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Differences between Treatment-Seeking and Nontreatment-Seeking Alcohol Dependent Research Participants: an Exploratory Analysis

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Abstract

Background—Alcoholism is a chronic relapsing disorder with complex behavioral and functional heterogeneity. To date, attempts to characterize subgroups of alcohol-dependent individuals has largely been focused on categorical distinctions based on behaviors such as ability to abstain, age of onset and drinking motives, but these have failed to yield predictors of treatment response and disease course. The distinction between alcohol dependent individuals who are or are not interested in treatment holds significant implications for interpreting results of human laboratory studies with nontreatment-seekers and clinical trials with treatment-seeking alcohol dependent patients. However, despite their crucial role in alcohol-related research, these two groups are poorly defined. In this exploratory analysis, we attempt to better define the phenotypic differences between these two experimentally relevant populations.

Methods—We analyzed data from alcohol-dependent individuals who participated in screening protocols to evaluate their suitability for participation in either treatment or nontreatment research studies at NIAAA. Scores on individual measures from a battery of behavioral, neuropsychological and blood laboratory measures were compared between those who presented seeking treatment for alcohol dependence and those who were not seeking treatment. Differences

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in each measure were assessed between the two groups. In addition, we explored whether significant differences were apparent when drinking behavior was used as a covariate.

Results—Treatment-seekers manifested more impairment compared to nontreatment seekers on a wide variety of measures in the following categories: alcohol drinking, personality, impulsivity, trauma/stress, cognition, aggression, mood and liver enzyme tests. Treatment seekers endorsed a greater number of alcohol dependence criteria. Several measures including elevations in liver enzyme tests, remained significantly different between the two groups when average daily alcohol consumption per drinking day was used as a covariate.

Conclusions—Treatment-seeking subjects, compared to nontreatment-seeking alcohol-dependent subjects who present for alcohol-related research studies, differ in characteristics beyond the quantity of alcohol consumption. Implications of these differences with respect to clinical research for treatments of alcohol dependence are discussed.

Keywords

alcohol use disorder; alcohol dependence; treatment; treatment seeking; nontreatment seeking

Introduction

Alcohol Dependence (AD) as defined by criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th edition, is a chronic relapsing disorder and a costly public health problem with a lifetime prevalence of 30.3% in the United States (Hasin et al., 2007). Alcohol Use Disorder as defined in DSM-5 has a comparable lifetime prevalence of 29.1% (Grant et al., 2015). Similar to other psychiatric illnesses such as depression, anxiety and psychosis, AD is a complex condition with tremendous behavioral and functional heterogeneity. Attempts to refine the classification of alcohol-dependent patients has largely been focused on categorical distinctions based on behaviors such as the ability to abstain, age of onset and motives for drinking. These approaches have failed to yield well-defined predictors of treatment response and disease course (Moos and Moos, 2006, Boschloo et al., 2012, Leggio et al., 2009). Defining, more precisely, individual behavioral differences within the AD population will aid in identifying effective treatments that may be matched to specific sub-groups of AD individuals.

An important but poorly understood feature of AD is the difference in characteristics between those who seek treatment compared to those who do not seek treatment for AD. Notably, only 8.4% of those with AD ever receive treatment (Substance Abuse and Mental Health Services Administration, 2014). The reasons for this are complex and stem from manifold societal and individual factors (Xu et al., 2008). According to the Health Belief Model (Bardsley and Beckman, 1988) and stress and coping models (Finney and Moos, 1995), important factors in the decision to seek treatment for addiction are more severe consequences of drinking and greater perceived severity of the illness; in addition, individuals with addiction who present to the criminal justice system are often court-mandated to treatment. Opposing these are barriers to seeking treatment such as resistance to reduce drinking, cost, stigma and accessibility of treatment (Xu et al., 2008, Andréasson et al., 2013, Substance Abuse and Mental Health Services Administration, 2009).

Epidemiological research, conducted largely in community cohorts, has identified factors associated with treatment-seeking behavior in AD individuals: older age, male sex, non-white race, as well as unemployed or unmarried status (Weisner, 1993). The relationship between social consequences and engagement in treatment is mixed, with studies finding positive, negative or no influence on treatment entry (Weisner, 1993, Weisner and Matzger, 2002, Finney and Moos, 1995). Impaired memory and executive function are also associated with reduced motivation for treatment in AD individuals (Le Berre et al., 2012).

