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Alcohol craving and withdrawal at treatment entry prospectively predict alcohol use outcomes during outpatient treatment

Jorge S. Martins [a,b], Nia Fogelman [a,b], Stephanie Wemm [a,b], Seungju Hwang [a,b], Rajita Sinha [a,b,c,*]

[a] Yale Stress Center, Yale School of Medicine, Yale University, USA
[b] Department of Psychiatry, Yale School of Medicine, Yale University, USA
[c] Department of Neuroscience, Yale School of Medicine, Yale University, USA

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ABSTRACT

Objective: Chronic alcohol use increases risk of alcohol craving and withdrawal symptoms (AW) as well as abstinence-related distress symptoms, in those entering alcohol use disorder (AUD) treatment. Here, we examined whether AW and alcohol craving in AUD patients entering outpatient treatment *prospectively* predicts future heavy drinking days/week (HDD) and additional alcohol use outcomes during 8-weeks of outpatient treatment, and their relationship to abstinence symptoms of depression, anxiety and sleep difficulties.

Methods: Participants were 80 treatment-seeking adults with current DSM-5 AUD (39% female; 43% White; 20–60 years) who completed assessments of AW and alcohol craving and also alcohol abstinence symptoms of depression, anxiety, and sleep quality at treatment intake. Participants were *prospectively* followed using daily diaries for alcohol intake during 8-week of standardized weekly relapse prevention counseling to support recovery.

Results: After accounting for demographic and pre-treatment alcohol use, greater alcohol craving at treatment entry predicted higher HDD ($p < .013$) as well as greater drinking days (DD: $p < .004$), average drinks per drinking day/week (AvgD: $p < .001$) and relapse to heavy drinking ($p < .05$), while higher levels of pretreatment AW symptoms interacted with treatment week to predict greater HDD ($p < .018$). Abstinence symptoms of depression, anxiety, and sleep difficulties were associated with craving and AW but did not predict any drinking-related outcomes.

Conclusions: These results provide evidence that increased alcohol craving and AW may serve as prognostic indicators of greater risk of heavy drinking in outpatient treatment. Findings suggest the need to evaluate craving and AW at outpatient treatment entry and develop targeted treatments to specifically address the effects of craving and AW on drinking outcomes in outpatient AUD treatment.

1. Introduction

Alcohol misuse and Alcohol Use Disorder (AUD) are significantly associated with adverse consequences and global disease burden (Griswold et al., 2018). Although there are efficacious treatments for AUD, treatment failure and high relapse rates remain a significant issue in AUD treatment (Sinha, 2011). The current FDA approved medications in the treatment of AUD have modest efficacy and heterogeneity in clinical symptomology of treatment-entering AUD patients contributes to the variability in the clinical course of AUD (Maisto, Kirouac and Witkiewitz, 2014). Recent initiatives aimed at addressing this heterogeneity to improve treatment of AUD (Litten et al., 2015; Witkiewitz et al., 2019) suggests a critical need to identify AUD features that differentiate those at increased risk for treatment failure and develop treatments targeted for those who are at risk of relapse to improve treatment outcomes and increase treatment success rates. For example, new research suggests that medication efficacy of gabapentin and prazosin for AUD treatment is moderated by alcohol withdrawal symptoms (AW) at treatment entry (Anton et al., 2020; Sinha et al., 2021). Previous work also suggests that alcohol craving at treatment entry levels may

* Correspondence to: Foundations Fund Professor of Psychiatry, and of Neuroscience and of Child Study, Chief of Psychology Section in Psychiatry, Director, Yale Stress Center, 2 Church Street South, Suite 209, New Haven, CT 06519, USA.
E-mail address: rajita.sinha@yale.edu (R. Sinha).

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moderate naltrexone effects in AUD treatment (Monterosso et al., 2001). Notably, AW and alcohol craving are common clinical features of AUD among patients entering treatment. However, systematic evaluation of these symptoms for their impact on predicting AUD treatment response has been limited thus far.

Recent research has demonstrated that early alcohol abstinence is associated with disruptions in the stress and reward brain neurocircuitry resulting from chronic alcohol use (Koob, 2003). In humans, chronic alcohol effects on stress biology has been documented by disruptions in prefrontal-striatal brain function and in peripheral autonomic and hypothalamic-pituitary-adrenal axis functioning (Duka et al., 2011; Milivojevic and Sinha, 2018; Blaine et al., 2020) that are accompanied by increased risk of associated clinical symptoms such as AW, craving, greater distress, including depression, anxiety and sleep difficulties (Fox et al., 2007; Sinha et al., 2011; Milivojevic and Sinha, 2018). This profile of stress biological dysfunction as well as associated distress symptoms characterize chronic alcohol-related stress pathophysiology in AUD, which is also associated with greater subjective stress and alcohol cue reactivity (Fox et al., 2007; Sinha et al., 2011), and increased risk of relapse that jeopardizes alcohol recovery (Sinha, 2011). Despite existing evidence of relapse and treatment failure risk in those showing such AUD-related stress pathophysiology (Sinha, 2001; Koob and Schulkin, 2018; Milivojevic and Sinha, 2018), research to specifically assess whether stress-related clinical features of AUD significantly impact alcohol use outcomes in outpatient treatment has lagged behind.

