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Use of Therapeutic Ethanol for Patients with Acute Alcohol Withdrawal Syndrome in the Intensive Care Unit

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Abstract
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Methods: An extensive search was performed using the databases EBMR, MEDLINE-Ovid, and Web of Science. The following keywords were used: alcohol, withdrawal, ethanol, delirium, and seizure. The search also necessitated studies to have at least one of the following terms: intensive care unit, ICU, inpatient, trauma, or critical care. The results were then reviewed for quality based on GRADE criteria.

Results: The query above generated 494 results that were reviewed for relevancy. Two studies met inclusion criteria, both of which were non-blinded, randomized, controlled trials with patients being treated for AWS in the ICU using EtOH. One study found mild benefit to using EtOH, while the other study found current therapy with BZD to be superior. Quality of the studies was either low or very low according to GRADE profile.

Conclusion: It is unclear whether patients benefit from EtOH, either as an adjunct or as mono-therapy, in the management of AWS compared to use of BZD. More research is needed to determine the efficacy of therapeutic EtOH.

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First Advisor
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Use of Therapeutic Ethanol for Patients with Acute Alcohol Withdrawal Syndrome in the Intensive Care Unit

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A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

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Biography

[Redacted for privacy]
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Keywords: Alcohol withdrawal syndrome, delirium, seizure, ethanol, intensive care unit, inpatient, critical care
Acknowledgements

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List of Abbreviations

AWS…………………………………………………………….Alcohol Withdrawal Syndrome
BZD…………………………………………………………….Benzodiazepine
CNS………………………………………………………………Central Nervous System
DT………………………………………………………………..Delirium Tremens
EtOH……………………………………………………………..Ethanol
IV…………………………………………………………………..Intravenous
MI………………………………………………………………..Myocardial Infarction
RSAS……………………………………………………………Riker Sedation-Agitation Scale

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Appendix A…………………………………………………………….Riker Sedation-Agitation Scale
Use of Therapeutic Ethanol for Patients with Acute Alcohol Withdrawal Syndrome in the Intensive Care Unit

BACKGROUND

Alcohol withdrawal syndrome (AWS) is a problematic and dangerous complication that affects up to 31% of patients across intensive care unit (ICU) settings. Its symptomatology begins with disorientation, agitation, and tachycardia, which can often progress to delirium tremens (DT), seizures, hallucinations, cardiovascular collapse, and even death. Chronic alcohol use and subsequent AWS is associated with increased morbidity and mortality due to elevated risk of infection, sepsis, and countless other complications as shown in Table I.

While AWS is detrimental to patient care, it also has a notable impact on healthcare associated costs. In one retrospective review of trauma patient visits spanning nearly 5 years, patients who experienced AWS incurred average hospital charges that were nearly 3 times higher than patients who did not experience AWS. Patients suffering from AWS also spent, on average, 4.28 more days in the ICU and required significantly more invasive procedures compared to non-AWS patients.

Historically, ethanol (EtOH) has been used in the management of AWS, though in recent times, it has largely been replaced by benzodiazepines (BZD) as the first line treatment of choice. With this shift in treatment approach has come criticism of adverse effects of BZD, namely that it increases the risk of excess sedation,
respiratory depression, immune system down-regulation, drug induced delirium, and subsequent drug dependence and abuse. \textsuperscript{2,4,6-8} Advocates of BZD for treatment of AWS suggest that administering EtOH to alcohol dependent patients reinforces their addictive behavior, which can be misconstrued as providers condoning their continued alcohol abuse. \textsuperscript{3,10}

As a treatment modality, many studies\textsuperscript{1,6,8} have shown EtOH to be both a safe and effective way to rapidly improve AWS symptoms. Proponents of therapeutic EtOH note that previous studies, which demonstrate EtOH as being ineffective, have often been confounded by improper dosing that didn’t reflect patient body weight.\textsuperscript{1} Dissenters of therapeutic EtOH note its association with increased risk of gastric irritation, drug interactions, and hepatic injury, all in the setting of having both a narrow therapeutic index and variable rate of hepatic elimination.\textsuperscript{3,4}

