Annals of Pharmacotherapy
2016, Vol. 50(5) 389–401

DOI: 10.1177/1060028016629161
aop.sagepub.com
SAGE

Treatment of Severe Alcohol Withdrawal

Kyle J. Schmidt, PharmD[1], Mitesh R. Doshi, PharmD[2], Jenna M. Holzhausen, PharmD, BCPS[3], Allycia Natavio, PharmD[3], Megan Cadiz, PharmD[3], and Jim E. Winegardner, PharmD, BCPS, BCCCP[3]

Abstract

Objective: Approximately 50% of patients with alcohol dependence experience alcohol withdrawal. Severe alcohol withdrawal is characterized by seizures and/or delirium tremens, often refractory to standard doses of benzodiazepines, and requires aggressive treatment. This review aims to summarize the literature pertaining to the pharmacotherapy of severe alcohol withdrawal. **Data Sources:** PubMed (January 1960 to October 2015) was searched using the search terms *alcohol withdrawal, delirium tremens, intensive care*, and *refractory*. Supplemental references were generated through review of identified literature citations. **Study Selection and Data Extraction:** Available English language articles assessing pharmacotherapy options for adult patients with severe alcohol withdrawal were included. **Data Synthesis:** A PubMed search yielded 739 articles for evaluation, of which 27 were included. The number of randomized controlled trials was limited, so many of these are retrospective analyses and case reports. Benzodiazepines remain the treatment of choice, with diazepam having the most favorable pharmacokinetic profile. Protocolized escalation of benzodiazepines as an alternative to a symptom-triggered approach may decrease the need for mechanical ventilation and intensive care unit (ICU) length of stay. Propofol is appropriate for patients refractory to benzodiazepines; however, the roles of phenobarbital, dexmedetomidine, and ketamine remain unclear. **Conclusions:** Severe alcohol withdrawal is not clearly defined, and limited data regarding management are available. Protocolized administration of benzodiazepines, in combination with phenobarbital, may reduce the need for mechanical ventilation and lead to shorter ICU stays. Propofol is a viable alternative for patients refractory to benzodiazepines; however, the role of other agents remains unclear. Randomized, prospective studies are needed to clearly define effective treatment strategies.

Keywords

severe, refractory, alcohol withdrawal, delirium tremens, benzodiazepine, critical care, intensive care, phenobarbital, propofol, dexmedetomidine

Introduction

There are an estimated 136.9 million people older than 12 years in the United States who are reported to be current users of alcohol, according to the 2013 National Survey on Drug Use and Health.[1] More than 8 million people are affected by alcohol dependence in the United States on an annual basis, with approximately 50% of these patients experiencing symptoms of alcohol withdrawal when alcohol intake is either reduced or discontinued.[2,3] Diagnostic criteria and related signs and symptoms for alcohol withdrawal as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) are listed in Table 1.[4] To be classified as alcohol withdrawal, these signs and symptoms must result in clinically significant distress or impairment in normal daily functions that cannot be attributable to any other medical conditions.[4]

Most patients experiencing alcohol withdrawal have mild symptoms and can be effectively managed as an outpatient. However, approximately 5% of these patients will present with severe alcohol withdrawal, potentially including seizures and/or delirium tremens (DT).[3] A consistent definition of severe alcohol withdrawal in the literature is lacking. Some studies have used a combination of elevated Clinical Institute Withdrawal Assessment (CIWA) scores and symptoms refractory to high doses of benzodiazepines (8 mg lorazepam within 6 hours or ≥40 mg diazepam in 1

[1]Spectrum Health Butterworth Hospital, Grand Rapids, MI, USA
[2]St John Hospital and Medical Center, Grosse Pointe, MI, USA
[3]Beaumont Hospital, Royal Oak, MI, USA

Corresponding Author:
Kyle J. Schmidt, Department of Pharmacy, Spectrum Health Butterworth Hospital, 100 Michigan St, NE MC001, Grand Rapids, MI 49503, USA.
Email: kyle.schmidt@spectrumhealth.org

Table 1. *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) Diagnostic Criteria for Alcohol Withdrawal.

A.	Cessation of (or reduction in) alcohol use that has been heavy and prolonged
B.	Two (or more) of the following, developing within several hours to a few days after criterion A
	1. Autonomic hyperactivity
	2. Increased hand tremor
	3. Insomnia
	4. Nausea or vomiting
	5. Transient visual, tactile, or auditory hallucinations or illusions
	6. Psychomotor agitation
	7. Anxiety
	8. Generalized tonic-clonic seizures

hour) to define severe alcohol withdrawal.[5-8] Whereas the management of uncomplicated or mild to moderate alcohol withdrawal is well established, management of severe alcohol withdrawal is less clear. The objective of this review article is to summarize the current literature regarding the management of severe alcohol withdrawal.

Data Sources and Selection

A PubMed search was conducted to identify relevant articles in the management of severe alcohol withdrawal. This search was limited to available articles published in English from January 1960 through October 2015. The search used a combination of the following search terms: *alcohol withdrawal, delirium tremens, intensive care*, and *refractory*. Articles describing the management of severe alcohol withdrawal in adult patients were included. The initial search yielded 739 articles, which were evaluated for inclusion by 2 independent reviewers. References from identified articles were examined to identify additional appropriate articles for inclusion. A total of 27 articles, which are summarized in the appendix, were selected through consensus decision for inclusion.

Pathophysiology

Alcohol's inhibitory effects in the brain are primarily achieved via the neurotransmitter γ-aminobutyric acid (GABA). Three different types of GABA receptors have been identified ($GABA_A$, $GABA_B$, and $GABA_C$), the most prominent of which is $GABA_A$. Stimulation of the ligand-gated $GABA_A$ receptor produces membrane hyperpolarization by enhancing chloride ion influx, resulting in a global slowing of neurotransmission, manifesting as anxiolysis, sedation, and anticonvulsant activity. Several pharmacological agents target the $GABA_A$ receptor to elicit these actions, including benzodiazepines, barbiturates, and propofol. Acute alcohol ingestion causes an increased release of the GABA neurotransmitter and enhances the sensitivity of $GABA_A$ receptor subtypes, resulting in an overall increase of inhibitory neurotransmission.[9,10]

In addition to the direct stimulation of the $GABA_A$ receptors, alcohol also produces physiological changes in excitatory neurotransmission. Alcohol competitively inhibits the binding of glycine to the *N*-methyl-D-aspartate (NMDA) receptors in the brain, consequently preventing the action of the major excitatory neurotransmitter glutamate on the NMDA receptors.[9]

The human brain undergoes functional adaptations that eventually result in tolerance in the presence of chronic alcohol ingestion. To compensate for the persistent inhibition of glycine binding to NMDA receptors, there is a progressively higher expression of excitatory NMDA receptors and a compensatory downregulation of $GABA_A$ receptors. This compensation gives rise to tolerance and a resultant need for higher blood levels of alcohol to produce the same effect.[9,10] Provided the presence of alcohol is constant, the balance in excitatory and inhibitory actions is sustained. Elimination of alcohol from the body exposes the inappropriately upregulated glutamate neurotransmission and suppressed GABA activity, resulting in the clinical manifestations of alcohol withdrawal.