In contrast to community treatment settings for AD, research settings for AD are unique in that both treatment- and nontreatment-seeking AD subjects participate in clinical studies. Nontreatment-seeking individuals with AD are often recruited for participation in early stage studies that evaluate a potential therapeutic drug for AD for safety and tolerability when given in combination with alcohol. These studies involve alcohol administration paradigms where the effect of an experimental drug to reduce alcohol craving and self-administration is also measured. If promising, further larger clinical trials are conducted in the treatment-seeking AD population (Litten et al., 2016). Given this, the characteristics of these two groups are important to understand in order to evaluate potential therapeutic strategies, both psychosocial and pharmacologic. In particular, it is important to know if the nontreatment-seeking group has distinct characteristics that might independently affect study outcome measures, thereby creating a confound in this field of clinical research.

Accordingly, in this study, we sought to compare psychological and physiological characteristics of treatment-seeking vs. nontreatment-seeking AD individuals among participants interested in participating in alcohol-related research studies. We sought to identify underlying characteristic differences within our research population to characterize the individual variability across these two experimentally and clinically relevant groups.

Methods

Participants

Data was analyzed from three protocols at the National Institute on Alcohol Abuse and Alcoholism (NIAAA) implemented to screen treatment- and nontreatment-seeking, AD research participants from 2008 to 2015. Participants were recruited through word of mouth, community outreach, the National Institutes of Health (NIH) website, as well as online and newspaper advertisements. Subject preference to receive treatment or not was determined through a phone screen. A health care practitioner later confirmed the treatment or nontreatment-seeking status at the time of the in-person outpatient visit (for nontreatment-seeking subjects) or inpatient admission (for the treatment-seeking subjects). These protocols were approved by the NIH Institutional Review Board and individuals gave written informed consent before participating. Only participants who met criteria for AD were included in this study (n = 791). Among them, 615 were treatment-seekers and 176 were nontreatment-seekers. Participants were not simultaneously in both groups.

Screening Measures

As part of these screening protocols, both treatment- and nontreatment-seekers participants underwent a large battery of medical, psychological and psychiatric tests. Broadly, their measures fall into the following categories: personality, impulsivity, trauma/stress, drinking, cognition, aggression, and mood. These measures consisted of continuous and categorical variables with scales that varied from yes/no questions to Likert scale responses. These measures were chosen by NIAAA investigators to give a comprehensive assessment of neuropsychological factors related to AD, general health as well as to determine suitability for other research protocols.

The Structured Clinical Interview for DSM Disorders (SCID)(First et al., 2002), was conducted to assess psychiatric as well as alcohol and substance use disorders (DSM-IV). DSM-IV criteria were parsed into two groups. One contained the AD criteria that reflects the positive reinforcing effect of drinking: tolerance and drinking more than planned; the other contained criteria associated with the negative effects of AD: unsuccessful attempts to cut down, missed activities because of drinking, psychological problems because of drinking and withdrawal symptoms. Group differences in the number of criteria endorsed in each of these two categories as well as the total number of AD criteria endorsed were assessed. Family history density of AD was also measured using the Family Tree Questionnaire (FTQ) (Mann et al., 1985). Recent alcohol use was assessed using a timeline follow-back questionnaire (TLFB)(Sobell and Sobell, 1996).

Subjects also underwent assessments of cognitive ability [Wechsler Abbreviated Scale of Intelligence (WASI)](Wechsler, 1999), mood [Comprehensive Psychopathological Rating Scale (CPRS)](Mattila-Evenden et al., 1996), impulsivity [Barratt Impulsivity Scale (BIS) (Patton et al., 1995) and UPPS-P Impulsive Behavior Scale](Lynam et al., 2006), personality (Neuroticism-Extraversion-Openness (NEO))(Costa and McCrae, 1997), aggression (Buss-Perry Aggression Questionnaire (BPAQ)(Buss and Perry, 1992)) and early life stress/trauma (Early Life Stress Questionnaire (ELSQ)(McFarlane et al., 2005), Childhood Trauma Questionnaire (CTQ)(Bernstein et al., 2003)).

