A Complicated Course: Severe Alcohol Withdrawal with Dexmedetomidine Infusion

July 31, 2023
Duong T, Boctor N, Bourgeois JA. A Complicated Course: Severe Alcohol Withdrawal with Dexmedetomidine Infusion. PSNet [internet]. 2023.
https://psnet.ahrq.gov/web-mm/complicated-course-severe-alcohol-withdrawal-dexmedetomidine-infusion

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At the conclusion of this educational activity, participants should be able to:

- Explain why benzodiazepines are the mainstay of care for management of severe alcohol withdrawal.
- Review commonly used medications for alcohol withdrawal and the risks associated with these medications.
- Recognize the importance of standardized medication order sets especially for continuous weight-based infusions within the intensive care unit.
- Identify methods to improve physician-nursing communication, especially for high-risk medications.
- Distinguish the importance of discussing treatment for alcohol use disorder once patients are out of withdrawal.
- Articulate how to minimize clinician bias in assessment of substance use disorders.

The Case

A 65-year-old man weighing 71 kg with a past medical history of alcohol use disorder and prostate cancer presented to an emergency department (ED) 36 hours after his last alcoholic drink with signs and symptoms of alcohol withdrawal. On arrival, he was noted to be tachycardic and hypertensive. Laboratory studies revealed elevated liver-associated enzymes, hyponatremia, and hypomagnesemia. Abdominal ultrasound revealed increased echogenicity of the hepatic parenchyma consistent with diffuse hepatocellular disease, likely hepatic steatosis. The patient was placed on the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) protocol and the intensive care team was consulted. Initially, the patient was agitated and had a very high CIWA score (CIWA > 25), so he was given dexmedetomidine IV (intravenous) 0.3 mcg/kg/hr and lorazepam. The patient was admitted to an intensive care step down unit for close observation as his CIWA scores fell to 7-9. As the patient's agitation and CIWA scores improved with initial treatment, the physicians' plan (communicated by a free text order in the electronic health record) was to wean the dexmedetomidine to 0.2 mcg/kg/hr and then by 0.1 mcg/kg/hr per day until discontinued. The patient was also on valproic acid 250 mg IV q6h for mood stabilization (i.e., 14 mg/kg/24 hours, within the usual dose range, 10-20 mg/kg/24 hours), thiamine 500 mg IV every 8 hours, propranolol 20 mg IV twice daily, tamsulosin, and folic acid 1 mg IV.

Two days after admission, the patient was obtunded with normal vital signs, but he had not received a dose of lorazepam for approximately 48 hours. Medical record review revealed that he had been titrated upward to dexmedetomidine IV 0.6 mcg/kg/hr (for unclear reasons) and maintained on that increased dose for about four hours. Supplemental oxygen by nasal cannula was started at 5 L/minute; mechanical ventilation was not necessary. He remained somnolent for two subsequent days, during which time he developed aspiration pneumonia. Following the completion of antibiotics for pneumonia, he was diagnosed with *Clostridioides difficile* colitis, which further prolonged his hospital stay and strained relationships among the patient's family, the nursing staff and medical team.

The Commentary

by Theresa Duong, MD, Noelle Boctor, MD, and James Bourgeois, OD, MD

Background

This case describes a 65-year-old man with alcohol use disorder who presented to a hospital 36 hours after his last alcoholic drink and was found to be in severe alcohol withdrawal. The patient's Clinical Institute Withdrawal Assessment (CIWA) score was very high, indicating signs and symptoms of severe alcohol withdrawal. Upon presentation, the patient was evaluated by the intensivist team who recommended admission to the intensive care step down unit. He was treated with symptom-triggered dosing of benzodiazepines utilizing the CIWA protocol and dexmedetomidine continuous infusion. The treating team had planned to wean the infusion by 0.1 mcg/kg/hr daily from the initial dose of 0.3 mcg/kg/hr. However, the following day, the patient was noted to be obtunded on dexmedetomidine IV infusion at 0.6 mcg/kg/hr, which is a high dose used for ICU (Intensive Care Unit) sedation.[1,2] Although dexmedetomidine was likely the main cause of his somnolence and subsequent complications, a potential contributing medication was valproic acid, which can cause hyperammonemia with delirium, including decreased level of consciousness.[3,4] Recommended treatment for hyperammonemia is to hold the offending medication and monitor ammonia levels, though carnitine can be used to more rapidly reverse hyperammonemia.

