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Effects of initiating abstinence from alcohol on daily craving and negative affect: Results from a pharmacotherapy clinical trial

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Abstract

Background—Craving and negative affect are distressing and commonly experienced during alcohol use disorder (AUD) treatment. Patients may assume that initiating abstinence will intensify their cravings and negative affect despite limited empirical data to support this assumption. The present study extends and replicates, under improved methodological conditions, previous work that found reductions in daily craving associated with initiating abstinence.

Methods—Seventy-eight adults (80.8% male, 57.1% Caucasian) in a clinical trial testing prazosin for AUD provided daily reports of drinking, craving, and negative affect for up to 12 weeks (mean=64.77 daily reports). Participants were classified into 3 subgroups based on whether and when they initiated 14 days of continuous abstinence, including: (1) ‘abstinence initiators’ who quit drinking during treatment ($n=17$), (2) ‘already abstainers’ who were abstinent at the start of treatment ($n=20$), and (3) ‘continued drinkers’ who never initiated abstinence ($n=41$). The timing and degree of change in craving and negative affect were compared across these groups using multivariate growth curve modeling.

Results—All participant subgroups reported gradual reductions in craving over the course of treatment, with ‘abstinence initiators’ reporting additional sudden reductions in craving upon initiating abstinence from alcohol. ‘Continued drinkers’ reported higher levels of craving than ‘already abstainers’ throughout the full course of treatment. Negative affect followed a different pattern of change, with ‘abstinence initiators’ experiencing gradual reductions in negative affect after initiating abstinence but no changes prior to or immediately upon initiating abstinence, and with ‘already abstainers’ and ‘continued drinkers’ experiencing no changes in negative affect over time.

Conclusions—Initiating abstinence is associated with immediate reductions in craving, followed by gradual reductions in both craving and negative affect. Results provide insight into the timing

and magnitude of changes in theoretically and clinically important variables and may help patients anticipate when to expect improvement in craving and negative effect.

Keywords

alcohol craving; depression; drinking urges; negative affect; substance abuse treatment

Introduction

Craving and negative affect are subjectively distressing and commonly experienced by individuals in alcohol use disorder (AUD) treatment. Craving and negative affect are increasingly recognized as core clinical features of AUD (American Psychiatric Association, 2013; Hasin et al., 2007; Murphy et al., 2014) and as clinically important targets in AUD recovery (Epstein et al., in press; Kavanagh et al., 2013; Tiffany & Wray, 2012). Patients in AUD treatment may make the intuitive assumption that both craving and negative affect will intensify when abstinence is initiated, contributing to reluctance to quit drinking. However, there is limited empirical evidence about how craving and negative affect respond to abstinence initiation, which is a clinically relevant question that the present study addresses.

Contemporary behavioral models of AUD often present drinking as both influencing and being influenced by craving and negative affect (Epstein & McCrady, 2009; Schlauch et al., 2013; Sher et al., 2005; Witkiewitz & Villarreal, 2009). For example, situational cues and negative affect may elicit craving (Richardson et al., 2008), and drinking is often conceptualized as a behavioral coping response that temporarily alleviates the discomfort associated with craving and negative affect (Anker et al., 2017; Law et al., 2016). Through this process, drinking may also help maintain or intensify longer-term craving and negative affect through negative reinforcement learning in which associations between situational cues, craving, negative affect, and alcohol consumption are strengthened (Köpetz et al., 2013). Chronic heavy drinking may alter stress, arousal, and reward systems that lead to heightened craving and negative affective reactivity in response to stressful and alcohol-related cues (Koob et al., 2004; Sinha et al., 2009). Continued alcohol consumption, especially in response to craving or negative affect, is therefore hypothesized to maintain longer-term craving and negative affect. Sustained abstinence from alcohol is hypothesized to help extinguish these associations of craving and negative affect states with drinking by both eliminating the negative reinforcement caused by drinking and removing alcohol as a potent source for cueing and maintaining future cravings and negative affect. However, it could be reasonable to expect that the transition from drinking to abstinence would be associated with a temporary worsening of craving and negative affect, particularly if alcohol was used to alleviate discomfort due to craving and negative affect.