Standard clinical laboratory biomarkers conducted at the NIH Clinical Center included a hepatic panel (alanine aminotransferase (ALT); aspartate aminotransferase (AST); alkaline phosphatase, gamma-glutamyl transferase (GGT)), a mineral panel (calcium, magnesium, phosphorus, potassium and sodium), albumin, hemoglobin, mean corpuscular volume, hepatitis B antigen, and hepatitis C antibody.

Analysis

For continuous measures, means, standard deviations (SD) and 95% confidence intervals (CI) are presented for each group. Group differences were tested for significance via independent samples t-tests (if normally distributed) or independent samples Mann-Whitney U tests (if non-normally distributed). Normality was tested by the Shapiro Wilk Test. For categorical measures, frequencies and prevalence rates are presented; and group differences were tested for significance via Pearson's chi-square test (or Fishers Exact tests). Odds ratios (ORs) and 95% CIs were obtained for dichotomous measures via logistic regression.

To determine whether alcohol consumption accounted for group differences, all models were re-run with drinks per drinking day included as covariate. In the case for continuous measures, analysis of covariance (ANCOVA) and rank analysis of covariance (Quade, 1967) were used for normally and non-normally distributed measures, respectively. For dichotomous variables, logistic regression was used.

For all statistical tests, $p < 0.05$ (two-tailed) was considered statistically significant. As this is an exploratory analysis, no adjustments were made for multiple tests. Data were analyzed using SPSS (IBM© SPSS© Version 20).

Results

Group Differences in Demographics:

Treatment seekers, as compared to non-treatment seekers, were more likely to be women and white (Table 1). The groups did not differ significantly by age.

Group Differences in Behavioral and Neuropsychological Measures:

Group differences on the behavioral and neuropsychological measures are shown in Table 2. As each of these measures was not normally distributed, group differences were tested using the Mann-Whitney U Test. Treatment-seekers reported drinking significantly more total alcohol drinks, drinks per drinking day and heavy drinking days. Treatment-seekers, compared to non-treatment seekers, scored significantly higher on measures of personality (neuroticism and conscientiousness), impulsivity (almost every subscale of the BIS and UPPS), and trauma/stress (early life stress events, childhood emotional abuse, and physical neglect). They also scored significantly higher on aggression, and endorsed more symptoms of depression and anxiety. Treatment seekers also had significantly higher IQ, and scored higher on measures cognitive complexity and cognitive instability.

After covarying for drinking behavior, 18 of 26 of the neuropsychiatric measures remained significantly different between groups and 2 group differences emerged on measures of physical aggression (Nontreatment > Treatment) and years of education (Treatment > NonTreatment) (Table 2).

Group Differences in DSM-IV Criteria for AD:

In addition to endorsing significantly greater number of total AD criteria [Mean (SD): 5.70(1.61) vs 4.51(1.39); $F(1,757)=75.13$, $p < .001$], treatment seekers endorsed more negative reinforcing AD criteria compared to nontreatment seekers (Table 2). There was no group difference in the number of positive reinforcing criteria endorsed. The group differences in number of total AD criteria and negative dependence criteria remained significant after average drinks per drinking day was used as a covariate. In addition, there were group differences in the individual criteria endorsed: unsuccessful attempts to cut down on drinking, spending a lot of time drinking, missing activities because of drinking, psychological problems because of drinking and withdrawal were more frequently endorsed in treatment seekers compared to non-treatment seekers (Table 3).

Group Differences in Blood Biomarkers:

Significant group differences in liver enzyme tests (ALT, AST and GGT) clinically used as biomarkers of alcohol use were observed (Table 2), with treatment-seekers having higher levels for each as compared to non-treatment seekers. Notably, group differences in these persisted after controlling for drinking behavior. Statistically significant group differences were also found for hemoglobin, MCV, iron, albumin and sodium, but both groups fell within the “normal” range, therefore suggesting that this variability was not clinically relevant (*data not shown*). No group differences were observed for the prevalence of serum Hepatitis B surface antigen or Hepatitis C antibody.

Discussion

This exploratory study examined differences between treatment-seeking and nontreatment-seeking AD research participants who were characterized with a comprehensive battery of behavioral, neuropsychological, and clinical measures as well as diagnostic (DSM-IV) criteria. These results are relevant to designing and interpreting results from clinical research studies of AD individuals. An exploratory approach applied to a large number of neurobehavioral measures identified categories where multiple measures therein were significantly different between groups. The categories were measures related to: alcohol drinking, personality, impulsivity, trauma/stress, cognition, and mood. In general, the treatment-seeking group showed more severe behaviors in several of the measures included in each of these categories. When compared based on their desire to engage in treatment, these two groups diverge with respect to their scores in diverse domains and remain divergent after controlling for drinking behavior.