Thus, a *prospective* observational study was conducted to examine whether specific AUD clinical features of AW and craving predicted subsequent risky drinking in AUD patients entering early outpatient treatment. On the basis of previous work (Sinha, 2011; Litten et al., 2015; Milivojevic and Sinha, 2018; Sinha et al., 2021), we selected AW and craving as co-primary predictors to assess their specific *prospective* impact on the primary outcome of heavy drinking days/week (HDD) during treatment, after accounting for baseline levels of alcohol intake prior to study entry, abstinence days after study entry and prior to first treatment session, age, gender, race and education. We chose HDD as the primary outcome due to increasing emphasis on HDD and risky drinking as clinically informative outcomes in clinical trials that align more closely with patient goals (Falk et al., 2010, 2019; Witkiewitz et al., 2020). In addition, specific alcohol-related covariates of recent alcohol consumption for 90 days prior to study entry, and abstinence days between intake and first treatment session were selected on the basis of previous work indicating their association with drinking outcomes during treatment (Sinha et al., 2011; Blaine et al., 2020), but more importantly, to assess specifically the effect of AW and craving *over and above* the quantitative effects of chronic alcohol use and abstinence/recovery days. Based on previous work (Sinha, 2001; Koob and Schulkin, 2018; Milivojevic and Sinha, 2018), we predicted that high levels of AW and craving would prospectively predict greater number of HDD during treatment. Additionally, we conducted secondary analyzes to determine if AW and craving predicted other alcohol use outcomes (average drinks per drinking day for each week [AvgD], number of drinking days [DD] for each week, time to dropout, time to lapse, and time to relapse) to determine consistency of effects of the primary predictors across drinking outcomes. Finally, because of the close association between AW and craving and other alcohol abstinence features of depression, anxiety and sleep difficulties, we conducted *post-hoc* exploratory analyzes to assess the association between these commonly reported abstinence-related distress symptoms and AW, craving and also alcohol use at intake and *prospectively* with alcohol use outcomes.

2. Method

2.1. Participants

Participants were 80 AUD treatment-seeking community adults with current moderate to severe AUD (38.8% female; 42.5% White; aged 20–60 years; M_{age} = 36.6, SD = 11.24) who were recruited from the Greater New Haven area. Participants were recruited using flyers, brochures, newspapers, website announcements, social media, and referrals from local addiction treatment facilities (see Supplementary Materials for eligibility and exclusion criteria). The study protocol was approved by the Yale University School of Medicine's Human Investigation Committee and registered on ClinicalTrials.gov (NCT02616094) to study the clinical and neurobiological predictors of AUD treatment outcome.

2.2. Procedure

Interested individuals were interviewed and screened via telephone by trained research assistants to determine their eligibility. Participants first completed additional in-person intake screenings (including urine toxicology screens for recent alcohol and drug use), provided informed consent, and completed measures of AW, craving, depression, anxiety, and sleep difficulties at intake. Two eligible participants completed intake procedures and opted to receive medical detoxification at Yale's Clinical Neuroscience Research Unit (CNRU) prior to initiating outpatient treatment. All participants were then *prospectively* followed while they participated in weekly standard manualized evidence-based behavioral treatment as described below for eight weeks with a trained master's level addiction counselor or clinical psychologist to reduce craving, alcohol intake and relapse risk while initiating and maintaining alcohol recovery. Alcohol intake was measured with daily diaries via mobile phone and corroborated with weekly timeline follow-back assessments using the Substance Use Calendar method (Miller and Del Boca, 1994).

2.3. Measures and materials

2.3.1. Initial visits and baseline assessments at intake

At intake, participants provided demographic information, including age, gender, race, annual household income, and years of education. Participants also completed the Clinical Institute of Withdrawal Assessment for Alcohol-revised (CIWA-Ar; (Sullivan et al., 1989)), Alcohol Urge Questionnaire (AUQ; (Bohn, Krahn and Staehler, 1995)), Hamilton Anxiety Scale (HAS; (Maier et al., 1988)), Beck Depression Inventory (BDI; (Beck et al., 1961)), and the Pittsburgh Sleep Quality Index (PSQI; (Buysse et al., 1988)). Internal consistency estimates of reliability were satisfactory for all these measures (see Table 1). Baseline alcohol intake for 90 days prior to study entry was assessed using the 90-day Substance Use Calendar (SUC; (Miller and Del Boca, 1994)). In addition, alcohol use was assessed daily after study entry up to the first treatment session to account for days of abstinence prior to the 8-week treatment. Finally, the Structured Clinical Interview for DSM-5 (SCID-5; (First et al., 2015)) was administered to assess DSM-5 criteria for AUD and other psychiatric conditions (see Supplemental Methods).

2.3.2. Weekly behavioral counseling and assessments during 8-week treatment

Participants participated in once-weekly treatment sessions for 8 weeks with empirically validated standardized 12-Step and relapse prevention approach as outlined in the NIAAA Project MATCH manuals (Kadden et al., 1994; Nowinski, Baker and Carroll, 1994). In addition, twice-weekly sessions were conducted to assess their alcohol use with timeline follow-back assessments using the 7-day SUC (Miller and Del Boca, 1994) (see Supplemental Methods). Participants also received contingency management (CM) reinforcing treatment attendance, in the form of 'fishbowl' draws in values of $1, $5, $10, and $25, in acordance with fishbowl CM techniques (Petry et al., 2000). All patients were referred to suitable continued treatment and aftercare at the end of the 8-week study treatment period.

Table 1
Demographics and Clinical Characteristics at Intake, Overall and Broken Down by Females and Males.

