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ORIGINAL ARTICLE

Differences between treatment-seeking and non-treatment-seeking participants in medication studies for alcoholism: do they matter?

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ABSTRACT

Background: Medication development for alcoholism typically includes experimental pharmacology studies with non-treatment-seeking individuals with alcohol use disorder (AUD) paving the way for randomized controlled trials in treatment-seekers with AUD. *Objectives*: The goal of this study is to provide a direct comparison between AUD treatment-seeking research participants and non-treatment-seeking participants on demographic and clinical variables and to test whether variables that differentiate the two groups are associated with clinical outcomes. *Method*: Non-treatment-seeking AUD participants (n = 213; 76.3% male) who completed behavioral pharmacology studies were compared to treatment-seekers who completed the COMBINE Study (n = 1383; 69.1% male) on demographic and clinical variables. Analyses examined whether the variables that differentiated the two groups predicted treatment outcomes in the COMBINE Study. *Results*: Analyses revealed that treatment-seeking participants were older, had more years of education, higher Alcohol Dependence Scale scores, higher Drinker Inventory of Consequences scores, higher Obsessive Compulsive Drinking Scale scores, a greater number of DSM-IV symptoms of AUD, longer duration of AUD, and consumed more standard drinks and more drinks per drinking day (i.e., in the past 30 days) compared to non-treatment-seeking participants. Nearly all characteristics that differed between the groups predicted at least one of the primary clinical outcomes of the COMBINE Study. *Conclusions*: This study highlights a host of clinical and demographic factors that differ between non-treatment-seeking and treatment-seeking research participants and the clinical significance of these variables. Differences between samples should be considered and addressed in order to promote greater consilience across stages of medication development.

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Introduction

The distinction between treatment-seekers and non-treatment-seekers with alcohol use disorder (AUD) is relevant in clinical and research domains, particularly in medication development efforts. Whereas behavioral pharmacology studies typically enroll non-treatment-seekers (1), treatment-seeking is a common requirement in randomized controlled trials for AUD. While individuals with AUD who enroll in behavioral pharmacology studies may reduce their drinking over the course of study participation and after brief intervention (2), the extent to which non-treatment-seeking samples are representative of treatment-seeking samples in randomized controlled trials for AUD remains poorly understood. Oftentimes, findings from human laboratory studies do not consistently and reliably translate to clinical trials' outcomes (3). Although reasons for these discrepancies remain unknown, one possibility is that treatment-seeking individuals respond differently to medications compared to non-treatment-seeking individuals. This hypothesis is supported by the tobacco literature which suggests that motivation to quit smoking significantly influences the effect of smoking cessation medications, such that nicotine replacement therapy (i.e., nicotine patch), for example, increased abstinence in treatment-seekers but had no significant effect on smokers not seeking treatment (4).

Given the prominent role of behavioral pharmacology efforts in medication development for AUD (5), particularly safety and initial efficacy screening, understanding the degree to which treatment-seeking and non-treatment-seeking samples are comparable is relevant for informing treatment development. Furthermore, if differences between samples are identified, it is important to determine whether such differences are in fact predictive of treatment outcomes, which would help inform the

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translation of findings from behavioral pharmacology studies to randomized controlled trials. A similar approach to comparing clinical samples has been useful in understanding discrepancies in the clinical literature, namely by elucidating differences between prominent clinical trials of naltrexone and acamprosate (i.e., comparing the COMBINE Study and the Predict Study) (6).

To advance medication development for AUD, the goal of this study is to compare non-treatment-seeking participants with AUD who completed behavioral pharmacology studies in our laboratory with treatment-seekers who completed a clinical trial for AUD. In order to use a large and nationally representative clinical trial for AUD, the behavioral pharmacology sample is compared with the sample recruited for the COMBINE Study (7). The present study addresses the following aims: (a) compare treatment-seekers to non-treatment-seekers on demographic and clinical variables for AUD, and (b) test whether the variables, found to differ across samples (if any), are predictive of clinical outcomes in the COMBINE Study. Based on epidemiological data suggesting that there is an average lag of 8-years between AUD onset and treatment-seeking (8) and the clinically-accepted recognition that longer duration of symptoms is associated with increased clinical severity, we hypothesized that treatment-seekers will be older and have a more severe AUD presentation, as compared to non-treatment-seekers. Lastly, we predicted that variables indexing clinical severity will significantly predict outcomes in the COMBINE Study.