With respect to DSM-IV criteria, predictably, treatment-seeking participants endorsed more DSM-IV dependence criteria and preferentially endorsed the criteria related to negative consequences of use. Indeed, perceived severity of the illness is an important factor in treatment entry (Bardsley and Beckman, 1988). In line with this, treatment-seekers endorsed more severe drinking patterns and this was supported by correspondingly higher levels of liver-related blood biomarkers of alcohol use in the treatment-seekers. That said, covarying for average drinks per drinking day removed neither significant group differences in DSM-IV AD criteria nor group differences in these biomarkers, suggesting that some other biobehavioral aspect of their drinking behavior is responsible for this group difference.

Another interesting observation in our study is that related to the group differences in family history of AD. This observation also suggests potential influence from genetic or environmental factors impacting treatment-seeking status. This is consistent with previous work, including twin studies and prospective cohort studies, which have indicated that genetic and shared environmental influences account for approximately 40% of the variance in help seeking for alcohol problems; that family history of alcohol dependence is associated with help seeking and higher healthcare utilization; and that a history of help seeking for alcohol problems among family members of offspring is associated with the offspring's own alcohol problem recognition (True et al., 1997, True et al., 1999, Milne et al., 2009, Glass et al., 2015).

Beyond drinking patterns and traditional DSM-IV AD criteria, this in depth characterization of this population of AD individuals across multiple neurobehavioral domains allows for identification of subdomains that allow for more detailed characterization of those who do and do not seek treatment for AD. This can inform approaches to AD treatment. Previous studies (Weisner, 1993, Weisner and Matzger, 2002, Kessler et al., 2001) indicate that aggression or a history of stress and trauma leads to more drinking related problems, comorbidity and thus, engagement in treatment. In each category of characterization measures, there were several measures that were significantly different and the majority of these significant differences remained after controlling for average drinking per drinking day. This suggests that these two populations with the same diagnosis differ in ways that cannot be attributed to alcohol consumption itself. Significantly greater depression and anxiety in treatment-seekers highlight the psychological heterogeneity of this AD population as does the differences in early life stress events and physical neglect scores which all remained significantly different after covarying for drinking behavior. Similarly, the treatment seeking group is more impulsive and hostile, again, regardless of the quantity of alcohol consumed.

These measures, therefore, may represent separate targets for behavioral and/or pharmacologic intervention that are focused on remediating directly, for example, impulsivity, aggression, depression and anxiety. Addressing these in combination, with interventions that reduce drinking such as behavioral (e.g.: motivational interviewing) and/or pharmacotherapy treatments may improve outcomes for subsets of patients with impairments in these domains. For treatment-seekers, this approach to identify subgroups of alcohol dependent individuals has also been used to predict response to pharmacologic treatments based on other (*i.e.*, genetic variation) endophenotypes (for reviews: see: (Kenna, 2010, Kranzler and McKay, 2012)).

Identifying factors associated with not seeking treatment provides an opportunity to define a population at risk and intervene before drinking progresses. For nontreatment seekers, the results of this study indicate that the absence of several DSM-IV criteria (Table3) as well as the presence of either tolerance or endorsing drinking more than planned are significantly associated with not seeking treatment. In addition, confidence intervals (95%) for each measure shown in Table 2 provide a guide for categorizing patients into one of the two groups. Obviously, defining the nontreatment-seeking group presents an opportunity to intervene in this population, perhaps with motivational interviewing that focuses on entities such as loss of control over drinking to prevent progression to increasingly severe AD.