Clinical Manifestations

Symptoms associated with alcohol withdrawal can be variable but are typically a reflection of an increase in autonomic activity and sympathetic outflow as well as psychomotor agitation.[3,4,11] Common symptoms of autonomic hyperactivity include diaphoresis, nausea, vomiting, tremor, and anxiety.

Severe alcohol withdrawal may manifest as the previously mentioned symptoms progressing to seizures and/or DT, the most severe consequence of alcohol withdrawal.[12] The diagnosis of DT is confirmed when patients present with alcohol withdrawal and delirium. Delirium is defined as a decrease in attention and awareness associated with changes in neurological status from baseline, fluctuating in severity during the day. Disturbances in attention, awareness, memory, orientation, language, visuospatial ability, and perception are common. These fluctuations occur in the absence of coma or other evolving neurocognitive disorders. Approximately 3% to 5% of patients hospitalized for alcohol withdrawal will meet clinical criteria for the diagnosis of DT.[3,4] Given the short duration of action of alcohol, symptoms may appear as early as 8 hours from a patient's last drink or as late as 72 hours, typically not lasting more than 7 days.[3,11]

Identifying patients at risk for alcohol withdrawal poses a significant challenge because a lack of consistency reported in several trials has resulted in the failure to identify reliable diagnostic criteria. The risk of development

linearly increases with the quantity and frequency of alcohol consumption but is most commonly seen in those drinking more than 8 drinks per day for multiple days.[4] Past medical or family history significant for episodes of alcohol withdrawal is the strongest predictor of future episodes.[11]

Medical Management

The main goal of treatment is to reduce the severity of symptoms and prevent progression of alcohol withdrawal to DT. Sedative hypnotics are recommended as first-line therapy for treatment in combination with supportive and adjunctive therapies.[9,11,13,14]

Supportive and Nonpharmacological Therapy

The management of alcohol withdrawal involves supportive measures to help keep patients safe while they experience withdrawal. The treatment of underlying conditions and the prevention of progressing symptoms associated with alcohol withdrawal are additional goals of therapy. Medical staff should help reorient the patient to time, place, and date; ensure adequate airway protection; and frequently monitor patients' vital signs. Patients must also be assessed for adequate hydration because volume depletion is commonly seen in these patients.[3,10]

Vitamin and Electrolyte Replenishment

Along with appropriate supportive measures, patients presenting with alcohol withdrawal must be provided with adequate nutritional support. Thiamine levels are often deficient in patients presenting with alcohol withdrawal, which can lead to the development of Wernicke's encephalopathy, typically manifesting as altered mental status, ophthalmoplegia, and ataxia. Thiamine is an important cofactor for carbohydrate metabolism. Deficiency can lead to impaired use as well as decreased absorption of glucose and should, therefore, be addressed prior to glucose administration. The daily recommended requirement of thiamine is 1 to 2 mg; however, higher doses are commonly used for rapid repletion.[15] Current literature fails to define a universally accepted regimen; however, 100 mg daily is commonly cited for prophylaxis. For acute treatment of Wernicke's encephalopathy, much higher daily doses of thiamine, up to 1500 mg, are initially utilized.[15,16] Folate supplementation is recommended on the basis of findings that chronic alcohol use is associated with hyperhomocysteinemia, thought to be a result of folate deficiency.[17] Multivitamins containing the daily recommended allowance of folic acid may help replenish nutritional deficiencies associated with chronic alcohol use.

Electrolyte imbalances resulting from inadequate nutrition and hydration are frequently encountered in alcohol withdrawal. Hypokalemia can be corrected with potassium supplementation, adjusting for renal function as necessary. Although patients may present with hypomagnesemia, routine supplementation of magnesium is not recommended.[18] Finally, hypophosphatemia is also commonly seen in alcohol withdrawal. Given the lack of data supporting phosphate replenishment in asymptomatic, moderate hypophosphatemia (1-2 mg/dL), self-correction with proper nutrition is preferred.[18]

Benzodiazepines

The majority of effects exerted by benzodiazepines are a result of their actions on the central nervous system, most prominently sedation, hypnosis, and anticonvulsant activity. Benzodiazepines bind directly to a specific site on the $GABA_A$ receptor, distinct from where GABA binds, causing enhanced GABA-induced ionic currents through the $GABA_A$ receptor channel, augmenting the inadequate inhibitory GABA activity present in alcohol withdrawal.[9] Benzodiazepines do not have an effect on $GABA_A$ receptor function in the absence of GABA. Some available data suggest that variations in $GABA_A$ receptor subunits may influence clinical effects of benzodiazepines; however, agent selection is still primarily based on pharmacokinetic considerations.

The benzodiazepines most commonly used to treat alcohol withdrawal include lorazepam, chlordiazepoxide, oxazepam, and diazepam. Table 2 highlights key pharmacokinetic characteristics of these agents, along with general dosing for alcohol withdrawal. It should be noted that dosing of benzodiazepines in severe alcohol withdrawal is higher than doses used for sedation and anxiolysis. The role of benzodiazepines in the management of alcohol withdrawal was first established in a 1969 study that randomized more than 500 patients to 1 of 4 different medications (chlordiazepoxide, chlorpromazine, hydroxyzine, or thiamine) or placebo for the treatment of alcohol withdrawal. Patients in the chlordiazepoxide group had the lowest incidence of DT and alcohol withdrawal seizures, which led to the establishment of benzodiazepines as first-line treatment for alcohol withdrawal.[19]

Despite data suggesting an influence on clinical effects of $GABA_A$ subunit variations, benzodiazepines have been shown to be similarly efficacious in reducing the signs and symptoms of withdrawal.[9,20] The choice of agent primarily depends on available dosage forms, pharmacokinetics, patient-specific factors, and cost.[20]

Symptom-triggered benzodiazepine administration has become the standard of treatment for alcohol withdrawal in the hospital setting. The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar; Table 3), originally created to determine patient risk for severe alcohol withdrawal, consists of 10 domains assessed and scored

Table 2. CIWA-Ar Scale (Adapted From Sullivan et al[21]).