	Range	*n*	Overall (*N* = 80)		Female			Male		
			Mean	SD	Mean	SD	*n*	Mean	SD	*n*
Demographics										
Gender (% Female)	0–1	31	38.75	–	–	–	–	–	–	–
Age (in years)	20–60	80	36.55	11.24	36.00	10.10	31	36.90	12.00	49
Race (% White)	0–1	34	32.5	–	32.26	–	10	48.98	–	24
Income	1–8	80	3.20	1.72	3.00	1.46	31	3.33	1.86	49
Education (in years)	9–20	80	13.82	2.31	14.26	2.38	31	13.63	2.25	49
SES (in percentile)	0–100	80	49.59	31.06	50.81	31.3	31	48.81	31.2	49
Psychiatric Disorders[a]										
Lifetime major depressive disorder (%)	0–1	30	37.5	–	48.39	–	15	30.61	–	15
Lifetime anxiety disorder (%)	0–1	13	16.25	–	19.35	–	6	14.29	–	7
Lifetime PTSD (%)	0–1	19	23.75	–	35.48	–	11	16.33	–	8
Alcohol Use										
Years of alcohol use	0.3–40	79	12.66	10.59	9.78	9.71	31	14.51	10.80	49
Past 90-day average drinks per drinking day	1.33–39.30	76	6.37	4.79	5.00	2.85	31	7.17	5.50	49
Past 90-day % drinking days	0–100	79	60.31	29.03	56.14	26.4	31	62.87	30.5	49
Past 90-day % heavy drinking days	0–100	79	39.26	30.89	33.38	25.8	31	42.86	33.4	49
Age at onset of alcohol use	6–28	80	15.20	3.12	16.00	3.41	31	14.7	2.84	49
Other Drug Use										
Past 90-day tobacco use (in cigarettes)	0.25–25	38	7.60	6.65	7.65	7.06	13	7.57	6.59	25
Past 90-day marijuana use (in joints)	0–20	27	1.65	3.77	0.73	0.79	11	2.11	4.84	16
Past 90-day cocaine use (in grams)	0–50	12	10.94	16.79	24.72	23.4	10	4.05	6.69	8
Alcohol Abstinence-Related Symptoms										
Alcohol Withdrawal (CIWA; α = 0.71)	0–15	80	4.55	3.84	4.06	3.84	31	4.86	3.84	49
Craving (AUQ; α = 0.92)	1–7	80	2.81	1.70	2.92	1.63	31	2.74	1.76	49
Depression (BDI; α = 0.93)	0–50	80	10.97	10.92	12.39	9.97	31	10.08	11.50	49
Anxiety (HAM-A; α = 0.85)	0–29	79	10.16	7.72	10.06	8.47	31	10.23	7.29	49
Sleep Difficulties (PSQI; α = 0.74)	0–17	80	8.04	4.09	8.06	4.12	31	8.02	4.12	49

Note. Income = annual household income, where 1 = "$0" and 8 = "More than $200,000"; [a] Lifetime DSM-5 diagnosis as determined by the SCID for DSM-5; *SD* = standard deviation. Means and associated *SDs* that differ significantly between men and women at the level of $p < .05$ are shown in bold.

2.3.3. Daily alcohol use surveys

Participants also reported their daily alcohol intake during treatment using brief surveys administered in a smartphone application (MetricWire, Inc.). Surveys on the total number of drinks consumed (beer, wine, and liquor) were obtained from daily morning and evening prompts triggered on their smartphones every day at 8:00 a.m. and 8:00 p.m. We calculated an index of the total number of drinks per day Overall, compliance was acceptable (69%), consistent with other daily diary studies monitoring everyday alcohol use (Piasecki, 2019).

2.3.4. Clinical predictors and drinking outcomes

The co-primary predictors of interest were AW and alcohol craving and the primary outcome was heavy drinking days/week (HDD). Heavy drinking days were operationalized as days in which patients had 4 + drinks (women) and 5 + drinks (men). Participants reported their daily alcohol use during treatment using diary reports via mobile phone and weekly timeline follow-back assessments using the 7-day SUC. Note that if drinking data from daily surveys via mobile phone were missing, timeline follow-back data obtained using the 7-day SUC was utilized to obtain alcohol intake data weekly. To assess consistency in effects of AW and craving predictors on alcohol intake, secondary measures of drinking outcomes, namely drinking days/week (DD), the average drinks per drinking day for each week (AvgD), time to dropout (i.e., time to withdraw from the study), time to lapse (i.e., time to first drink), and time to relapse (i.e., time to first heavy drinking day) were included.

3. Data analytic approach

To determine the extent to which varying levels of AW and craving prior to treatment initiation were prospectively associated with HDD during treatment, linear mixed-effects (LME) regression models were estimated in R (R Core Team, 2020) using the 'lme4' (Bates et al., 2015) and 'lmerTest' (Kuznetsova, Brockhoff and Christensen, 2017) packages. A single separate model was utilized to examine the effects of each of the co-primary predictors of AW and craving using continuous scores for each, and their interactions with treatment week (week 1–8) on HDD.[1] Thus, a separate LME regression model included age, gender, race, education, baseline total drinks, days of abstinence, AW and treatment week, as well as AW X treatment week effect on primary HDD outcome during treatment. Similarly, a separate LME regression model including age, gender, race, education, baseline total drinks, days of abstinence, Craving and treatment week, as well as Craving X treatment week assessed the effects on primary HDD outcome (2 LME models). We corrected for multiple comparisons using a Bonferroni correction across the two co-primary predictor models for HDD, considering significant effects to be below $p < .025$ (0.05/2). Each of the two LME models specified a random intercept varying by participant and were estimated using restricted maximum likelihood (REML) estimation. Between-person continuous covariates were grand-mean-centered. We used *t*-tests and 95% confidence intervals (CIs), along with Satterthwaite-approximated denominator degrees of freedom to determine the significance of fixed-effect parameters at the level of $p < .05$.