Criteria for Admission to Different Inpatient Units

The patient in this case was admitted to a stepdown unit. Stepdown units offer an intermediate level of care for patients with care needs between intensive care and what a general ward can provide. The heterogeneity of the US healthcare system leads to substantial variability in the criteria for admission to stepdown units, based on locally available resources (e.g., nurse staffing, addiction medicine expertise).[5]

Although there are no strict guidelines for level of care for patients presenting to the hospital with alcohol withdrawal, there are general guidelines from the American Society of Addiction Medicine (ASAM) based on the Clinical Institute Withdrawal Assessment-Revised scale (CIWA-Ar, see Table 1). A score of <10 is considered minimal withdrawal and can be treated in the outpatient setting.[6] A score of 10-18 indicates mild to moderate withdrawal, while a score of 19 or greater represents severe withdrawal (although some authors use lower thresholds, such as 16).[7] *Uncomplicated* severe withdrawal (i.e., without seizure, delirium and/or hallucinations) may sometimes be treated on an outpatient basis by an experienced provider.[3] However, ASAM recommends that patients with *complicated* severe alcohol withdrawal be treated in the inpatient setting for their delirium, seizures, and/or hallucinations. Risk stratification scores, such as the CIWA-Ar score and the Prediction of Alcohol Withdrawal Severity Scale (PAWSS), can be helpful in guiding clinicians as to the safest level of hospital care for the patient.[2] Given that the best single predictor of alcohol withdrawal seizures is a *previous* alcohol withdrawal seizure, a patient's prior alcohol withdrawal history, when obtainable, is also helpful.[8] Other considerations supporting ICU level of care include a history of or active evidence of delirium tremens, and the presence and severity of comorbid cardiopulmonary or renal conditions.[9] The patient in this case presented with a high CIWA score (> 25). He should have been admitted to the ICU for IV benzodiazepines with consideration of adjunctive dexmedetomidine, which requires titration and close monitoring in an ICU, as higher doses of dexmedetomidine require airway management and possibly intubation.

Table 1. The ten alcohol withdrawal symptoms of CIWA-Ar and range of scoring scale. https://sciwheel.com/work/citation?ids=3405656&pre=&suf=&sa=0&dbf=0[10]	
Nausea or vomiting (0-7)	Tactile disturbances (0-7)
Tremor (0-7)	Auditory disturbances (0-7)
Paroxysmal sweats (0-7)	Visual disturbances (0-7)
Anxiety (0-7)	Headache (0-7)
Agitation (0-7)	Orientation and clouding of sensorium (0-4)
Total score is the total sum of each item score (maximum score is 67).	

Brief Review of Pathophysiology of Alcohol Withdrawal

Alcohol disrupts two major central nervous system (CNS) pathways – (1) the inhibitory gamma-aminobutyric acid (GABA) pathway and (2) the excitatory N-Methyl-D-aspartate (NMDA glutamate) pathway. Alcohol consumption augments GABA inhibition activity on GABA receptors and blocks the excitatory action of glutamate on NMDA receptors, leading to its sedative and CNS depressant effects.[2]

Chronic exposure to alcohol causes downregulation of GABA receptors and an upregulation of NMDA receptors to maintain homeostasis. The sudden cessation or reduction of alcohol results in decreased GABA inhibitory activity and increased glutamatergic action causing autonomic overactivity and the excitatory state seen in alcohol withdrawal syndrome (AWS), such as agitation, tremors, tachycardia, hypertension, hallucinations, seizure activity, and delirium tremens.[5]

