Published in final edited form as:

Am J Crit Care. 2013 September ; 22(5): 398–406. doi:10.4037/ajcc2013283.

Alcohol Withdrawal Prevention: A Randomized Evaluation of Lorazepam and Ethanol (AWARE) Pilot Study

Joyce E. Fullwood, RN, BSN¹, Zhila Mostaghimi, RN, BSN², Christopher B. Granger, MD³, Jeffrey B. Washam, PharmD⁴, Wanda Bride, RN⁵, Yanfang Zhao, MS⁶, and Bradi B. Granger, RN, PhD⁷

¹Nurse Manager, Operations, Cardiac Intensive Care Unit, Duke University Hospital, Durham, NC

²Clinical Nurse IV, Cardiac Intensive Care Unit, Duke University Hospital, Durham, NC

³Medical Director Cardiac Intensive Care, Duke Clinical Research Institute, Durham, NC

⁴Clinical Pharmacist, Cardiac Intensive Care Unit, Duke University Hospital, Durham, NC

⁵Associate Chief Nursing Officer, Cardiovascular Services, Duke University Hospital

⁶Statistician, Duke Translational Nursing Institute, Durham, NC

⁷Cardiovascular Clinical Nurse Specialist, Duke University Health System and Associate Professor, Duke University, School of Nursing, Durham, North Carolina

Abstract

Background—Alcohol withdrawal syndrome, characterized by a hyperadrenergic state with confusion, agitation and hallucinations, has detrimental effects on patient safety in the context of acute myocardial infarction (MI). Unexpected hospitalization and sudden cessation of alcohol consumption may result in adverse outcomes including in-hospital complications, increased length of stay, and death. Strategies for safe and effective patient management have not been rigorously studied.

Purpose—We conducted a randomized evaluation of lorazepam and ethanol/lorazepam to evaluate the safety and efficacy of two strategies for the prevention of alcohol withdrawal syndrome in patients with acute coronary syndromes.

Methods—Patients (n=57) with myocardial infarction were screened for alcohol dependence using the CAGE questionnaire and randomized to lorazepam or to ethanol with lorazepam. Demographic group differences and complication rates were analyzed using chi square (categorical variables) and t-tests (continuous variables). Safety (composite complication rates) of the treatment strategy was evaluated using Fisher's exact test. Length of stay was analyzed using Wilcoxon rank-sum test.

Results—Safety-associated complication rates (self-extubation, delirium tremens, re-infarction) were not different between groups (24% lorazepam vs. 18% ethanol; p=0.56). A trend toward fewer complications in the ethanol group was noted. In addition, no difference was detected

Correspondence: Bradi B. Granger DUMC 3322, Trent Drive Durham, NC 27710 Bradi.granger@dm.duke.edu.

All work for this study was performed at Duke University Hospital and School of Nursing

between the treatment groups for days spent in the CCU (6.9% lorazepam vs. 2.4% ethanol; $p = 0.32$) or overall hospital stay (6.2% lorazepam vs. 6.4% ethanol; $p = 0.72$).

Conclusions—These findings suggest that a randomized evaluation of treatment strategies to prevent complications associated with alcohol withdrawal in acute MI is safe and feasible. A larger study may provide important evidence for improving clinical outcomes for patients experiencing alcohol withdrawal during acute myocardial infarction.

Keywords

lorazepam; ethanol; alcohol withdrawal syndrome; randomized controlled trial; patient safety; acute myocardial infarction; CAGE questionnaire

Introduction

Alcohol withdrawal syndrome, characterized by altered mental status, confusion, tremors, seizures, and delirium in its most severe form, is the physiologic response to withdrawal of the central nervous system depressant effect of alcohol (1). Delirium tremens is most consistently defined as a hyperadrenergic state (fever, tachycardia, and/or hypertension) with confusion, severe agitation, and/or hallucinations (2). While the relationship of this response to coronary artery disease and the nature of its effects in myocardial infarction are unclear, we have observed increased morbidity among patients experiencing myocardial infarction and alcohol withdrawal syndrome in our patient population. Studies have demonstrated an increased risk for coronary artery disease among heavy drinkers (3, 4). However, alcohol intake when consumed in moderation has been shown in some studies to be associated with a lower risk of mortality from coronary artery disease and myocardial infarction (5-11). While alcohol may be protective against the occurrence of myocardial infarction, the abrupt cessation of alcohol increases the risk of adverse outcome in the event that a myocardial infarction occurs (12). This is in part explained by the hyperadrenergic state of alcohol withdrawal, which may increase the risk of recurrent myocardial infarction, arrhythmias, and death (1, 12).

