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Treatment of Severe Alcohol Withdrawal: A Focus on Adjunctive Agents

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Abstract

Objective: To review adjunctive treatment options for severe alcohol withdrawal. **Data Sources:** The search strategy included a search of Ovid MEDLINE using keywords *alcohol withdrawal*, *severe alcohol withdrawal*, *AWS*, *delirium tremens*, *delirium*, *dexmedetomidine*, *propofol*, *anticonvulsants*, *clonidine*, and *phenobarbital* and included articles dated from January 1990 to March 2017. **Study Selection and Data Extraction:** All English-language clinical trials and case reports assessing the efficacy of adjunctive agents in severe alcohol withdrawal were evaluated. **Data Synthesis:** Although first-line pharmacotherapy for alcohol withdrawal continues to be benzodiazepines, literature does not clearly define adjunctive treatment options for severe alcohol withdrawal. During severe alcohol withdrawal patients may become unable to tolerate or may become unresponsive to high-dose benzodiazepines. Large doses of benzodiazepines may also result in oversedation, respiratory insufficiency, and worsening delirium. **Conclusions:** Phenobarbital and dexmedetomidine are both viable adjunctive treatment options for severe alcohol withdrawal. Current evidence has shown these agents decrease the dose requirements of benzodiazepines with limited incidence of adverse reactions. Propofol may also be a viable option in mechanically ventilated patients, but its lack of clear safety and efficacy advantages over current treatment options may limit its use in practice. Clonidine, oral anticonvulsants, and ketamine require further controlled clinical trials to clearly define their role in the treatment of severe alcohol withdrawal.

Keywords

alcohol withdrawal, severe alcohol withdrawal, delirium tremens, dexmedetomidine, propofol, clonidine, Phenobarbital

Introduction

Alcohol use disorder affected approximately 16.3 million adults in the United States in 2014, and of those, 1.5 million adults required treatment in a specialized facility.[1,2] Approximately 88 000 people die from alcohol-related causes annually, making it the fourth leading preventable cause of death in the United States.[3] In addition, up to 20% of hospitalized patients abuse alcohol, and approximately 8% experience alcohol withdrawal symptoms during hospitalization.[4,5] Special patient populations at increased risk of severe alcohol withdrawal include the elderly, those with cirrhosis, those with a history of delirium tremens (DTs), or patients in the intensive care unit (ICU) who require mechanical ventilation.[6,7]

Alcohol withdrawal occurs after abrupt cessation or reduction in alcohol intake following prolonged use.[8] As a result of chronic alcohol use, there is a downregulation of γ-aminobutyric acid (GABA) receptors (inhibitory neurotransmitter) and an increase in *N*-methyl-D-aspartate (NMDA) receptors (excitatory neurotransmitter).[9] On discontinuation or reduction of consumption of alcohol, there is increased central nervous system (CNS) excitation as a result of NMDA receptors no longer being inhibited by alcohol.[9] This results in autonomic hyperactivity, psychomotor agitation, anxiety, and seizures.[8]

Based on the *Diagnostic and Statistical Manual of Mental Disorders* (5th edition), the diagnosis of alcohol withdrawal is based on the following 4 criteria being met[8]: (1) cessation of (or reduction in) alcohol use that has been heavy and prolonged, (2) 2 or more symptoms of alcohol withdrawal developing within several hours to a few days after cessation of alcohol use (refer to Table 1), (3) symptoms causing clinically significant distress or affecting social/occupational functioning, and (4) the signs and symptoms must not be attributable to any other cause.[8] Of note, withdrawal symptoms typically last 4 to 5 days.[8] Withdrawal symptoms can first appear 6 to 12 hours following last alcohol consumption and may increase to severe

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Table 1. Symptoms of Alcohol Withdrawal (*DSM-5*)[8,a].