Neurobehavioral differences between treatment and nontreatment-seekers are also relevant as they may be confounding factors in AD treatment research. Experimental outcomes in pharmacotherapy clinical trials may be influenced by characteristics of the study population itself. Early efficacy proof-of-concept human laboratory studies of putative treatments are often done with nontreatment-seeking individuals, especially if alcohol administration procedures take place (Enoch et al., 2009). The characteristics of the nontreatment-seeking individuals, which we report here diverge from treatment seekers, might directly affect the outcome measures themselves presenting a confound for studies that evaluate potential treatments for AD. Results from these studies may not translate to the treatment-seeking

population. For example, it is possible that factors such as impulsivity, aggression and mood independently affect outcomes in human laboratory studies that measure craving, physiologic tone in response to alcohol cues and the decision to drink at the expense of monetary reward (Ray et al., 2010, Plebani et al., 2012). Treatments thought ineffective based on results from studies in nontreatment-seekers in proof-of-concept human laboratory studies may be prematurely rejected before proceeding to larger clinical trials with treatment-seekers. As such, it is valuable to characterize AD subjects beyond DSM-IV criteria and self-reported drinking behavior.

Results of this study explore categories that significantly differ between treatment and nontreatment-seeking AD research participants. These results provide novel neurobehavioral-based information and are a first step to understanding in a more refined way the characteristics of this research population of AD individuals. Further study of the categories identified here might help to explain variance in clinical trial outcomes.

This study has several limitations. The study was exploratory, therefore multiple uncorrected tests were conducted. Our approach is consistent with (Bender and Lange, 2001) who suggested that exploratory analyses be done without multiplicity adjustment but confirmed in follow up studies. As such, a separate sample will be necessary to confirm the present findings. For the 64 group comparisons conducted, one would expect 3 to be significant by chance alone. We report 38 significant group comparisons (including biomarkers with statistically significant though not clinically significant group differences). No attempt was made to covary for factors other than drinking behavior that might affect the individual outcomes, such as age of onset of AD. The fact that in each category, multiple measures were significantly different and remained different when alcohol consumption was taken into account indicates that these categories provide a basis for further work to characterize the heterogeneity of this complex population with AD. The sample was also relatively small and not equally balanced between the two groups. The fact that participants were compensated for participation may have affected their performance on certain measures. Also, compensation levels may have varied between subjects in both groups due to each person's time spent involved in research procedures. We also did not have follow-up data to determine if phenotypic differences were predictive of relapse in the treatment-seekers. Importantly, those who participate in alcohol research protocols, both treatment and nontreatment seekers, are not necessarily reflective of the corresponding groups in the general population. While future analyses will require larger samples and advanced analytic approaches, the present findings hold significant importance as they illustrate the utility of better characterizing relevant clinical and research phenotypes using broad behavioral and neuropsychological measures.

In conclusion, this study provides novel information on neurobehavioral phenotypes that distinguish between individuals who seek, or do not seek, treatment for AD, in a research setting. It is clear that the diagnosis of AD comprises large phenotypic variation and we have presented data on phenotypic differences in two clinically relevant subgroups of alcohol dependent individuals. Understanding how these two groups differ especially beyond drinking behavior is vital to refining clinical research in AD, especially given that current

research on AD treatment often depends on translating results obtained in the nontreatment-seeking population to treatment-seekers.

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Table 1:

Group Differences in Demographic Characteristics

		Nontreatment-Seeking Participants	Treatment-Seeking Participants	<i>p</i> -value
N		176	615	
Mean Age, years (SD)		42.3(12.1)	43.1(10.2)	
Range		21.0–65.9	19.0–64.4	.438 ^a
Mean Education, years (SD)		13.5 (3.0)	13.8 (2.7)	
Range		2–24	1–24	0.166
Mean IQ (SD)		91.5 (25.3)	97.4 (14.7)	
Range		58–241	57–210	<.001
Gender	Female: n (%)	38 (21.6%)	187 (30.4%)	.022 ^b
	Male: n (%)	138(78.4%)	428 (69.6%)	
Race	African American: n (%)	130 (73.9%)	238 (38.7%)	<.001 ^b
	White: n (%)	35 (19.9%)	323 (52.5%)	
	Other: n (%)	11 (6.3%)	54 (8.8%)	

^aindependent samples t-test^bChi-Square

Table 2:

Group Differences in Neuropsychiatric Measures, DSM-IV Alcohol Dependence Criteria and Blood Biomarkers

