to take oral medications
    - Patient commitment to frequent follow-up visits
    - Patient with friend or relative who can monitor patient and administer medications
    - Age 16 years or older [22]
- General criteria for discharge with referral for outpatient alcohol dependence treatment program
  - Clinical Institute Withdrawal Assessment for Alcohol (Revised) score less than 8 to 10 [42, 3, 5]
  - Patient not currently intoxicated (alcohol or other drugs) [3]
  - No history of complicated alcohol withdrawal syndrome (ie, seizures, hallucinosis, delirium tremens) [3]
  - No significant medical or psychiatric comorbidity or suicidal ideation [42, 3]
  - Patient ability to maintain regular outpatient visits and therapy [3]
- General criteria for outpatient detoxification
  - Clinical Institute Withdrawal Assessment for Alcohol (Revised) score 15 or less [3]
  - No symptoms or history of delirium tremens or alcohol withdrawal seizures [42, 3]
  - Ability to take oral medications [3]
  - Presence of a family member or close contact who can stay with the patient [3]
  - Lack of unstable medical condition [3]
  - No psychosis or suicidality [3]
  - Ability to commit to daily medical visits and adequate follow-up [3]
- Admission criteria
  - Admission criteria to medical unit or inpatient medically supervised detoxification center [5]
    - Patients with more than mild alcohol withdrawal plus all of the following:
      - No underlying medical or surgical condition requiring ICU-level care [3]
      - Normalization or near-normalization of vital signs within emergency department [3]
      - Clear sensorium [3]
      - Responsive to 10 to 20 mg diazepam and tolerating 2 to 4 hours between benzodiazepine doses [3]

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- Clinical Institute Withdrawal Assessment for Alcohol (Revised) score higher than 15 [42]
- Clinical Institute Withdrawal Assessment for Alcohol (Revised) score 8 to 15 and a history of delirium tremens or alcohol withdrawal seizures [42]
- Patients at high risk for progression to worsening stage of withdrawal (ie, mild withdrawal despite a detectable ethanol concentration, concomitant use of benzodiazepines, history of severe withdrawal [17])
- Patients with concomitant major electrolyte disorder, decompensated medical illness, [42] psychiatric illness, or pregnancy [17]
- Presence of medical or psychiatric condition or suicidal ideation requiring inpatient admission [3]

- Criteria for ICU admission
  - Intubation or other respiratory support requirement [5]
  - Severe hemodynamic abnormalities [5]
    - Significant tachycardia or hypotension
  - Persistent fever higher than 39°C [5]
  - Severe, or advanced stage 2 or greater, withdrawal [5]
    - Delirium
    - Recurrent seizures
    - Requirement for large or escalating doses of benzodiazepines or barbiturates [2, 3]
    - Moderate to severe withdrawal despite elevated blood alcohol concentration [3]
  - Consider for patients with:
    - Significant medical or surgical comorbidities (eg, cardiac disease, respiratory disease, renal insufficiency, acute serious infection, trauma) [3, 5]
    - Evidence of significant alcohol-related complications (eg, hepatic insufficiency, pancreatitis, gastrointestinal bleeding, rhabdomyolysis) [3]
    - History of complicated alcohol withdrawal or severe withdrawal course [3]
    - Marked fluid or electrolyte abnormalities [5]
    - Patients requiring treatment of suspected Wernicke encephalopathy [3]
    - Older age [17]

- Recommendations for specialist referral
  - Treatment of severe withdrawal or patients at high risk for severe withdrawal (eg, comorbidity, concurrent acute illness) should be managed by a clinician well trained in management of alcohol withdrawal syndrome (eg, addiction medicine specialist) [10, 6]
  - Consult a medical toxicologist or addiction medicine specialist for patients with benzodiazepine-resistant withdrawal and severe withdrawal for further diagnostic and treatment recommendations

TREATMENT OPTIONS

- Resuscitation and stabilization is first aspect of care while assessing need for treatment of concurrent medical conditions [3]
  - Manage airway and administer oxygen as indicated clinically [17]
  - Initiate fluid resuscitation and start IV fluids when clinically indicated [17]
  - Treat concurrent medical conditions [17]
  - Treat hypoglycemia; begin thiamine administration before glucose (preferred) [8]
- Determine level of care and setting necessary for appropriate management
  - Patients with very mild withdrawal (ie, Clinical Institute Withdrawal Assessment for Alcohol [Revised] score of less than 8-10 with isolated stage 1) do not require pharmacologic management or admission if there is no progression or complicating factors [5, 10]
    - Some experts consider prescribing brief lorazepam regimen (2-4 mg every 4 hours) as needed for 3 to 5 days [42]
  - Patients with mild to moderate manifestations without significant comorbidity or significant risk of developing severe withdrawal may be managed in either: [9, 5, 18]
    - Outpatient setting with oral medications and daily follow-up when environment is conducive for recovery
    - Residential detoxification centers when home environment is unstable or not conducive for recovery
      - Centers may be medically managed by nursing staff with consulting physician or nonclinically managed by social workers and counselors
  - Stabilization in an emergency setting and medically monitored inpatient or residential admission is appropriate for patients presenting with: [9]
    - Moderate to severe manifestations [5]
    - Significant comorbid psychiatric, medical, or surgical conditions [5]
    - Patients at risk for severe withdrawal [18]
- Regional protocols are available to guide management strategy for both inpatient and outpatient treatment [22]

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- Standard inpatient alcohol withdrawal treatment with medical assistance [2]
  - Sedative hypnotics are the cornerstone of initial management [8]
    - Goal of initial treatment is rapid sedation with normalization of vital signs [2]
      - Consider alternative or concurrent diagnosis if appropriate sedation is achieved without normalization of vital signs [17]
      - Appropriately sedated patient is calm and sleepy but arousable without active hallucinations or seizures [21]
      - Early and adequate treatment minimizes morbidity; administration of adequate benzodiazepine dose based on high withdrawal score (Clinical Institute Withdrawal Assessment for Alcohol [Revised]) is indicated ***regardless of blood alcohol concentration***
    - Benzodiazepines are first line treatment [43, 37]
      - Treat psychomotor agitation and prevent progression to more serious withdrawal symptoms (eg, seizures, delirium tremens)
      - Act as GABA-A agonist to overcome loss of central nervous system GABA-A inhibitory effects [3]
      - Preferred methods of administration include:
        - IV route for severe symptoms; oral route for less severe symptoms [3]
        - Front-loading (loading dose) of benzodiazepines [44]
          - Decreases rate of seizures, achieves earlier symptom control, and decreases total cumulative dose of medication needed
          - Involves high initial doses repeated frequently (eg, every 2-3 hours)
          - Often a long-acting agent is used (eg, diazepam)
        - Rapid and repeated escalating dosing (ie, double subsequent doses if control not achieved) of benzodiazepines
          - Reduces risk of seizures, delirium tremens, and need for mechanical ventilation in patients with severe withdrawal [3]
          - Titrate based on sequential sedation scale scores [5]
          - No maximum dose of benzodiazepines exists for treatment of alcohol withdrawal [3]
          - Dose required to control manifestations is highly variable among patients [10]
      - Debate exists regarding which benzodiazepine is the best treatment option [3]
        - Some clinicians prefer IV diazepam or lorazepam for acute severe symptom control [3]
          - Diazepam has shorter onset of action when compared with lorazepam, which may allow more rapid determination of dose response and more frequent dose titration [8]
          - Longer duration of diazepam compared with lorazepam may allow for smoother downward titration [8]
          - Diazepam may require dose adjustment in patients with renal failure because active metabolites are eliminated by kidneys; avoid in patients with liver disease [8]
          - Lorazepam may be safer in patients with liver dysfunction and those at high risk of serious medical consequences after sedation (eg, elderly patients, those with severe pulmonary dysfunction) because lack of active metabolites leads to lower risk of overdose [6]
        - Exercise caution with routine use of more than 1 type of benzodiazepine in combination; experts recommend use of only a single benzodiazepine [6]
          - Use of 2 different benzodiazepines may be required in select scenarios including: [45]
            - Transitioning to tapering phase of treatment
            - Initial stabilization phase of treatment, particularly in patients with severe withdrawal
              - Some experts maintain that alternating doses of lorazepam and diazepam in patients with severe withdrawal may be more effective at arresting withdrawal than use of lorazepam alone and leads to less postwithdrawal sedation than use of diazepam alone
        - Benzodiazepine equivalents: diazepam 5 mg = lorazepam 1 mg = chlordiazepoxide 25 mg = oxazepam 15 mg [15]
    - Second line adjunct treatments for withdrawal resistant to benzodiazepines alone include phenobarbital and/or propofol [3]
      - Can work synergistically with benzodiazepines on the GABA-A receptor [2, 46]
        - Limited data suggest that a single dose of IV phenobarbital combined with symptom-triggered benzodiazepine treatment of acute withdrawal decreases rates of ICU admission without significant adverse effects [47]
      - Respiratory and cardiac depressant effects are more common than with benzodiazepines alone
      - Emerging adjunct treatments include dexmedetomidine and ketamine [3]
  - Continued inpatient alcohol withdrawal management with medical assistance
    - Dosing regimens
      - Symptom-triggered (as needed) dosing of benzodiazepines is preferred to scheduled dosing after initial stabilization of symptoms for most inpatients [44]
        - Symptom-triggered dosing based on severity scales allows for individualized dosing and results in shorter duration of therapy and lower cumulative medication doses [3, 8]