Method

Participants and studies

Data for the non-treatment-seekers in this study were taken from four human laboratory studies conducted at UCLA, which enrolled non-treatment-seekers with self-reported alcohol-related problems (n = 213). The sample analyzed herein were drawn from one study examining acute subjective response to alcohol administration (n = 113; 9) and three human laboratory studies examining quetiapine (n = 33; Ray et al., 2011), ivermectin (n = 27; 10), and ibudilast (n = 40; 11) as pharmacotherapies for AUD. All studies were approved by the Institutional Review Board at UCLA and were conducted in accordance with the Declaration of Helsinki.

For all studies, a community sample of non-treatment-seeking problem drinkers was recruited via online and print advertisements from the Los Angeles area. Interested individuals called the laboratory to complete a preliminary telephone-screening interview used to assess general eligibility requirements. Individuals who met these initial requirements were invited to the laboratory for an extensive in-person screening visit, during which informed, written consent was obtained.

All studies shared the following inclusion criteria: 1) consume ≥48 drinks per month in the 90 days prior to enrollment, 2) be fluent in English and 3) meet DSM criteria for a current alcohol use disorder (either DSM-IV abuse or dependence or DSM-5 alcohol use disorder of any severity). For the alcohol administration, quetiapine, and ivermectin studies, participants were required to be between the ages of 21–65, whereas the ibudilast study included participants aged 21–55 years. Additionally, all studies shared the following exclusion criteria: 1) be recently involved (<30 days) in any treatment program or currently interested in seeking treatment for drug or alcohol problems, 2) meet criteria for a DSM diagnosis of current dependence on any psychoactive substances other than alcohol and nicotine, 3) meet criteria for a DSM-IV diagnosis of lifetime schizophrenia, bipolar disorder, or other psychotic disorder, 4) attend the behavioral screen under the influence of alcohol, as indicated by a reading > 0.000 g/dl on the breathalyzer, 5) report having a significant medical condition, such as hepatitis, chronic liver disease, ulcer disease, seizure disorder, brain disease, cardiac disease, obstructed bowel, hypertension, glaucoma, hyperthyroidism, or circulatory disease, 6) report experiencing serious alcohol withdrawal symptoms as indicated by a score of 10 or higher on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (12), and 7) self-reported use of cocaine, methamphetamine, heroin or other illicit drugs (other than marijuana) in the previous 60 days.

The COMBINE Study collected data from 1383 treatment-seeking drinkers (7). During the in-person screening visit, all participants signed an informed consent form. Individuals were classified as treatment-seeking if they self-reported a desire to stop drinking. Inclusion criteria were: 1) meet DSM-IV criteria for current AD, 2) be abstinent for 4–21 days prior to beginning the study, and 3) report consuming >14 drinks (women) or >21 drinks (men) per week with at least 2 heavy drinking days (≥4 drinks/day for women and ≥5 drinks/day for men) during a consecutive 30-day period within the 90 days prior to baseline. Exclusion criteria were: (1) a history of other DSM-IV substance abuse or dependence disorder (other than nicotine or cannabis) in the prior 90 days (6 months for opioid abuse) as indicated by self-report or by positive urine drug screen, (2) possess a current psychiatric disorder requiring medication, and (3) report unstable medical conditions.

Outcome measures

The UCLA and the COMBINE Study samples were compared on several demographic and alcohol-related clinical variables. During the in person screening visit, UCLA participants completed a battery of measures including demographic (i.e., age, sex, ethnicity, years of education, and marital status), alcohol use disorder severity (i.e., Alcohol Dependence Scale; ADS (13)), negative consequences of alcohol use (i.e., Drinker Inventory of Consequences; DrInC-2r (14)), alcohol use over the previous 30 days (i.e., total number of drinks and drinks per drinking day as assessed by the Time Line Follow Back Interview; TLFB (15)), duration of DSM-IV alcohol dependence, and alcohol craving (i.e., Obsessive Compulsive Drinking Scale; OCDS (16)). The Structured Clinical Interview of DSM-IV (SCID (17);) or DSM-5 was administered by a master's level clinician to assess for current alcohol abuse and dependence or AUD symptoms, respectively. Readiness to change alcohol use (SOCRATES (18)) was assessed for the behavioral pharmacology studies only.

