Supplemental Information

Experimental Design

This is a double-blind active-controlled parallel group randomized clinical trial (RCT). Patients were evaluated at the time of enrollment in outpatient substance abuse treatment and followed weekly for 24 weeks. All patients received a psychosocial intervention based in a validated theoretical model (see below) as well as usual treatment for coexistent psychiatric conditions. In addition, they were randomized to receive either sodium valproate or naltrexone, a standard of care active comparator. Randomization was done stratifying by the frequency and intensity of the psychotherapeutic treatment [i.e. whether participants were enrolled in an intensive outpatient program (SAMHSA Level 2) or assisted to weekly appointments with an addiction counselor (SAMHSA Level 1)].
The evaluation of drinking outcomes was done by expert personnel from the Iowa Consortium for Substance Abuse. The Consortium is involved with many local and statewide evaluation projects and has a vast experience with data collection with the proposed target population. In addition, the staff is familiarized with Government Performance and Results Act that utilizes highly effective tracking and follow-up techniques. The Consortium conducts multiple follow-up evaluations related to treatment outcomes. The follow-up success rates on these projects are 80% or higher. Evaluators were not involved in any aspect of treatment and were blind to the randomized intervention status. However, evaluators had close contact with the patients to foster compliance and reduce attrition rates.

Study participants

Participants were male veterans 18 to 60 years old, with an AUD and no other substance use besides nicotine or cannabis. All subjects underwent successful detoxification before starting treatment. Veterans were enrolled at the outpatient substance abuse treatment programs in two sites: the Iowa City VA Medical Center in Iowa City, Iowa; and the Michael E DeBakey VA Medical Center in Houston, Texas. Veterans with psychotic disorders, with significant medical comorbidities that contraindicated the use of the interventional drugs, and Veterans who had multiple treatment failures during the 2 years before enrollment, were excluded from the study.

Inclusion Criteria:

1. Aged 18 to 60 years old.
2. Presence of a diagnosis of alcohol dependence according to DSM-IV criteria.
3. A recent history of heavy drinking defined as 5 or more drinks in a sitting at least two times in one week during the previous two months.
4. Absence of withdrawal symptoms as measured by the Revised Clinical Institute Withdrawal Assessment for Alcohol Scale (*119*).
5. Presence of a knowledgeable informant.

Exclusion Criteria:

1. Evidence of other substance abuse different from nicotine or cannabis assessed by DSM-IV criteria in the last 90 days or by two consecutive positive urine drug screens.
2. The veteran has an unstable medical condition such as severe heart disease, liver or renal failure or evidence of neoplasia. In addition, patient with liver enzymes (ALT, AST) serum levels > 3 times the upper limit of normal will be excluded from the study.
3. The veteran has an unstable psychiatric condition that requires treatment in more structured settings (e.g., active suicidal ideation, worsening psychotic symptoms or acute mania).
4. The veteran has a diagnosis of schizophrenia or schizoaffective disorder.
5. The veteran currently requires therapy with valproate or naltrexone or has a history of significant side effects from either study drug.
6. The veteran requires therapy with topiramate, lamotrigine or carbamazepine.
7. The veteran requires chronic treatment with opioid analgesics for refractory pain.
8. The veteran has failed three previous intensive alcohol treatment programs in the past 2 years.
9. The veteran is a woman.

Randomization Procedure

Patients were randomized using a permuted blocks randomization scheme. Treatment randomization was stratified by psychosocial rehabilitation treatment frequency as this might be a major predictor of recovery. Within each stratum we randomly assigned two block sizes and within each block we randomly assigned the two treatments. This randomization scheme provides a less unbalanced sample size in each stratum at the end of the study than a simple randomization technique while helping to keep the professionals assessing the patient from guessing the treatment allocation scheme. To further ensure this, the block sizes used were not disclosed to these professionals. The randomization tables were physically separated from them and only members of the research team not requiring blinding had access to them.

Primary and secondary outcomes

The primary outcome variable was the time to relapse to heavy drinking as defined by having 5 or more drinks in a sitting and was assessed using the Timeline Followback (TLFB) method (*112*). Thus, a structured questionnaire reviewed the amount of alcohol that the patient had consumed on each of the days of the previous week. Additional outcomes include time to the first drink as well as the percentage of drinking weeks during the follow-up period. The evaluation of drinking outcomes was done by experts from the Iowa Consortium for Substance Abuse. Information sources included the participants' report and the input of a knowledgeable informant. Evaluators were not involved in any aspect of treatment and were blind to the randomized intervention status.