Autonomic hyperactivity (eg, sweating or pulse greater than 100 bpm)
Increased hand tremor
Insomnia
Nausea
Transient visual, tactile, or auditory hallucinations or illusions
Psychomotor agitation
Anxiety
Generalized tonic-clonic seizures

[a]Two (or more) of these must have developed within several hours to a few days of cessation, or reduction in, alcohol use.

symptoms, such as DTs, 3 to 5 days after the last alcoholic drink.[8] DTs are associated with a 5% to 10% mortality rate.[7,10] Elderly patients are at a higher risk of experiencing severe alcohol withdrawal due to physiologic changes including decreased total body water, decreased hepatic blood flow, and increased permeability of the blood-brain barrier, which results in increased CNS symptoms including delirium and hallucinations.[6]

Once alcohol withdrawal is identified, patients should be frequently monitored with a validated scale to ensure proper and prompt treatment. The most commonly used scale in clinical trials and in practice appears to be the Clinical Institute Withdrawal Assessment Scale for Alcohol–Revised (CIWA-Ar).[11-14] The scale focuses on 10 categories of symptoms: nausea and vomiting, tremor, sweats, anxiety, agitation, headache, disorientation, tactile disturbances, auditory disturbances, and visual disturbances. The higher the score the worse the alcohol withdrawal; patients with a CIWA score of >8 benefit from treatment while those with a score of >20 are considered to be experiencing severe withdrawal and treatment in an ICU setting may be warranted.[5,11,13,14]

Benzodiazepines (BZDs) are the cornerstone of therapy; they bind to GABA receptors inhibiting CNS hyperactivity; this prevents life-threating symptoms such as seizures and DTs.[15] BZDs can be administered using different dosing strategies including front loading, fixed dosing, or symptom-triggered dosing.[15] When utilizing front loading administration, longer-acting BZDs such as chlordiazepoxide and diazepam are typically administered at a higher dose to achieve sedation initially and then administered as needed based on CIWA-Ar protocol.[15] Maldonado et al conducted a prospective, randomized clinical trial that revealed no difference in total BZD dose usage or symptom control between front loading versus symptom-triggered BZD administration.[16] Clinical trials show no difference in severe symptoms of alcohol withdrawal, such as seizures and DTs, between scheduled and symptom-triggered BZD administration. However, symptom-triggered administration may reduce the amount of BZDs administered and the length of hospital stay when compared to fixed dosing.[12,13,17] The most commonly utilized BZDs include lorazepam, oxazepam, diazepam, and chlordiazepoxide.[12-14] Long-acting BZDs with active metabolites including chlordiazepoxide and diazepam do not require tapering; however, they should be avoided in elderly patients and those with severe liver disease.[14] Intermediate acting BZDs, lorazepam and oxazepam, have no active metabolites and are safer options in the elderly and those with severe liver disease.[14] Although BZDs are effective as monotherapy for mild-moderate alcohol withdrawal, treatment of severe alcohol withdrawal is less defined in clinical practice. In severe alcohol withdrawal, patients may become resistant to BZDs and require greater than 6 mg of lorazepam or greater than 40 mg of diazepam in an hour, increasing risk of adverse effects.[18-20] Adjunctive agents may be utilized in severe alcohol withdrawal to reduce dose requirements of BZDs and control sympathetic symptoms.[4] The focus of this article will be a review of adjunctive agents studied in the treatment of severe alcohol withdrawal.

Data Source

The search strategy included a search of Ovid MEDLINE using keywords *alcohol withdrawal*, *severe alcohol withdrawal*, *alcohol withdrawal syndrome* (AWS), *delirium tremens*,*delirium*,*dexmedetomidine*,*propofol*,*anticonvulsants*, *clonidine*, and *phenobarbital*, including articles dated from January 1990 to March 2017. Article selection was limited to clinical trials (all phases), case series, case reports, and review articles, including only human subjects, published in English language, and in the critical care setting. Supplemental sources include the dexmedetomidine and propofol package inserts accessed via the manufacturers' website.