From the COMBINE Study, the relationship between demographic or alcohol-related variables and treatment outcomes were also examined. The primary end points from the COMBINE Study were percent days abstinent and time to first heavy drinking day, defined as ≥5 standard drinks per day for men, ≥4 for women, over the course of the 16-week treatment period. The secondary study outcome, labeled as good clinical outcome, was defined as abstinence or moderate drinking without problems. Moderate drinking referred to a maximum of 11 and 14 drinks per week for women and men, respectively, with ≤ two days on which > three drinks (women) or four drinks (men) were consumed, and problems were defined as endorsing 3 or more items on the DrInc-2r.

Data analysis

Analyses for continuous variables (i.e., age, years of education, ADS, DrInC-2r, OCDS, SCID, CIWA-AR) were conducted using an independent t-test to identify if these variables differed between treatment-seeking (i.e., participants from the COMBINE Study) and non-treatment-seeking (i.e., participants from the UCLA studies) individuals. When Levene's test suggested unequal variances between groups on a given outcome (i.e., Levene's test $p < 0.05$), we reported the result of the more conservative unequal variance t-test. Cohen's d effect size estimates were computed for each outcome with 95% confidence intervals to assess the magnitude of treatment-seeking group differences in R version 3.3.0 (19) via the compute.es package (20). Analyses for nominal variables (i.e., sex, ethnicity, marital status) were conducted using a chi-squared test. No chi-squared tests violated test assumptions. Cramer's V effect sizes (and 95% CI's) were computed for nominal variables in R via the DescTools package (21). Marital status and ethnicity variables in the UCLA studies were coded to match those of the COMBINE Study. All analyses were conducted in SPSS Statistics version 22.0.

No imputation procedure was undertaken for randomly missing data and a pairwise missing data approach was employed. Missing data was relatively uncommon for all outcomes (0.0%–2.1%) with the exception of DrINC-2 R, where 13.23% of participants in the COMBINE Study had missing data. Sample sizes for each comparison are presented in Table 1.

If significant differences were found between the COMBINE Study and UCLA samples, a secondary set of analyses was completed to examine whether these individual difference variables predicted treatment outcomes in the COMBINE Study (main outcomes were: time to relapse, percent days abstinent [PDA], and good clinical outcome [GCO]). The analytical strategy for this second study aim was consistent with the primary report from the COMBINE Study (7). For each outcome, a 2 × 2 × 2, Acamprosate × Naltrexone × Therapy between subjects factorial model was fit. Variables that differed between treatment-seeking and non-treatment-seeking individuals were singly entered into these models as fixed-effect subject-level covariates to assess whether they predicted overall treatment outcomes in the COMBINE Study.

Time to relapse was tested with a proportional hazards model (PROC PHREG) with exact estimation of failure time ties. Adjusted hazard ratios were computed in these multivariate proportional hazard models to estimate the effect sizes over and above treatment effects. Percent days abstinent was tested with a linear multilevel models via PROC MIXED where treatments factors and the individual difference variables were analyzed as fixed effects at Level 2 and month post randomization was entered as a Level 1 repeated-measures effect. In the multilevel modeling framework, there are no agreed upon standardized effect sizes (22), therefore we elected to report the fixed effect regression coefficient (B) and 95% confidence intervals. Though coefficients are not standardized effect sizes, they can be interpreted as the expected change in PDA with a one unit increase in the predictor variable, and thus provide valuable information on effect magnitude. Good clinical outcome was analyzed with a binomial logistic regression model (PROC LOGISTIC). Adjusted odds ratios were computed in these multivariate logistic regression models controlling for treatment effects. As a data

Table 1. Comparison between non-treatment-seeking and treatment-seeking alcohol dependent (AD) individuals on demographic and clinical variables of interest.