The potential for rapid onset of initial symptoms following cessation of alcohol intake (as early as eight hours), and the potential for rapid progression to delirium tremens has been well documented (13). Hospitalization for acute myocardial infarction forces sudden discontinuation of alcohol consumption and may precipitate alcohol withdrawal, thus increasing the patient's risk for complications following MI and poor outcomes. Moreover, in contrast to most patients without life-threatening underlying disease, patients with acute myocardial infarction are at extremely high risk for serious complications, including death, when experiencing alcohol withdrawal. In fact, in a retrospective review of historical cases identified as high risk for acute alcohol withdrawal in one cardiac intensive care unit (ICU), approximately 24% developed delirium tremens, and of these, 11% died, and an additional 56% had serious complications (14).

Increased circulating catecholamines and increased myocardial oxygen consumption which occur during withdrawal are counter-productive to stabilization and myocardial healing and may in fact precipitate ventricular fibrillation and sudden death. In addition, patient-induced

complications such as self-extubation, attempts to get out of bed with large gauge femoral lines in place, and patient removal of enteral feeding tubes are a few examples of behavioral complications often observed during delirium tremens which contribute to a poor prognosis (15-17). Other common complications include delayed bypass (CABG) surgery, aspiration pneumonia, encephalopathy, gastrointestinal bleeding, and prolonged length of stay (15-17).

As a result of these common complications, costs to both the patient and the health care system are a significant factor in providing safe care for these patients. For example, one hospital bill at discharge totaled \$89,818.50 for a patient with an acute MI who suffered alcohol withdrawal, as compared to an average hospital charge of \$22,300.00 per case for patients with acute MI in the same fiscal year, and that reported over a decade ago, is an underestimate of costs that might be incurred in this same population today (14). The impact of the problem of alcohol withdrawal on the health care system in terms of personnel, resources, supplies, and financial strain is significant (18).

The relative impact of the therapeutic use of alcohol versus benzodiazepines to prevent or suppress withdrawal during the acute stage of myocardial infarction is unclear. In our cardiac ICU, both Lorazepam and ethanol were used, often interchangeably depending on the rounding physician each week. After reviewing over a year of historical cases of patient treatment for alcohol withdrawal in the setting of acute MI in our cardiac ICU, 74% of patients received benzodiazepines alone, and 26 % received alcohol with or without benzodiazepines. These data demonstrated that alcohol was often used for these patients, and yet the safety, benefits and possible risks had not been systematically evaluated nor published in the literature. The safety and efficacy of these different strategies remains unknown. The purpose of this study was to evaluate the safety of two strategies for the management of alcohol withdrawal in the setting of acute MI by conducting the AWARE pilot study: *Alcohol Withdrawal Prevention: A Randomized Evaluation of Lorazepam and Ethanol (AWARE)*. The first strategy, using lorazepam alone, was dose-designed to provide pharmacologic suppression of the physiologic effects of withdrawal.

The second strategy, using a combination of ethanol and lorazepam, was designed to delay physiologic withdrawal and in addition, to suppress breakthrough symptoms and prevent onset of alcohol withdrawal syndrome until the MI was stabilized. Our hypothesis was that prevention of the physiologic response to withdrawal in the setting of acute MI would provide opportunity for cardiovascular stabilization prior to subsequently going through withdrawal and would therefore be a safer approach to treatment. In addition, we hypothesized that delay of acute withdrawal using a treatment strategy of ethanol in addition to benzodiazepines would result in fewer acute complications and result in a shorter CCU length of stay, avoiding the incremental costs of care associated with complications and prolonged acute care hospital stay. The theoretical basis for this study was that the most effective approach to preventing alcohol withdrawal would be to provide alcohol itself, rather than an alternative central nervous system depressant. Since studies found a high rate of mortality with alcohol withdrawal in the setting of acute coronary syndromes, the strategy of preventing alcohol withdrawal, even without beginning the cessation of alcohol ingestion, was believed to be warranted as a strategy to study.

Methods

Design, Sample and Setting

This was a prospective, randomized, controlled pilot study in patients with unstable angina or acute myocardial infarction who were admitted to the cardiac intensive care unit and were identified as being at high risk for alcohol withdrawal. Fifty-seven (n=57) patients were screened and randomized to one of two strategies, lorazepam or ethanol and lorazepam in combination (Figure 1). The choice of agent used in the study design was made in consultation with the clinical pharmacist, cardiologist and alcohol and addictions program chair. Lorazepam was selected as the benzodiazepine since it is the current practice standard in our hospital and has fewer drug interactions, being conjugated rather than oxidized like diazepam. The choice of ethanol (wine, beer, vodka or whiskey) was based on the patient's drinking history. In a cardiac population we took into consideration the volume-related issues in patients with volume overload or LV dysfunction. As alcohol has its own diuretic effect, we did not encounter issues with volume overload.