		Nontreatment-Seeking Participants					Treatment-Seeking Participants					
Instrument	Measure	Mean (SD)	Min	Max	95% CI		Mean (SD)	Min	Max	95% CI		p-value
Personality												
NEO-PI-R(Costa and McCrae, 1997)	Neuroticism	50.9	29	77	49.4	52.3	57.2 (10.6)	24	90	56.3	58.1	<.001
	Conscientious	48.1 (10.6)	0	79	46.4	49.8	43.9 (12.2)	−3	76	42.9	44.9	<.001
	Extraversion	52 (9.5)	27	78	50.5	53.6	53 (10.6)	17	85	52.1	53.9	0.192
	Openness	50.8 (9.5)	29	82	49.3	52.4	51.4 (10.5)	26	87	50.5	52.3	0.437
	Agreeable	46.9 (10.7)	11	72	45.2	48.6	47.3 (12.3)	0	79	46.3	48.4	0.545
Impulsivity												
Barratts Impulsivity Scale (Patton et al., 1995)	Attention	9.5 (2.4)	5	15	9.2	9.9	10.7 (3.1)	5	19	10.5	11	<.001
	Self-Control	12.4 (3.1)	6	20	11.9	12.8	14 (3.9)	6	24	13.7	14.4	<.001
	Cognitive Complexity	12 (2.6)	5	18	11.6	12.4	13.1 (2.8)	6	20	12.8	13.3	<.001
	Perseverance	8 (2)	4	14	7.7	8.3	8.7 (2.2)	4	16	8.5	8.9	<.001
	Attentional Impulsivity	14.9 (3.5)	8	22	14.4	15.5	16.8 (4.2)	8	29	16.4	17.2	<.001
	Motor Impulsivity	23.5 (4.1)	14	35	22.9	24.1	25 (4.6)	15	41	24.6	25.4	<.001
	Nonplanning Impulsivity	24.4 (4.9)	13	37	23.7	25.1	27.1 (5.8)	14	43	26.6	27.6	<.001
	Motor	15.5 (3)	10	24	15	16	16.3 (3.4)	7	28	16.1	16.6	0.003
	Cognitive Instability	5.4 (1.7)	3	10	5.1	4.7	6.1 (1.8)	3	12	5.9	6.2	<.001
UPPS-P (Lynam et al., 2006)	Negative Urgency	2.1 (0.7)	1	4	2	2.3	2.7 (0.8)	1	4	2.6	2.7	<.001
	Positive Urgency	1.9 (.7)	1	4	1.8	2.0	2.1 (.8)	1	4	2.0	2.2	0.047
	Premeditation	1.9 (0.5)	1	3	1.8	1.9	2 (0.6)	1	4	1.9	2.1	0.029
	Perseverance	1.9 (0.6)	1	3	1.8	1.9	2 (0.6)	1	4	1.9	2.1	0.007
	Sensation Seeking	2.6 (0.8)	1	4	2.5	2.7	2.6 (0.7)	1	4	2.6	2.7	0.499
Trauma/Stress												
CTQ(Bernstein et al., 2003)	Emotional Abuse	8.5 (4.3)	5	24	7.9	9.2	9.9 (5.3)	5	25	9.4	10.4	0.007
	Sexual Abuse	6.4 (3.7)	5	25	5.9	7	7.5 (5.4)	5	25	7	7.9	0.264
	Physical Abuse	8.2 (3.9)	5	25	7.6	8.8	8.7 (4.4)	5	25	8.3	9.1	0.365
	Emotional Neglect	10.2 (4.6)	5	25	9.5	10.9	10.5 (5.1)	5	25	10	10.9	0.929
	Physical Neglect	7.9 (3.4)	5	22	7.4	8.5	7.6 (3.6)	4	25	7.2	7.9	0.016
ELSQ(McFarlane et al., 2005)	Early life Stress Events	2.7 (2.4)	0	12	2.4	3.1	3.8 (3)	0	14	3.5	4	<.001
Alcohol Drinking												
TLFB(Sobell and Sobell, 1996)	Total Drinks	603.9 (477.5)	60	3352	531.8	676	996.1 (639.8)	0	3349	944.6	1047.5	<.001
	Average Drinks Per Drinking Day	8.6 (5.6)	2	37	7.7	9.4	13.6 (7)	0	49	13.1	14.2	<.001
	Heavy Drinking Days	50.2 (28.2)	0	90	45.9	54.4	65.4 (25.8)	0	90	63.3	67.5	<.001