Selective Review of Medications in Severe Alcohol Withdrawal

Benzodiazepines

Benzodiazepines (BZDs) are the mainstay of therapy in AWS and are the only class of medication with proven efficacy in preventing complicated forms of AWS, such as seizures and delirium tremens.[11] BZDs stimulate GABA receptors, increasing the inhibitory effect of GABA on neuronal excitability, and thereby mimicking the neurodepressant effect of alcohol.[12,13] This mechanism reduces the incidence of alcohol-related withdrawal seizures and delirium.[6] Long-acting BZDs (e.g., diazepam, chlordiazepoxide) are metabolized by the liver; therefore, in patients with AWS with liver injury or liver dysfunction, a short acting BZD (e.g., lorazepam) is preferred.[12] Studies have shown that the use of a continuous infusion of lorazepam (which is metabolized via a pathway in the liver that does *not* produce active metabolites) following a symptom-based protocol does not increase the risk of severe complications including aspiration pneumonia, respiratory depression, or the need for intubation.[14] There are BZD refractory cases where the patient has a cross-tolerance to standard BZD protocol therapy. In these cases, alternative GABA agents such as propofol and phenobarbital and/or adjunctive medications with a different mechanism of action, such as dexmedetomidine, may be used.

Dexmedetomidine

Dexmedetomidine is an $alpha_2$-adrenergic agonist. It is used as a sedative in intravenous form in general anesthesia in the ICU and for monitored anesthesia care. In alcohol withdrawal syndrome, it is used off-label, including as monotherapy. ASAM recommends use of dexmedetomidine as an adjunct to benzodiazepine therapy to control autonomic hyperactivity and anxiety when these symptoms are not well controlled by optimized dosing of benzodiazepines alone.[6] Dexmedetomidine inhibits the release of norepinephrine, reducing central sympathetic output and thereby reducing autonomic hyperactivity such as tachycardia and hypertension *without* causing significant respiratory depression.[15] An important side effect of dexmedetomidine is that it frequently causes bradycardia. It is typically dosed in mcg/kg/hour, which is an unusual dosing unit that may increase the risk of medication errors.

Crispo et al. conducted a retrospective study comparing clinical outcomes in non-intubated patients with severe AWS treated with continuous infusions of short-acting BZDs versus dexmedetomidine.[13] The dexmedetomidine group showed a benzodiazepine sparing effect, demonstrating the possible benefits of using this medication in severe AWS. However, this end point should be interpreted with caution.[8]

Dexmedetomidine attenuates the hemodynamic symptoms of withdrawal that would otherwise trigger symptom-based administration of benzodiazepines. This effect may *worsen* progression of AWS, if benzodiazepines are not adequately administered. For this reason, dexmedetomidine should almost always be used as adjunctive therapy with BZDs.[13]

Propofol

Propofol is a sedative-hypnotic agent. In the ICU, it is used in patients with AWS who require mechanical ventilation, have refractory AWS but are not candidates for other adjuvant therapies, or have seizure activity or refractory delirium tremens. Propofol has predictable metabolism and ease of titration. Additionally, it acts as an agonist of a subset of GABA receptors different from those stimulated by BZDs, has NMDA antagonistic properties, and antiepileptic properties that may provide some benefit in AWS.[16] A major side effect of propofol is respiratory depression; therefore, propofol typically requires patients to be mechanically ventilated. The most common adverse effect is hypotension. Prolonged use can also cause hypertriglyceridemia and propofol-related infusion syndrome, a life-threatening condition with multiorgan failure caused by prolonged propofol exposure.[17] The typical units for propofol infusion are *mcg/kg/min* (while dexmedetomidine infusions are in *mcg/kg/hr*), which adds complexity when patients are concurrently receiving multiple infusions.