Alpha-2 Agonists

Two α-receptor agonists, oral clonidine and intravenous (IV) dexmedetomidine, have been studied. Alpha-receptor agonists reduce norepinephrine release, which then reduces the sympathetic symptoms associated with alcohol withdrawal including tremors, tachycardia, increased agitation, and hypertension. There is stronger supporting literature regarding the use of dexmedetomidine over clonidine for the treatment of severe alcohol withdrawal.[21,22]

Spies et al conducted a study in critically ill patients comparing the use of 3 different alcohol withdrawal regimens, flunitrazepam with clonidine, chlormethiazole with haloperidol, and flunitrazepam with haloperidol. Clonidine was administered intravenously up to 1.2 mg and haloperidol was administered intravenously up to a total dose of 40 mg. Flunitrazepam and chlormethiazole were administered as an IV bolus, followed by an IV infusion. Therapies were titrated to achieve a CIWA score of less than 10. A BZD dose reduction was shown when comparing the clonidine combination to the haloperidol combinations. The study

also found that the addition of clonidine to a BZD regimen resulted in a shorter duration of mechanical ventilation when compared to haloperidol. Literature suggests that clonidine may be effective as an adjunct agent, but should not be used as monotherapy in AWS.[23]

Dexmedetomidine (DEX, Precedex) induces sedation, analgesia, and anxiolysis, without causing respiratory depression like other sedatives such as BZDs and propofol.[20] While BZDs and propofol induce sedation by directly increasing the activity of GABA neurons, DEX induces sedation by inhibiting noradrenergic neuron release at the locus ceruleus, leading to GABA activation and reduced sympathetic output.[20,24] DEX is currently indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting and for sedation of nonintubated patients prior to and/or during surgical procedures, each with a duration of therapy no more than 24 hours.[24] However, because of its lighter "cooperative" sedation, absence of respiratory depression and delirium, and its ability to decrease the BZD and opioid requirements, DEX has been studied as an adjunct to BZDs in the treatment of AWS.[20] Due to its inherent mechanism of action, it has been hypothesized that use of DEX would reduce autonomic hyperactivity in patients with AWS. DEX's ability to control tremors, hypertension, and tachycardia would make it a suitable adjunct to BZDs.[20]

In a prospective, randomized, double-blind, placebo-controlled dose range study of DEX as adjunctive therapy for AWS, Mueller et al studied the change in total lorazepam requirement within the first 24 hours after DEX was initiated compared to the 24 hours prior to the initiation of DEX. However, the study was only powered on the outcome of the difference in 7-day lorazepam requirements. The study included 24 adult patients with a CIWA score >15, despite being administered over 16 mg of lorazepam over a 4-hour period per University of Colorado Hospital protocol. Patients were excluded if not admitted the ICU, comatose, patients with active myocardial infarction (MI), heart block, liver disease, or pregnancy. Patients received a symptom-triggered CIWA protocol for severe AWS with ICU admission (lorazepam 2-4 mg every 30 minutes for CIWA >15) and were randomized to receive DEX 1.2 μg/kg/h (high dose), 0.4 μg/kg/h (low dose), or placebo as adjunctive therapy for up to 5 days or until resolution of withdrawal symptoms. High-dose and low-dose groups were combined as a single DEX group for the primary analysis with a secondary analysis exploring a dose-response relationship. The results showed that the difference in 24-hour lorazepam requirements pre-DEX versus post-DEX were significantly greater in the pre-DEX group (−56 mg vs −8 mg, $P = .037$). With regard to safety, bradycardia occurred more frequently in the DEX group versus placebo group (25% vs 0%), with the majority of bradycardia occurring in the high-dose group (37.5%) over the low-dose group (12.5%). Neither endotracheal intubation nor seizure occurred in any group while on study drug, and no significant differences in cardiovascular adverse effects were seen.[18] While DEX decreased the BZD requirements within the first 24 hours, the study failed to show significant statistical differences in the 7-day cumulative lorazepam requirements (159 mg in the combined treatment groups vs 181 mg in the placebo group), which was the outcome that the power was studied to detect.[18] Other study limitations include small sample size and insufficient power of clinical outcomes, such as need for intubation or length of stay.