Variable	Non-treatment-seeking mean (SD) or %	Treatment-seeking mean (SD) or %	N per Group	Effect size, 95% CI
Sex (% Male)	76.3%	69.1%	211/1383	Cramer's V = 0.054, 95% CI [0.00, 0.10]
Age (Years)	32.40 (10.50)	44.43 (10.19)	211/1383	d = 1.18, 95% CI [1.03, 1.33]
Years of education	14.05 (3.26)	14.55 (2.73)	204/1356	d = 0.18, 95% CI[0.03, 0.33]
Ethnicity				
Caucasian	40.1%	76.8%	207/1383	Cramer's V = 0.315, 95% CI [0.26, 0.36]
African American	26.6%	7.9%		
Hispanic/Latino	15.0%	11.2%		
Other	18.4	4.1		
Relationship status				
Committed relationship	13.9%	46.3%	209/1382	Cramer's V = 0.335, 95% CI [0.29, 0.38]
Single	74.6%	27.8%		
Previously married	11.5%	25.9%		
ADS Score1	12.39 (8.76)	16.68 (7.32)	208/1378	d = 0.57, 95% CI [0.42, 0.72]
DrInC Score	40.35 (23.75)	55.73 (20.53)	193/1200	d = 0.73, 95% CI [0.58, 0.89]
OCDS Score[1]	20.80 (9.36)	26.65 (8.21)	203/1379	d = 0.70, 95% CI [0.55, 0.85]
Number of DSM-IV AD Symptoms[1]	4.29 (1.51)	5.53 (1.28)	207/1378	d = 0.95, 95% CI [0.80, 1.10]
Number of drinks (30 days pre-randomization)[1]	230 (168)	263 (193)	210/1362	d = 0.18, 95% CI [0.03, 0.32]
Number of drinks per drinking day (30 days pre-randomization)[1]	10.06 (6.27)	12.15 (7.95)	210/1362	d = 0.27, 95% CI [0.13, 0.42]
Duration of AUD (Years)[1]	8.12 (8.62)	13.9 (10.8)	207/1378	d = 0.55, 95% CI [0.40, 0.70]

For these outcomes, Levene's tests for equality of variance between groups was significant (at $p < 0.05$), therefore unequal variance t-tests are reported. The unequal variance t-test significantly reduces test statistic degrees of freedom.

reliability check, all outcomes presented in the primary manuscript from the COMBINE Study were replicated prior to any model testing for this study. Consistent with the primary COMBINE Study analyses, all analyses controlled for baseline percent days abstinent (PDA). Analyses of the COMBINE data were conducted in SAS version 9.4. Furthermore, to control for multiple comparisons, alpha correction was employed in order to maintain a false discovery rate below 0.05 for each of the COMBINE study outcomes (23).

Results

Sample characteristics

Full demographic and baseline drinking characteristics can be found in the primary report from the COMBINE Study (7). A summary of the variables analyzed in the present study is presented in Table 1. A total of 1383 (n = 428 women) treatment-seeking individuals with AUD were randomized to the COMBINE Study. The majority of participants identified as white (n = 1062) while the remainder of the sample identified as Hispanic or Latino (n = 155), African American (n = 109), or other (n = 57). About half of the participants reported being in a committed relationship (n = 640), approximately one quarter reported they were not in a committed relationship and had never been married (n = 384), and the remaining subjects reported being previously married (n = 358).

Among the non-treatment-seeking participants with AUD who completed behavioral pharmacology studies at UCLA, 213 were eligible and included in this analysis (n = 50 women). The majority of participants identified as white (n = 83) while the remainder of the sample identified as African American (n = 55), Hispanic or Latino (n = 31), or other (n = 38). About three quarters of participants had never been married and were not currently in a committed relationship (n = 156), while a significantly smaller proportion of participants reported being in a committed relationship (n = 29) or having been previously married (n = 24).

Comparing non-treatment-seekers vs. treatment-seekers

Analyses comparing participant demographics from the COMBINE Study (treatment-seeking) and UCLA (non-treatment-seeking) studies revealed a significant effect of treatment-seeking status across a range of demographic and clinical variables. A summary of the results is provided in Table 1. Briefly, treatment-seeking participants were older ($t(1592) = -15.90$, $p < 0.001$), had more years of education ($t(1558) = -2.36$, $p = 0.018$), higher ADS score ($t(253) = -6.71$, $p < 0.001$), higher DrInC score ($t(1391) = -9.44$, $p < 0.001$), higher OCDS score ($t(250) = -8.43$, $p < 0.001$), consumed more drinks in the 30 days prior to assessment ($t(301) = -2.62$, $p = 0.009$), and more drinks per drinking day ($t(323) = -4.34$, $p < 0.001$), had a longer duration of AUD ($t(308) = -8.34$, $p < 0.001$) and met more DSM-IV symptoms of AD ($t(253) = 11.24$, $p < 0.001$) compared to non-treatment-seeking participants. Furthermore, additional demographic variables

including relationship status ($\chi^2(2) = 178.57$, $p < 0.001$), ethnicity ($\chi^2(3) = 157.89$, $p < 0.001$), and sex ($\chi^2(1) = 4.58$, $p = 0.032$) were not equally represented between treatment-seeking and non-treatment-seeking participants. Average readiness to change score for non-treatment-seekers was 5.23 (SD = 2.64).