Nausea and vomiting: Ask, "Do you feel sick to your stomach? Have you vomited?" Observation 0, No nausea or vomiting 1, Mild nausea or vomiting 2 3 4, Intermittent nausea with dry heaves 5 6 7, Constant nausea, frequent dry heaves and vomiting	Tactile disturbances: Ask, "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation 0, None 1, Very mild itching, pins and needles, burning, or numbness 2, Mild itching, pins and needles, burning, or numbness 3, Moderate itching, pins and needles, burning, or numbness 4, Moderately severe hallucinations 5, Severe hallucinations 6, Extremely severe hallucinations 7, Continuous hallucinations
Tremor: Arms extended and fingers spread apart. Observation 0, No tremor 1, Not visible but can be felt fingertip to fingertip 2 3 4, Moderate, with patient's arms extended 5 6 7, Severe, even with arms not extended	Auditory disturbances: Ask, "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation 0, Not present 1, Very mild harshness or ability to frighten 2, Mild harshness or ability to frighten 3, Moderate harshness or ability to frighten 4, Moderately severe hallucinations 5, Severe hallucinations 6, Extremely severe hallucinations 7, Continuous hallucinations
Paroxysmal sweats: Observation 0, No sweat visible 1, Barely perceptible sweating, palms moist 2 3 4, Beads of sweat obvious on forehead 5 6 7, Drenching sweats	Visual disturbances: Ask, "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation 0, Not present 1, Very mild sensitivity 2, Mild sensitivity 3, Moderate sensitivity 4, Moderately severe hallucinations 5, Severe hallucinations 6, Extremely severe hallucinations 7, Continuous hallucinations
Anxiety: Ask, "Do you feel nervous?" Observation 0, No anxiety, at ease 1, Mildly anxious 2 3 4, Moderately anxious, or guarded, so anxiety is inferred 5 6 7, Equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions	Headache, fullness in head: Ask, "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity 0, Not present 1, Very mild 2, Mild 3, Moderate 4, Moderately severe 5, Severe 6, Very severe 7, Extremely severe
Agitation: Observation 0, Normal activity 1, Somewhat more than normal activity 2 3 4, Moderately fidgety and restless 5 6 7, Paces back and forth during most of the interview, or constantly thrashes around	Orientation and clouding of sensorium: Ask, "What day is this? Where are you? Who am I?" 0, Oriented and can do serial additions 1, Cannot do serial additions or is uncertain about date 2, Disoriented for date by no more than 2 calendar days 3, Disoriented for date by more than 2 calendar days 4, Disoriented for place or person
Patients with score <10 do not usually need additional medication for withdrawal	Total CIWA-Ar Score (maximum = 67): _____ Rater's initials: _____

Abbreviations: CIWA-Ar, Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised.

Table 3. Pharmacological Properties of Benzodiazepines Used in Alcohol Withdrawal.[24]

Drug	Routes of Administration	Onset of Action (minutes)	po Dosing Range	Intermittent IV Dosing Range	$t_{1/2}$ (hours)	Metabolism
Chlordiazepoxide	PO, IV, IM	Oral: 30-120	Initial: 50-100 mg; repeat as necessary, up to 300 mg per 24 hours	N/A	10 ± 3.4	Hepatic (active)
Diazepam	PO, IV, IM, rectal	IV: 2-5	10 mg, 3-4 Times during the first 24 hours; then, 5 mg, 3-4 times daily as needed	5-10 mg Every 10-15 minutes	43 ± 13	Hepatic (active)
Lorazepam	PO, IV, IM	IV: 15-20	2-4 mg Every 1 hour as needed (symptom triggered)	1-4 mg Every 5-15 minutes	14 ± 5	Hepatic (inactive)
Oxazepam	PO	120-180	15-30 mg 3-4 Times/d	N/A	8 ± 2.4	Hepatic (inactive)

Abbreviation: PO, by mouth; IV, intravenous; IM, intramuscularly.

independently to yield a possible maximum of 67 points, with scores of 20 or greater indicating severe alcohol withdrawal. The amount of medication administered is linearly related to the CIWA score.[21] Within the intensive care unit (ICU), use of the CIWA-Ar scale for guiding treatment of alcohol withdrawal may be complicated by lack of patient cooperation and/or communication as well as the presence of influential patient comorbidities such as ICU delirium.[22] Some studies performed in ICU patients have reported successful use of quicker assessments, such as the Richmond Agitation Sedation Scale (RASS), Riker Sedation Analgesia Scale, and the Minnesota Detoxification Scale, to guide treatment.[7,22,23]

Phenobarbital

Phenobarbital is a barbiturate historically used in the treatment of epilepsy. The clinical effects of phenobarbital can be attributed to its interaction with the $GABA_A$ receptor subtype in a manner distinct from GABA and benzodiazepines. Phenobarbital potentiates synaptic inhibition by the $GABA_A$ receptor by enhancing the binding of GABA to the receptor and through increasing the duration of $GABA_A$-mediated inhibitory currents. Barbiturates at high concentrations may also be GABA mimetic and directly activate the chloride channel. Each of these actions is different from that of benzodiazepines, which are known only to increase the frequency of $GABA_A$ receptor channel opening.[9,24] These pharmacological differences form the basis of utilizing phenobarbital in combination with benzodiazepines for synergistic effects. Weight-based and fixed doses ranging from 65 to 260 mg of phenobarbital intravenously have been reported in the literature.[7,22,25-27] The onset of action of intravenously administered phenobarbital is 5 minutes, achieving maximal effect within 30 minutes. Despite a long elimination half-life (53-140 hours), the duration of action is approximately 4 to 10 hours.[16]

Evidence supporting the use of phenobarbital in the treatment of alcohol withdrawal is limited.[7,22,25-27] A retrospective review of patients admitted with DT evaluated differences in outcomes between patients treated with diazepam or phenobarbital. The authors concluded that phenobarbital was a safe, possibly more efficient, alternative to diazepam. There was no difference in the primary outcomes of DT duration or length of stay and no significant difference in safety outcomes.[25] One prospective study performed in the emergency department found that administration of a 1-time IV dose of 10 mg/kg phenobarbital in addition to symptom-triggered therapy, compared with symptom-triggered therapy alone, resulted in significantly fewer ICU admissions for alcohol withdrawal.[26] Many of the patients included presented with either an altered level of consciousness (58% in the phenobarbital arm, 68% in the placebo arm) and/or auditory/visual disturbances (40% in the phenobarbital arm, 41% in the placebo arm). Two recent studies have described utilizing phenobarbital as part of a protocolized approach in the treatment of alcohol withdrawal within the ICU and will be discussed in detail later in this review.[7,22]

Propofol

Propofol works as an agonist at the $GABA_A$ receptor within the central nervous system, causing hyperpolarization of neurons.[9] Hyperpolarization limits the ability for neuronal firing and produces sedation and anxiolysis. In addition,

propofol also inhibits the NMDA glutamate receptors, which may provide additional benefit in patients treated for alcohol withdrawal.[28]

Propofol use in alcohol withdrawal has been primarily reserved for severe withdrawal refractory to benzodiazepine therapy, in patients requiring mechanical ventilation. Several case reports, cohort analyses, and retrospective reviews have described the successful use of propofol in patients with refractory DT.[29-33] Although effective, propofol addition to escalating doses of benzodiazepines compared with benzodiazepines alone was reported to increase hospital and ICU length of stay, increase the need for mechanical ventilation, and lead to more complicated hospital stays in one review.[8] In contrast, Sohraby et al[34] retrospectively evaluated the effects of benzodiazepine monotherapy versus propofol-containing regimens in patients requiring mechanical intubation for alcohol withdrawal symptoms. No difference was noted in terms of days of withdrawal symptoms, length of stay, or mechanical ventilation. They concluded that propofol-containing regimens appear to be safe and effective for patients not able to be adequately managed with benzodiazepines alone and should be considered for patients in alcohol withdrawal who fail benzodiazepine therapy and require mechanical ventilation.[34]