Barbiturates

Phenobarbital is a barbiturate that has been used to successfully treat alcohol withdrawal since the 1920s.[11] When phenobarbital binds to the GABA channel, it increases the duration of the channel opening, causing increased GABA effect, which can cause sedation. It also directly blocks excitatory glutamate signaling. Despite these mechanisms, which are helpful in AWS, it has a narrow therapeutic window and important side effects including hypotension, bradycardia, hypothermia and pulmonary edema.[6] Nevertheless, phenobarbital continues to be used for moderate to severe AWS, especially for patients who have contraindications to BZDs. It has also been used to augment BZD action when co-administered with a BZD, as it promotes BZD binding to the $GABA_A$ receptor.[11] In patients on high doses of BZDs or refractory to BZD treatment in the ICU, phenobarbital has been shown to decrease days on mechanical ventilation and ICU length of stay, and to improve symptom management.[11,18]

?$_2$-Agonist and ?-Blocker Use in AWS

Other medications that have been used in the treatment of AWS are alpha-2-agonists, such as clonidine, beta-blockers, and antipsychotics. These medications control autonomic hyperactivity and decrease sympathetic activation; however, they do not treat the underlying pathophysiology of AWS. They can mask the elevated adrenergic state seen in AWS and cause a false perception that these symptoms are being appropriately treated. As such, they should not be utilized alone to treat seizures or delirium related to withdrawal, but they may have an adjunctive role when agitation is not controlled by BZDs or dexmedetomidine alone.[6] Indeed, antipsychotics decrease the seizure threshold, which makes them relatively contraindicated in severe AWS, and clearly inferior to benzodiazepines for preventing seizures (e.g., relative risk [RR] 0.24, 95% confidence interval [CI] 0.07 to 0.88, in a meta-analysis of 4 studies with 633 participants).[19]

Inpatient Care for Patients with Severe Alcohol Withdrawal

Thiamine for Prevention of Wernicke's Encephalopathy

Thiamine should be provided to all patients presenting with AWS with concern for poor nutrition, malabsorption, and/or severe complications of alcohol withdrawal, and patients admitted to the ICU to treat AWS. Intravenous or intramuscular thiamine (minimum daily dose 500 mg) is the modality of choice for patients with moderate or severe alcohol withdrawal to prevent Wernicke's encephalopathy, which is characterized by delirium with amnesia, ataxia, and ophthalmoplegia. Other common deficiencies that are seen in patients with AWS are hypokalemia, hypomagnesemia, and hypophosphatemia, all of which should be repleted.[6]

Decrease Aspiration Risk in Alcohol Withdrawal

Chronic alcohol use disorder impairs the cough reflex. It also causes patients to have relatively immunocompromised systems by impaired cellular and innate immunity including pulmonary immune response.[20,21] Therefore, pneumonia is common in patients with AWS. Prevention strategies for hospital acquired pneumonia on admission vary depending on the patient's level of arousal and/or cognitive function. Swallow evaluations, aspiration precaution orders (such as oral hygiene and "elevated head of bed") are options for decreasing aspiration risk. The best supported prevention strategy in mechanically ventilated patients is oral hygiene;[22,23] for example, toothbrushing reduced the incidence of ventilator-associated pneumonia (RR 0.61, 95% CI 0.41 to 0.91) and the duration of ICU stays (mean difference -1.89 days, 95% CI -3.52 to -0.27 days), compared to oral hygiene without toothbrushing, in a recent meta-analysis.[24] Early clinical suspicion and repetitive evaluation of the high-risk patient for potential pneumonia is recommended, especially as sedating medications are titrated in patients with AWS.[20]

Systems Change Options and Quality Improvement Approach

Tools to Determine Appropriate Level of Care for Patients with AWS

Criteria for admitting patients with AWS to the ICU vary across hospitals. The Society of Critical Care Medicine created the "ICU Admission, Discharge, and Triage Guidelines," which provide a comprehensive framework for admission criteria, triaging patients to different levels of care, and discharge timing.[23] This framework can be used to create policies for institution-specific patient populations depending on the institutional resources available (size of the ICU, nursing availability etc.) Computerized clinical decision support (CDS) can help identify patients at high risk of clinical deterioration by analyzing CIWA scores and creating an interruptive alert to the admitting physician or advanced practice provider (APP). When the CIWA-Ar protocol scores are entered by nursing staff, consecutive high scores can create an alert that prompts the provider to consider ICU level of care on admission. The system requires the clinician to act on the alert to complete the workflow.