Predicting treatment outcomes

After establishing that treatment-seekers and non-treatment-seekers differed on several demographic and clinical measures (Table 1), additional analyses were conducted to determine whether these patient characteristics predicted the main clinical outcomes in the COMBINE Study (i.e., time to relapse, percent days abstinent, and probability of good clinical outcome). As shown in Table 2, with the exception of marital status and AUD duration, every variable that differed between treatment-seeking and non-treatment-seeking participants predicted at least one of the primary clinical outcomes reported in the COMBINE Study (*false discovery rate < 0.05*). Time to relapse in the COMBINE Study was significantly predicted by age ($\chi^2(1) = 19.20$, $p < 0.001$), AD symptom count ($\chi^2(1) = 12.43$, $p < 0.001$), OCDS total score ($\chi^2(1) = 18.41$, $p < 0.001$), and ADS total score ($\chi^2(1) = 5.88$, $p = 0.015$). Percent days abstinent during the 16-week trial was predicted by ethnicity ($F(3,3489) = 10.04$, $p < 0.001$), sex ($F(1,2979) = 8.20$, $p = 0.004$), drinks per drinking day ($F(1,3440) = 23.73$, $p < 0.001$), total drinks in the 30-days prior to randomization ($F(1,3441) = 30.42$, $p < 0.001$), DrInC-2 R total score ($F(1,3054) = 9.51$, $p = 0.002$), and ADS total score ($F(1,3480) = 14.23$, $p < 0.001$). Lastly, probability of a good clinical outcome was significantly predicted by years of education ($\chi^2(1) = 6.19$, $p = 0.013$), age ($\chi^2(1) = 6.40$, $p = 0.011$), AD symptom count ($\chi^2(1) = 8.36$, $p = 0.004$), DrInC-2 R total score ($\chi^2(1) = 14.38$, $p < 0.001$), ADS total score($\chi^2(1) = 5.40$, $p = 0.020$), and OCDS total score ($\chi^2(1) = 6.09$, $p = 0.014$).

Discussion

Characterizing differences between AUD non-treatment-seekers and treatment-seekers may promote the translation of findings from behavioral pharmacology studies to randomized controlled trials for AUD. The present study identified a host of demographic and clinical variables that differed between a sample of non-treatment-seekers participating in behavioral pharmacology studies and treatment-seeking individuals enrolled in the COMBINE Study. Specifically, treatment-seeking participants from the COMBINE Study were older, had more years of education, greater ADS scores, DrInC scores, and OCDS scores, reported more DSM-IV symptoms of AUD, had a longer duration of AUD symptoms, and consumed more standard drinks and more drinks per drinking day (i.e., in the past 30 days) compared to non-treatment-seeking participants. The two samples also differed on demographic variables, such that the COMBINE Study enrolled a higher percentage of female participants, a less ethnically diverse sample, and individuals who were more likely to be in a committed relationship compared to non-treatment-seekers. Nearly all sample characteristics found to differ between treatment-seeking and non-

Table 2. Demographic and clinical variables that differentiated between treatment-seeking and non-treatment-seeking samples were tested for whether each variable predicted clinical outcomes in the COMBINE Study, controlling for baseline PDA and treatment conditions (i.e., Naltrexone, Acamprosate, CBI, and their interactions).