Dexmedetomidine

Dexmedetomidine (DEX) is a centrally acting α_2 adrenergic receptor agonist, similar to clonidine, which activates receptors in the medullary vasomotor center, leading to a decrease in norepinephrine synthesis and sympathetic outflow. Clinical effects seen with DEX include sedation, anxiolysis, analgesia, and sympatholysis. Specificity for the α_2 receptor versus α_1 is much higher than that of clonidine (1600:1 vs 200:1), resulting in different clinical effects.[35] In addition, DEX also increases parasympathetic tone, allowing increased firing of inhibitory neurons.[35] Compared with other agents used to treat alcohol withdrawal, DEX does appear to have the advantage of an apparent lower incidence of respiratory depression. Delirium incidence was initially thought to be lower with DEX compared with benzodiazepines, but recent literature has suggested conflicting evidence, citing a potentially higher rate of delirium.[36-39] DEX lacks the GABA receptor activity required to prevent withdrawal-related seizures, making it an inappropriate option for monotherapy in severe alcohol withdrawal. The Food and Drug Administration–approved administration is through continuous infusion of 0.2 to 0.7 µg/kg/h titrated to desired effect; however, higher doses have been reported in the literature.[37,38,40]

Multiple case reports and series have been published, highlighting successful use of DEX in alcohol withdrawal patients.[41-45] Most patients were experiencing refractory severe withdrawal despite standard therapy, and the addition of DEX to standard therapy resulted in clinical improvement. As a result of this, several retrospective analyses have been performed to evaluate the effects addition of DEX had in patients with alcohol withdrawal.[5,46-51] DEX is consistently reported to lower benzodiazepine requirements and blunt autonomic hyperactivity associated with alcohol withdrawal when compared with benzodiazepine monotherapy. Crispo et al[49] evaluated nonintubated patients with severe alcohol withdrawal being treated with standard medical therapy plus continuous infusion of sedatives (benzodiazepines vs DEX). Consistent with other reports, DEX appeared to lower benzodiazepine requirements as well as requirements for olanzapine administration. There was no difference in the composite end point of respiratory distress requiring intubation and alcohol withdrawal–related seizures. However, 1 of the 28 patients in the DEX group did experience a seizure compared with none of the 33 patients in the benzodiazepine group. There was a higher cost associated with DEX use comparatively. Given the small number of patients in the trial (61 in total), the authors concluded that the protective effect of DEX could not be excluded; however, they did find a significantly higher cost and rate of adverse drug events with DEX use, necessitating caution when using DEX adjunctively.[49] These results are further bolstered by 2 other retrospective reviews that compared addition of DEX with addition of propofol or benzodiazepine infusions to patients unable to be adequately treated with standard benzodiazepine therapy.[50,51] Each review was designed to include patients experiencing severe alcohol withdrawal requiring continuous intravenous sedation. DEX was reported to be associated with decreased use of mechanical ventilation, suggesting a potential benefit of utilizing DEX later in the treatment strategy rather than earlier.[50,51]

Choice of Therapy

Despite several controlled trials evaluating other medications, benzodiazepines remain the first-line agents for severe alcohol withdrawal treatment because they are known to prevent both withdrawal and withdrawal-related seizures. When selecting a benzodiazepine, consideration should be given to several key pharmacokinetic differences among agents. An ideal agent for alcohol withdrawal would possess a quick onset of action for management of acute agitation episodes while also possessing a long serum half-life to allow longer control of agitation and easier titration off the medications. Comparing the 2 most widely used benzodiazepines, diazepam and lorazepam, diazepam exhibits a significantly shorter onset of action, allowing a quicker determination of therapy response and more frequent dose titration.[52] The longer serum half-life of diazepam also confers benefit by allowing an easier downward titration. Caution should be exercised in patients with

significant renal dysfunction because the active metabolite of diazepam is primarily renally cleared. In the setting of hepatic dysfunction, a common comorbidity in patients experiencing alcohol withdrawal, the duration of action of both lorazepam and diazepam can be significantly prolonged.[16,52]

Phenobarbital in alcohol withdrawal is an attractive option to achieve synergistic effects when given with benzodiazepines.[9] Given the paucity of data describing monotherapy with phenobarbital for alcohol withdrawal, it should be reserved for patients deemed to be refractory to benzodiazepine therapy (doses of >150 mg diazepam or approximately >30 mg lorazepam).[7,16,22,25-27]

Propofol appears to be safe and effective for use in mechanically ventilated alcohol withdrawal patients refractory to benzodiazepines.[29-34] Compared with a benzodiazepine infusion, the quicker onset and offset of propofol allows more frequent neurological assessments.[16,52] Inhibition of NMDA by propofol may provide an additional reason for the observed efficacy in treatment of severe alcohol withdrawal.

DEX appears to be an effective adjunctive agent for the treatment of alcohol withdrawal syndrome and has been successfully used in patients with severe refractory withdrawal in combination with other medications. The available literature suggests a potential benzodiazepine-sparing effect of DEX when used adjunctively to treat severe alcohol withdrawal.[5,41-51] In addition, an apparent lower effect on the respiratory drive by DEX may be of potential benefit in decreasing the need for mechanical ventilation. Emphasis should be placed on adjunctive use because DEX does not exert any action on GABA neurotransmission. Therefore, monotherapy would inappropriately expose patients to a higher risk for alcohol withdrawal seizures.

Ketamine, an NMDA antagonist, has largely remained unstudied for the treatment of severe alcohol withdrawal. One retrospective review did report safe use of ketamine infusion in patients resistant to benzodiazepine therapy, with a trend toward lower benzodiazepine use. However, the place in therapy of ketamine remains undetermined given the lack of data showing significant efficacy.[53]

Protocolized Dose Escalation Strategy

Benzodiazepines are the standard treatment modality for alcohol withdrawal, but the manner in which they are administered varies. Historically, fixed-schedule dosing was used and resulted in predetermined amounts of benzodiazepines being administered over 3 to 5 days.[54,55] Use of a fixed-schedule regimen did not allow individualization of the amount of medication being administered, regardless of the severity and the amount of medication needed to control symptoms. Symptom-triggered dosing of benzodiazepines, compared with fixed-schedule dosing, allows for individualization and has been shown to result in a shorter duration of treatment and less benzodiazepine use in multiple randomized controlled trials.[54] The use of symptom-triggered therapy, in particular the CIWA-Ar protocol, has yet to be validated in the ICU and may be inappropriate in patients requiring intensive care for severe alcohol withdrawal refractory to increasing doses of benzodiazepines.