Procedures for Screening

Patients were screened for alcohol use using a two-step process developed in collaboration with the hospital Alcoholism and Addictions Program. First, nurses assessed each patient on admission using the standard medical history assessment question, "how many alcoholic drinks do you have each day: 0, 1-2, 3 or more?" Patients who reported five or more drinks per week were then evaluated further using a four question survey, the CAGE (Cut down, Annoyed, Guilty, Eye-opener) screening survey (19), selected through consultation with the hospital Alcoholism and Addictions Program. A CAGE score of 2 or more has been shown to be associated with a sensitivity of 74% and specificity 91%, and was determined to be the most accurate and reliable for screening this population in the acute care setting. Patients were asked to participate in the study if they reported three or more drinks per day and scored 2 or more on the CAGE screening survey. If the patient was not able to provide admission assessment information or informed consent due to his or her medical condition, the family member was asked to provide a medical history and informed consent. A modification and waiver of consent was approved for this purpose from the institutional review board. Informed consent was obtained on 57 patients, and 57 completed the study and were included in this analysis.

Inclusion criteria for participation in the study included average consumption of 3 or more drinks a day, a positive CAGE score, and admission diagnosis of acute myocardial infarction or unstable angina. Exclusion criteria included a history of allergic reaction or history of prior intolerance of benzodiazepines and pregnancy, due to potential for birth defects related to study medications. Randomization was accomplished by sealed envelopes assigned to consecutively eligible, consented patients, each containing the assigned study arm which was derived using a computer-generated randomization scheme.

Procedures for Treatment Randomization

Dosing for both strategies was determined in collaboration with a consulting clinical pharmacologist using a weight-based algorithm. Although an accurate determination of daily

alcohol intake is frequently impossible, the best estimate was determined by taking into account patient and family history, medical records, and the patient's alcohol level at the time of admission, if available. Patients were randomized into one of two arms:

Strategy 1. Lorazepam—Lorazepam was administered beginning at 2 milligrams (mg) intravenously (IV) every 6 hours. If the patient's signs and symptoms progressed, he was advanced as defined by the weight-based, symptom driven algorithm. Lorazepam 2mg IV was given systematically every 30 minutes until sedated (sedation was assessed using a modified Ramsey Scale as calm and/or arousable to verbal or tactile stimulation). Once sedated, Lorazepam dosing was maintained at 2mg IV every 4 hours or as directed by the physician in consultation with the clinical pharmacist and the nursing care team.

Strategy Two: Ethanol and Lorazepam Combination—Patients in the ethanol arm were dosed beginning at 50% of estimated daily intake, offered in the form of either beer or vodka, depending on patient preference. The dose was given orally or via nasogastric tube every 4-6 hours over a 24 hour period. Patients in this alcohol/lorazepam arm were advanced to 100% of reported ethanol intake based symptomatic progression. Lorazepam 2mg IV every 12 hours was also given in combination with the ethanol arm. If symptoms progressed in patients receiving 100% of reported ethanol intake, the Lorazepam was increased as needed. Patients were reassessed for sedation using the Ramsey Scale and for withdrawal symptoms every 2-4 hours and as needed according to the CCU usual care practice.

The study treatment continued with both arms until signs and symptoms of alcohol withdrawal subsided with the minimum of 3 days and the maximum of one week. Further treatment was available at the discretion of the attending physician.

Outcome Measure

The primary endpoint was a composite score for CCU complications. This endpoint was defined based on the cumulative frequency of complications that threaten patient safety and included: the development of delirium tremens, recurrent ischemia, re-infarction, self-extubation, ventricular tachycardia/fibrillation, aspiration pneumonia, requirement of four-point restraints, and failure to complete at least 3 days of assigned study arm treatment strategy. The secondary endpoints were the CCU length of stay, overall hospital length of stay and death during the patient hospitalization.

Statistical Analysis

Demographic variables were analyzed using descriptive statistics for each of the two treatment groups. The continuous variables were reported in percentiles (e.g., mean, median), and discrete variables were reported in frequencies and percentages. For comparisons of groups with respect to continuous variables, the Wilcoxon rank-sum test was used. Group comparisons for discrete variables were done using a conventional chi-square test. The primary outcome, composite CCU complication rate, was analyzed using Fisher's exact test. Statistical comparisons were performed using two-sided significance tests. An alpha level of 0.05 was used for interpreting significance of the treatment comparisons. All analyses were performed using the SAS version 9.0 (Cary, NC).

Results

Of the 57 patients who qualified for this study, the mean age was 53 years (standard deviation 12.4 years), the majority were male (93%; n=53), and Caucasian (65%; n=37), and were more likely to have a primary diagnosis of acute MI (83%; n=48) as compared to acute unstable angina. Nineteen percent (n=11) of all patients had a prior history of documented alcohol withdrawal. When baseline characteristics were evaluated by treatment group assignment, baseline demographics were similarly distributed and not statistically significantly different with the exception of one factor (Table 1). The patients were slightly older in the Lorazepam group as compared to the Ethanol/Lorazepam group (54 versus 48.5 years). The majority of the patients in both groups were male (n=27 and n=26, respectively) and Caucasian (58.6% and 71.4%; n=17 and n=20, respectively). The baseline vital statistics including median heart rate, heart rhythm, respiratory rate and body temperature did not differ by treatment group, nor did baseline laboratory values (clotting factors, albumin and blood alcohol level). There were slightly more patients with a history of alcohol withdrawal in the Lorazepam group as compared to the Ethanol/Lorazepam group (27.5% vs. 25 %), however this was not a significant baseline difference ($p=0.86$).