	Clinical outcome					
	Time to relapse		PDA		GCO	
	Hazard ratio [95% CI]	*p*-value	B [95% CI]	*p*-value	Odds ratio [95% CI]	*p*-value
Years of Education	0.98 [0.96, 1.01]	0.209	−0.47 [−1.01, 0.08]	0.092	**0.93 [0.89, 0.99]**	**0.013**
Marital Status						
Committed Relationship vs. Previously Married	0.85 [0.72, 1.01]	0.023	3.87 [0.27, 7.48]	0.087	0.73 [0.52, 1.03]	0.069
Single vs. Previously Married	1.05 [0.88, 1.26]		3.64 [−0.40, 7.68]		1.04 [0.72, 1.51]	
Ethnicity						
White vs. Other	1.11 [0.77, 1.60]	0.037	**15.44 [7.86, 23.02]**	**<0.001**	0.41 [0.22, 0.79]	0.045
African American vs. Other	0.76 [0.48, 1.18]		**24.81 [15.81, 33.82]**		0.36 [0.16, 0.79]	
Hispanic/Latino vs. Other	1.17 [0.78, 1.76]		**13.87 [5.27, 22.46]**		0.48 [0.23, 1.02]	
Sex (Male vs. Female)	1.15 [1.00, 1.33]	0.051	**−4.65 [−7.83, −1.46]**	**0.004**	1.08 [0.81, 1.46]	0.592
Age (Years)	**0.99 [0.98, 0.99]**	**<0.001**	−0.01 [−0.15, 0.14]	0.94	**0.98 [0.97, 1.00]**	**0.011**
Drinks per Drinking Day	1.00 [0.99, 1.01]	0.933	**0.46 [0.28, 0.65]**	**<0.001**	1.01 [1.00, 1.03]	0.157
Total Drinks (past 30 days)	1.00 [1.00, 1.00]	0.615	**0.02 [0.01, 0.02]**	**<0.001**	1.00 [1.00, 1.01]	0.325
AD Symptoms	**1.10 [1.04, 1.16]**	**<0.001**	0.35 [−0.81, 1.52]	0.553	**1.18 [1.06, 1.32]**	**0.004**
DrInC-2 R	1.00 [1.00, 1.01]	0.065	**0.12 [0.04, 0.19]**	**0.002**	**1.01 [1.01, 1.02]**	**<0.001**
OCDS	**1.02 [101, 1.03]**	**<0.001**	0.02 [−0.16, 0.20]	0.801	**1.02 [1.00, 1.04]**	**0.014**
ADS	**1.01 [1.00, 1.02]**	**0.015**	**0.39 [0.19, 0.59]**	**<0.001**	**1.02 [1.00, 1.04]**	**0.02**
Duration of AUD (Years)	0.99 [0.99, 1.00]	0.063	−0.01 [−0.16, 0.13]	0.848	1.00 [0.98, 1.01]	0.724

Bolded values were statistically significant after false discovery rate correction. Hazard and odds ratios were adjusted based on treatment condition and baseline PDA. B = fixed effect coefficient, or the expected change in PDA with a one unit increase in the predictor.

treatment-seeking participants predicted at least one clinical outcome in the COMBINE Study. These results provide initial evidence that demographical and clinical differences between treatment-seekers and non-treatment-seekers with AUD are significantly related to treatment outcomes. And while in-depth analyses of moderators of response to each intervention in the COMBINE Study (i.e., Acamprosate, Naltrexone, and CBI) are beyond the scope of the present study, recent studies have proposed a host of putative moderators, including craving for alcohol (24), reward and relief drinking dimensions (25), social network (26), and body mass index (BMI) (27). In the context of this study, we sought to examine the clinical significance (i.e., prediction of clinical outcome) of the variables found to differ between treatment-seekers and non-treatment-seekers, as opposed to investigate their potential moderating role.

Although literature reviews have often suggested differences in treatment-seeking and non-treatment-seeking individuals may be partially responsible for the inconsistencies observed in the translation from human laboratory studies to clinical trials for medication development (for review see (28)), results from the current study not only identify the specific characteristics that differ between the samples but also illustrate the clinical significance of such variables. The present results are consistent with those by Rohn and colleagues (in press) comparing non-treatment-seekers (n = 150) and treatment-seekers (n = 528), who participated in research screening protocols at the NIAAA Intramural Research Program (29). Similar to our findings, Rohn et al. reported that treatment-seekers differed from non-treatment-seekers in quantity and pattern of alcohol consumption (i.e., heavier drinking among treatment-seekers), in addition to showing significant group differences on mood variables, impulsivity, neuroticism, and family history of alcoholism. While our data do not allow for direct replication of the group differences in mood and personality factors reported by Rohn et al., the two studies coalesce in noting that non-treatment-seekers with AUD are generally not representative of treatment-seekers enrolling in AUD clinical trials.