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- Numerous regional guidelines exist outlining individual treatment protocols, with a great deal of variability among them; insufficient evidence is available to recommend one individual protocol above another
  - Refer to individual hospital-driven and regional protocols for specific dosing recommendations [17, 6]
  - Widely used regimen is available [48]
- Fixed-tapering-dose regimen may be best suited for outpatient detoxification and for patients in whom sedation scales cannot be accurately applied (eg, severe comorbid illness)

– Use objective measurement of symptom severity to determine frequency of administration targeted to treatment goals [3]
- Several scales assess severity of withdrawal
  - General target treatment goals include prevention of withdrawal seizures and delirium tremens, normalization of vital signs, and reduction or elimination of sensory disturbances (eg, agitation, anxiety, hallucinations)
  - Clinical Institute Withdrawal Assessment for Alcohol (Revised) is most commonly used [3]
    - Goal of treatment is a calm awake state [15]
    - Suggested treatment response to score [6]
      - Less than 10: no need for pharmacotherapy
      - 11 to 20: clinical judgment is necessary regarding need for pharmacotherapy
      - Greater than 21: requires pharmacotherapy
    - Not validated for patients requiring ICU level of care [8]
  - ICU sedation scales are often used for patients with severe withdrawal or withdrawal requiring intubation [3]
    - Richmond Agitation-Sedation Score is most commonly used [5]
      - Score of 0 to −2 indicates patient is in a calm, arousable state [3]

– Tapering
- Usually benzodiazepines can be tapered down from peak dosing after about 48 to 72 hours [6]
- General guideline is to taper by about 20% of total daily benzodiazepine equivalent dose [45]
- Some experts prefer chlordiazepoxide for scheduled tapering protocol; other experts prefer lorazepam given by a symptom-triggered tapering strategy [45]

o Manifestation-specific treatment

– Seizures
- Benzodiazepines are first line treatment [3]
- Barbiturates and propofol are second line treatment options for seizures recalcitrant to benzodiazepines
- Avoid other anticonvulsants (eg, carbamazepine, phenytoin, valproic acid, levetiracetam) for treatment or prophylaxis of seizures because most seizures are self-limited and inconsistently responsive to anticonvulsants other than benzodiazepines and barbiturates [3]
- Long-term anticonvulsant therapy is ***not*** necessary unless patient has underlying seizure disorder or epilepsy [5]
- Refractory status epilepticus may require management in consultation with specialists (eg, medical toxicologist, neurologist) and infusion of phenobarbital, pentobarbital, propofol, or midazolam [4]

– Alcoholic hallucinosis
- Benzodiazepines are first line treatment [3]
- Avoid routine use of antipsychotics (eg, phenothiazines, butyrophenones) because they lower seizure threshold, often have anticholinergic effects (worsening hypertension, tachycardia, etc.), mask symptoms of worsening withdrawal, [17] and increase risk of respiratory complications [3, 5]
  - May be beneficial for patients with known or suspected thought disorders (eg, schizophrenia) [3]
  - May be used in outpatient setting to diminish craving

– Autonomic hyperactivity
- Adjunct medications that may be useful to diminish symptoms but do not prevent seizures or delirium tremens include: [5]
  - β-blockers
    - May diminish symptoms such as tremor, tachycardia, cardiac arrhythmias, hypertension, and craving
  - Clonidine (α_2 agonist)
    - May diminish severity of symptoms in mild to moderate withdrawal

– Delirium and severe agitation
- Management requires aggressive sedation [5]
  - Extremely high benzodiazepine dosing may be required to achieve sedation goals
  - Titrated IV infusion may be required
  - Adjunct measures for benzodiazepine-resistant withdrawal may be required
- Potential need for endotracheal intubation and mechanical ventilation is high [5]
- Maintain high awareness for potential complications such as development of pneumonia and sepsis [5]