More recently, another prospective study by Bielka et al aimed to evaluate if the addition of DEX to BZD treatment of AWS is safe and effective for patients in the ICU. The study was a single-center, randomized, controlled trial that enrolled 72 patients. Thirty-six patients received a DEX infusion at a starting dose of 0.2 to 1.4 μg/kg/h, titrated to achieve a target Richmond Agitation-Sedation Scale (RASS) score of −2, with symptom-triggered diazepam 10 mg boluses as needed, and 36 patients received only symptom-triggered 10 mg boluses of diazepam. The primary outcomes were 24-hour diazepam consumption and cumulative diazepam consumption. The study also compared length of ICU stay, sedation and communication quality, and haloperidol requirements. The results demonstrated that the average 24-hour and cumulative diazepam consumption was significantly less in the DEX group than the BZD monotherapy group (20 mg vs 40 mg, $P < .001$; 60 mg vs 90 mg, $P < .001$). Furthermore, the DEX group had significantly better nurse-assessed patient communication and also required significantly less haloperidol during their treatment for AWS ($P < .001$ and .02, respectively). Bradycardia was seen more in the DEX group than in the BZD group (10 incidences vs 2 incidences, $P = .03$) and the length of hospital stay was 2 days shorter in the DEX group ($P = .034$). The limitations of the study were the small sample size, exclusion of patients who developed DTs, and absence of a placebo control. Overall, DEX reduced BZD requirements, haloperidol requirements, length of stay, and was associated with improved sedation and patient communication.[25]

A retrospective study by Rayner et al was conducted in a 23-bed mixed medical-surgical ICU at Fairview-Southdale Hospital. It compared BZD (diazepam equivalents) and haloperidol requirements, CIWA score, heart rate, and blood pressure in 20 patients during 24 hours prior to DEX administration versus 24 hours after DEX administration. The trial included patients who were diagnosed with AWS and received DEX only for the purpose of the management of AWS symptoms. The study excluded patients with severe comorbid disease, including CNS trauma, cerebrovascular accidents, end-stage metastatic carcinoma, and severe sepsis. The results showed that after the administration of DEX, BZD dosing decreased an average of 32.4 mg (61.5%)

per 24 hours ($P < .001$; 95% confidence interval [CI] = 16.7 to 48.1) and haloperidol dosing decreased an average of 5.6 mg (46.7%) per 24 hours ($P = .052$; 95% CI = −0.03 to 11.23). The CIWA score also decreased 1.9 points after the administration of DEX (21.1%, $P < .015$; 95% CI = 0.44 to 3.36). Conversely, adverse effects of bradycardia and hypotension were noted following DEX administration. Heart rates decreased an average of 23.4 bpm (22.8%, $P < .001$; 95% CI = 18.4 to 28.4) and systolic blood pressure decreased an average of 13.5 mm Hg (9.6%, $P = .002$; 95% CI = 3.8-15.4). Of these 20 patients, one patient on DEX was intubated for respiratory failure and one patient discontinued DEX due to significant bradycardia.[26]

There have been many additional retrospective case studies investigating the use of DEX as adjunctive treatment in AWS. Dailey et al conducted a retrospective chart review of 10 patients with AWS who were treated with DEX as an adjunctive agent. The mean dose of DEX was 0.7 μg/kg/h, and the mean infusion time was 50 hours. After initiation of DEX, patients' mean CIWA score significantly decreased from 26 to 13 ($P = .014$). The mean diazepam dose decreased from 13 mg/h to 3 mg/h in the 24 hours after DEX administration. No patients required intubation, although one developed pneumonia. Hypotension (systolic blood pressure <100 mm Hg) occurred in 5 patients, and DEX was temporarily held in 2 patients due to episodes of significant hypotension (systolic blood pressure <75 mm Hg).[27]

Ludtke et al studied sedation with a continuous infusion of DEX compared to propofol and lorazepam in ICU patients experiencing alcohol withdrawal from 2002 to 2009. The primary outcomes of the study were incidence of mechanical ventilation, length of mechanical ventilation, and length of ICU and hospital stay. Of the 32 patients studied, 15 patients received a continuous infusion of DEX and 17 patients received a continuous infusion of propofol and lorazepam. The results showed that in the DEX group, 2 patients required intubation and mechanical ventilation, compared to 10 patients in the propofol/lorazepam group (13.3% vs 58.8%, respectively, $P = .006$). The length of ICU stay was significantly lower in the DEX group compared to the propofol/lorazepam group (53 vs 115 hours, $P = .016$). Additionally, the length of the total hospital stay was significantly less in the DEX group (136 vs 241 hours, $P = .008$). Although patients who were administered continuous infusions of DEX had an initially higher CIWA score at the time of admission, they were less likely to require mechanical ventilation.[28] The retrospective nature of these studies and the small sample sizes were study limitations.