Despite the shift towards BZD use, EtOH remains on the formulary at more than 66\% of major teaching hospitals in the United States, and use of therapeutic EtOH varies significantly from provider to provider.\textsuperscript{6,9} Though some academic reviews, notably “Ethanol for alcohol withdrawal: The end of an era,”\textsuperscript{10} suggest a consensus of the literature surrounding therapeutic EtOH, its continued widespread use indicates there is not a consensus in clinical practice for the management of a particularly common and problematic complication in critical care medicine.
METHODS

An extensive search was performed using the literature databases EBMR, MEDLINE-Ovid, and Web of Science, using the keywords: alcohol, withdrawal, ethanol, delirium, and seizure. In order to identify proper disease management settings, the search also necessitated studies to have one of the following terms: trauma, intensive care unit, ICU, inpatient, or critical care. The search was then narrowed to English language studies that had been performed within the past 10 years. The remaining studies were then reviewed for quality based on GRADE criteria.12

RESULTS

Based on the search performed above, 494 results were generated. From there, studies were reviewed for relevancy and duplicate results were removed. A total of 2 studies (Weinberg et al11, AWARE study9) were selected for inclusion based on comparison of treatment efficacy for EtOH versus BZD in the inpatient setting. Study GRADE Profile is included in Table II. Summary of findings is included in Figure I and II.

Weinberg et al

During 2007, Weinberg et al11 conducted a non-blinded, randomized, controlled trial over the course of 15 months with the goal of evaluating BZD compared to therapeutic EtOH for management of AWS. Prospective enrollees for the
study were selected from patients being admitted to the trauma ICU, who reported daily alcohol intake of 5 or more alcoholic beverages per day for the previous 6 months. Patients with anticipated hospital stay of less than 4 days were excluded.\textsuperscript{11}

Patients meeting inclusion criteria were randomized into therapeutic groups for either BZD or EtOH management using computerized coin flip simulation. Those in the EtOH therapy group received initial EtOH 50mL/hr IV infusion, were evaluated regularly using the Riker Sedation Agitation Scale (RSAS), and had EtOH dose adjustments with aim of RSAS score of 4 (a score that represents a patient who is calm and cooperative; see Appendix A). Those in the BZD therapy group received diazepam 5mg every 6 hours, were regularly evaluated using RSAS, and had BZD dose adjustments for target RSAS score of 4.\textsuperscript{11}

Of the 58 patients who met inclusion criteria, 26 were assigned to the EtOH group and 24 were assigned to the BZD group. Eight patients were excluded from the study based on exclusion criteria related to age, comorbidities, past medical history, and ability to provide informed consent. Additionally, 1 patient opted to withdraw from the study, and 1 patient was removed from the study due to receiving additional BZD beyond study protocol. There was 1 patient in the EtOH therapeutic arm that failed treatment despite reaching max dosing of EtOH (200mL/hr) and required additional BZD therapy to control symptoms.\textsuperscript{11}
Despite expecting EtOH to be the more successful therapeutic treatment, the authors state they found BZD to be superior in the management of AWS. Overall, the EtOH arm of treatment had significantly more deviations from RSAS score of 4 (p=0.020) with the majority of deviations falling in the category of insufficient sedation (meaning there was increased patient agitation). All patients were successfully weaned from AWS medications.\textsuperscript{11}

**AWARE Study**

During 2013, Fullwood et al\textsuperscript{9} conducted a non-blinded, randomized, controlled trial with the goal of evaluating BZD as mono-therapy versus BZD with adjunctive EtOH in the management of AWS. Prospective enrollees for the study were patients who were admitted to the cardiac ICU following a myocardial infarction (MI) and were at risk for AWS (as determined by both stated alcohol consumption and scoring a 2 or greater on the CAGE alcohol screening survey).\textsuperscript{9}

Patients meeting inclusion criteria were randomized into either BZD or BZD with EtOH therapeutic groups via computer-generated randomization. Of the 57 patients who fulfilled inclusion criteria, 29 were selected for the BZD mono-therapy group and 28 were selected for the BZD with adjunctive EtOH group. All participants completed the study except 1 patient death in the BZD group, which was attributed to MI.\textsuperscript{9}
Patients in the BZD mono-therapy group received lorazepam 2mg IV every 6 hours, were evaluated regularly for sedation levels based off a modified Ramsey Scale, and had BZD dose maintained at 2mg IV every 4 hours to maintain sedation. Dosing adjustments were permitted to maintain appropriate level of sedation.9