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        - Physical restraints may be temporarily required; however, take care to avoid prolonged physical restraints without appropriate sedation owing to increased risk for rhabdomyolysis [15, 2]
        - Intermittent verbal reorientation to time, place, and date are important after stabilization [8]
    - Benzodiazepine-resistant withdrawal
      - Clear definition is lacking; many experts define as lack of symptom control after the following doses:
        - At least 40 to 50 mg diazepam or 8 to 10 mg lorazepam within the first hour of treatment [3, 8]
        - More than 200 mg diazepam or 40 mg lorazepam within 3 hours of treatment [3]
      - If rapid escalation of benzodiazepines fails to control symptoms, adjunct treatment options include phenobarbital, propofol, ketamine, and dexmedetomidine [3]
        - Dexmedetomidine and ketamine use has not been studied as much as phenobarbital and propofol use [3]
      - Consider alternative or concurrent diagnosis [17]
      - Refractory withdrawal and delirium tremens may require intubation and mechanical ventilation [3]
      - Most experts ***do not*** recommend treating with ethanol [17] or baclofen (selective GABA-B receptor agonist) [3]
    - Treat concurrent acute illness and comorbid conditions in standard manner
      - May include treatment of other pathologic processes leading to alcohol withdrawal such as: [3]
        - Infection (eg, pneumonia, sepsis, meningitis/encephalitis)
        - Gastrointestinal disease (eg, pancreatitis, hepatitis, alcoholic gastritis, bleeding esophageal varices)
        - Trauma (eg, head trauma)
        - Metabolic derangements (eg, hypoglycemia, electrolyte abnormalities)
        - Intracerebral hemorrhage
        - Acute coronary syndrome
        - Drug overdose
- Outpatient alcohol withdrawal treatment with medical assistance
    - Aggressive counseling and rehabilitation are essential adjuncts to medication-assisted withdrawal to sustain recovery process and prevent relapse and subsequent episodes of withdrawal
    - Options include oral benzodiazepines, anticonvulsants, [3] β-blockers, and α_2-adrenergic agonists [9]
      - Benzodiazepines
        - Choice of specific benzodiazepine
          - Long-acting benzodiazepines (eg, diazepam, chlordiazepoxide) are preferred in most patients [9]
          - Intermediate-acting benzodiazepines (eg, lorazepam, oxazepam) are also effective and preferred in patients with liver dysfunction owing to lack of active metabolites [9]
          - Chlordiazepoxide and oxazepam have less misuse potential than diazepam and lorazepam and may be preferred in patients at high risk for substance use disorders [9]
        - Stress importance of abstinence from alcohol intake during treatment with benzodiazepine [9]
          - Increased risk of respiratory depression and death is associated with alcohol and benzodiazepine coingestion
        - Administration technique
          - Either fixed-dose or symptom-triggered schedule may be used [9]
            - Administration of dose during symptom-triggered management should be given for: [9]
              - Short Alcohol Withdrawal Score of 12 or higher, or
              - Clinical Institute Withdrawal Assessment for Alcohol (Revised) score higher than 9
          - Front-loading (loading dose) is ***not*** routinely recommended [9]
        - Tapering
          - In general, doses can be gradually tapered down when Clinical Institute Withdrawal Assessment for Alcohol (Revised) score is less than 10 or Short Alcohol Withdrawal Score is less than 12 until eventual discontinuation [9]
          - Symptoms usually resolve by day 7 following last alcohol use [9]
      - Anticonvulsants
        - Data are limited; [49] carbamazepine, valproic acid, and gabapentin may be used to reduce craving and prevent early relapse [9]
        - Anticonvulsants do not prevent withdrawal seizures or delirium tremens [9]
      - β-blockers and α_2-adrenergic agonists
        - Atenolol and clonidine may be used as adjunct medications in combination with benzodiazepines to reduce adrenergic symptoms [9]
        - β-blockers and α_2-adrenergic agonists do not prevent withdrawal seizures or delirium tremens
- Counseling and rehabilitation
    - Cornerstone to recovery and adjunct to medication-assisted withdrawal
    - Refer all patients with alcohol withdrawal for alcohol use disorder treatment (eg, alcohol abstinence counseling, long-term rehabilitation) [5]
    - American Society of Addiction Medicine placement criteria can guide placement after detoxification process [17, 50]

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- Provide patient with resources for assistance in long-term abstinence such as:
  - Alcoholics Anonymous[51]
  - National Council on Alcoholism and Drug Dependence[52]
  - National Institute on Alcohol Abuse and Alcoholism[53]
  - Substance Abuse and Mental Health Services Administration[54, 55]
- Drug therapy
  - Benzodiazepines[2]
    - Diazepam
      - Rapid onset of action allows for ease of titration with less risk of dose stacking than with lorazepam[3]
      - Active metabolites result in a longer duration of action compared with lorazepam[3]
      - Readminister drug in an escalating dose fashion every 5 to 10 minutes until sedation goals and normalized vital signs are achieved[3]
        - Common escalating dosing pattern for diazepam:[3]
          - Initial dose is 10 mg, then observe for 5 to 10 minutes for clinical effects
          - When required, administer second dose of 20 mg then observe for 5 to 10 minutes for effects
          - When required, administer third dose of 40 mg then observe for 5 to 10 minutes for effects
          - Extremely high doses may be required for management of manifestations
            - Requirement of up to 500 mg for initial front-loading dose and cumulative dose of up to 2000 mg over 48 hours are reported[3]
      - Can be administered intravenously, orally, or rectally
        - Diazepam Solution for injection; Adults: 10 mg IV initially, followed by 5 to 10 mg IV every 3 to 4 hours PRN. Doses of 5 to 10 mg IV may be given every hour if required. Hold if sedated.
      - Example of outpatient oral diazepam dosing regimens[9]
        - Fixed-schedule
          - Diazepam Oral tablet; Adults: Day 1: 10 mg PO every 6 hours; Day 2: 10 mg PO every 8 hours; Day 3: 10 mg PO every 12 hours; Day 4 and 5: 10 mg PO at bedtime.
        - Symptom-triggered schedule
          - Diazepam Oral tablet; Adults: Day 1:10 mg PO every 4 hours PRN; Day 2 and 3: 10 mg PO every 6 hours PRN; day 4 and 5: 10 mg PO every 12 hours PRN.
    - Lorazepam
      - Slower time to peak effect than diazepam; therefore, dose stacking may occur if re-dosed before peak effect
      - Lack of active metabolites results in shorter half-life compared with diazepam[3]
      - Less liver metabolism than other benzodiazepine options; may be preferred in patients with liver failure
      - Readminister drug in an escalating dose fashion every 15 to 20 minutes until sedation goals and normalized vital signs are achieved[3]
        - Common escalating dosing pattern:[3]
          - Initial dose is 4 mg, then observe for 15 to 20 minutes for effects
          - When required, administer second dose of 8 mg then observe for 15 to 20 minutes for effects
          - When required, administer third dose of 16 mg then observe for 15 to 20 minutes for effects
          - Extremely high doses may be required for management of manifestations
      - Can be administered intravenously, intramuscularly, or orally
        - Bolus dosing
          - Lorazepam Solution for injection; Adults: Initially 1—2 mg PO/IM/IV q8h. Titrate for desired clinical response. MAX: 4 mg/dose. NOTE: Dosing is highly variable; some patients require high doses of benzodiazepines to treat acute ethanol withdrawal.
        - Continuous infusion
          - For use in patients requiring frequent treatment
          - Infusion carries risk of propylene glycol toxicity and excessive accumulation of drug (ie, dose stacking)
          - Lorazepam Solution for injection; Adults: 1 to 4 mg/hour continuous IV infusion; titrate to effect. Max: 14 mg/hour.[56]
      - Example of outpatient oral lorazepam dosing regimens[9]
        - Fixed-schedule
          - Lorazepam Oral tablet; Adults: Day 1 and 2: 2 mg PO every 8 hours; Day 3: 1 mg PO every 8 hours; Day 4: 1 mg PO every 12 hours; Day 5: 1 mg PO at bedtime.
        - Symptom-triggered schedule
          - Lorazepam Oral tablet; Adults: Day 1 and 2: 2 mg PO every 6 hours PRN; Day 3: 1 mg PO every 8 hours PRN; Day 4 and 5: 1 mg PO every 12 hours PRN.