[1] Daily drinking data was aggregated to obtain average weekly heavy drinking and secondary drinking measures to match with weekly treatment provided. Time (treatment week) was treated as a discrete, within-subject variable (week 1–8) in the analyzes. We adopted this modeling approach based on two main methodological and practical considerations. First, given that treatment was provided on a weekly basis, aggregating HDD at the weekly level allows best to characterize treatment responses throughout the entire treatment period. Note that recent work (Hallgren, Atkins and Witkiewitz, 2016) suggests that analyzes of clinical trials based on aggregated drinking data produced nearly identical Type I error rates, statistical power, and bias in estimating treatment effects, compared to analyzes using completely disaggregated daily drinking data. Second, obtaining aggregate drinking data over the week over weekly intervals and specifying treatment week as a discrete, within-subject variable allows the interpretation of the main effects of interest as averaged effects across the entire treatment period.

Both full model and primary predictors variance contributions was provided with marginal and conditional R^2 (Rights et al., 2019) using 'partR^2' package (Stoffel et al., 2020). To aid in the interpretation, the estimated marginal means of the primary HDD outcome were calculated based on the ± 1 standard deviation levels of the craving and AW predictors.

Similar to the model described above for the primary HDD drinking outcome, we conducted analyzes for the secondary drinking outcomes during treatment using a separate LME regression model for AW and a separate model for craving with the covariates specified above, to assess their effect on number of drinking days per week (DD) and separately for average drinks per drinking day per week (AvgD) (4 LME regression models). For the secondary drinking outcomes of time to drop out, time to lapse and time to relapse (3 outcomes), we utilized separate right-censored Cox Proportional-Hazards (CPH) regression models in R using the 'survival' (Therneau, 2021) and 'survminer' (Kassambara et al., 2020) packages for each of the pretreatment AW and craving predictors to assess their prospective effect on time to dropout, time to lapse, and time to relapse during treatment. Thus, separate models were estimated to examine the effects of baseline AW and craving on each time-to-event outcome (total of 6 models). All CPH models were estimated using partial likelihood (PL) estimation. The day of lapse or relapse for patients who withdrew from the study without having reported a lapse or relapse was considered censored at the day that they withdrew (i.e., lapse coded as a 0 but the study day was censored at point of dropout). Efron's approximation method was used to handle ties. Wald χ^2 and 95% CIs were used to determine the significance of hazard ratios (HRs) at the level of two-tailed $p < .05$.

Additional *post-hoc* exploratory LMEs, same as the separate LME regression models described above, were conducted to assess the separate effects of anxiety, depression, sleep problems and alcohol intake at pre-treatment and also to assess whether depression, anxiety and sleep problems predicted alcohol use outcomes during treatment.

3.1. Covariate adjustment

Given the evidence that alcohol use outcomes during treatment could be influenced by the number of abstinence days (Blaine et al., 2020) and levels of recent alcohol use (Breslin et al., 1997) upon study entry, all models controlled for the effects of the number of abstinence days after study entry and prior to the first of the 8 treatment sessions and past 90-day alcohol use upon study entry, in addition to age, sex, race, and education.

4. Results

4.1. Description of the analytic sample

Table 1 summarizes demographic information and clinical characteristics of the sample overall and separately for men and women. Overall, the sample consisted of 80 treatment-entering patients with current DSM-5 moderate to severe AUD who were middle-aged (M_{age} = 36.6, *SD* = 11.24), predominantly male (62.2%), and non-White (57.5%). Participants regularly consumed alcohol for 12.66 (*SD* = 10.59) years, on average, with a mean age at onset of drinking at 15.20 (*SD* = 3.12) years. During the 90 days prior to study entry, participants reported, on average, 6.37 (*SD* = 4.79) drinks per drinking day, 60.31 (*SD* = 29.03) percent drinking days, and 39.26 (*SD* = 30.89) percent of heavy drinking days. On average, participants reported 14.04 (*SD* = 62.26) abstinence days between intake and prior to the 8-week outpatient treatment initiation. Most participants reported having experienced some degree of AW symptoms (90%), craving (80%), depression (83.4%), anxiety (94.9%), and sleep difficulties (98.8%) at treatment entry. No sex differences were found between men and women in their levels of pretreatment alcohol abstinence-related symptoms (all *ps* > .05). Participants completed, on average, 7.42 sessions (*SD* = 1.60) throughout the entire treatment period, with most participants (83.8%) remaining in the study until the end of treatment.

4.2. Pretreatment alcohol craving ad AW predicting percent heavy drinking days

4.2.1. Pretreatment alcohol craving

Alcohol craving levels at treatment entry significantly predicted higher HDD overall through the 8-weeks of treatment ($F_{1,71.65} = 6.53$, p =[0.013 Conditional R^2: Full Model = 0.66, Alcohol Craving = 0.63; Marginal R^2: Full Model = 0.08; Alcohol Craving= 0.05) (Fig. 1a). Thus, in the real-world context, individuals with a low craving score (−1 *SD* = 1.79) had approximately 0.78 (*95% CI*: 0.–1.76) heavy drinking days on average per week, whereas an individual with a high craving score (+1 *SD* = 5.24) would have 1.28 (*95% CI*: 0.66–1.89) heavy drinking days per week. Notably, other than the co-primary predictor of alcohol craving, none of the covariates of age, sex, race, education, baseline drinking and pretreatment abstinence days yielded a significant effect on HDD during treatment. These data indicate that alcohol craving accounted for the majority of variance in HDD each week over the 8-week period.