In 2007, Gold et al[7] published the results of a retrospective cohort study of 95 patients admitted to the medical ICU for alcohol withdrawal, DT, and alcoholic hallucinosis. The vast majority (98%) of these patients met the DSM-IV criteria for DT. Patients treated with standard of care at the time were compared with those treated according to a protocolized approach featuring escalating doses of diazepam and titration of phenobarbital according to the Riker Sedation Analgesia Scale (goal 3-4), similar in concept to a successful diazepam-loading strategy described by Wasilewski and colleagues.[56] Figure 1 outlines the protocol used in the study. Data were collected on patients treated for alcohol withdrawal prior to implementation of the protocol and compared with data from patients treated after the protocol was implemented. Mechanical ventilation use was significantly less in the post-protocol implementation compared with preprotocol (21.9% vs 47.3%, $P = 0.008$). Protocol implementation was also associated with a nonsignificant decrease in ICU length of stay and nosocomial complications. The major limitation of this study was the lack of a prospective design.

A recent retrospective pre-post trial reported similar findings in patients, suggesting a true benefit to the protocolized approach.[22] Duby et al[22] evaluated 135 patients admitted to the ICU with alcohol withdrawal (CIWA-Ar score of 8-20), regardless of ICU admission diagnosis. Patients in the preintervention group were treated in a non-protocolized fashion, whereas patients in the postintervention group were treated according to a protocol similar to that of Gold et al.[7] Duby et al escalated the benzodiazepine dose based on level of sedation, with a goal RASS score of 0 to −2. Patients were reassessed every 15 minutes until an effective dose was identified, which was continued as needed to maintain adequate sedation. If individual doses greater than 120 mg of diazepam were required, phenobarbital was added in a similar escalating fashion. The primary outcome—namely, ICU length of stay—was found to be significantly lower in the postintervention period compared with the preintervention period (5.2 days vs 9.6 days, respectively, $P = 0.0004$). Similar to Gold et al,[7] a significant reduction in mean days on the ventilator and rate of intubation was also observed.

In summary, a protocolized approach using escalating doses of diazepam and additional phenobarbital use when large doses of diazepam are being administered may lead to lower rates of mechanical ventilation and ICU length of stay in patients presenting to the ICU with severe alcohol withdrawal.

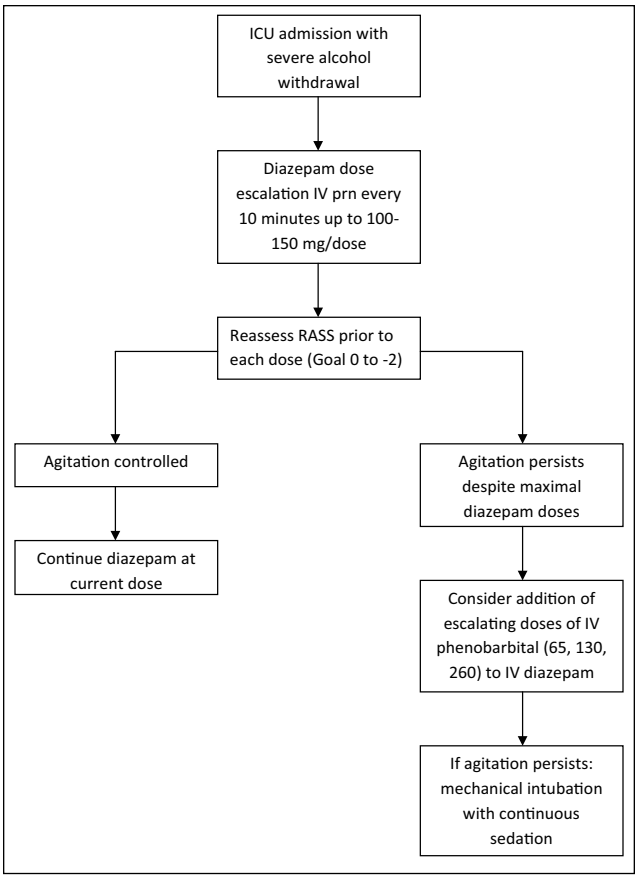

Figure 1. Overview of symptom-triggered, dose escalation protocol.

Conclusion

Severe alcohol withdrawal presents a unique set of problems, including the lack of a standardized definition and limited available literature to guide management. Despite evidence supporting the use of several other medications, benzodiazepines remain the mainstay for treatment of alcohol withdrawal. Diazepam possesses favorable pharmacokinetic characteristics that make it the best-suited available benzodiazepine for the treatment of severe alcohol withdrawal agitation and DT. The manner in which benzodiazepines are administered continues to evolve. Use of a protocolized benzodiazepine escalation approach in combination with phenobarbital appears to reduce the need for mechanical ventilation and may lead to shorter ICU stays. In patients with alcohol withdrawal refractory to benzodiazepines and requiring mechanical ventilation, propofol is an appropriate alternative. The role of DEX remains unclear but could play an adjunctive role in severe alcohol withdrawal by reducing benzodiazepine requirements and potentially decreasing the need for mechanical ventilation. The lack of randomized prospective studies limits the validity of this strategy and should be the target of future trials.

Appendix

Summary of Articles Identified for Inclusion in the Review.

First Author (year)	Sample Size and Population	Design	Treatment Arm(s)	Outcomes	Results
Baddigam et al (2005)[41]	n = 3; Postcardiothoracic surgery patients experiencing withdrawal behavior	Case series	DEX infusion	N/A	DEX infusion effectively treated withdrawal symptoms in 3 postoperative patients regardless of the agent patients were withdrawing from
Coomes and Smith (1997)[29]	n = 1; 42-Year-old man with history of alcohol withdrawal and DT presented with seizure	Case report	Propofol bolus and continuous infusion	N/A	100 mg Bolus of propofol followed by continuous infusion controlled agitation in patient experiencing seizures and DT refractory to high-dose BZD therapy
Crispo et al (2014)[49]	n = 61; Nonintubated, AWS patients who received infusion of BZD or DEX for severe AWS	Retrospective cohort study	Continuous infusion lorazepam/midazolam versus continuous infusion DEX	Composite of endotracheal intubation and seizure	No significant difference in primary outcome (BZD 9.1% vs DEX 7.1%), $P > 0.99$; DEX associated with higher cost and more adverse effects
Darrouj et al (2008)[43]	n = 1; 30-Year-old man admitted for altered mental status and agitation	Case report	DEX infusion monotherapy	N/A	Treated in the ICU with BZD (oxazepam, lorazepam, midazolam) with a poor response. DEX titrated to 0.7 µg/kg/h resulted in alleviation of alcohol-related agitation

(continued)

Appendix (continued)