Patients in the BZD with EtOH adjunct group received enteral preparations of half of their stated daily EtOH intake every 4-6 hours with dose adjustment to maintain an appropriate level of sedation. These patients also received scheduled lorazepam 2mg IV every 12 hours. The BZD dose was increased if patients remained symptomatic refractory to maximal EtOH therapy (defined as 100% of stated daily intake of EtOH, given every 4-6 hours, with scheduled 2mg BZD dose noted above).9

Endpoints used for results analysis included complications as shown in Figure II. There was no significant difference in the complication rates between the 2 groups (p=0.564), though there was an overall trend towards decreased complication rates seen in the BZD with adjunctive EtOH group. Patients in the BZD group on average stayed for 1 extra hospital day compared to the BZD with adjunctive EtOH group (p=0.323).9

DISCUSSION

The future of EtOH in AWS management is unclear. The studies9,11 discussed above come to disparate conclusions with one study11 demonstrating BZD as the superior treatment modality, and the other suggesting EtOH, when used as an adjunct,
may improve AWS management. Both studies have significant shortcomings that restrict the implications of their findings. Higher-powered studies are needed to develop definitive conclusions.

In regard to Weinberg et al, there were several limitations that detracted from the study’s reliability. Using EtOH as a mono-therapy in the experimental group, rather than as an adjunct to BZD, may have lead to its decreased efficacy. Additionally, previous studies have established the importance of weight-based dosing of EtOH for AWS. The lack of such a dosing regimen in the Weinberg et al study may have lead to sub-therapeutic EtOH levels and subsequent decreased EtOH efficacy. The authors of the study acknowledged this problem and noted in their discussion that blood alcohol levels were undetectable in most of their patients using the study’s EtOH dosing regimen.

The Weinberg et al study also did not fully disclose some of the patient demographics, which may have affected the results. This was particularly notable in that 8% of participants were identified as having experienced AWS in the past, though it was not identified which treatment groups these patients fell into. Given that patients with a history of previous AWS have the greatest risk for symptomatology, the lack of disclosure of which cohort these patients fell into may have confounded the results.
Both studies\textsuperscript{9,11} suffered from lack of blinding given that the study designs included alterations in therapy dosing regimens based on subjective findings (RSAS and Ramsey scale). This may have lead to sub or supra-therapeutic dosing regimens in either cohort. Additionally, this subjectivity may have influenced the results in the Weinberg et al study\textsuperscript{11} due to outcome measurements being derived from the same subjective scoring system.

Specific patient populations were not appropriately represented in both studies.\textsuperscript{9,11} Critically-ill patients who were unable to provide informed consent were excluded from both of the studies, which unfortunately limits the implications of their results for acute care management. Female patients were also underrepresented, with 93\% male patients in the AWARE study and 96\% male patients in the Weinberg et al study. Notably, the patients in the AWARE study were all post-MI, which presents its own assortment of mortality and morbidity risk factors that make the cohort not particularly representative of typical ICU patients.

Perceived ethical implications have most likely contributed to the paucity of well-constructed studies evaluating therapeutic EtOH. It has been postulated that oral ethanol given by providers acts as a trigger for further alcohol addiction behavior and demonstrates permission by staff for continued abuse.\textsuperscript{3} This was particularly noticeable in the AWARE study,\textsuperscript{9} whose authors acknowledged discontinuity in support for therapeutic EtOH throughout the trial due to ethical concerns of certain
providers and nursing staff. This bias against EtOH use lead to decreased patient enrollment and may have affected results of the trial.\textsuperscript{9} It can be surmised that personal ideologies surrounding alcoholism and addiction management may be detracting from both provider objectivity and the ability to treat AWS as a purely pathophysiologic process separate from the behavior of alcohol abuse.