The primary outcome of the study, CCU complication rates, did not differ significantly in incidence or frequency between the two treatment groups (Table 2). When comparing the two treatment groups regarding the overall number of CCU complications, no significant difference was found in incidence or frequency of complications between the two groups ($p=0.564$). When comparing the two treatment groups on a composite of CCU complications, no significant difference was found between the two treatment groups ($p=0.747$) (Table 3). When comparing the groups on the number of all other CCU complications that occurred and were considered unrelated to alcohol dependence, no significant difference was detected between the groups ($p=0.399$). When comparing the two treatment groups to ensure adequate ability of patients to withdraw from the randomized, assigned drug regimen within three days, once the myocardial infarction had stabilized, no significant difference in ability to safely withdraw from therapy was detected between groups ($p=0.151$). One death occurred in the benzodiazepine group (Strategy 1) and was attributed to the acute myocardial infarction.

The secondary endpoints of the study included CCU length of stay and hospital length of stay (Table 4). The mean CCU length of stay differed by one day, with patients in the Lorazepam group having a slightly longer CCU length of stay as compared to those in Ethanol/Lorazepam group ($p=0.323$). The difference in overall hospital length of stay was also not significantly different ($p=0.718$). Therefore, overall, no significant differences are reported in this analysis to suggest that a combination of ethanol and lorazepam was less safe for patients or resulted in a difference in CCU or overall hospital length of stay.

Discussion

Results of this pilot study suggest that a randomized comparison of treatment strategies for the prevention of complications associated with alcohol withdrawal in the setting of acute myocardial infarction is safe and feasible. Though the inherent risks of alcohol withdrawal

are undisputed, a recently published study concluded that the mortality rate attributed to alcohol withdrawal syndrome has decreased since the beginning of the last century, especially in critical care units (20, 21). A number of factors have contributed to these improved survival rates, including improved management of delirium tremens, placement of patients in a carefully monitored ICU setting, and increased rates of timely *endotracheal* intubation (21, 22). Improved nursing management of these patients has also led to improved survival through early identification of patients at risk and development of standardized care protocols (17, 23, 24).

Risks

Despite these advances, the risks associated with alcohol withdrawal persist and are in fact more dangerous in patients experiencing critical illness. Hospital complications from alcohol withdrawal include the increased risk for and longer duration of mechanical ventilation in the ICU patient (21, 25), sepsis, septic shock and hospital mortality (15). For patients with the concomitant risks associated with myocardial infarction, mortality rates have not appreciably declined in the last decade (14). In fact, the risk of myocardial infarction has been reported to be greater among alcoholics (26), suggesting that the proportion of cardiac ICU patients that are likely to withdrawal is higher than that in the general population. The nature of the physiologic response to alcohol withdrawal, characterized by an increased risk of sepsis, seizures, shock and death (17, 18, 21, 27), when added to the increased risk of heart rate abnormalities, ventricular dysrhythmias, re-infarction, shock and death that occur in the acute phase of myocardial infarction (28, 29), pose a significant risk of increased mortality for this vulnerable patient population. For this reason, the rationale to suppress or delay the withdrawal from alcohol until the myocardium has stabilized is one approach that has physiologic merit, but scant evidence to support safe treatment strategies.

Current Treatment

The first line of therapy for the prevention of alcohol withdrawal is benzodiazepines (30-32). Though some studies have evaluated the use of symptom-based alternatives (25, 31, 33), most have focused on excessive sedation is a primary concern with multiple drug regimens (34), as opposed to the overriding risk of multiple morbidity and mortality in the context of acute MI. As an example, studies have focused various intervention strategies on patient airway management and ventilator concerns *during* alcohol withdrawal without considering the option to prevent onset of withdrawal in the setting of acute concomitant decompensation. As reported by Gold and colleagues (2007), the strategy of escalating doses of benzodiazepines and phenobarbital administration was studied and found to reduce the need for mechanical ventilation in delirium tremens, once it occurred (35). This study supports the ability to safely manage the airway and avoid potentially dangerous mechanical ventilatory interventions. The importance of these findings cannot be underestimated and represent one solution to a critical patient safety concern; however the primary aim of this pilot study was to *prevent* the onset of withdrawal symptoms *before* they occurred.

Few studies of benzodiazepines in conjunction with ethanol have been reported. However, among those who have reported the use of ethanol in acute care settings, results and recommendations have been both negative (36), and positive(37). Most recently studies have

reported alcohol as a therapeutic intervention to be safe and effective in isolated acute care settings (37). These circumstances include critical care scenarios similar to myocardial infarction in which the risk of withdrawal may outweigh the minimal risk of temporary, carefully monitored infusion of alcohol for therapeutic management.