First Author (year)	Sample Size and Population	Design	Treatment Arm(s)	Outcomes	Results
DeCarolis et al (2007)[23]	n = 36; Patients admitted to medical ICU for primary diagnosis of severe AWD	Retrospective observational	Symptom-driven BZD protocol (MINDS) versus nonprotocolized BZD infusion	Time to reach symptom control, total BZD dose, duration of BZD infusion, LOS	Significantly lower time to symptom control (symptom-driven 7.7 ± 4.9 hours vs nonprotocol 19.4 ± 9.7 hours; $P = 0.002$). Cumulative BZD dose and duration of BZD infusion were significantly lower with symptom-driven protocol. ICU and hospital LOS were not significantly different
Duby et al (2014)[22]	n = 135; AWS patients admitted to the ICU	Retrospective, pre-post study	Nonprotocolized BZD versus symptom-triggered, protocolized dose escalation of diazepam and phenobarbital	ICU LOS, BZD use, MV use	ICU LOS was significantly lower with protocolized delivery (5.2 ± 6.4 days vs 9.6 ± 10.5 days, $P = 0.0004$); significantly fewer intubations for AWS with protocolized delivery (5% vs 22%, $P < 0.001$). Protocolized delivery resulted in significantly less time on the ventilator, more ventilator-free days, less need for continuous sedation, and shorter duration of sedation
Frazee et al (2014)[48]	n = 33; Critically ill adults with primary diagnosis of AWS	Retrospective case series	DEX infusion	BZD requirements, changes in vital signs	DEX significantly reduced BZD requirements by median of 20 mg lorazepam equivalents in the 12 hours after initiation compared with the 12 hours before. MAP and HR were also significantly lower in the 12 hours following DEX initiation compared with 12 hours before
Gold et al (2007)[7]	n = 54; Patients admitted to medical ICU solely for treatment of AWS	Retrospective cohort study	Nonprotocolized BZD versus symptom-triggered, protocolized dose escalation of diazepam and phenobarbital	MV use, BZD use, ICU LOS	Protocolized dose escalation associated with significant reduction in MV (22% vs 47%, $P = 0.008$). Maximum individual doses and total amount of diazepam were higher in the protocolized dose escalation period. Trends toward reduced ICU LOS and nosocomial pneumonia were noted
Hayner et al (2009)[27]	n = 1; 28-Year-old man with new-onset seizure and advanced DT	Case report	IV phenobarbital in addition to high-dose continuous infusion lorazepam (>40 mg/h)	N/A	Phenobarbital in escalating doses of 65 mg, followed by 130 mg 15 minutes later resulted in control of severe agitation
Hughes et al (2013)[32]	n = 1; 42-Year-old man presenting with alcohol withdrawal with hallucinations	Case report	Propofol infusion	N/A	CIWA scores became increasingly worse (noted up to 46) despite administration of 62 mg of lorazepam, 10 mg of diazepam, and 5 mg of haloperidol. Initiation of propofol infusion resulted in a drastic reduction in CIWA scores without the need for MV. On propofol discontinuation, the severe agitation returned
Lizotte et al (2014)[50]	n = 41; Patients with AWS who received propofol or DEX infusions in addition to standardized AWS protocol	Retrospective cohort study	Propofol continuous infusion versus DEX continuous infusion	BZD and haloperidol use, MV use, LOS	Mean BZD use and haloperidol were significantly lower in the 24-hour period following initiation of either infusion compared with the 24-hour period before. There were no significant differences between groups in BZD or haloperidol use. MV was shorter in the DEX group compared with propofol group (19.9 hours vs 97.6 hours, $P = 0.002$). There was no significant difference in ICU LOS
Lorentzen et al (2014)[33]	n = 15; Patients admitted for alcohol detoxification with DT refractory to up to 1-2 g of diazepam and/or chlordiazepoxide	Retrospective cohort study	Propofol continuous infusion for 48 hours	Clinical effects of treatment	13/15 Patients experienced prolonged sedation following discontinuation of propofol. Average propofol infusion rate of 4.22 mg/kg/h was required to maintain sedation

(continued)

Appendix (continued)

First Author (year)	Sample Size and Population	Design	Treatment Arm(s)	Outcomes	Results
Ludtke et al (2015)[51]	n = 32; Patients with diagnosis for alcohol withdrawal treated with continuous infusion of DEX, propofol, or lorazepam	Retrospective cohort study	DEX infusion versus propofol and/or lorazepam infusion	MV use, LOS	Significantly fewer patients treated with DEX required MV (13.3% vs 58.8%, $P = 0.006$). Duration of MV was not statistically different (DEX 0.95 days vs propofol/ lorazepam 4.1 days, $P = 0.264$). ICU LOS was shorter in the DEX group (2.2 days vs 4.87 days, $P = 0.016$). Hospital LOS was shorter in the DEX group (5.7 days vs 10 days, $P = 0.08$)
Mahajan et al (2010)[31]	n = 1; 32-Year-old man experiencing DT refractory to standard BZD therapy	Case report	Propofol infusion	N/A	Propofol and lorazepam continuous infusion with intermittent boluses of diazepam successfully controlled BZD-refractory DT
McCowan and Marik (2000)[30]	n = 4; Patients experiencing DT refractory to standard BZD therapy	Case series	Propofol infusion	N/A	Each patient's BZD-refractory DT was successfully managed with propofol infusion
Michaelsen et al (2010)[25]	n = 194; Patients with DT who received treatment	Retrospective cohort study	Phenobarbital 100-200 mg po or IV hourly versus diazepam 10-20 mg IV hourly	Duration of DT, LOS, mortality, rate of pneumonia	No significant difference noted for duration of DT, LOS, mortality, or rate of pneumonia
Mueller et al (2014)[6]	n = 24; Patients with CIWA-Ar score ≥15 despite ≥16 mg of lorazepam over a 4-hour period	Prospective, randomized, double-blind, placebo-controlled trial	Symptom-triggered CIWA-Ar protocol with lorazepam plus DEX 1.2 µg/kg/h, or DEX 0.4 µg/kg/h, or placebo	Lorazepam requirements, MV use, seizure, AWS symptom severity	Difference in lorazepam requirement 24 hours prior to and after study drug initiation was significantly greater in the DEX group versus placebo group (−56 vs −8 mg, $P = 0.037$). There was no difference between higher- and lower-dose DEX infusions on lorazepam requirements. There were no intubations or seizures after study drug initiation. No significant differences in CIWA-Ar or Riker scores in the first 24 hours of study drug initiation between study groups
Muzyk et al (2012)[44]	n = 5; ICU patients with AWS and no other acute concurrent medical illnesses	Case series	DEX infusion	N/A	Use of DEX infusion adjunctively with BZDs resulted in a reduced need for BZDs, concomitant agitation medications, and restraint use in 4 of the 5 patients reported
Rayner et al (2012)[47]	n = 20; ICU patients treated with DEX for BZD-refractory alcohol withdrawal	Retrospective cohort study	DEX infusion	AWS severity scores, medication doses 24 hours before and after DEX initiation	Significant reduction in mean alcohol withdrawal severity scale; BZD requirement significantly reduced by 61.5%; $P < 0.001$.
Rosenson et al (2013)[26]	n = 102; Patients presenting to the emergency department with acute AWS	Prospective, randomized, double-blind, placebo-controlled trial	Lorazepam-based alcohol withdrawal protocol plus phenobarbital 10 mg/kg IV once or placebo	Initial level of hospital admission, BZD use, LOS	Patients who received phenobarbital had a slower ICU admission rate compared with the placebo group (8% vs 25%). Continuous infusion lorazepam was used less frequently in the phenobarbital group (4% vs 31%). Total lorazepam requirements were also lower in the phenobarbital group. No differences were noted in adverse effects or LOS
Rovasalo et al (2006)[42]	n = 1; 50-Year-old man admitted for severe delirium and violent behavior	Case report	DEX infusion	N/A	Over a 48-hour period, 360 mg diazepam and 12.5 mg haloperidol failed to control agitation. DEX infusion was started in the ICU, which resulted in rapid control of the severe agitation within 2 hours