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- Midazolam
  - Has the most rapid onset of action (1-2 minutes) but short duration of action
  - Can be administered intravenously, intramuscularly, or orally
    - Midazolam Hydrochloride Solution for injection; Adults: Midazolam may be considered as an alternative to commonly used benzodiazepines (e.g., lorazepam). Doses of 1 to 5 mg IV every 1 to 2 hours for mild to moderate alcohol withdrawal symptoms and 1 to 20 mg every 1 to 2 hours by continuous IV infusion for delirium tremens have been suggested from retrospective data. Case reports of larger doses exist in the literature; in 1 report delirium tremens was successfully treated with a total of 2,850 mg of midazolam administered over a 5-day period, with a rate of infusion ranging from 20 to 55 mg/hour. Until more data become available, the lowest effective dose should be used in conjunction with close monitoring for potential adverse effects on respiratory and cardiovascular function. It is advisable to periodically assess the patient for signs of fluid overload.
- Oxazepam
  - Preferred in patients with liver dysfunction owing to lack of active metabolites
    - Oxazepam Oral capsule; Adults: 15—30 mg PO 3—4 times daily; geriatric patients may need a reduced initial dose.
- Chlordiazepoxide
  - Longer onset and duration of action
    - Inpatient dosing
      - Chlordiazepoxide Hydrochloride Oral capsule; Adults: The suggested initial dose is 50 to 100 mg PO, may repeat q4h to q6h PRN until agitation is controlled. Then reduce to lowest maintenance dose. Max: 300 mg/day PO. Hold doses if overly sedated or lethargic.
  - Example of outpatient oral chlordiazepoxide dosing regimens[9]
    - Fixed-schedule
      - Chlordiazepoxide Hydrochloride Oral capsule; Adults: Day 1: 25 to 50 mg PO every 6 hours; Day 2: 25 to 50 mg PO every 8 hours; Day 3: 25 to 50 mg PO every 12 hours; Day 4 and 5: 25 to 50 mg PO at bedtime.
    - Symptom-triggered schedule
      - Chlordiazepoxide Hydrochloride Oral capsule; Adults: Day 1: 25 to 50 mg PO every 4 hours PRN; Day 2 and 3: 25 to 50 mg PO every 6 hours PRN; Day 4 and 5: 25 to 50 mg PO every 12 hours PRN.

Benzodiazepines for alcohol withdrawal syndrome.

Drug	Time to onset	Active metabolites	Half-life in hours	Typical initial dose
Diazepam	1 to 5 minutes intravenous	Yes	43 ± 13	10 to 20 mg intravenous or oral
Lorazepam	5 to 20 minutes intravenous	No	14 ± 5	2 to 4 mg intravenous or oral
Midazolam	2 to 5 minutes intravenous/intramuscular	Yes	2 ± 1	2 to 4 mg intravenous or intramuscular
Oxazepam	2 to 3 hours oral	No	8 ± 2	15 to 30 mg oral every 8 hours
Chlordiazepoxide	2 to 3 hours oral	Yes	10 ± 3	50 to 100 mg oral

From Long D et al: The emergency medicine management of severe alcohol withdrawal. Am J Emerg Med. 35(7):1005-11, 2017, Table 4.

- Barbiturates[47, 57]
  - Phenobarbital[58]
    - Effective when used in combination with benzodiazepines for resistant withdrawal and delirium tremens[3]
    - Paucity of data exists for use as monotherapy; therefore, monotherapy should only be considered in a patient whose condition is refractory to benzodiazepines[8]
    - Patients requiring phenobarbital may require intubation and mechanical ventilation
    - Bolus dosing
      - Phenobarbital Sodium Solution for injection; Adults: 65 to 260 mg IV bolus every 15 to 30 minutes until control of symptoms is usually adequate.[3]
    - Infusion
      - Phenobarbital Sodium Solution for injection; Adults: 10 mg/kg IV infusion over 30 minutes.[3]
        - NOTE: Not readily titratable due to delayed peak onset of action
- Propofol[59, 60]
  - Reserved for severe withdrawal refractory to benzodiazepine therapy in patients requiring intubation and mechanical ventilation[8]

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- Propofol Emulsion for injection; Adults: Dosages from 5 to 100 mcg/kg/minute (0.3 to 6 mg/kg/hour) IV have been used to reduced alcohol withdrawal symptoms. Development of hypotension may occur. Evaluate clinical effects and CNS function daily to determine minimum effective dosage.[61]

- α_2 receptor agonists
  - May reduce autonomic signs and symptoms of alcohol withdrawal as an adjunct therapy without an increase in benzodiazepine cumulative doses[62, 63, 64]
  - Clonidine[9]
    - May be beneficial adjunct in mild withdrawal states to diminish symptoms in outpatient setting
    - Clonidine Hydrochloride Oral tablet; Adults: In one study, clonidine was dosed initially as 0.2 mg PO at 9PM on day 1; at 9AM, 1PM, and 6PM on day 2; at 9AM and 6PM on day 3; and a final dose at 9AM on day 4.
  - Dexmedetomidine[65]
    - Clinical effects include sedation, anxiolysis, analgesia, and sympatholysis; incidence of respiratory depression is lower compared with other adjunct agents available for severe, refractory withdrawal[8]
    - Adjunct treatment may lower benzodiazepine requirements and decrease need for mechanical ventilation in patients with severe, refractory withdrawal[8]
    - Does not prevent or treat withdrawal seizures and may increase rate of delirium, although available data are conflicting[8]
    - Dexmedetomidine Hydrochloride Solution for injection; Adults: Adjunctive therapy: Initiate infusion at 0.2 mcg/kg/hour IV; titrate by 0.2 mcg/kg/hour every 15 minutes to maintain desired clinical effect (Max dose: 1.4 mcg/kg/hour).[3]

- β-blockers
  - Atenolol
    - May be a beneficial adjunct in mild withdrawal states to diminish symptoms in outpatient setting
      - Atenolol Oral tablet; Adults: 50 to 100 mg PO once daily has been studied.
        - Pulse 50 to 79 beats per minute: 50 mg typical dose[9]
        - Pulse 80 beats per minute or higher: 100 mg typical dose[9]

- Ketamine
  - Very limited data demonstrate safety when used as an adjunctive therapy for benzodiazepine resistant withdrawal[66, 8]
    - Ketamine Hydrochloride Solution for injection; Adults: Initially, a loading dose of 0.3 mg/kg, followed by 0.2 mg/kg/hour continuous IV infusion.[56, 67]

- Anticonvulsants
  - May be a beneficial adjunct in mild withdrawal states to diminish craving in outpatient setting[68]
  - Carbamazepine
    - Carbamazepine Oral capsule, Extended-Release; Adults: 300 mg PO twice daily on Days 1 through 3, 300 mg PO daily on Day 4, and 100 mg PO daily on Day 5. Individualize dosage based on clinical response and tolerability.[69, 70]
  - Valproic acid
    - Valproic Acid Oral capsule; Adults: 600 mg PO twice daily for Days 1 and 2, 300 mg PO daily on Days 3 and 4. Individualize dosage based on clinical response and tolerability.[9, 71]
  - Gabapentin[9]
    - Misuse has been reported and caution should be taken especially in patients with substance use disorder[72, 73]
    - Gabapentin Oral capsule; Adults: Use not FDA-approved, but has been studied. Initially, 300 mg PO at bedtime on day 1; then 300 mg PO twice daily on day 2; then 300 mg PO 3 times per day on Day 3; and then titrated upward over days 4 to 7 to reach final dosage. Doses from 600 mg/day to 1,800 mg/day PO have improved abstinence rates and relapse-related symptoms (i.e., insomnia, dysphoria, craving) in some patients.