Among the α-2 receptor agonists, both clonidine and DEX have been studied as adjuncts in treating AWS.[18,23,25-27] Clonidine used as an adjunct agent to BZDs may be safe and efficacious in treating severe AWS, in comparison to haloperidol.[23] DEX has stronger supporting evidence and is shown to be safe and efficacious in the management of alcohol withdrawal symptoms, while avoiding respiratory depression and decreasing the BZD dose requirements.[18,25-27]

Sedatives

Propofol is one of the most commonly used sedatives in the hospital setting. Propofol induces anesthesia and sedation by decreasing the rate of dissociation of GABA from the receptor, increasing the duration of the GABA-activated opening of the chloride channels, resulting in hyperpolarization of cell membranes.[29,30] In addition to opening chloride channels, propofol may also antagonize amino acids that are upregulated during DTs.[2] Historically, propofol has been used in the treatment of AWS patients that are resistant to high doses of BZDs.[30] The following clinical trials demonstrate propofol's safety and efficacy in AWS treatment.

In a study completed by Lorentzen et al, the authors investigated the effects of propofol infusions in alcohol withdrawal–induced refractory DTs in patients who failed to respond to high doses of BZDs. This was a retrospective, single-centered cohort analysis of 15 patients admitted from May 2012 to September 2013. Patients enrolled in the study had previously received 1500 mg of diazepam, 2000 mg of chlordiazepoxide, or 1200 mg of phenobarbital without treatment success before receiving propofol (mean prior treatment time = 1.87 days). The patients were intubated and mechanically ventilated in the ICU prior to propofol infusion. An average dose of 4.22 mg/kg/h of propofol was infused over 48 hours. In addition, 13 patients received adjunct opioids and 7 patients received vasopressor infusions. Twelve out of the 15 patients were successfully treated and symptom free, while 3 patients required further treatment of DTs for 5, 6, and 11 days, respectively.[31] There were several study limitations in the trial, which included lack of randomization, retrospective analysis that could have led to selection bias, and patients receiving varied doses of propofol. The 86.7% success rate of treating DTs refractory to BZDs shows that propofol may be a viable option in treating AWS.

Another study by Sohraby et al compared the use of propofol-containing regimens versus BZD regimens for treatment of AWS that required mechanical ventilation. Sixty-four patients were included for analysis, which included 46 cases of propofol-containing regimens and 18 cases of BZD infusion monotherapy. The time to resolution of AWS symptoms, median hospital and ICU length of stay, and days mechanically ventilated were not significantly different between the 2 groups ($P = .34$, >.92, and .98, respectively).[32] This study was limited by the fact that it was single-centered and included mostly uninsured patients, excluded patients with comorbidities, and lack of assessment of concomitant medications.

Wong et al compared BZD dose escalation with and without propofol in BZD-resistant alcohol withdrawal in a retrospective study to investigate if propofol would minimize the adverse effects seen with high doses of BZDs and improve AWS symptoms in 66 patients (33 BZD and 33 BZD + propofol). The results of the trial showed that the time to resolution of AWS symptoms was significantly longer in the propofol group than in the BZD only group (7 vs 5 days, P = .025). Moreover, patients receiving propofol had an increased duration of mechanical ventilation (4.5 days longer), ICU stay (6 days longer), and hospital stay (9.5 days longer; P = .017, <.001, and <.001, respectively). Additionally, the patients in the propofol group required more BZDs than those receiving the BZD regimen (167 mg more diazepam equivalents) and experienced more bradycardia, AWS complications, DTs, hallucinations, and pneumonia.[19]

Last, a study completed by Lizotte et al compared propofol to DEX as adjunctive therapy in AWS. The results showed that the BZD and haloperidol doses were decreased in both groups without a significant difference between the DEX and propofol treatments (20.9 to 8.5 mg and 17.4 to 8.7 mg, P = .933 and .465, respectively). Patients receiving propofol experienced hypotension more frequently (28.5% vs 17.6%) and required longer mechanical ventilation (97.6 vs 19.9 hours), but had less bradycardia (0% vs 17.6%).[33] The study limitations included the retrospective design, small sample size, and uneven distribution of patients in the treatment groups. Propofol and DEX have similar efficacy in reducing the doses of BZDs and haloperidol, but propofol may not be advantageous over DEX due to its mechanical ventilation requirement and other safety measures.[33]