Prevention of Medication Administration Errors

Medication errors are common in the hospital setting and can cause adverse drug events.[25] Up to 33% of reported medication errors concern medication *administration* and 22% concern medication *delivery*.[25] Multiple methods have been utilized to decrease the rate of inpatient medication errors, including computerized provider order entry (CPOE), barcode identification of patients and medications, and medication reconciliation performed by pharmacists.[26]

Information from the Joint Commission hospital survey shows that citations related to infused medications typically occur because key components of orders are missing.[27] Subsequently, the Joint Commission has required institutions to have policies for continuous infusion orders that include the following: initial starting rate, incremental units by which the rate can be adjusted without a change in orders, the range for frequency of changing the infusion rate, the maximum dose, and the clinical objective endpoint for the reason for titration (such as Richmond Agitation Sedation Scale (RASS) score).[27] The creation of titration order sets should include a multidisciplinary team that includes but is not limited to APPs, nurses, physicians, and pharmacists.[28] In this case, an order that contained pre-written hold parameters for the sedating effect of dexmedetomidine and the titration frequency with dosing increments may have reduced the likelihood of the medication error that seems to have occurred.

A system-wide protocol for standardized two-person verification of high-risk intravenous medications (such as continuous infusions that are weight based) has also been shown to reduce medication errors and increase error detection.[29,30] This method can be implemented by two nurses who verify the correct dosage adjustment is being made for a medication via continuous infusion, such as dexmedetomidine.

Once a medication error is identified, institutions should consider root cause analyses (RCAs) of the error and systems-focused, non-punitive feedback programs to prevent this outcome from recurring. In this patient’s case, it may have been beneficial for the CDS system to include AWS-specific clinical parameters for interval up-titration or down-titration and a default range for safe dexmedetomidine infusion. Feedback programs can involve “working backwards” with bedside staff to identify what component(s) of the medication order set contributed to the error and require modification. Another potential educational tool is to create a realistic simulation on medication administration errors specific to the ICU setting, which would involve APPs, nurses, physicians, and pharmacy personnel. Debriefing after such simulations may provide information and perspectives to support participants’ learning and to improve system design. Clinical simulation on medication use errors in other settings has been found to be effective, relevant, and educational about critical processes.[31]

Concerns with Free Text Communication Orders

The clinician in this case used a free text order to communicate the medication titration plan. Free text communication is a type of order that providers can use to instruct nurses about how to titrate medication doses. In a retrospective analysis of six hospitals, the proportion of communication orders that contained medication information was 15-62% across patient care settings.[32] In one hospital system, the most common action in free text orders was to discontinue medications due to lack of this functionality within structured orders in the electronic health record (EHR).[33] Free text orders for medications may not be visible to pharmacists, which may lead to more medication errors reaching patients.[32]

Nursing Communication and Documentation

In this case, it is unclear why the dexmedetomidine infusion rate was not reduced according to plan. It is possible that there was a staffing change and the nurse who received the free text order did not confirm it and communicate it to other nurses. Another potential explanation is that the patient's agitation worsened overnight, and the dose was increased according to standing orders in the unit. In either case, there should have been a clear explanation in the nursing documentation of the behavior change and the change in medication dosage. The nurses should have alerted the physician staff about the change and more importantly, when the patient's level of consciousness decreased. Implementation of an electronic SBAR (situation, background, assessment, response) documentation template could have alerted the physician to the dose change and why medication weaning was impossible.