There has been limited research to date that formally quantifies the timing and extent to which craving and negative affect increase or decrease in response to initiating abstinence. Previous studies have shown that negative affect is inversely related to the duration of abstinence within the first year of alcohol and drug cessation (Sutherland, 1997), and that both craving and negative affect typically improve over the course of receiving naltrexone, inpatient AUD treatment, and alcohol detoxification treatment (Brown et al., 1991; Brown &

Schuckit, 1988; Helstrom et al., 2016; Myrick et al., 2008; Oslin et al., 2009; Petit et al., 2017; Richardson et al., 2008; Witkiewitz et al., 2013). Studies have also shown that reduced alcohol craving and negative affect may facilitate sustained improvements in alcohol consumption, both in the near-term (e.g., in subsequent hours or days; Fazzino et al., 2013; Fatseas et al., 2015; Witkiewitz & Villarroel, 2009) and in the longer-term (e.g., in subsequent months or years; Bottlender & Soyka, 2004; Coates et al., 2017; Subbaraman et al., 2013; Witkiewitz et al., 2010, 2013). However, studies have typically modeled craving and negative affect as predictors of drinking, rather than vice versa, and few studies have evaluated the day-by-day manner with which craving and negative affect improve during AUD treatment, especially with regard to how these changes may correspond with the initiation of abstinence.

There is currently little empirically-derived information available to patients and healthcare providers that may help them anticipate how much and when craving and negative affect may be expected to change in association with initiating abstinence in AUD treatment. Moreover, many patients and some providers may worry that initiating abstinence will exacerbate craving and negative affect, especially during the first several days of abstinence, rather than provide relief. These fears are clinically relevant, as they could lead to some hesitation to initiate abstinence due to worries about worsening craving and negative affect that create negative expectancies about abstinence goals. In contrast, having empirical information about the timing and degree of change in craving and negative affect that are expected to occur when one initiates abstinence could help guide patients in setting treatment goals about drinking and abstinence (Hallgren et al., in press), potentially creating more positive expectancies about treatment and abstinence.

A previous study (Hallgren et al., 2016) evaluated the extent to which daily alcohol craving changed in relationship to initiating abstinence. In that study, outpatients in individual- and couple-based cognitive-behavioral treatments recorded their daily alcohol consumption and whether they experienced any cravings each day via hand-written daily diary cards. The participants who initiated abstinence during treatment reported experiencing alcohol cravings on most days (60–80% of days) before they initiated abstinence, followed by an immediate decrease in the number of days with alcohol craving starting within the first days after initiating abstinence (50–55% of days) with continued declines in the frequency of daily cravings after that (20–40% of days up to four months after initiating abstinence). In contrast, participants who never initiated abstinence started treatment with a high proportion of craving days (70–80% of days) that declined modestly throughout treatment (60–70% of days four months after starting treatment) and participants who initiated abstinence prior to treatment started treatment with a lower proportion of craving days (35–45% of days) that declined throughout treatment (20% of days four months after starting treatment).

The present study aims to replicate this previous study that found reductions in daily craving associated with initiating abstinence (Hallgren et al., 2016) under improved methodological conditions, including the use of interactive voice response (IVR) technology to ensure same-day data collection (versus hand-written daily diaries asking patients to report on urges when they occur) and the use of multiple items that assessed different facets of daily craving including frequency and intensity (versus a single item assessing the presence or absence of

any daily cravings). The present study also extends this previous work by evaluating changes in daily negative affect (versus only craving) and by studying these changes in the context of a pharmacotherapy trial with no behavioral intervention (versus cognitive-behavioral treatments that include substantial education and psychotherapy around craving and negative affect). These findings could potentially help advance a greater understanding of the timing and magnitude of change in hypothesized mechanisms of behavioral change and key AUD treatment targets (Hallgren et al., in press), and may also help providers and patients better anticipate the expected timing and degree of change in the intensity of craving and negative affect, both over time and in relationship with initiating abstinence, providing evidence-based information that can support treatment goals and clinical decision-making.

Materials and Methods

Participants

The present study is a secondary analysis of data from a randomized controlled trial comparing the effect of prazosin versus placebo medication on alcohol consumption (Simpson et al., under review). In brief, the parent trial found a small but significant treatment $\times$ time effect where participants receiving prazosin had greater rates of change in percentages of heavy drinking days over the 12-week medication period. However, there were no absolute differences between the treatment conditions in the percentage of heavy drinking days for any week during treatment, and there were no main effects for treatment condition or treatment $\times$ time interactions on the percentage of days abstinent (PDA).