Ketamine, an NMDA receptor antagonist, was studied by Wong et al in a small single-centered, retrospective study from April 2011 to March 2014. The study reviewed 23 adult patients who received adjunctive ketamine infusions (doses ranging from 4.5 to 14.2 mg) in addition to AWS standard of care treatment. Patients received BZDs hourly as first-line treatment for AWS and ketamine was initiated the 34th hour of treatment and discontinued at hour 56. The primary outcome was the change in BZD requirement 12 and 24 hours post ketamine infusion. BZD usage was documented as diazepam equivalents. The addition of ketamine appeared to lower the BZD dose requirement 12 and 24 hours post ketamine infusion (−40 mg, 95% CI = −106.7 to 21.7; −13.3 mg, 95% CI = −86.7 to 50). However, the difference in BZD dose required was not found to be statistically significant at 12 hours (P = .110) or 24 hours (P = .330) post ketamine infusion. The trial depended on prior documentation of adverse effects and it was unclear whether hemodynamic parameters (temperature, heart rate, respiratory rate, and blood pressure) were rising due to ketamine administration or due to the nature of AWS. The results of this retrospective analysis did not show a clinical benefit in the use of adjunctive ketamine.[34]

For the treatment of severe AWS using sedatives as adjuncts, there is limited evidence for their recommended usage. Propofol may be a viable option but it is lacking advantages over other alternative treatment options currently in use.[19,31-33] Ketamine also lacks supporting evidence for its use and requires more clinical trial data.[34]

Anticonvulsants

Phenobarbital is a long-acting barbiturate with sedative, hypnotic, and anticonvulsant properties. These effects are mediated by the increase (or upregulation) of GABA.[35] The inherent pharmacologic effects of phenobarbital have led clinicians to further investigate its place in therapy for the treatment of AWS. However, limited data provided by small and insufficiently powered studies leave this clinical question unanswered.

Rosenson et al conducted a prospective, randomized, double-blind, placebo-controlled study of emergency department (ED) patients presenting with acute AWS. In the study, 102 patients were randomized to receive a single dose of IV phenobarbital 10 mg/kg or placebo while in the ED.[36] In addition, all patients were placed on a symptom-guided lorazepam-based modified CIWA protocol. The primary outcome of this study was the initial level of hospital admission from the ED, based on ED provider judgement. The results of the study found that patients receiving a single dose of phenobarbital had a decreased ICU admission rate (8% vs 25%; difference 17%, 95% CI = 4% to 32%); however, it was not specified whether the result was of statistical significance. There was no significant difference between phenobarbital and placebo in length of stay or incidence of adverse outcomes, falls, or mortality. The single dose of phenobarbital resulted in decreased use of continuous infusion lorazepam (4% vs 31%; 95% CI = 14% to 41%) and total lorazepam required (26 vs 49 mg; 95% CI = 7-40). The results of this small study provide some evidence that phenobarbital and lorazepam may have synergistic effects when used for treatment of AWS.[36]

Certain patients may be unique in having low levels of endogenous GABA or acquired conformational changes in the GABA receptor, which may render the use of BZDs suboptimal or ineffective for the treatment of AWS. In the case of these specific patients, phenobarbital may be a preferred option due to the drug's additional effects on glutamate and other CNS neurotransmitters.[35] A published case report presents a 28-year-old Hispanic male who presents to the ED unresponsive and actively seizing with an ethanol level of 320 mg/dL (legal limit of intoxication = 80 mg/dL).[35] The patient had no known history of BZD use or abuse but was unresponsive to 20 mg/h of lorazepam. The patient was administered escalating doses of IV phenobarbital 65 mg, followed by 130 mg 15 minutes later. Following the second phenobarbital dose, the patient's vital signs and

CIWA-Ar score improved within 15 minutes. The patient continued to be treated with lorazepam for breakthrough symptoms and required up to 44 mg/h over the next 4 days to achieve symptom control. On hospital day 4, the patient experienced propylene glycol toxicity, potentially due to the lorazepam injectable solution used and the high dose requirements for symptom control. The patient was unable to be managed solely by the weaning of the lorazepam, requiring scheduled phenobarbital to be initiated. The patient was eventually able to be weaned off of the phenobarbital and successfully discharged.[35] This case report highlights phenobarbital's potential as an adjunctive agent to BZDs in the treatment of AWS, specifically in patients who are unresponsive or require large doses of BZDs.