Systems of Care to Prevent Recurrent Hospitalization in Patients with Alcohol Use Disorder

Medical ICU survivors treated for AWS were found to have higher healthcare utilization in the presence of additional psychiatric comorbidity.[34] This finding emphasizes the importance of longitudinal multidisciplinary care for this patient population, including access to consultation-liaison psychiatrists, who can evaluate patients with substance use disorder for commonly comorbid psychiatric illnesses. Strong discharge planning support is needed to refer the patient to appropriate resources, such as substance abuse treatment programs, other psychiatric care when needed, social interventions and primary care follow-up for medication refills. Receiving medication treatment within the first month after an episode of AWS is associated with significantly less chance of readmission.[35] FDA approved pharmacologic treatments for alcohol use disorders include naltrexone and acamprosate.[36] When the patient is no longer in AWS, pharmacologic treatment should be discussed with the patient and prescribed if appropriate. Acamprosate or naltrexone can be initiated in-hospital once the AWS has been medically stabilized.

Clinicians also need to be attentive to the social stigma surrounding alcohol use disorder (AUD) and other substance use disorders (SUD). Stigma can cause patients to feel isolated or ashamed, and social stigma may be internalized which impacts their willingness to seek care.[37] Health care providers are also susceptible to conscious or unconscious biases from the stigma related to AUD, which may include the idea that patients with AUD have "chosen" their condition, that they have "complete control" over the AUD, and/or have "character flaws".[38] Health care providers can reduce stigma by the following: (1) explore the patient's understanding of their alcohol use, (2) use non-stigmatizing, encouraging language, (3) discuss that AUD is a common health condition, (4) discuss that effective evidence-based treatments exist, and (5) encourage patient autonomy in picking treatment options.[38]

Conclusion

Alcohol withdrawal syndrome is a serious, life-threatening condition that requires diligent medical care and thorough evaluation of the patient's risk of developing severe AWS with complications. Such patients would likely benefit from admission to the ICU. There are several medications that have are utilized to mitigate AWS, some of which are titrated continuous infusions, which require closer monitoring in the ICU. Effective physician-nursing communication is paramount to ensure accurate medication administration. Methods that have been implemented to assist this include developing and implementing order sets that give clear clinical endpoints for titration and holding parameters. Prior to discharge from the hospital, patients who presented with AWS should be prescribed medications, if amenable, for alcohol use disorder treatment, educated that AUD is a health condition with effective treatments, and provided with psychosocial resources to prevent readmissions.

Take-Home Points

- Understanding a patient's prior alcohol withdrawal syndrome history and utilizing risk scores to predict severe alcohol withdrawal helps to determine the appropriate level of care for patients presenting with acute AWS.
- Benzodiazepines remain the cornerstone of treatment for patients with severe AWS; however, other medications that address the elevated sympathetic response seen in AWS, such as dexmedetomidine, are also widely utilized.
- Tools to prevent medication administration errors, such as standardized order sets and clear clinical endpoints for titration and holding parameters, can decrease the risk of errors.
- Free-text orders are not the safest or most effective method for communicating medication management plans; improved computerized physician order entry options may improve safety.
- Electronic SBAR (situation, background, assessment, response) documentation templates may facilitate alerting clinicians to changing circumstances or medication management plans.
- Discharging physicians and APPs should work to reduce stigma, emphasize that alcohol use disorder is a health condition with effective treatments, and apply a shared decision-making model for medication management on discharge.

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This project was funded under contract number 75Q80119C00004 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services. The authors are solely responsible for this report's contents, findings, and conclusions, which do not necessarily represent the views of AHRQ. Readers should not interpret any statement in this report as an official position of AHRQ or of the U.S. Department of Health and Human Services. None of the authors has any affiliation or financial involvement that conflicts with the material presented in this report. View AHRQ Disclaimers