In general, data from the present study support the notion that treatment-seekers have a more severe AUD presentation compared to non-treatment-seekers. This is consistent with a study suggesting that individuals with AUD who have never received treatment have lower alcohol use over time compared to AUD-treated individuals (30). Interestingly, while it has been reported that there is an average lag of 8-years between AUD onset and treatment-seeking (8), participants in the behavioral pharmacology studies reported an average of approximately 8 years since onset of AUD while those from the COMBINE study reported an average of approximately 14 years since onset of AUD symptoms, suggesting that the gap between AUD onset and AUD treatment-seeking may be longer than initially thought. More recent data from the National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC III), confirm the low rates of treatment-seeking for 12-month and lifetime DSM-5 AUD (7.7% and 19.8%, respectively) and suggest a 3 year lag between the mean ages at onset and at treatment (31). Importantly, NESARC II data suggest that treatment-seeking is associated with severity of AUD, such that treatment-seeking increased from mild to moderate to severe AUD in both the 12-month and lifetime prevalence analyses (31). As such, consideration of AUD severity may be a critical component of the distinction between treatment-seekers and non-treatment-seekers.

A primary concern regarding enrollment of treatment-seekers in behavioral pharmacology studies consists of the ethical issues surrounding alcohol administration to AUD treatment-seekers. Although the National Advisory Council on Alcohol Abuse and Alcoholism's recommended council guidelines on alcohol administration in human experimentation suggests that behavioral pharmacology studies involving alcohol administration should enroll non-treatment-seeking individuals (1), they also acknowledge that these guidelines can be circumvented given a strong scientific justification. The data presented in this study emphasize the importance of recruiting participants with comparable characteristics in behavioral pharmacology studies and in clinical trials. Various studies have shown that alcohol administration in the laboratory does not increase future alcohol use in research subjects, easing the ethical concerns associated with administering alcohol to individuals seeking AUD treatment (32,33). Thus, enrolling treatment-seeking individuals with AUD may be ethically justified and methodologically relevant to facilitate the translation of findings from behavioral pharmacology trials to clinical trials.

In addition to examining group differences, it would be relevant to consider the underlying construct of readiness to change across the two groups. While direct comparisons were not possible given that the two samples did not administer an identical measure of readiness to change, descriptive data suggest that the non-treatment-seeking sample had an average readiness to change score between 5 ("I definitely plan to reduce my drinking in the next 6 months") and 6 ("I definitely plan to reduce my drinking in the next 30 days"). This

readiness score among non-treatment-seekers suggests that although they may not be specifically seeking treatment, on average, they do have future plans to reduce alcohol use.

The present study should be considered in light of its strengths and limitations. Study limitations include the use of a single site for the behavioral pharmacology sample (i.e., UCLA) as compared to a multisite trial represented in COMBINE. Similarly, recruitment methods and inclusion criteria were different between the behavioral pharmacology studies and the COMBINE Study. Nevertheless, single site studies conducted in the US and abroad are routinely incorporated into the scientific literature on medications development for alcoholism; hence contrasting single site studies to one another and to multisite trials provides a unique perspective on how single site trials should be properly interpreted. Another limitation of this study is the sample size imbalance between the two groups. The lack of moderator analyses for the variables that differentiated treatment-seekers from non-treatment-seekers (i.e., investigating each variable as a potential moderator of clinical response to each specific intervention in the COMBINE Study) may also represent a limitation; however, such analyses are beyond the scope of this manuscript and studies of moderators of outcome in the COMBINE Study have been briefly reviewed above. Study strengths include the careful matching of assessments across the two groups and the strong rationale for investigating differences between treatment-seekers and non-treatment-seekers in order in inform medications development for AUD.

In conclusion, the results presented herein suggest that the treatment-seeking individuals differ significantly from non-treatment-seeking individuals on clinical and demographic variables and that these variables are, in turn, predictive of clinical outcomes. Given that behavioral pharmacology studies generally enroll individuals not seeking treatment and that clinical trials, by definition, enroll individuals seeking treatment, such differences should be carefully considered in medications development for AUD. Specifically, efforts to enroll treatment-seekers in behavioral pharmacology studies appear justified in order to achieve a more comparable sample which in turn may promote consilience across stages of medication development.

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