- Thiamine (vitamin B_1)[15]
  - Prophylactic dose
    - Vitamin B_1 (Thiamine Hydrochloride) Oral tablet; Adults: 100 mg PO once daily for 3 to 5 days.[42]
    - Vitamin B_1 (Thiamine Hydrochloride) Solution for injection; Adults: 100 mg IV once daily for 3 to 5 days.[3, 8]
  - Treatment dose for Wernicke encephalopathy
    - Thiamine should be given before any glucose administration to avoid precipitating Wernicke encephalopathy;[8] several dosing regimens are available[74]
    - Vitamin B_1 (Thiamine Hydrochloride) Solution for injection; Adults: 500 mg IV every 8 hours for 5 days, followed by 250 mg IV once daily for 3 to 5 days depending on response.[3, 10, 22, 75]

- Folate supplementation
  - Folic Acid Oral tablet; Adults: 1 mg PO once daily for 3 to 5 days.[3]
  - Folic Acid Solution for injection; Adults: 1 mg IV once daily for 3 to 5 days.[3]

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

	Chlordiazepoxide	Diazepam	Lorazepam	Midazolam	Phenobarbital	Propofol
Class of drug	Benzodiazepine	Benzodiazepine	Benzodiazepine	Benzodiazepine	Barbiturate	Hypnotic
Intermittent initial dose	50 to 100 mg (oral)*	10 mg (intravenous)	2 mg (intravenous)	1 to 5 mg (intravenous)	65 mg (intravenous)	Not applicable[61]
Route of dose	Oral	Intravenous, intramuscular, oral, rectal	Intravenous, intramuscular, oral	Intravenous, intramuscular, oral	Intravenous, intramuscular, oral, rectal	Intravenous
Infusion dosing	Not applicable	Not applicable	1 to 4 mg/hour†[56]	1 to 20 mg/hour, titrate up to effect§	10 mg/kg intravenous over 30 minutes**[3]	0.3 to 6 mg/kg/hour as needed for appropriate sedation[61]
Time to effect onset	2 to 3 hours	1 to 5 minutes (intravenous); 15 to 30 minutes (intramuscular); 30 to 90 minutes (oral); 10 to 45 minutes (rectal)	5 to 20 minutes	2 to 5 minutes	5 to 30 minutes (peak brain concentrations at 20 to 40 minutes)	1 to 2 minutes
Half life	5 to 30 hours (active metabolite 30 to 200 hours)	30 to 60 hours (active metabolite 30 to 100 hours)	9 to 21 hours	2 to 6 hours	50 to 140 hours	10 minutes to 12 hours (longer if prolonged use)
Duration of action	Long	Long	Short to medium	Short	Long	Short to medium
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic, gut	Hepatic	Hepatic
Excretion	Renal	Renal	Renal, fecal	Renal	Renal	Renal
Dose adjustment	Renal (creatinine clearance less than 10): 50% dose reduction; hepatic impairment: risk of accumulation	Hepatic impairment; renal impairment	Renal impairment: dose reduction	Renal failure (creatinine clearance less than 10): dose reduction	Renal failure (GFR less than 10): increase dosing interval and dose reduction; caution in hepatic impairment	None
Notes	Extremely long-acting active metabolite, so not recommended in elderly patients	Phlebitis; erratic absorption if given intramuscularly	If more than 25 mg/hour, risk of acute tubular necrosis, lactic acidosis, and hyperosmolar state because of solvent; no active metabolite	Prolonged sedation if obese and/or low albumin; active metabolite	May cause hypotension	Risks: propofol infusion syndrome, injection site pain, hypertriglyceridemia; more hypotension than other sedative-hypnotics; may discolor urine. Caution: soy or egg allergy

*All doses on the table are for the IV form of the drug except for chlordiazepoxide because the IV form of this drug has been discontinued in the United States. †Based on longer half-life of lorazepam (and diazepam), infusion dosing generally not recommended. §Case reports of infusion rates up to 520 mg/hour. (Wolf KM et al: Prolonged delirium tremens requiring massive dosages of medication. J Am Board Fam Pract. 6(5):502-4, 1993) **Generally, not given in true infusions.

Adapted from Stehman CR et al: A rational approach to the treatment of alcohol withdrawal in the ED. Am J Emerg Med. 31(4):734-42, 2013, Table 1.

- Nondrug and supportive care
  - Electrolytes
    - Electrolyte abnormalities are common in patients with long-term alcohol use and those with severe withdrawal; correct in standard manner when indicated[24]
      - Hypokalemia is not uncommon; usually results from dietary deficiency
        - Potassium may require repletion depending on severity of deficiency and presence of symptoms related to deficiency[3]

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        - Hypomagnesemia and hypophosphatemia may occur; usually result from dietary deficiency
            - Routine supplementation is not recommended [8]
            - Supplementation may be required, especially when symptomatic, given supporting laboratory evidence of severe deficiency
            - Self-correction with proper nutrition is preferred treatment for asymptomatic, mild to moderate deficiency
            - IV repletion is not routinely required [3]
    - Fluids
        - IV fluid resuscitation may be necessary in patients with severe withdrawal
        - Increased fluid losses are not uncommon in patients with hyperthermia, hyperventilation, diaphoresis, and/or agitation [2]
    - Nutrition [5]
        - Thiamine
            - Thiamine is a critical cofactor in carbohydrate metabolism; deficiency results in decreased glucose utilization [3]
            - Thiamine deficiency is often present and increases risk of Wernicke encephalopathy (eg, altered mental status, ophthalmoplegia, ataxia) [3]
            - Administer prophylactic dose for presumed thiamine deficiency to all patients presenting in withdrawal [3, 15]
            - Administer treatment dose to any patients with concerning manifestations for Wernicke encephalopathy [3]
            - Administer thiamine before (preferred) or with glucose administration [8]
        - Folate
            - Supplementation is recommended owing to low dietary folate intake, which may lead to megaloblastic anemia in patients with long-term alcohol use disorder [3]
            - Multivitamins containing daily recommended allowance of folic acid are often used [8]
        - Provide nutritional support to those with long-term alcohol use to prevent and/or treat ketoacidosis
            - Route of administration is individualized [5]
                - Enteral is preferred (oral, nasogastric, or nasoduodenal)
                - Parenteral may be required
        - Glucose
            - Some patients may require glucose supplementation for hypoglycemia because of increased metabolic requirements in the setting of diminished glycogen stores [2]
            - Untreated hypoglycemia can lead to alcoholic ketoacidosis (hyperketonemia with anion gap metabolic acidosis without significant hyperglycemia), complicating withdrawal management
            - Avoid glucose administration alone (without thiamine administration) in patient at risk for Wernicke encephalopathy
    - Procedures
- Comorbidities
    - Liver failure
        - IV lorazepam and oral oxazepam may be preferred in patients with advanced cirrhosis, hepatitis, and liver failure owing to the lower degree of hepatic metabolism compared with other benzodiazepines [2, 3]
        - Duration of any benzodiazepines may be significantly prolonged in patients with hepatic dysfunction; dose adjustment may be required [3]
    - Renal insufficiency
        - Most benzodiazepines and their metabolites are eliminated by the kidney; dose adjustment may be necessary, particularly in agents with active metabolites [24]
    - Wernicke encephalopathy
        - Administer treatment dose of thiamine for duration of 3 to 5 days to any patients with concerning manifestations for Wernicke encephalopathy [3, 10]
        - Administer thiamine before (preferred) or with glucose administration to avoid precipitating Wernicke encephalopathy in patients at risk [8, 10]
- Special populations
    - Pregnant women
        - There are no structured guidelines or high-level studies regarding optimal treatment of alcohol withdrawal in pregnancy [76]
        - As maternal health is vitally important to fetal health, benzodiazepines should still be considered first line treatment
        - Manage in consultation with specialist (eg, substance misuse medicine, high-risk obstetrician)