(continued)

Appendix (continued)

First Author (year)	Sample Size and Population	Design	Treatment Arm(s)	Outcomes	Results
Sohraby et al (2014)[34]	n = 64; Intubated patients admitted with AWS who received benzodiazepine or propofol infusion	Retrospective cohort study	Continuous infusion lorazepam or midazolam versus continuous infusion propofol	Time to resolution of AWS symptoms, LOS, MV use, mortality	No significant difference was noted in time to resolution of AWS symptoms. Hospital and ICU LOSs were not different. Days of MV and in-hospital mortality were not significantly different
Tolonen et al (2013)[45]	n = 18; Patients with AWD who either failed standard BZD treatment or were determined to be at risk for large amounts of BZD and haloperidol	Prospective cohort study	DEX infusion in addition to standard therapy	LOS, time to AWD resolution, MV use	Time to resolution of AWD was 3.8 days. ICU LOS was 7.1 days, with a hospital LOS of 12.1 days. None of the included patients required intubation
VanderWeide et al (2014)[5]	n = 42; Patients admitted to the ICU for >24 hours for AWS who received DEX within 60 hours of hospital admission	Retrospective cohort study	DEX infusion plus standard BZD therapy versus standard BZD therapy	BZD use, LOS, MV use	DEX use resulted in a significantly higher reduction in 12-hour pre-post BZD requirements. Hospital LOS, ICU LOS, and MV incidence were not significantly different between the 2 groups
Wasilewski et al (1996)[56]	n = 96; Patients with AWD	Prospective, randomized trial	Diazepam po 10-20 mg every 1-2 hours versus diazepam in divided doses	Psychosis duration	Psychosis duration was significantly shorter in the diazepam loading group (6.9 ± 4.8 hours vs 33.8 ± 25.7 hours, $P < 0.001$)
Wong et al (2015)[53]	n = 23; ICU patients administered ketamine for management of AWS	Retrospective cohort study	Ketamine continuous infusion	BZD use, effect on sedation scores	Nonsignificant decreases in 12- and 24-hour pre-post diazepam equivalent doses were noted (40 and 13.3 mg, respectively). No significant changes in sedation scores were noted with ketamine
Wong et al (2015)[8]	n = 66; Patients with severe alcohol withdrawal resistant to BZD therapy	Retrospective cohort study	Dose escalation of BZDs versus BZDs plus propofol	Time to AWS resolution, MV use, LOS	Significantly shorter time to resolution of AWS in BZD-only group (5 vs 7 days, $P = 0.025$); significantly longer duration of MV and higher rate of nosocomial pneumonia in the propofol group; hospital and ICU LOS significantly longer in the propofol group

Abbreviations: AWD, alcohol withdrawal delirium; AWS, alcohol withdrawal syndrome; BZD, benzodiazepine; CIWA-Ar, Clinical Institute Withdrawal Assessment, revised; DEX, dexmedetomidine; DT, delirium tremens; HR, heart rate; ICU, intensive care unit; LOS, length of stay; MAP, mean arterial pressure; MINDS, Minnesota Detoxification Scale; MV, mechanical ventilation.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Results from the 2013 national survey on drug use and health: summary of national findings. http://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.pdf. Accessed January 18, 2016.
2. Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. *N Engl J Med*. 2003;348:1786-1795.
3. Schuckit MA. Recognition and management of withdrawal delirium (delirium tremens). *N Engl J Med*. 2014;371:2109-2113.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
5. VanderWeide LA, Foster CJ, MacLaren R, Kiser TH, Fish DN, Mueller SW. Evaluation of early dexmedetomidine addition to the standard of care for severe alcohol withdrawal in the ICU: a retrospective controlled cohort study [published online October 16, 2014]. *J Intensive Care Med*. doi:10.1177/0885066614554908.
6. Mueller SW, Preslaski CR, Kiser TH, et al. A randomized, double-blind, placebo-controlled dose range study of dexmedetomidine as adjunctive therapy for alcohol withdrawal. *Crit Care Med*. 2014;42:1131-1139.