Valproate and carbamazepine are commonly used in Europe for the treatment of alcohol withdrawal.[37] Current evidence supports the hypothesis that anticonvulsants demonstrate antikindling activity by blocking the development of progressive neuronal responsiveness.[37] Kindling is a phenomenon that occurs after repeated withdrawal episodes, which leads to increased neuronal excitability and worsening of future withdrawal-related symptoms.[38] Reoux and colleagues conducted a randomized, double-blind, placebo-controlled study to determine the efficacy of oral divalproex sodium in the treatment of AWS. All patients enrolled in the study received an initial dose of oxazepam 30 mg and additional doses following the institution's CIWA-Ar protocol. Following 7 days of treatment, 36 patients were included in the final analysis, which found that a significantly lower total amount of oxazepam was required in patients treated with divalproex (85 vs 117 mg; $P = .033$). Similar rates of improvement in mean withdrawal symptom severity were achieved by both groups. However, nearly half of the patients in the placebo group did not require medication in addition to the baseline dose of oxazepam, which may have placed bias against the divalproex group and prevented demonstration of a stronger treatment effect.[37] The results of this study suggest that valproate may be useful as an adjunct agent to BZDs for the treatment of AWS.

Eyer et al conducted a retrospective chart review of 827 patients admitted to the alcohol detoxification department for alcohol detoxification with moderate to severe AWS who received either carbamazepine or valproic acid from January 2000 to December 2009. The investigators found that the duration of medical treatment of AWS and median length of stay were significantly longer in patients receiving carbamazepine over valproic acid ($P < .001$). In addition, patients receiving carbamazepine required intensive care treatment significantly more often than patients receiving valproic acid, although the reasons for ICU transfers are not discussed in the article ($P = .001$). There was no significant difference in occurrence of DTs between patients receiving carbamazepine or valproic acid ($P = .52$). The results of this retrospective chart review continues to fail to answer the question whether anticonvulsants have a general place as adjuncts in the treatment of severe AWS; however, the results do suggest that valproic acid may offer additional benefits with regard to length of stay and intensity of care over carbamazepine in patients with moderate to severe AWS.[39]

Although various anticonvulsants have been extensively studied for the treatment of AWS, the current available evidence remains conflicting. The supporting evidence suggests that anticonvulsants, specifically phenobarbital and valproate, may be indicated as adjunct agents to BZDs and may have a synergistic effect, decreasing the total amount of BZDs required for symptom control (see Table 2). However, current evidence does not support the use of anticonvulsants as monotherapy for the treatment of AWS; nevertheless, further studies are warranted.[37,38,40,41]

Discussion

Evidence continues to show support for the use of BZDs as the first-line treatment for patients with AWS. However, current evidence supports the use of adjunct agents in patients with severe AWS, patients who are unresponsive to large doses of BZDs, and patients who are unable to tolerate BZDs. In patients with severe AWS, high doses of BZDs are required that could lead to oversedation, respiratory insufficiency, worsening of delirium, as well as increased risk of aspiration, intubation, length of stay, and hospital costs.[20]

Literature has shown that adjunctive clonidine has the potential to decrease the BZD requirement and resulted in lower mechanical ventilation when compared to haloperidol. The use of DEX as an adjunctive agent has proven to be efficacious in sedation, analgesia, and inhibition of the sympathetic nervous system, without causing respiratory depression.[20,24] DEX has minimal to no delirium compared to BZDs, rapid onset, short half-life, and a favorable side effect profile.[20,24] DEX was associated with an increased incidence of bradycardia, and therefore should be avoided in hemodynamically unstable patients.[20,24] In comparison to other pharmacological agents used in the management of alcohol withdrawal, DEX rapidly decreases autonomic hyperactivity while avoiding respiratory depression.[1,2] Although DEX is not indicated for the treatment of AWS, literature demonstrates that DEX is a promising adjunct agent for the management of alcohol withdrawal symptoms, with the potential to be BZD dose sparing.