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MONITORING

- Admitted patients with alcohol withdrawal syndrome and patients at risk for developing alcohol withdrawal syndrome
  - Serial measurements using a validated withdrawal severity scale are required to guide symptom-triggered treatment[5]
    - Frequency of scoring depends on stage of management and degree of symptom control
      - Frequent evaluations (eg, every 10-15 minutes) may be required during initial stages of treatment[3]
      - Scoring evaluations may be spaced to hourly once treatment goals are reached[3]
  - Maintain awareness and assess for other coexistent conditions and alternate medical causes for patient decompensation other than worsening or recalcitrant withdrawal[3]
  - Monitor for adequacy of airway protection, frequent vital signs, and hydration status[8]
- Outpatient monitoring for patients requiring treatment
  - Guide monitoring type and frequency based on symptom severity and characteristics of individual patient and environment[9]
  - Daily reassessments are required in most patients until symptoms abate, including:[9]
    - Measurement of vital signs
    - Random alcohol breath analysis
    - Withdrawal symptom severity scale assessment (eg, Short Alcohol Withdrawal Score, Clinical Institute Withdrawal Assessment for Alcohol [Revised])
  - Refer for long-term outpatient treatment when symptoms are minimal, benzodiazepines are no longer required, and patient has abstained from alcohol intake for at least 3 days[9]
  - Refer to addiction medicine specialist or inpatient treatment program if patient does not adequately respond to benzodiazepine therapy, misses an appointment, or resumes drinking alcohol[9]
- Refer to regional protocols to guide monitoring strategy[22]

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS

- Death
  - Cause of death usually results from hyperthermia, cardiac arrhythmias, complications of withdrawal seizures, or concomitant medical disorders (eg, pneumonia, acute coronary syndrome[6])[10]
- Aspiration pneumonia and/or respiratory depression requiring tracheal intubation and mechanical ventilation
  - May result from oversedation
- Rhabdomyolysis
  - May result from severe agitation, hyperthermia, prolonged seizures, and/or prolonged use of physical restraints
- Wernicke encephalopathy
  - Alcohol use disorder may result in chronic thiamine deficiency characterized by cell damage to the mammillary body, thalamus, and hippocampus[15]
    - May lead to the permanent amnestic syndrome or Korsakoff encephalopathy
  - Prevalence may be as high as 3%[6]
  - Classically presents with confusion, ataxia, and ophthalmoplegia[15]
  - Glucose administration without thiamine replacement can precipitate syndrome in thiamine-deficient patients[15]
  - Diagnosis may be missed if nystagmus and ataxia are not appreciated; mental status changes may be attributed to delirium tremens[6]

PROGNOSIS

- Overall prognosis is best among patients without other acute medical problems[5]
- Morbidity and mortality are increased among patients with comorbidity, concurrent disease related to alcohol use disorder that complicates management,[5] and older age[12]
  - Failure to identify an underlying medical or surgical issue leading to decreased alcohol intake places patient at increased risk for morbidity and mortality
- Mortality among hospitalized patients with delirium tremens is about 1% to 4%[3]
- Long-term mortality among patients who experience seizures or delirium tremens associated with withdrawal episode is guarded
  - Up to 50% of patients die within 10 years[8]
- Clinical course
  - Symptoms of acute withdrawal usually improve markedly by several days after abstinence[1]
  - Persistent symptoms (eg, anxiety, insomnia, autonomic dysfunction) may occur in some patients for up to 6 months[1]
    - Symptoms occur at lower level of intensity than during acute withdrawal
  - About 5% of patients who develop acute withdrawal will progress to severe withdrawal without treatment[77]
  - About one-third of patients who develop seizures will progress to delirium tremens without treatment[3]

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- Average length of hospitalization for acute withdrawal
  - General inpatients: about 5.4 days[5]
  - ICU patients: about 12.5 days[5]
- Patients who develop delirium
  - Delirium usually subsides within a few days; rarely persists for up to 2 weeks[5]
  - Return to baseline mental status may require several weeks for some patients[5]
- Long-term abstinence from alcohol among patients with alcohol use disorder[9]
  - First step is successful treatment of withdrawal
  - Enrollment in a long-term treatment program greatly increases likelihood of long-term abstinence

- Recurrent withdrawal
  - Subsequent episodes of alcohol withdrawal tend to increase in severity[78]

SCREENING AND PREVENTION

SCREENING

- At-risk populations
  - Hospitalized and patients with active alcohol use disorder may be at increased risk
- Screening tests
  - Prediction of Alcohol Withdrawal Severity Scale may predict complicated withdrawal among ***hospitalized*** patients[7]
    - Score of 4 or higher suggests high risk for developing moderate to severe withdrawal[17]
      - Sensitivity is approximately 93% and specificity is approximately 99%[7]
    - Scoring questions are as follows:[79]
      - Have you consumed any amount of alcohol within the last 30 days? Or did the patient have a positive blood alcohol content on admission?
        - If no, then stop. Prediction of Alcohol Withdrawal Severity Scale is negative
        - If yes, then continue to score 1 point for each of the following:
          - Have you been recently intoxicated/drunk, within the last 30 days?
          - Have you ever undergone alcohol use disorder rehabilitation treatment or treatment for alcoholism?
          - Have you ever experienced any previous episodes of alcohol withdrawal, regardless of severity?
          - Have you ever experienced blackouts?
          - Have you ever experienced alcohol withdrawal seizures?
          - Have you ever experienced delirium tremens or DTs?
          - Have you combined alcohol with other "downers" like benzodiazepines or barbiturates, during the last 90 days?
          - Have you combined alcohol with any other substances of abuse, during the last 90 days?
          - Was the patient's blood alcohol content on presentation 200 mg/dL or higher?
          - Is there evidence of increased autonomic activity (eg, heat rate above 120 beats per minute, tremor, sweating, agitation, nausea)?

PREVENTION

- Ask all patients about their alcohol use[2,80]
  - Counsel patients with frequent alcohol use to limit consumption to a safe level
  - Consider referral to an alcohol or substance use specialist if patient cannot self-limit alcohol intake
- Enrollment in long-term treatment program after an episode of withdrawal decreases likelihood of relapse and future episodes of withdrawal[9]

SYNOPSIS

KEY POINTS

- Alcohol withdrawal may occur after cessation or reduction of heavy and prolonged alcohol use; manifestations are characterized by autonomic hyperactivity and central nervous system excitation
- Alcohol withdrawal can start as early as 6 hours from the last drink and early manifestations are characterized by sympathomimetic symptoms, tremor, anxiety, insomnia, nausea, and vomiting[4]
- Manifestations may worsen without treatment; progression to severe symptom manifestations including seizures and delirium tremens occurs in up to 5% of patients[3]
- Withdrawal is a clinical diagnosis and a diagnosis of exclusion; *DSM-5* diagnostic criteria define the diagnosis[1]
- Ancillary testing does not usually aid in diagnosis; obtain routine baseline studies (eg, metabolic panel, liver function testing) to evaluate for concurrent problems in patients with moderate to severe withdrawal manifestations requiring admission

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- Obtain individualized studies based on presentation to identify concurrent conditions that may have contributed to precipitation of withdrawal
- Outpatient alcohol withdrawal treatment with medical assistance may be used for select patients with mild to moderate withdrawal without significant comorbidity
- Inpatient alcohol withdrawal treatment with medical assistance is required for patients with severe withdrawal and patients at risk for progression to severe withdrawal
- Sedative hypnotics (ie, benzodiazepines) are the cornerstone of initial management
- With effective treatment, progression of disease and development of delirium tremens may be avoided
- Administer thiamine and folate supplementation in patients presenting in withdrawal; replenish potassium to correct hypokalemia[3]
- Refer all patients with alcohol withdrawal for alcohol use disorder treatment (eg, alcohol abstinence counseling, long-term rehabilitation)
- Overall prognosis is best among patients without other acute medical problems
- Morbidity and mortality are increased among patients with comorbidity, concurrent disease related to alcohol use disorder that complicates management,[5] and older age[12]
- Prevention of withdrawal may be possible with screening, early identification, and rehabilitation of patients with alcohol use disorder