Valproate and Naltrexone Dosing

Sodium valproate extended release tablets were initiated at a dosage of 250 mg per day, taken approximately 30 minutes after a meal. Dosage was increased up to a dose of 1000 mg per day. We used a fixed dose of valproate to minimize side effects and increase tolerability within a population with mild liver abnormalities. However, serum valproate levels in our subjects were

within a therapeutic range. Naltrexone was given once per day in a dose of 25 mg for the first 4 days and 50 mg thereafter up to completion of the protocol. All naltrexone and valproate pills were identical in appearance. Compliance was assessed weekly concurrently with the determination of alcohol consumption.

Adverse Events

An adverse event was defined as any undesirable medical event with new onset or significant exacerbation during the study, regardless of the fact it was considered to be related to the study medication. Adverse events were graded on a three-point ordinal scale: 1) Mild = Discomfort noticed, but no disruption to daily activity; 2) Moderate = Discomfort sufficient to reduce or affect normal daily activity; 3) Severe = Inability to perform normal daily activity. Adverse events were recorded in *ad hoc* clinical report forms (CRF).

Criteria for Early Termination of the Study

1) Patient experiences an allergic or idiosyncratic reaction to the study drug.
2) Patient develops an intercurrent illness during the study that requires treatment that is not consistent with the protocol requirements or represents too great a risk for continued participation in the trial.
3) Patient experiences a serious adverse event or presents a serious laboratory abnormality that constitutes an unacceptable risk.
4) Patient requests to be withdrawn from the study.
5) Non-compliance or refusal of treatment or assessment.
6) Patient develops severe psychiatric symptoms, including suicidality or psychosis. These patients will be evaluated in emergency settings to determine if they require a more intensive level of care and need to be discharged from the study. Patients and relatives will be given emergency contact numbers with psychiatric help available on a 24/7 basis. They will be instructed to bring the patient to the emergency room at the VAMC in Iowa City or in other VA facilities near their home. In addition, medications will be dispensed to patients on a 2-week basis so they will never have a large amount of medication on hand.

Psychosocial Intervention

AUD Treatment programs provided by the Mental Health services at the Iowa City VAMC and the Michael E DeBakey VA Medical Center (MEDVAMC) are based on the Matrix Intensive Outpatient Drug and Alcohol Treatment Model. This model is an integrated therapeutic approach incorporating evidence-based treatment modalities including: cognitive behavioral therapy, motivational enhancement therapy, couples and family therapy and education, twelve-step facilitation, group therapy and social support, and individual supportive psychotherapy and education. Patients were seen at least 1 time per week in the context of this model. This flexible approach was adopted to include those veterans with alcohol use disorders who seek rehabilitation treatment but have limited time to assist to the program because of their work obligations. Although these patients present less severe forms of alcohol dependence they might be significantly impaired (e.g. about their interpersonal and family functioning) and require specialized treatment to resolve these problems and to prevent progression to more severe form of the disease. Typically, however, the patients assisted to the IOP at least 3 times per week for the initial 4 weeks, at least 2 times per week during weeks 5 to 8, once weekly during

weeks 9 to 12, 16, 20 and 24. The treatment team had flexibility to increase the number of encounters attending to the circumstances of a case.

More specifically, the Matrix Model is a comprehensive, multi-format 16-week intensive outpatient treatment program with up to 52 weeks of follow-up social support group sessions made up of the following components:

- Individual / Conjoint therapy sessions: three fifty-minute meetings during the intensive phase of treatment between the client and his counselor.
- Early recovery group sessions: this group meets twice weekly and consists of eight fifty-minute group sessions during the first month of treatment.
- Relapse prevention group sessions: this group meets twice weekly and consists of thirty-two ninety-minute group sessions for sixteen weeks.
- Family education group sessions: this group meets once weekly and consists of twelve ninety-minute group sessions for the first three months.
- Social support group sessions (Continuing Care): this group meets weekly and consists of thirty-six ninety-minute group sessions, beginning at week thirteen.

Neuropsychiatric Assessment

Diagnosis of comorbid psychiatric conditions was made using the Mini-International Neuropsychiatric Interview (M.I.N.I.) * while the severity of depressive, anxiety and PTSD symptoms was measured by the Hamilton Depression Rating Scale (HDRS)*, the Hamilton Anxiety Rating Scale (HARS)* and the Patient Checklist (PCL)*. Severity of AUD was assessed through the Alcohol Use Disorders Identification Test (AUDIT)*. Ascertainment of the presence and severity of TBI was done using the Ohio State University TBI Inventory*.
The full psychiatric assessment took about 2 hours to complete and was divided into two 1-hour sessions. Psychiatric assessments will be obtained at baseline, 12-week and 24-week visits.