Resources Allocated for Care

Findings in this study suggest that increased awareness, early screening and prompt initiation of therapy may provide an opportunity to curtail ICU resource use associated with acute alcohol withdrawal. The risk of longer duration of mechanical ventilation and ICU stay (25), and the independent association of alcohol withdrawal with the onset of sepsis, septic shock and increased all-cause hospital mortality(21, 38) support the notion of resource-consciousness as a desirable outcome in cases of alcohol withdrawal. In this study patients were screened and identified early for enrollment, providing an opportunity to initiate early treatment. Providing a more proactive, preventive approach may have contributed to the trend in decreased length of stay among patients in the ethanol arm.

Although this study was focused on safety and resource use rather than costs, actual costs of untreated withdrawal have been reported in many studies as a major concern (18). Standardized treatment strategies have been evaluated and have been effective in improving early identification of patients at risk (39). Advantages of early treatment initiation were also noted in this study, and a trend toward greater benefit in the ethanol arm was observed. For example patients in the ethanol / lorazepam arm experienced less agitation, fewer episodes of feeding tube displacement, and shorter CCU as well as overall hospital length of stay.

In summary, the efficacy of treatment strategies in the high risk acute MI patient population is difficult to evaluate in a rigorous, randomized, controlled trial. This study demonstrates that a randomized, controlled evaluation of treatment strategies can be safely conducted. Early screening and identification of high risk patients is feasible in the acute MI setting. .

Limitations

Several factors posed limitations in the conduct of the study including provider-perceived ethical issues and intermittent lapse in support for the intervention that was physician-dependent. House staff, attending physicians and some nurses were in disagreement with regard to the ethical nature of the treatment arm, and felt that administration of alcohol to patients who struggled with dependency was unethical. These differences resulted in some patients not being enrolled due to provider opposition and bias, which ultimately led to important discussions on the lack of empirical evidence in this patient population. These discussions also led to increased transparency among the care team and with families, which exposed differences in the level of acceptability of social norms for alcohol consumption. Differences in perspective limited the study in that some patients were removed from the study early, for example upon transfer to the step-down unit, based on concerns by the accepting physicians. In addition, some family members voiced similar ethical concerns.

Implications for Clinical Practice

This study appeared to have a positive influence on the management of alcohol withdrawal through changes in the standard approach to screening and management of high risk alcohol dependent patients experiencing acute MI, as well as changes in the overall unit culture related to alcohol withdrawal. First, the study resulted in provider consensus around a standard approach for treatment as well as patient assessment and screening for increased risk of alcohol withdrawal. Although treatment guidelines exist (32, 39, 40), consensus on the approach is not universal and no guidelines exist in the setting of acute MI. Therefore the local effort to study two strategies promoted increased collaboration among physicians and nurses, social workers, psychologist and pharmacists to identify a common practice. Others have implemented similar approaches in different patient populations that have been found to be successful (24, 39). As a result, not only did screening occur earlier in the acute MI treatment process, but in addition many patients were transitioned to the Duke Alcohol and Addictions Program following stabilization of the MI, and there received the opportunity for more person-centered care and long-term, community-based follow up.

Culturally, the frequent discussion of the study led to increased sensitivity of alcohol dependency, monitoring of patients for withdrawal, and discussion with patients and families issues surrounding alcohol dependence. By recognizing the prevalence of the problem of alcohol dependence and having tools to better identify and manage symptoms early, staff were more likely to engage with families and the health care team was able to present a more cohesive, systematic plan to the patients' families. The overall result appeared to be improved communication, both among the care provider team and between the team and the families. Plans for care and open discussion of the transition to ambulatory care and home following stabilization of the acute MI were observed to be more transparent and more frequent among participants during the study period.

Conclusions

This pilot study suggests that an alternative treatment strategy to *prevent* withdrawal in patients with alcohol dependence and experiencing acute myocardial infarction is safe. Treatment that includes alcohol in low dose, in conjunction with lorazepam, may prevent complications associated with alcohol withdrawal in the acute phase of acute coronary syndromes. The measures used to evaluate safety (the incidence and severity of CCU complications following MI) in this study were measures that might be used to show meaningful improvement in clinical outcomes in a larger study of treatment efficacy. Although this pilot study was not powered to test efficacy, patients receiving the non-traditional treatment strategy of alcohol in conjunction with benzodiazepines appeared to experience "safe passage" through a high risk and potentially lethal acute myocardial infarction event.

Acknowledgments

This publication was made possible by Grant Number 1 UL1 RR024128-01 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH.