4.2.2. Pretreatment alcohol withdrawal symptoms (AW)

Continuous scores of AW at treatment entry interacted with treatment week to predict significantly higher HDD during treatment ($F_{7,474.82} = 2.44$, $p = .018$; Conditional R^2: Full Model = 0.67, AW X Treatment Week = 0.65; Marginal R^2: Full Model=0.07; AX x Treatment Week = 0.05). During the first study week, an individual who experienced low AW (−1 *SD* = 1.56) at baseline experienced 0.98 (*95% CI*: 0.76 – 1.19) heavy drinking days per week; similarly, a high AW score (+1 *SD* = 9.62) was associated an average of 0.82 (*95% CI*: 0.54–1.10) heavy drinking days. However, assessing the effect of AW at Week 6, low AW was associated with 0.42 (*95% CI*: − 0.01 to 0.86) but high AW was associated with an average of 1.82 (*95% CI*: 0.70–1.85) heavy drinking days. Again, the covariates did not contribute significantly to the variance in HDD outcomes over 8 weeks in this model. As shown in Fig. 1b, individuals with higher AW at treatment entry maintained had a higher frequency of HDD each week, whereas individuals low in AW had fewer HDD episodes as they progressed from week 1 through week 8 in the study. Fig. 1c also provides actual raw number of heavy drinking days for each treatment week for the high and low AW individuals.

4.3. Secondary analyses of pretreatment alcohol craving and AW on secondary alcohol use outcomes

4.3.1. Pretreatment alcohol craving

Pretreatment craving significantly predicted higher DD during treatment ($F_{1,70.65} = 9.29$, $p < .004$; Conditional R^2: Full Model = 0.77, Alcohol Craving = 0.71; Marginal R^2: Full Model = 0.13; Alcohol Craving = 0.07) and AvgD ($F_{1,70.23} = 12.07$, $p < .001$, Conditional R^2: Full Model = 0.53 Alcohol Craving = 0.49; Marginal R^2: Full Model = 0.11; Alcohol Craving = 0.08) (see Fig. 2a and b). Furthermore, higher pretreatment alcohol craving levels significantly predicted a higher risk of subsequent time to relapse to heavy drinking during treatment in the CPH models (HR: 1.20; 95% CI [1.00–1.44], $p = .049$), where each one-unit increase in craving at intake was associated with a 20% increase in the risk of subsequent relapse to heavy drinking during treatment (see Fig. 2c). Pretreatment craving did not significantly predict risk of subsequent time to alcohol lapse or dropout during treatment (all *ps* > .05).

4.3.2. Pretreatment alcohol withdrawal symptoms (AW)

Pretreatment AW continuous scores did not significant predict DD, AvgD, nor risk of subsequent lapse, relapse, or dropout during treatment (all *ps* > .05).