7. Gold JA, Rimal B, Nolan A, Nelson LS. A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. *Crit Care Med*. 2007;35:724-730.
8. Wong A, Benedict NJ, Lohr BR, Pizon AF, Kane-Gill SL. Management of benzodiazepine-resistant alcohol withdrawal across a healthcare system: benzodiazepine dose-escalation with or without propofol. *Drug Alcohol Depend*. 2015;154:296-299.
9. Brunton L, Chabner B, Knollmann B, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York, NY: McGraw-Hill; 2011.
10. Yip L. Ethanol. In: Nelson L, Lewin N, Howland M, Hoffman R, Goldfrank L, Fomenbaum N, eds. *Goldfrank's Toxicologic Emergencies*. 9th ed. New York, NY: McGraw-Hill; 2011. http://0-accesspharmacy.mhmedical.com.libcat.ferris.edu/content.aspx?. Accessed December 18, 2014.
11. Sarff M, Gold JA. Alcohol withdrawal syndromes in the intensive care unit. *Crit Care Med*. 2010;38:S494-S501.
12. Awissi D-K, Lebrun G, Fagnan M, Skrobik Y. Alcohol, nicotine, and iatrogenic withdrawals in the ICU. *Crit Care Med*. 2013;41:S57-S68.
13. Carlson RW, Kumar NN, Wong-Mckinstry E, et al. Alcohol withdrawal syndrome. *Crit Care Clin*. 2012;28:549-585.
14. Mayo-Smith MF, Beecher LH, Fischer TL, et al. Management of alcohol withdrawal delirium. *Arch Intern Med*. 2004;164:1405-1413.
15. Latt N, Dore G. Thiamine in the treatment of Wernicke encephalopathy in patients with alcohol use disorders. *Intern Med J*. 2014;44:911-915.
16. Lexi-Comp, Inc. (Lexi-Drugs). Lexi-Comp, Inc.; May 11, 2015.
17. Cravo ML, Glória LM, Selhub J, et al. Hyperhomocysteinemia in chronic alcoholism: correlation with folate, vitamin B-12, and vitamin B-6 status. *Am J Clin Nutr*. 1996;63:220-224.
18. Doering PL, Li R. Substance-related disorders: alcohol, nicotine, and caffeine. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York, NY: McGraw-Hill; 2011:chap 75. http://accesspharmacy.mhmedical.com/content.aspx?bookid=462&Sectionid=41100850. Accessed December 22, 2014.
19. Kaim S, Klett C, Rothfeld B. Treatment of the acute alcohol withdrawal state: a comparison of four drugs. *Am J Psychiatry*. 1969;125:1640-1646.
20. 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*. 1997;278:144-151.
21. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict*. 1989;84:1353-1357.
22. Duby JJ, Berry AJ, Ghayyem P, Wilson MD, Cocanour CS. Alcohol withdrawal syndrome in critically ill patients: Protocolized versus nonprotocolized management. *J Trauma Acute Care Surg*. 2014;77:938-943.
23. DeCarolis DD, Rice KL, Ho L, Willenbring ML, Cassaro S. Symptom-driven lorazepam protocol for treatment of severe alcohol withdrawal delirium in the intensive care unit. *Pharmacotherapy*. 2007;27:510-518.
24. Katzung B, Trevor A, eds. *Basic and Clinical Pharmacology*. 13th ed. New York, NY: McGraw-Hill; 2015.
25. Michaelsen IH, Anderson JE, Fink-Jensen A, Allerup P, Ulrichsen J. Phenobarbital versus diazepam for delirium tremens: a retrospective study. *Dan Med Bull*. 2010;57:A4169.
26. Rosenson J, Clements C, Simon B, et al. Phenobarbital for acute alcohol withdrawal: a prospective randomized double-blind placebo-controlled study. *J Emerg Med*. 2013;44:592-598.e2.
27. Hayner CE, Wuestefeld NL, Bolton PJ. Phenobarbital treatment in a patient with resistant alcohol withdrawal syndrome. *Pharmacotherapy*. 2009;29:875-878.
28. Orser BA, Bertlik M, Wang LY, MacDonald JF. Inhibition by propofol (2,6 di-isoprpylphenol) of the *N*-methyl-D-aspartate subtype of glutamate receptor in cultured hippocampal neurons. *Br J Pharmacol*. 1995;116:1761-1768.
29. Coomes TR, Smith SW. Successful use of propofol in refractory delirium tremens. *Ann Emerg Med*. 1997;30:825-828.
30. McCowan C, Marik P. Refractory delirium tremens treated with propofol: a case series. *Crit Care Med*. 2000;28:1781-1784.
31. Mahajan R, Singh R, Bansal P, Bala R. Use of propofol as adjuvant therapy in refractory delirium tremens. *Ind Psychiatry J*. 2010;19:58-59.
32. Hughes DW, Vanwert E, Lepori L, Adams BD. Propofol for benzodiazepine-refractory alcohol withdrawal in a non-mechanically ventilated patient. *Am J Emerg Med*. 2014;32:112.e3-112.e4.
33. Lorentzen K, Lauritsen AO, Bendtsen AO. Use of propofol infusion in alcohol withdrawal-induced refractory delirium tremens. *Dan Med J*. 2014;61:A4807.
34. Sohraby R, Attridge RL, Hughes DW. Use of propofol-containing versus benzodiazepine regimens for alcohol withdrawal requiring mechanical ventilation. *Ann Pharmacother*. 2014;48:456-461.
35. Gerlach AT, Murphy CV, Dasta JF. An updated focused review of dexmedetomidine in adults. *Ann Pharmacother*. 2009;43:2064-2074.
36. Skrupky LP, Drewry AM, Wessman B, et al. Clinical effectiveness of a sedation protocol minimizing benzodiazepine infusions and favoring early dexmedetomidine: a before-after study. *Crit Care*. 2015;19:136.
37. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. 2009;301:489-499.
38. Pandharipande PP, Sanders RD, Girard TD, et al. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. *Crit Care*. 2010;14:R38.
39. Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics*. 2009;50:206-217.
40. Jones GM, Murphy CV, Gerlach AT, Goodman EM, Pell LJ. High-dose dexmedetomidine for sedation in the intensive care unit: an evaluation of clinical efficacy and safety. *Ann Pharmacother*. 2011;45:740-747.

41. Baddigam K, Russo P, Russo J, Tobias J. Dexmedetomidine in the treatment of withdrawal syndromes in cardiothoracic surgery patients. *J Intensive Care Med*. 2005;20:118-123.
42. Rovasalo A, Tohmo H, Aantaa R, Kettunen E, Palojoki R. Dexmedetomidine as an adjuvant in the treatment of alcohol withdrawal delirium: a case report. *Gen Hosp Psychiatry*. 2006;28:362-363.
43. Darrouj J, Puri N, Prince E, Lomonaco A, Spevetz A, Gerber DR. Dexmedetomidine infusion as adjunctive therapy to benzodiazepines for acute alcohol withdrawal. *Ann Pharmacother*. 2008;42:1703-1705.
44. Muzyk A, Revollo J, Rivelli S. The use of dexmedetomidine in alcohol withdrawal. *J Neuropsychiatry Clin Neurosci*. 2012;24:E45-E46.
45. Tolonen J, Rossinen J, Alho H, Harjola VP. Dexmedetomidine in addition to benzodiazepine-based sedation in patients with alcohol withdrawal delirium. *Eur J Emerg Med*. 2013;20:425-427.
46. DeMuro JP, Botros DG, Wirkowski E, Hanna AF. Use of dexmedetomidine for the treatment of alcohol withdrawal syndrome in critically ill patients: a retrospective case series. *J Anesth*. 2012;26:601-605.
47. Rayner SG, Weinert CR, Peng H, Jepsen S, Broccard AF. Dexmedetomidine as adjunct treatment for severe alcohol withdrawal in the ICU. *Ann Intensive Care*. 2012;2:12.
48. Frazee EN, Personett HA, Leung JG, Nelson S, Dierkhising RA, Bauer PR. Influence of dexmedetomidine therapy on the management of severe alcohol withdrawal syndrome in critically ill patients. *J Crit Care*. 2014;29:298-302.
49. Crispo AL, Daley MJ, Pepin JL, Harford PH, Brown CVR. Comparison of clinical outcomes in nonintubated patients with severe alcohol withdrawal syndrome treated with continuous-infusion sedatives: dexmedetomidine versus benzodiazepines. *Pharmacotherapy*. 2014;34:910-917.
50. Lizotte RJ, Kappes JA, Bartel BJ, Hayes KM, Lesselyoung VL. Evaluating the effects of dexmedetomidine compared to propofol as adjunctive therapy in patients with alcohol withdrawal. *Clin Pharmacol*. 2014;6:171-177.
51. Ludtke K, Stanley K, Yount N, Gerkin R. Retrospective review of critically ill patients experiencing alcohol withdrawal: dexmedetomidine versus propofol and/or lorazepam continuous infusions. *Hosp Pharm*. 2015;50:208-213.
52. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41:278-280.
53. Wong A, Benedict NJ, Armahizer MJ, Kane-Gill SL. Evaluation of adjunctive ketamine to benzodiazepines for management of alcohol withdrawal syndrome. *Ann Pharmacother*. 2015;49:14-19.
54. Daeppen JB, Gache P, Landry U, et al. Symptom-triggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal. *Arch Intern Med*. 2002;162:1117-1121.
55. Saitz R, Mayo-Smith MF, Roberts MS, Redmond HA, Bernard DR, Calkins DR. Individualized treatment for alcohol withdrawal: a randomized double-blind controlled trial. *JAMA*. 1994;272:519-523.
56. Wasilewski D, Matsumoto H, Kur E, et al. Assessment of diazepam loading dose therapy of delirium tremens. *Alcohol Alcohol*. 1996;31:273-278.