References

1. Kumar S, Porcu P, Werner DF, Matthews DB, Diaz-Granados JL, Helfand RS, et al. The role of GABA(A) receptors in the acute and chronic effects of ethanol: a decade of progress. *Psychopharmacology (Berl)*. 2009; 205(4):529–64. Epub 2009/05/21. [PubMed: 19455309]
2. Bouchard NC, Meltzer A, Hoffman RS. Treatment of delirium tremens. *Arch Intern Med*. 2005; 165(5):587. author reply Epub 2005/03/16. [PubMed: 15767540]
3. Di Castelnuovo A, Costanzo S, di Giuseppe R, de Gaetano G, Iacoviello L. Alcohol consumption and cardiovascular risk: mechanisms of action and epidemiologic perspectives. *Future cardiology*. 2009; 5(5):467–77. Epub 2009/09/01. [PubMed: 19715411]
4. Stockley CS. Is it merely a myth that alcoholic beverages such as red wine can be cardioprotective? *Journal of the science of food and agriculture*. 2012; 92(9):1815–21. Epub 2012/04/17. [PubMed: 22505227]
5. Bertelli AA, Das DK. Grapes, wines, resveratrol, and heart health. *Journal of cardiovascular pharmacology*. 2009; 54(6):468–76. Epub 2009/09/23. [PubMed: 19770673]
6. Sacanella E, Vazquez-Agell M, Mena MP, Antunez E, Fernandez-Sola J, Nicolas JM, et al. Down-regulation of adhesion molecules and other inflammatory biomarkers after moderate wine consumption in healthy women: a randomized trial. *The American journal of clinical nutrition*. 2007; 86(5):1463–9. Epub 2007/11/10. [PubMed: 17991660]
7. Lakshman R, Garige M, Gong M, Leckey L, Varatharajalu R, Zakhari S. Is alcohol beneficial or harmful for cardioprotection? *Genes & nutrition*. 2010; 5(2):111–20. Epub 2009/12/17. [PubMed: 20012900]
8. Krenz M, Korthuis RJ. Moderate ethanol ingestion and cardiovascular protection: from epidemiologic associations to cellular mechanisms. *Journal of molecular and cellular cardiology*. 2012; 52(1):93–104. Epub 2011/11/02. [PubMed: 22041278]
9. Thun MJ, Peto R, Lopez AD, Monaco JH, Henley SJ, Heath CW Jr. et al. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. *The New England journal of medicine*. 1997; 337(24):1705–14. Epub 1997/12/11. [PubMed: 9392695]
10. Tolstrup J, Jensen MK, Tjønneland A, Overvad K, Mukamal KJ, Gronbaek M. Prospective study of alcohol drinking patterns and coronary heart disease in women and men. *BMJ*. 2006; 332(7552):1244–8. Epub 2006/05/05. [PubMed: 16672312]
11. Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB, De Gaetano G. Meta-analysis of wine and beer consumption in relation to vascular risk. *Circulation*. 2002; 105(24):2836–44. Epub 2002/06/19. [PubMed: 12070110]
12. Adinoff B, Ruether K, Krebaum S, Iranmanesh A, Williams MJ. Increased salivary cortisol concentrations during chronic alcohol intoxication in a naturalistic clinical sample of men. *Alcohol Clin Exp Res*. 2003; 27(9):1420–7. Epub 2003/09/25. [PubMed: 14506402]
13. Alcohol withdrawal syndrome: how to predict, prevent, diagnose and treat it. *Prescrire Int*. 2007; 16(87):24–31. Epub 2007/02/28. [PubMed: 17323538]
14. Bartrug B, Fullwood J, Rogers L, Bride W. Delirium tremens in acute myocardial infarction. *Heart Lung*. 1994; 23(1):21–6. Epub 1994/01/01. [PubMed: 8150640]
15. Bard MR, Goettler CE, Toschlog EA, Sagraves SG, Schenarts PJ, Newell MA, et al. Alcohol withdrawal syndrome: Turning minor injuries into a major problem. *J Trauma*. 2006; 61(6):1441–5. discussion 5-6. Epub 2006/12/13. [PubMed: 17159688]
16. Compton P. Caring for an alcohol-dependent patient. *Nursing*. 2002; 32(12):58–63. quiz N242. Epub 2002/12/07. [PubMed: 12468945]
17. McKinley MG. Alcohol withdrawal syndrome overlooked and mismanaged? *Crit Care Nurse*. 2005; 25(3):40–2. 4–8. quiz 9. Epub 2005/06/11. [PubMed: 15946927]
18. Genther DJ, Gourin CG. The effect of alcohol abuse and alcohol withdrawal on short-term outcomes and cost of care after head and neck cancer surgery. *Laryngoscope*. 2012 Epub 2012/05/09.
19. Buchsbaum DG, Buchanan RG, Centor RM, Schnoll SH, Lawton MJ. Screening for alcohol abuse using CAGE scores and likelihood ratios. *Ann Intern Med*. 1991; 115(10):774–7. Epub 1991/11/15. [PubMed: 1929025]