In order to definitively demonstrate the effectiveness, or lack thereof, of therapeutic EtOH, randomized controlled trials need to be done with large sample sizes. These studies would benefit from using weight-based dosing for EtOH to ensure therapeutic levels.\textsuperscript{1} It would most likely be beneficial for EtOH to be evaluated in the setting of adjunctive therapy to BZD rather than as mono-therapy given that current evidence leans towards the combination being more efficacious.\textsuperscript{9,11} Additionally, modifying EtOH delivery to either be via nasogastric tube or IV would help to negate possible behavior cues triggered by oral intake of therapeutic EtOH. Lastly, using the CIWA-Ar scale to evaluate response to therapy would bolster the applicability of future studies as it is the most commonly employed AWS symptom evaluation criteria.\textsuperscript{7}

**CONCLUSION**

There is not currently enough evidence to support or disavow the use of EtOH in the management of AWS. Of the two studies reviewed, the AWARE trial showed a
minor trend towards benefit in using EtOH as an adjunct for BZD therapy and Weinberg et al demonstrated BZD use as more effective than EtOH mono-therapy.

Currently, more than 66% of major teaching hospitals in the United States have EtOH on their formulary and 70% of hospitals surveyed acknowledged that they have not constructed any specific guidelines for its administration.\textsuperscript{2,6} Between the numerous small population size studies demonstrating benefit of EtOH, and the frequency at which therapeutic EtOH is already being used, it is clear that a comprehensive study with a large population size is indicated to determine efficacy. Given the significant morbidity and mortality associated with AWS in the ICU setting, an evaluation of how providers can improve management of this condition is imperative.
References


Table I. Morbidity and Mortality associated with AWS\textsuperscript{5}

| Hospital Course and Complications of patients with AWS compared to non-AWS patients |
|---------------------------------|--------------------------------------------------|
| Length of ICU stay              | +4.28 days longer stay                           |
| Duration of ventilator treatment| +3.32 days of ventilation                        |
| Total length of stay            | +11.0 days total increased length of stay        |
| Average hospital charges        | +316% increased cost                             |
| Total mortality                 | +2.27% incidence                                 |
| Respiratory failure             | +22.4% incidence                                 |
| Pneumonia                       | +17.1% incidence                                 |
| Sepsis                          | +7.0% incidence                                  |
| Need for tracheostomy           | +11.6% incidence                                 |
| Need for percutaneous endoscopic gastrostomy | +11.8% incidence     |

Table II. Characteristics of Reviewed Studies: GRADE Profile

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<th>Quality Assessment</th>
<th>Downgrade Criteria</th>
<th>Upgrade</th>
<th>Quality</th>
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<td>Design</td>
<td>Limitations</td>
<td>Indirectness</td>
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<tr>
<td>Weinberg, et al\textsuperscript{11}</td>
<td>RCT</td>
<td>Serious\textsuperscript{a}</td>
<td>Serious\textsuperscript{b}</td>
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<tr>
<td>AWARE\textsuperscript{9}</td>
<td>RCT</td>
<td>Serious\textsuperscript{a}</td>
<td>Not Serious</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Non-blinded study using subjective patient assessments for determining treatment
\textsuperscript{b} Low starting dose of EtOH not comparable to control therapy of benzodiazepine
\textsuperscript{c} Small patient size
Figure I. Summary of Findings: Weinberg et al.\textsuperscript{11}

Percentage (%) of patients deviating from RSAS score of 4 (calm and cooperative) over their course of treatment
Figure II. Summary of Findings: AWARE Study

Percentage (%) of patients who had various complications secondary to AWS management with either BZD or BZD with adjunctive EtOH
Appendix A: Riker Sedation-Agitation Scale

<table>
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<th>Value</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Unarousable</td>
</tr>
<tr>
<td>2</td>
<td>Very sedated</td>
</tr>
<tr>
<td>3</td>
<td>Sedated</td>
</tr>
<tr>
<td>4</td>
<td>Calm and cooperative</td>
</tr>
<tr>
<td>5</td>
<td>Agitated</td>
</tr>
<tr>
<td>6</td>
<td>Very agitated</td>
</tr>
<tr>
<td>7</td>
<td>Dangerous Agitation</td>
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