		Nontreatment-Seeking Participants					Treatment-Seeking Participants					
Instrument	Measure	Mean (SD)	Min	Max	95% CI		Mean (SD)	Min	Max	95% CI		p-value
Family Tree Questionnaire (Mann et al., 1985)	<u>Family History</u>	0.1 (.1)	0	0.5	0.1	0.1	0.2 (.2)	0	1	0.2	0.2	<.001
<i>Cognition</i>												
WASI (Wechsler, 1999)	<u>IQ</u>	91.5 (25.3)	58	241	87.4	95.6	97.4 (14.7)	57	210	96.1	98.6	<.001
	<u>Years of Education</u>	13.5 (3)	2	24	13	13.9	13.8 (2.7)	1	24	13.6	14	0.166
<i>Aggression</i>												
BPAQ(Buss and Perry, 1992)	<u>Physical</u>	21.2 (7.9)	9	42	20	22.4	20.2 (8.4)	9	45	19.5	20.9	0.074
	Verbal	13.9 (3.8)	5	25	13.4	14.5	14.1 (4.5)	5	25	13.7	14.5	0.798
	Anger	15.3 (5.7)	7	30	14.4	16.1	16.3 (6.2)	7	33	15.7	16.8	0.077
	<u>Hostility</u>	43.2 (5.7)	33	56	42.3	44.1	45.2 (6.3)	33	61	44.7	45.8	<.001
	Total Aggression	93.6 (20)	59	146	90.6	96.6	95.7 (21.1)	54	160	93.9	97.6	0.261
<i>Mood</i>												
CPRS (Mattila-Evenden et al., 1996)	<u>Anxiety</u>	5.1 (5.2)	0	23	4.2	6.0	11 (7)	0	37	10.5	11.6	<.001
	<u>Depression</u>	5.2 (6.3)	0	31	4.1	6.2	15.5 (9.5)	0	46	14.7	16.2	<.001
<i>Group Differences in DSM-IV Alcohol Dependence Criteria</i>												
DSM-IV (First et al., 1997)	<u>Negative</u>	2.0 (1.2)	0	4	1.8	2.2	3.2	0	4	3.1	3.3	<.001
	Positive	1.7 (0.5)	0	2	1.6	1.8	1.6 (0.6)	0	2	1.6	1.7	0.278
<i>Group Differences in Blood Biomarkers</i>												
Liver function tests	<u>ALT(U/L)</u>	34.1 (32.3)	9	308	29.3	39	59.9 (55.4)	5	435	55.8	64.6	<.001
	<u>AST(U/L)</u>	29.2 (26.6)	7	181	25.2	33.2	62.9 (74.4)	3	585	57.1	69	<.001
	<u>GGT(U/L)</u>	72.1 (102.9)	10	664	56.9	87.8	183.5 (313.8)	9	2833	159.1	209.2	<.001

Items Underlined and **Bolded** were significant after controlling for average drinks per drinking day; Physical aggression and years of education became significant after covarying for drinking ($p=.002$ and $p=.006$, respectively).

Legend: NEO-5: Neuroticism-Extraversion-Openness; UPPS-P: UPPS-P Impulsive Behavior Scale [(negative)Urgency, (lack of)Premeditation, (lack of)Perseverance, Sensation Seeking]; CTQ: Childhood Trauma Questionnaire; ELSQ:Early Life Stress Questionnaire; TLFB: Timeline Follow Back; WASI: Wechsler Abbreviated Scale of Intelligence; BPAQ: Buss-Berry Aggression Questionnaire; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase

Table 3:

Group Differences in Individual DSM-IV Alcohol Dependence Criteria

Criterion	Nontreatment-Seeking Participants (%)	Treatment-Seeking Participants (%)	B	Wald χ^2	p-value	Odds Ratio ^a	95% Confidence Interval
Drinking more than planned	88.1	86.3	-0.2	0.4	0.538	0.8	0.5 1.4
Unsuccessful attempts to cut down	59.5	84.6	1.3	46.2	<.001	3.7	2.6 5.5
Spend lots of time drinking	76.6	84.8	0.5	6	0.014	1.7	1.1 2.6
Missed activities because of drinking	42.8	79.7	1.3	53.2	<.001	3.8	2.6 5.4
Psychological problems because of drinking	48.2	87.6	2	104.2	<.001	7.6	5.1 11.2
Tolerance	83.3	76.2	-0.4	3.8	0.05	0.6	0.4 1
Withdrawal	50.3	73.2	1	30.2	<.001	2.7	1.9 3.8

^aRelative to the nontreatment seeking group