20. Monte R, Rabunal R, Casariego E, Bal M, Pertega S. Risk factors for delirium tremens in patients with alcohol withdrawal syndrome in a hospital setting. *Eur J Intern Med.* 2009; 20(7):690–4. Epub 2009/10/13. [PubMed: 19818288]
21. Monte R, Rabunal R, Casariego E, Lopez-Agreda H, Mateos A, Pertega S. Analysis of the factors determining survival of alcoholic withdrawal syndrome patients in a general hospital. *Alcohol Alcohol.* 2010; 45(2):151–8. Epub 2010/01/16. [PubMed: 20075027]
22. Mennecier D, Thomas M, Arvers P, Corberand D, Sinayoko L, Bonnefoy S, et al. Factors predictive of complicated or severe alcohol withdrawal in alcohol dependent inpatients. *Gastroenterol Clin Biol.* 2008; 32(8-9):792–7. Epub 2008/09/02. [PubMed: 18757147]
23. Tran DT, Stone AM, Fernandez RS, Griffiths RD, Johnson M. Changes in general nurses' knowledge of alcohol and substance use and misuse after education. *Perspect Psychiatr Care.* 2009; 45(2):128–39. Epub 2009/04/16. [PubMed: 19366423]
24. Crumpler J, Ross A. Development of an alcohol withdrawal protocol: a quality of care initiative. *J Nurs Care Qual.* 2005; 20(4):297–301. Epub 2005/09/24. [PubMed: 16177579]
25. Rayner SG, Weinert CR, Peng H, Jepsen S, Broccard AF. Dexmedetomidine as adjunct treatment for severe alcohol withdrawal in the ICU. *Annals of intensive care.* 2012; 2(1):12. Epub 2012/05/25. [PubMed: 22620986]
26. Lee JH, Jang MK, Lee JY, Kim SM, Kim KH, Park JY, et al. Clinical predictors for delirium tremens in alcohol dependence. *J Gastroenterol Hepatol.* 2005; 20(12):1833–7. Epub 2005/12/13. [PubMed: 16336440]
27. Coffey R, Murphy CV. Effects of alcohol use and abuse on critically ill burn patients. *Critical care nursing clinics of North America.* 2012; 24(1):1–7. Epub 2012/03/13. [PubMed: 22405708]
28. Jochum T, Schulz S, Schein M, Schroder R, Voss A, Bar KJ. Heart rate turbulence during acute alcohol withdrawal syndrome. *Drug Alcohol Depend.* 2012; 122(3):253–7. Epub 2011/11/08. [PubMed: 22055013]
29. Bar KJ, Boettger MK, Koschke M, Boettger S, Groteluschen M, Voss A, et al. Increased QT interval variability index in acute alcohol withdrawal. *Drug Alcohol Depend.* 2007; 89(2-3):259–66. Epub 2007/03/14. [PubMed: 17350180]
30. Caputo F, Bernardi M. Medications Acting on the Gaba System in the Treatment of Alcoholic Patients. *Curr Pharm Des.* 2010 Epub 2010/05/21.
31. Barrons R, Roberts N. The role of carbamazepine and oxcarbazepine in alcohol withdrawal syndrome. *J Clin Pharm Ther.* 2010; 35(2):153–67. Epub 2010/05/12. [PubMed: 20456734]
32. Mayo-Smith MF, Beecher LH, Fischer TL, Gorelick DA, Guillaume JL, Hill A, et al. Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Arch Intern Med.* 2004; 164(13):1405–12. Epub 2004/07/14. [PubMed: 15249349]
33. Spies CD, Otter HE, Huske B, Sinha P, Neumann T, Rettig J, et al. Alcohol withdrawal severity is decreased by symptom-orientated adjusted bolus therapy in the ICU. *Intensive Care Med.* 2003; 29(12):2230–8. Epub 2003/10/15. [PubMed: 14557857]
34. Hecksel KA, Bostwick JM, Jaeger TM, Cha SS. Inappropriate use of symptom-triggered therapy for alcohol withdrawal in the general hospital. *Mayo Clin Proc.* 2008; 83(3):274–9. Epub 2008/03/05. [PubMed: 18315992]
35. 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(3):724–30. Epub 2007/01/27. [PubMed: 17255852]
36. Hodges B, Mazur JE. Intravenous ethanol for the treatment of alcohol withdrawal syndrome in critically ill patients. *Pharmacotherapy.* 2004; 24(11):1578–85. Epub 2004/11/13. [PubMed: 15537562]
37. Weinberg JA. Comparison of Intravenous Ethanol Versus Diazepam for Alcohol Withdrawal Prophylaxis in the Trauma ICU: Results of a Randomized Trial. *The Journal of Trauma Injury, Infection and Critical Care.* 2008
38. Khan A, Levy P, DeHorn S, Miller W, Compton S. Predictors of mortality in patients with delirium tremens. *Acad Emerg Med.* 2008; 15(8):788–90. Epub 2008/07/22. [PubMed: 18638029]