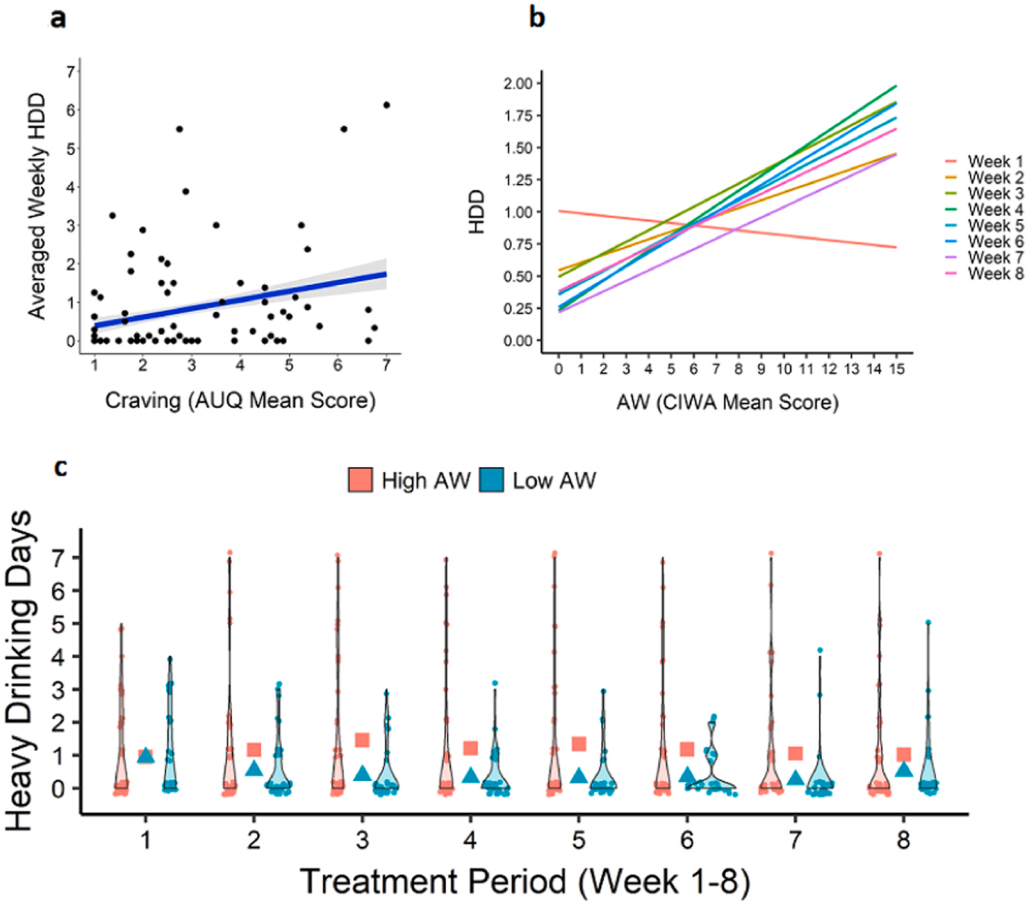

Fig. 1. Pretreatment alcohol craving and AW predicted subsequent heavy drinking days during treatment. 1a: Higher the AUQ Craving score, greater the HDD ($p < .013$) during treatment. Scores on the AUQ were averaged so that possible scores would fall between 1 and 7; 1b: Regression lines for AW continuous score X each treatment week is shown representing CIWA mean score in the sample by number of HDD each week, with greater the baseline AW being associated with higher HDD weekly after week 1, while lower AW predicted progressive reductions in HDD weekly ($p < .018$). 1c: Violin plots showing distribution of number of HDD for each treatment week for the Low (Blue data points and mean in Blue squares) and High (Red data points and Red squares) AW scores, using the median split cut-off of 3.5 to define low and high groups. Total scores for AW (measured by the CIWA) ranges between 0 and 67, although the range for the current sample was 0–15 as shown in Fig. 1b.

4.4. Post-Hoc exploratory analyzes

4.4.1. Association of pretreatment AW and craving with abstinence symptoms and alcohol intake

Pretreatment levels of AW and alcohol craving were moderately positively correlated ($r = 0.32$ $p < 0.004$) Pretreatment AW and alcohol craving were moderately to strongly associated with depression, anxiety, and sleep difficulties at treatment entry (mean value $|r| = .42$; range.32 to.65; all p's $< .05$; see Table S1 and Fig. S1). Craving was moderately correlated with pretreatment HDD ($r = 0.30$ $p < 0.007$). Higher AW tended to be related to increased baseline HDD but this association was not significant ($r = .21$, $p = 0.063$).

4.4.2. Pretreatment depression, anxiety and sleep difficulties on alcohol use outcomes

Although moderately to strongly correlated with AW and craving, pretreatment symptoms of depression, anxiety, and sleep difficulties did not significantly predict any drinking-related outcome during treatment after accounting for demographic and pretreatment alcohol use covariates (all $ps > .05$).

5. Discussion

This prospective observational study examined whether chronic alcohol intake-related AUD clinical features of AW and alcohol craving at pretreatment *prospectively* predicted alcohol treatment outcome, specifically heavy drinking days as the primary outcome and also secondary drinking outcomes of number of drinking days/week and average drinks/per drinking day each week in AUD patients entering outpatient treatment. Higher levels of pretreatment craving predicted a higher number of heavy drinking days across all weeks in the 8-week treatment period. Furthermore, higher pretreatment levels of AW interacted with treatment weeks to predict greater number of heavy drinking days each week for weeks 2–8. Remarkably, none of the other demographic (age, sex, education, race) or baseline drinking and pretreatment days of abstinence variables exerted any significant influence on weekly drinking outcomes during the 8-week treatment period, either in the craving model or the AW model. While it is possible that other temperament, personality or genetic factors not assessed in the current study may also influence treatment outcomes, it was notable that alcohol craving and AW each accounted for the majority of the variance in the primary outcome of number of heavy drinking days and secondary drinking outcomes of number of drinking days and average drinks per drinking day during the 8-week treatment in each of their respective models. Notably these significant effects of pre-treatment craving and AW occurred even in the context of the expected improvements in drinking outcomes with weekly empirically validated efficacious behavioral counseling being provided. Furthermore, higher craving also predicted swifter relapse to heavy drinking. Thus, the findings suggest that while the empirically validated 8-weeks of behavioral counseling treatment was effective in reducing alcohol misuse among patients with little or no craving or AW, it did not improve risky drinking in patients with higher levels of pretreatment AW or those with higher alcohol craving. The findings for HDD were significant even after adjusting for multiple comparisons and suggest that pretreatment AW and alcohol craving as assessed via Clinical Institute of Withdrawal Assessment for Alcohol (CIWA-Ar) and Alcohol Urge Questionnaire (AUQ), may serve as clinical prognostic indicators of alcohol use outcomes and AUD treatment response.

Current findings indicating that pre-treatment alcohol craving predicted heavy alcohol use during outpatient treatment are consistent with previous research assessing alcohol use and heavy drinking (Mchugh