URGENT ACTION

- Early and aggressive treatment of alcohol withdrawal will halt progression to more severe forms of withdrawal
- Treat moderate to severe withdrawal aggressively with rapid escalating doses of benzodiazepines initially
- Seizures should be terminated with benzodiazepines (first line); second line agents include barbiturates and/or propofol
- Wernicke encephalopathy requires urgent treatment doses of thiamine

PITFALLS

- Patients may develop manifestations of withdrawal despite a detectable serum alcohol concentration
  - Consider diagnosis even in patients who are not abstinent from alcohol because a decreased amount of consumption can lead to withdrawal
  - Early and aggressive treatment of withdrawal manifestations is a key measure to diminish morbidity when indicated *regardless of detectable blood alcohol concentration*
- Consider alcohol withdrawal diagnosis in patients admitted to hospital for other reasons if manifestations consistent with withdrawal develop
  - Up to 8% of patients admitted to hospitals with non–alcohol-related diagnoses exhibit signs of withdrawal[12]
  - Early recognition and aggressive treatment decreases morbidity
- Inadequate initial treatment of withdrawal symptoms may lead to worsening withdrawal
  - Treat aggressively to targeted treatment goals for sedation
- Accurate diagnosis is key to appropriate management of manifestations
  - For example, benzodiazepines are the treatment of choice for alcoholic hallucinosis; administration of antipsychotics can be detrimental if hallucinations are considered attributable to a psychiatric illness rather than withdrawal
- Acute illness may precipitate withdrawal episode
  - Maintain awareness for need to identify and treat any acute illness that occurs concurrent with withdrawal
- Monitor for other coexistent conditions and alternate medical causes for patient decompensation or recalcitrant withdrawal[3]
  - For example, persistent tachycardia may be a manifestation of alternate disease (eg, hypovolemia, sepsis, heart failure, thyrotoxicosis) rather than withdrawal alone
  - Failure to consider alternative and coexisting diagnosis may lead to increased morbidity and mortality
- Subsequent episodes of alcohol withdrawal tend to increase in severity
  - Encourage treatment and counseling for alcohol use disorder after an episode of acute withdrawal to prevent recurrent withdrawal episodes
- Prophylactic thiamine replacement is important to avoid increased risk of Wernicke encephalopathy[3]
  - Maintain high suspicion for Wernicke encephalopathy in patients presenting with suspicious manifestations (eg, ataxia, ophthalmoplegia) because mortality is high and diagnosis is frequently missed
  - Treatment thiamine dosing is higher and longer than prophylactic dosing for patients presenting with concern for Wernicke encephalopathy
  - Administer thiamine before (preferred) or with glucose administration in patients at risk for Wernicke encephalopathy because supplemental administration of glucose alone can precipitate encephalopathy

SELECTED REFERENCES

1 American Psychiatric Association: Alcohol withdrawal. In: Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013:499-501
2 Stehman CR et al: A rational approach to the treatment of alcohol withdrawal in the ED. Am J Emerg Med. 31(4):734-42, 2013
3 Long D et al: The emergency medicine management of severe alcohol withdrawal. Am J Emerg Med. 35(7):1005-11, 2017