Statistical Analysis

Power and Sample size

A total of 32 participants in each group, when patients receiving naltrexone are compared to patients receiving valproate, will allow us to have 85% power (at alpha 0.05) to detect a drop in the relapse to heavy drinking from 76% to 40% after the 24 weeks of treatment using the two-sample log rank test. This is equivalent to a 2.8 hazard ratio (HR). The rationale for targeting a large effect for this hypothesis is based on the large effect found by a double-blinded placebo-controlled clinical trial of valproate in patients with AUD and psychiatric co-morbidities (132), a sample similar in many aspects to the sample of participants that will be included in this study. We consider that a 60% reduction in the probability of completing 24 weeks of treatment without relapsing to heavy drinking (i.e., from 60% to 24%) is a clinically meaningful effect when it comes to determine if valproate is more effective than naltrexone to treat AUD. This power analysis is assuming that we will have a 20% of participants lost to follow-up in both groups.

Because recruitment delay resulting from moving from the Iowa City VA to the MEDVAMC, the final number of participants enrolled was 31 in each group. The power decreases slightly and equals to 83% under the final sample size.
We will use a two-sided alpha of 0.05 in all analyses. There is a single primary outcome, time to relapse to heavy drinking. Therefore, multiplicity is not an issue for the primary analysis. Secondary analyses and sensitivity analyses are not adjusted for multiple comparisons, and the results should be interpreted as exploratory.

Analysis for Aim 1.

Aim 1: To determine if valproate is more effective than naltrexone to treat AUD in a group of veterans with a high frequency of coexistent psychiatric disorders and history of TBI.
We hypothesized that time to relapse to heavy drinking would be longer in patients treated with valproate when compared with patients treated with naltrexone. In order to assess this hypothesis, we analyzed these data using survival techniques. The procedures for determining whether and when a participant relapsed to heavy drinking are detailed in the Primary and Secondary Outcomes section. The primary efficacy analysis was conducted using a two-sample log-rank test, to compare the event time between the two study groups. Analysis followed the intention-to-treat principle, and all randomized subjects were included.

Additional analyses were conducted to gain further insights. First, we computed a 24-week Kaplan-Meier survival curve by study group. Next, a sensitivity analysis will be conducted using the Cox proportional hazards (PH) hazards model with the exact partial likelihood, taking the psychosocial rehabilitation treatment frequency (the stratifying variable) and site into account. Specifically, model covariates included study group (Naltrexone vs. Valproate) and site (Texas vs. Iowa), and the psychotherapeutic treatment frequency (High vs. Low) was included as a stratification factor. Finally, we ran exploratory multivariate analyses to additionally adjust for important baseline characteristics and baseline characteristics that are not well-balanced in the Cox model. The covariate effects were summarized by hazard ratio (HR) and the corresponding 95% confidence intervals. P-values were obtained using the likelihood ratio tests. The PH assumption that underlies the Cox PH model was tested for all model covariates.

We also conducted secondary analyses to examine the effect of study group on the secondary outcomes, such as time to any drinking and the proportion of drinking weeks. Time to any drinking is an event time outcome and can be analyzed using similar strategies (i.e., log rank test and Cox PH models) as the primary outcome. To examine the proportion of drinking weeks, we adopted the Generalized Estimating Equation (GEE) with logit link, where the outcome is whether the participant drink or not during each follow-up week (Yes vs. No). The working independence correlation was used to handle intra-subject correlation.

Analysis for Aim 2

Aim 2: To determine whether the presence of prefrontal brain damage will be associated with poorer response to substance abuse treatment.

Aim 2.1. We hypothesized that time to relapse to heavy drinking would be shorter in veterans with TBI than in patients without TBI. To evaluate this, we adopted a Cox PH model that adjusts for baseline TBI severity (None, Mild, Moderate to Severe), with None being the reference level. The model also included study group and site as fixed terms, and rehabilitation treatment frequency as a stratification variable. Possible confounders included baseline PTSD status and time since injury. The coefficients corresponding to the TBI variable were tested using the likelihood ratio test.

Aim 2.2. We hypothesized that time to relapse to heavy drinking would be positively associated to prefrontal gray matter volume. This will be assessed in a Cox PH model with time to relapse as the outcome and prefrontal gray matter volume as the independent variable. Study arm, site and rehabilitation treatment frequency will be accounted for. We will also explore whether the association persists after adding to the model potential confounders, such as age, time since injury and total intracranial volume.

Aim 2.3. We hypothesize that time to relapse to heavy drinking will be significantly associated to Fractional anisotropy (FA) in major limbic pathways (i.e., cingulate bundle and uncinate fasciculus). Analytic strategies will be similar to those in Aim 2.2.