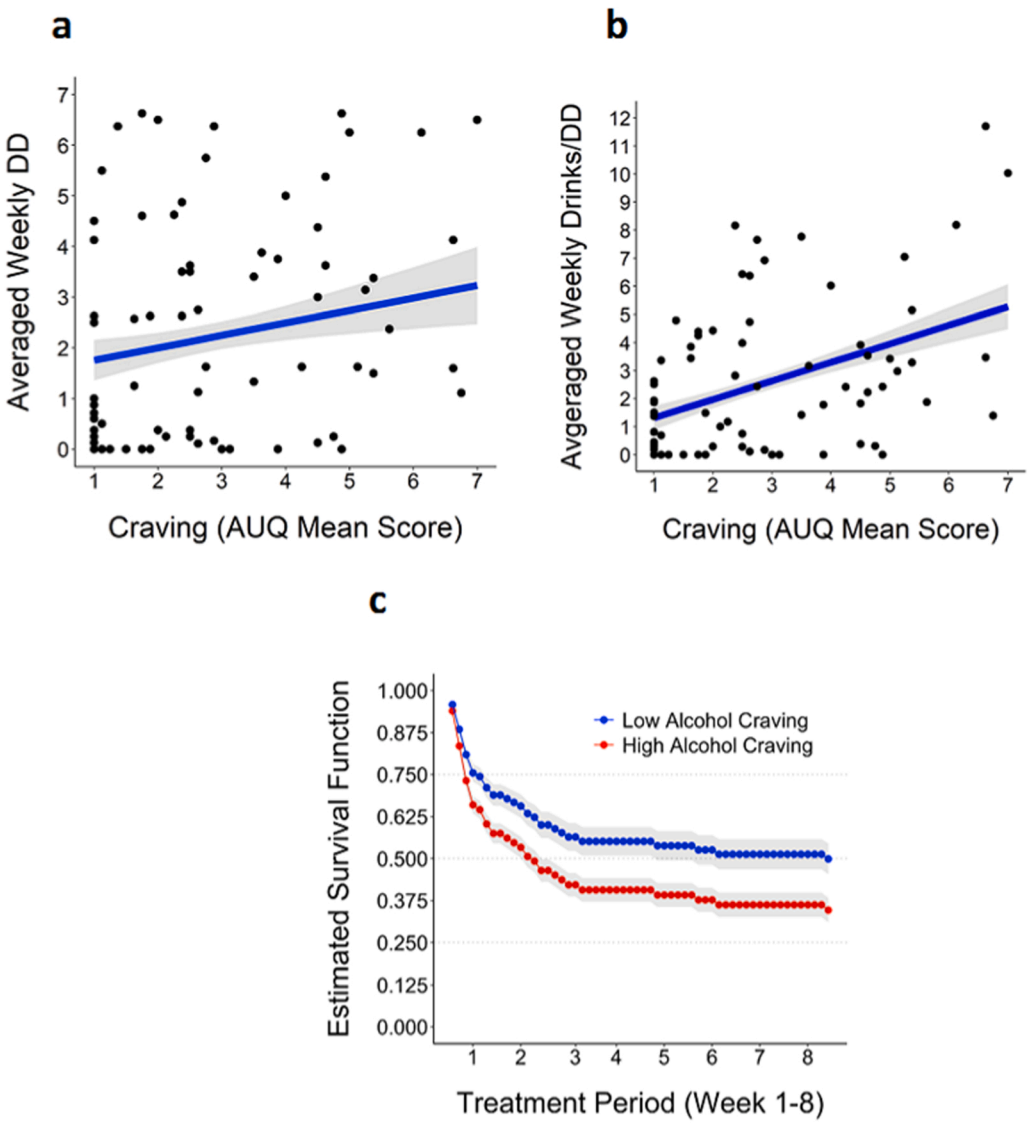

Fig. 2. Pretreatment alcohol craving predicting subsequent secondary alcohol use outcomes during treatment. Scores on the AUQ were averaged so that possible scores would fall between 1 and 7, which is the Likert scale range for each AUQ item. 2a–2b: Higher AUQ craving scores predicted significant greater DD ($p < .004$ and AvgD ($p < .001$) during treatment; 2c: Baseline AUQ alcohol craving (continuous scores) predicted risk of relapse to heavy drinking during treatment ($p = .049$). The survival function (or model-estimated predicted probability) is depicted across the entire treatment period (week 1–8). AUQ scores were median split at 2.5 to define high and low alcohol craving groups.

et al., 2017; Schlauch et al., 2019), and relapse (Higley et al., 2011; Sinha et al., 2011). Findings also indicated that baseline levels of AW interacted with treatment week to predict alcohol use and heavy drinking (O'Connor et al., 1991; Sinha et al., 2021). The significant interaction reflected sustained reductions in alcohol intake across treatment weeks in patients with little or no AW symptoms, but no such reductions were observed in those with higher levels of AW at treatment entry, and these effects were independent of demographic and baseline drinking variables. This is significant as it suggests that key AUD-related clinical features of craving and AW represent significant disease processes that impact AUD clinical course and drinking outcome during outpatient treatment.

Previous research has shown alcohol craving and AW are associated with disruptions in brain and peripheral stress physiology that also co-occur with additional abstinence related distress symptoms such as anxiety, depression and sleep problems, which together may represent stress pathophysiology of AUD beyond that attributable to chronic alcohol intake levels and drinking patterns (Koob, 2003; Fox et al., 2007; Duka et al., 2011; Blaine et al., 2018, 2020; Milivojevic and Sinha, 2018). Furthermore, preclinical and clinical research indicates that these alcohol-related changes in stress neurobiology involve alterations in noradrenergic, corticotrophin releasing factor (CRF) dopaminergic and Gamma-Aminobutyric Acid (GABA) pathways among others, that in turn, affect increased alcohol craving and relapse risk (Koob and Volkow, 2016; Koob and Schulkin, 2019). Recent pharmacotherapy development has focused on targeting individual differences in AW as well as stress-induced craving related changes that promote relapse risk and treatment failure. For example, evidence shows the utility of Gabapentin treatment for AUD in those with high AW (Anton et al., 2020) and we also reported that Prazosin, a noradrenergic alpha-1 antagonist showed benefit in AUD treatment outcomes only in those with significant AW and not in those with no or very few AW (Sinha et al., 2021). The prazosin findings are also consistent with human laboratory and real world ecological momentary assessment studies showing that Prazosin improves disruption in peripheral stress physiology and also reduced stress- and alcohol -cue- induced craving (Fox et al., 2012; Milivojevic et al., 2020), and that day-to-day stress and related craving significantly impacts increases in next day drinking in early treatment for AUD (Wemm et al., 2020). These findings underscore the need to assess AUD clinical features such as AW and craving at treatment entry as prognostic indicators of outcome, as these indicators add not only significant heterogeneity in clinical presentation (Litten et al., 2015), but also identify the need for targeted treatment development for those with higher levels of craving and AW can be of benefit in improving AUD drinking outcomes.