Published September 14, 2018

4 McMicken D et al: Alcohol-related seizures. Emerg Med Clin North Am. 29(1):117-24, 2011
5 Carlson RW et al: Alcohol withdrawal syndrome. Crit Care Clin. 28(4):549-85, 2012
6 Finn K: Inpatient management of alcohol withdrawal. Hosp Med Clin. 1(1):e132-47, 2012
7 Maldonado JR 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. 50(5):509-18, 2015
8 Schmidt KJ et al: Treatment of severe alcohol withdrawal. Ann Pharmacother. 50(5):389-401, 2016
9 Muncie HL Jr et al: Outpatient management of alcohol withdrawal syndrome. Am Fam Physician. 88(9):589-95, 2013
10 Schuckit MA: Recognition and management of withdrawal delirium (delirium tremens). N Engl J Med. 371(22):2109-13, 2014
11 Hall W et al: The alcohol withdrawal syndrome. Lancet. 349(9069):1897-900, 1997
12 Kosten TR et al: Management of drug and alcohol withdrawal. N Engl J Med. 348(18):1786-95, 2003
13 National Institute on Alcohol Abuse and Alcoholism: Drinking Levels Defined. NIAAA website. Accessed September 14, 2018. https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking
14 Goodson CM et al: Predictors of severe alcohol withdrawal syndrome: a systematic review and meta-analysis. Alcohol Clin Exp Res. 38(10):2664-77, 2014
15 Sachdeva A et al: Alcohol withdrawal syndrome: benzodiazepines and beyond. J Clin Diagn Res. 9(9):VE01-7, 2015
16 Alcohol, Ethanol. In: ToxED [database online]. Tampa, FL: Elsevier; 2018. Updated August 1, 2018. Accessed September 14, 2018. http://www.toxed-ip.com/ToxEdView.aspx?id=592345
17 Simpson SA et al: Psychiatric emergencies for clinicians: emergency department management of alcohol withdrawal. J Emerg Med. 51(3):269-73, 2016
18 Friedmann PD: Alcohol use in adults. N Engl J Med. 368(17):1655-6, 2013
19 Eyer F et al: Risk assessment of moderate to severe alcohol withdrawal--predictors for seizures and delirium tremens in the course of withdrawal. Alcohol Alcohol. 46(4):427-33, 2011
20 Sullivan JT et al: Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar). Br J Addict. 84(11):1353-7, 1989
21 Sessler CN et al: The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 166(10):1338-44, 2002
22 National Institute for Health and Care Excellence: Alcohol-use Disorders: Diagnosis and Management of Physical Complications. Clinical Guideline CG100. NICE website. Published June 2010. Updated April 2017. Accessed September 14, 2018. https://www.nice.org.uk/guidance/cg100
23 Awissi DK et al: Alcohol withdrawal and delirium tremens in the critically ill: a systematic review and commentary. Intensive Care Med. 39(1):16-30, 2013
24 Allison MG et al: Alcoholic metabolic emergencies. Emerg Med Clin North Am. 32(2):293-301, 2014
25 Bird RD et al: Alcohol withdrawal: what is the benzodiazepine of choice? Ann Pharmacother. 28(1):67-71, 1994
26 American Psychiatric Association: Delirium, diagnostic criteria. In: Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013:596-601
27 Wartenberg AA: Management of alcohol intoxication and withdrawal. In: Ries RK et al, eds: The ASAM Principles of Addiction Medicine. 5th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:635-51
28 Galameau DW et al: Benzodiazepine intoxication and withdrawal: assessment and management. Hosp Med Clin. 4(4):513-25, 2015
29 McKeon A et al: The alcohol withdrawal syndrome. J Neurol Neurosurg Psychiatry. 79(8):854-62, 2008
30 Ross JC et al: Acute intrathecal baclofen withdrawal: a brief review of treatment options. Neurocrit Care. 14(1):103-8, 2011
31 McMicken DB: Alcohol withdrawal syndromes. Emerg Med Clin North Am. 8(4):805-19, 1990
32 Ciccarone D: Stimulant abuse: pharmacology, cocaine, methamphetamine, treatment, attempts at pharmacotherapy. Prim Care. 38(1):41-58, v-vi, 2011
33 Schneider P et al: A case of mistaken identity: alcohol withdrawal, schizophrenia, or central pontine myelinolysis? Neuropsychiatr Dis Treat. 8:49-54, 2012
34 American Psychiatric Association: Schizophrenia. In: Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013:99-105
35 Davies H et al: Listeria meningoencephalitis masked by alcohol withdrawal. J R Soc Med. 92(4):196-7, 1999
36 Devereaux D et al: Hyperthyroidism and thyrotoxicosis. Emerg Med Clin North Am. 32(2):277-92, 2014
37 Amato L et al: Efficacy and safety of pharmacological interventions for the treatment of the alcohol withdrawal syndrome. Cochrane Database Syst Rev. CD008537, 2011
38 Jawa RS et al: Alcohol withdrawal syndrome in admitted trauma patients. Am J Surg. 208(5):781-7, 2014
39 Jung ME et al: Alcohol withdrawal and brain injuries: beyond classical mechanisms. Molecules. 15(7):4984-5011, 2010
40 Marra A et al: Intensive care unit delirium and intensive care unit-related posttraumatic stress disorder. Surg Clin North Am. 97(6):1215-35, 2017
41 Setters B et al: Delirium. Prim Care. 44(3):541-59, 2017
42 Stephens JR et al: Who needs inpatient detox? Development and implementation of a hospitalist protocol for the evaluation of patients for alcohol detoxification. J Gen Intern Med. 29(4):587-93, 2014
43 Guglielmo R et al: Pharmacological treatments in alcohol use disorders: state of art and new perspectives. Clin Ter. 166(6):262-70, 2015
44 Daeppen JB et al: Symptom-triggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal: a randomized treatment trial. Arch Intern Med. 162(10):1117-21, 2002
45 New York-Presbyterian Hospital: Alcohol Withdrawal (AWD) Symptom-triggered Therapy Guidelines (Pilot) for Medical Patients (NYP/CU: Emergency Department, Medical ICU/A and B, 6GN/S, and 7GS). Columbia University Medical Center website. Issued June 2009. Reviewed May 2010. Approved May 2012. Accessed September 14, 2018. http://www.hospitalist.cumc.columbia.edu/downloads/clinical%20references/Alcohol_Withdrawal_-Guideline_Adult_.pdf
46 Monte-Secades R et al: Inpatient alcohol withdrawal syndrome. Rev Clin Esp. 215(2):107-16, 2015
47 Rosenson J et al: Phenobarbital for acute alcohol withdrawal: a prospective randomized double-blind placebo-controlled study. J Emerg Med. 44(3):592-8.e2, 2013
48 Mayo-Smith MF: Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA. 278(2):144-51, 1997
49 Minozzi S et al: Anticonvulsants for alcohol withdrawal. Cochrane Database Syst Rev. CD005064, 2010
50 Mee-Lee D: Understanding and Utilizing ASAM Placement Criteria. National Association for Alcoholism and Drug Abuse Counselors website. Published March 14, 2012. Accessed September 14, 2018. https://www.naadac.org/assets/1959/2012-03-14_understanding_and_utilizing_asam_webinarslides.pdf
51 Alcoholics Anonymous website. Accessed September 14, 2018. https://www.aa.org/
52 National Council on Alcoholism and Drug Dependence (NCADD) website. Accessed September 14, 2018. https://www.ncadd.org/
53 National Institute on Alcohol Abuse and Alcoholism (NIAAA) website. Accessed September 14, 2018. https://www.niaaa.nih.gov/
54 Substance Abuse and Mental Health Services Administration: National Recovery Month. SAMHSA website. Accessed September 14, 2018. https://www.recoverymonth.gov/
55 Substance Abuse and Mental Health Services Administration (SAMHSA) website. Accessed September 14, 2018. https://www.samhsa.gov/
56 Shah P et al: Adjunctive use of ketamine for benzodiazepine-resistant severe alcohol withdrawal: a retrospective evaluation. J Med Toxicol. 14(3):229-36, 2018
57 Mo Y et al: Barbiturates for the treatment of alcohol withdrawal syndrome: a systematic review of clinical trials. J Crit Care. 32:101-7, 2016
58 Hendey GW et al: A prospective, randomized, trial of phenobarbital versus benzodiazepines for acute alcohol withdrawal. Am J Emerg Med. 29(4):382-5, 2011
59 Erstad BL et al: Management of alcohol withdrawal. Am J Health Syst Pharm. 52(7):697-709, 1995
60 Hughes JR: Alcohol withdrawal seizures. Epilepsy Behav. 15(2):92-7, 2009
61 Brotherton AL et al: Propofol for treatment of refractory alcohol withdrawal syndrome: a review of the literature. Pharmacotherapy. 36(4):433-42, 2016
62 Muzyk AJ et al: Dexmedetomidine for the treatment of alcohol withdrawal syndrome: rationale and current status of research. CNS Drugs. 27(11):913-20, 2013
63 Muzyk AJ et al: Role of α2-agonists in the treatment of acute alcohol withdrawal. Ann Pharmacother. 45(5):649-57, 2011
64 Linn DD et al: Dexmedetomidine for alcohol withdrawal syndrome. Ann Pharmacother. 49(12):1336-42, 2015

Published September 14, 2018

65 Mueller SW et al: A randomized, double-blind, placebo-controlled dose range study of dexmedetomidine as adjunctive therapy for alcohol withdrawal. Crit Care Med. 42(5):1131-9, 2014
66 Wong A et al: Evaluation of adjunctive ketamine to benzodiazepines for management of alcohol withdrawal syndrome. Ann Pharmacother. 49(1):14-9, 2015
67 Pizon AF et al: Adjunct ketamine use in the management of severe ethanol withdrawal. Crit Care Med. 46(8):e768-71, 2018
68 Barrons R et al: The role of carbamazepine and oxcarbazepine in alcohol withdrawal syndrome. J Clin Pharm Ther. 35(2):153-67, 2010
69 Malcolm R et al: The effects of carbamazepine and lorazepam on single versus multiple previous alcohol withdrawals in an outpatient randomized trial. J Gen Intern Med. 17(5):349-55, 2002
70 Schik G et al: Oxcarbazepine versus carbamazepine in the treatment of alcohol withdrawal. Addict Biol. 10(3):283-8, 2005
71 Lum E et al: Valproic acid management of acute alcohol withdrawal. Ann Pharmacother. 40(3):441-8, 2006
72 Drug Enforcement Administration, Office of Diversion Control, Drug & Chemical Evaluation Section: Gabapentin (Neurontin). US Department of Justice website. Published March 2018. Accessed September 14, 2018. https://www.deadiversion.usdoj.gov/drug_chem_info/gabapentin.pdf
73 Smith RV et al: Gabapentin misuse, abuse and diversion: a systematic review. Addiction. 111(7):1160-74, 2016
74 Latt N et al: Thiamine in the treatment of Wernicke encephalopathy in patients with alcohol use disorders. Intern Med J. 44(9):911-5, 2014
75 Lingford-Hughes AR et al: BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. J Psychopharmacol. 26(7):899-952, 2012
76 Bhat A et al: The management of alcohol withdrawal in pregnancy--case report, literature review and preliminary recommendations. Gen Hosp Psychiatry. 37(3):273.e1-3, 2015
77 Trevisan LA et al: Complications of alcohol withdrawal: pathophysiological insights. Alcohol Health Res World. 22(1):61-6, 1998
78 Monte R et al: Risk factors for delirium tremens in patients with alcohol withdrawal syndrome in a hospital setting. Eur J Intern Med. 20(7):690-4, 2009
79 Maldonado JR 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. 48(4):375-90, 2014
80 Heilig M et al: Acute withdrawal, protracted abstinence and negative affect in alcoholism: are they linked? Addict Biol. 15(2):169-84, 2010

Published September 14, 2018