39. Repper-DeLisi J, Stern TA, Mitchell M, Lussier-Cushing M, Lakatos B, Fricchione GL, et al. Successful implementation of an alcohol-withdrawal pathway in a general hospital. *Psychosomatics*. 2008; 49(4):292–9. Epub 2008/07/16. [PubMed: 18621934]
40. Hayanga A, Weiss E. A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. *Crit Care Med*. 2007; 35(7):1809–10. author reply 11-2. Epub 2007/06/22. [PubMed: 17581393]

Figure 1.
AWARE Study Enrollment and Randomization Algorithm

Table 1

Summary Of Participant Characteristics By Treatment Group

Demographic characteristic	Lorazepam n=29	Ethanol/Lorazepam n=28	P-value
Age			
Mean (SD)	54.4 (10.1)	51.4 (14.4)	0.18
Median	54	48.5	
Sex (n / %)			
Male	27 (93.1%)	26 (92.9%)	0.97
Female	2 (6.9%)	2 (7.1%)	
Race (n / %)			
White	17 (58.6%)	20 (71.4%)	0.32
Non-white	12 (41.4%)	8 (28.6%)	
Diagnosis (n / %)			
AMI	24 (82.8%)	24 (85.7%)	0.76
GI Bleed,NQWMI or USA	5 (17.2%)	4 (14.3%)	
Location of MI (n / %)			
Anterior	4 (17.39%)	5 (22.73%)	0.29
Inferior	12 (52.17%)	10 (45.45)	
Inferior-lateral	0 (0%)	1 (4.55)	
Anterior-lateral	1 (4.35)	4 (18.18%)	
Non Q-wave	6 (26.09%)	2 (9.09%)	
Comorbid Illnesses (n / %)			
Diabetes	4 (20%)	3 (15.79%)	0.74
HTN	16 (80%)	16 (84.21%)	
Current Smoker (n / %)			
Yes	21 (72.41%)	19 (63.33%)	0.46
No	8 (27.59%)	11(36.76%)	
History of Alcohol Withdrawal (n / %)			
Yes	8 (27.5%)	21 (72.4%)	0.86
No	7 (25%)	21 (75%)	

Table 2

Characteristics For Cardiac Care Unit (CCU) Course By Treatment Group

Factor	Lorazepam n=29	Ethanol/Lorazepam n=28	P-value
Delirium Tremens			
Yes	6 (20.69%)	5 (17.86%)	0.79
No	23 (79.31%)	23 (82.14%)	
(Re)infarction			
Yes	29 (100%)	27 (96.43%)	0.31
No	0	1 (3.57%)	
Ischemia			
Yes	1 (3.45%)	1 (3.57%)	0.98
No	28 (96.55%)	27 (96.43%)	
Intubations			
Yes	3 (10.34%)	1 (3.57%)	0.30
No	26 (89.66%)	27 (96.43%)	
Death			
Yes	1 (3.45%)	0	0.33
No	28 (96.55%)	28 (100%)	
Extubation			
Yes	1 (3.45%)	1 (3.57%)	0.98
No	28 (96.55%)	27 (96.43%)	
Displaced Feeding Tubes			
Yes	1 (3.45%)	0	0.33
No	28 (96.55%)	28 (100%)	
Ventricular Tachycardia			
Yes	1 (3.45%)	0	0.33
No	28 (96.55%)	28 (100%)	
Agitation			
Yes	11 (37.93%)	6 (21.43%)	0.18
No	18 (62.07%)	22 (78.57%)	
Orientation			
Yes	14 (48.28%)	6 (21.43%)	0.04
No	15 (51.72%)	22 (78.57%)	
Hyperadrenergic State			
Yes	7 (24.14%)	6 (21.43%)	0.81
No	22 (75.86%)	22 (78.57%)	

Table 3

Summary of Complications by Treatment Group

Endpoint	Lorazepam n=29	Ethanol/ Lorazepam n=28	p-value
CCU Complications (count)			0.56
0	22 (75.86)	23 (82.14)	
1-4	7 (24.14)	5 (17.86)	
Composite Complications			0.75
0	22 (75.86)	23 (82.14)	
1	7 (24.14)	5 (17.86)	
Number of Other CCU Complications			0.40
0	14 (24.56)	19 (67.86)	
1-5	15(51.72)	9(32.14)	
Withdrew from drug regimen within 3 days			0.15
Yes	7 (12.28)	24 (42.11)	
No	22 (38.60)	4 (7.02)	

Table 4

CCU Length Of Stay And Hospital Length Of Stay By Treatment Group

Factor	Lorazepam n=29	Ethanol/Lorazepam n=28	p-value
CCU Length of Stay			
Mean (SD)	4 (6.9)	2 (2.1)	
Median	2	1	p=0.32
Hospital Length of Stay			
Mean (SD)	8 (6.2)	7.7 (6.4)	
Median	6	5	p=0.72