Consistent with our previous work (Sinha et al., 2021) additional

post-hoc exploratory analyses also revealed that higher baseline levels of AW and craving were associated with symptoms of depression, anxiety, and sleep difficulties at treatment entry, and depression and sleep difficulties were also associated with baseline levels of alcohol intake. Despite these positive associations with craving, AW, and pretreatment drinking, post-hoc exploratory analyses showed that baseline symptoms of depression, anxiety, and sleep difficulties did not predict subsequent alcohol use outcomes during 8-weeks of behavioral AUD treatment. These results suggest that these symptoms are related, but conceptually and functionally distinct constructs. Nevertheless, attesting to their clinical significance in AUD treatment, these clinical symptoms are associated with higher alcohol craving in AUD patients, thereby increasing the risk of drinking episodes during treatment (Witkiewitz, Bowen and Donovan, 2011; Wemm et al., 2020). Given that individuals high in AW and craving at treatment entry are more likely to experience symptoms of depression, anxiety, and sleep difficulties during treatment, these additional clinical symptoms may further reduce their ability to cope with stressful events and resist alcohol cravings, thereby increasing their risk of relapse. Thus, these findings support the need to evaluate and monitor clinical symptoms associated with AUD-related stress pathophysiology during outpatient treatment and indeed throughout treatment to promote AUD treatment success. The findings also suggest that assessments of AW and craving at treatment entry may serve as relevant modifiable clinical prognostic factors influencing AUD drinking outcome, while broader, transdiagnostic AUD-related clinical phenotypes of negative mood or emotionality or measures of depression, anxiety, and sleep difficulties may be associated with AW and craving but may not directly impact drinking outcomes in treatment.

The current study has several strengths that address common shortcomings of AUD treatment studies. First, the current study used daily diary self-reports to capture daily drinking in close temporal proximity to the actual drinking experiences, which augments the validity and accuracy of weekly timeline follow-back drinking data obtained during treatment by reducing recall bias (Piasecki, 2019). Moreover, the hypotheses were tested using linear mixed-effects (LME) regression models which factors in week-by-week variance in drinking outcomes to more powerfully model prospective treatment effects. Furthermore, this approach also has many advantages over more traditional regression-based techniques for analyzing data from treatment-based daily diary studies (Shiffman, Stone and Hufford, 2008), including its ability to handle missing observations without excluding the entire patient's data while still providing unbiased parameter estimates. An additional strength is that we chose to focus the riskiest level of drinking, namely heavy drinking days, as our primary outcome of interest to emphasize the clinical utility of these measures. Finally, even though baseline 90 days of recent past alcohol use and number of abstinence days prior to treatment initiation have been shown to influence AUD treatment outcomes (Breslin et al., 1997; Blaine et al., 2020), current findings build on previous work indicating the clinical relevance of alcohol withdrawal (Malcolm et al., 2000; Schuckit, 2014) and craving (Fazzino et al., 2013) in AUD treatment course by showing that the effects of AW and craving on subsequent alcohol use outcomes during treatment were present even after accounting for any potential influence of these alcohol use measures prior to the 8-week treatment period.

The current study has some limitations that need to be discussed and addressed in future research. First, we collected data from 80 treatment-entering AUD patients, consisting of mostly men, which may have prevented us from having adequate statistical power for detecting differences between men and women. Because previous research has shown some evidence of sex differences in the chronic course of AUD (Peltier et al., 2019; Guinle, 2020), future studies should replicate our findings with larger samples of women to adequately test for gender differences. In addition, the current study relied exclusively on patients' reports on their alcohol intake during treatment. Although there is evidence for the validity of self-report drinking data in patients receiving treatment for AUD (Mundle et al., 1999; Babor et al., 2000), researchers should nevertheless replicate the current findings using more objective measures obtained from wearable technology with biosensors and other biochemical measures of recent alcohol intake as additional outcome measures in future studies. Also, future research may benefit from advanced statistical techniques such as multivariate approaches, including structural equation modeling, to account for the potentially covarying effects or multiple related drinking variables, AW, craving and other abstinence symptoms. Finally, future research to replicate current findings and also determine specific cut-off scores for CIWA-Ar and AUQ that are sensitive to treatment response could be of benefit to clinicians in outpatient treatment settings to help them identify patients at risk for relapse and poor alcohol use outcomes during treatment, to further improve AUD treatment efficacy.

In conclusion, the current study provides evidence that increased levels pre-treatment craving and AW place patients with AUD at increased risk for treatment failure, thus jeopardizing their recovery efforts. Our findings extend previous research showing that higher levels of craving at treatment entry predict heavy alcohol use and a higher risk of subsequent relapse to heavy drinking during outpatient treatment, and also provide the first evidence that AW at treatment entry interacted with treatment week to predict treatment response. Individuals with more AW symptoms at treatment entry maintained high levels of alcohol use, whereas those individuals low in withdrawal showed improvements with evidence-supported AUD behavioral therapy with significant reductions in their alcohol use during treatment. These findings are consistent with the notion that AW and craving may serve as useful and clinically meaningful prognostic indicators of treatment response, and suggest the need for both assessment of AW and craving at treatment entry, and the development of treatments that specifically target AW and craving to facilitate early alcohol recovery and improve drinking outcomes in AUD.

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CRediT authorship contribution statement

JSM was responsible for data analyses, contributed to interpretation of the results, and was a major contributor to manuscript preparation. NF assisted with data analysis and interpretation and contributed to manuscript preparation. SW and SH made critical revisions of the manuscript for intellectual content. RS conceptualized and designed the study, and was a major contrbutor to data analytic strategy, interpretation of study findings, manuscript preparation and made critical revisions of the manuscript.

All authors have approved the manuscript for submission to Drug and Alcohol Dependence.

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Conflict of Interest Statement

All authors declare no financial relationships with commercial interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2021.109253.

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