Propofol is a viable option as an adjunct to BZDs in the treatment of severe AWS in mechanically ventilated patients, but its lack of clear safety and efficacy advantages over current treatment options may limit its use in practice.[19] A trial comparing BZD requirements before and after ketamine infusions showed no statistical difference in the BZD requirements 12 hours and 24 hours post ketamine infusion. Due to the limited evidence currently available,

Table 2. Comparision of Studied Adjunctive Agents in Severe Alcohol Withdrawal.

Study Medications	Dosing Ranges Used	Average Duration of Use	Outcomes	Side Effects Observed
Clonidine[23]	0.15-0.9; 3-4 times per day	~3 days	BZD dose reduction and shorter duration of mechanical ventilation in combination with flunitrazepam when compared to chlormethiazole/haloperidol and flunitrazepam/haloperidol	Hypotension, bradycardia, AV node block
Dexmedetomidine[18,25-28,33]	0.4-1.2 µg/kg/h	24 hours	Decrease in BZD requirement 24 hours and cumulative BZD consumption post-DEX administration compared to placebo. Also, with DEX, required less haloperidol requirements and had shorter length of hospital stay. When compared with propofol, DEX had a significantly less BZD requirements. No observed respiratory depression or worsening of delirium.	Bradycardia, hypotension
Propofol[31,33]	Mean 4.22 mg/kg/h	48 hours	Reduced symptoms in patients with AWS refractory to BZDs	Hypotension, respiratory acidosis, hypertriglyceridemia
Ketamine[34]	4.5-14.2 mg infusion	24 hours	Lowered BZD requirement but not statistically significant compared to placebo	Oversedation
Phenobarbital[36]	10 mg/kg single dose; serum concentrations 15-38 µg/mL	~9 days	Single dose of phenobarbital in the ED had a decreased ICU admission rate and decreased BZD requirement	Bradycardia, hypotension
Valproate[37]	300-500 mg q6-8h	122 hours	Decreased BZD requirement compared to placebo	Thrombocytopenia, hepatotoxicity
Carbamazepine[39]	200 mg q8h or 400 mg q12h	91 hours	Duration of treatment longer and hospital stay longer in carbamazepine when compared to valproate	Hypersensitivity reaction, nausea, vomiting

Abbreviations: BZD, benzodiazepine; DEX, dexmedetomidine; AWS, alcohol withdrawal syndrome; ED, emergency department; ICU, intensive care unit.

more studies must be completed before ketamine can be recommended in the treatment of AWS.[34] Phenobarbital was shown to decrease the need for continuous infusions of BZDs, lower the overall BZD requirement, and to be a potential adjunctive agent in patients who require high doses of BZDs.[41] A trial comparing valproic acid to carbamazepine as an adjunctive agent in moderate-severe alcohol withdrawal in an alcohol detoxification unit found that the carbamazepine arm had longer hospital stays and more ICU admissions and there was no difference in the incidence of DTs.[39] Due to limited evidence currently available, more studies should be completed on valproic acid in severe alcohol withdrawal before considering it as an adjunctive agent.

Although haloperidol is commonly utilized in practice to treat agitation and hallucinations commonly associated with severe AWS, its efficacy and safety has not been studied in clinical trials. In addition, haloperidol may lower seizure threshold and therefore should be reserved for patients with comorbid psychiatric conditions.[11,17]

Conclusion

Patients with severe AWS, who require high doses of BZDs, or are resistant to BZDs, may have improved clinical outcomes with the use of the adjunctive agents included in this review. Current evidence is lacking a cost-benefit analysis to determine the overall cost reduction associated with the use of these agents with BZDs, as the trials reviewed have shown a decrease in the length of ICU stay with the use of DEX and phenobarbital. With the data currently available, the use of adjunctive clonidine, DEX, or phenobarbital should be highly considered when treating patients with severe AWS.

Author Contributions

EG: Contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted manuscript, critically revised manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

JR: Contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted manuscript, critically revised manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

KK: Contributed to design, contributed to acquisition, analysis, and interpretation, drafted manuscript, critically revised manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AF: Contributed to design, contributed to acquisition, analysis, and interpretation, drafted manuscript, critically revised manuscript, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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