Participant inclusion criteria included current DSM-IV alcohol dependence, a treatment goal of abstinence from alcohol, at least 14 or 21 drinks consumed per week for women or men, respectively, and two heavy drinking days per week for at least four consecutive weeks in the last 90 days at baseline. Exclusion criteria included a diagnosis of post-traumatic stress disorder, uncontrolled psychiatric disorder that included psychotic symptoms or cognitive impairment, unstable psychiatric medication dosing in the past month, use of alcohol treatment medications (e.g., disulfiram, acamprosate, naltrexone) within the past month, current opioid dependence, positive drug screen for opioids, benzodiazepines, or sedative hypnotics, significant acute or chronic illness, pre-existing systolic blood pressure <100 mmHg or orthostatic hypotension, history of prazosin sensitivity or use of prazosin in the past 30 days, or participation in a drug- or addiction-related study in the past month. In addition, men were excluded if they used trazodone, tadalafil, or vardenafil in the past month; women of childbearing age could participate only if they reported using contraception. Participants could not receive behavioral or medication treatment for AUD outside of the study but could participate in Alcoholics Anonymous and receive supportive counseling.

Among 92 participants in the parent study, a total of $N=78$ had enough daily IVR drinking data to assess an abstinence status over 14 or more consecutive days. Following identical procedures to Hallgren et al. (2016), these 78 participants were classified into three groups based on whether and when they first initiated 14 consecutive days of abstinence from alcohol during treatment. *Abstinence initiators* ($n=17$) drank on at least one of the first 14 days of treatment then eventually obtained at least 14 consecutive days of abstinence during

the treatment period. *Already abstainers* ($n=20$) were abstinent throughout the first 14 days of treatment. *Continued drinkers* ($n=41$) drank during the first 14 days of treatment and never obtained 14 consecutive days of abstinence. Although the AUD treatment literature has had numerous definitions of drinking “remission” (Maisto et al., 2016), the 14-day window for classifying abstinence initiation in the present study was informed by previous research suggesting a low likelihood of 14 or more consecutive days of abstinence between drinking episodes before and during alcohol treatment (Epstein et al., 2004; Hallgren et al., 2016). In the present sample, only four participants (4.4% of original sample) had any abstinence periods lasting 14 or more days between drinking episodes within the baseline period, suggesting that achieving abstinence for 14 consecutive days would likely reflect a deliberate transition in drinking behavior rather than being part of a pre-existing drinking pattern. The three drinking pattern groups were defined identically as they were in Hallgren et al. (2016), and whereas Hallgren et al. reported more abstinence initiators and already abstainers than continued drinkers, the present study had a larger proportion of continued drinkers.

Drinking statuses were considered unknown if data were unavailable for at least 70% of days within a 14-day window; however, participants were classified as drinking if any drinking days were observed during a 14-day window even if less than 70% of daily data were available. Participants who resumed drinking beyond the first 14 days of abstinence were not reassigned to different classes, but of note, PDA was high after the first 14-days of abstinence for both abstinence initiators ($M=95.83$, $SD=5.05$) and already abstainers ($M=99.44$, $SD=1.42$). Already abstainers reported a mean of 11.40 days of continuous abstinence ($SD=18.02$) prior to baseline interviews.

Participant demographic and PDA summaries are presented in Table 1. In brief, the sample was predominantly male (80.8%) and Caucasian (57.1%), with sizeable proportions of African American (31.2%) and veteran participants (21.8%). Mean age was 48.49 and participants were employed on average for 17.33 of the last 90 days prior to baseline. There were no differences between the drinking subgroups for any of the demographic variables except veteran status, in which case there was a larger proportion of veterans in the abstinence initiator group compared to the continued drinker group. Consistent with how the three subgroups were defined, already abstainers had higher baseline PDA than abstinence initiators and continued drinkers, but baseline PDA did not differ between abstinence initiators and continued drinkers. Also consistent with the subgroup definitions, within-treatment PDA was highest for already abstainers, lowest for continued drinkers, and intermediate for abstinence initiators (see Table 1). The 14 individuals who lacked enough daily drinking data to assess an abstinence status did not differ from the 78 participants included in the present analysis on demographic variables, baseline PDA, or baseline craving; however, the excluded participants did have significantly higher baseline depression ratings (difference=3.39, $SE=1.62$, $p=.04$).

Measures

Daily drinking, craving, and negative affect during treatment—Participants were asked to provide daily measures of previous-day drinking, craving, and negative affect each

day during the 12-week treatment period using a telephone-based IVR system. These daily IVR measures were used in the primary analyses presented here. The 78 participants included in the present study provided IVR data on a mean of 64.77 days (77.1% of all possible days, $SD=20.54$ days, range=14 to 83 days)¹. On average, continued drinkers provided about 9 fewer days of IVR data compared to abstinence initiators and already-abstainers, respectively; however, these differences in rates of IVR assessment completion did not reach statistical significance (see Table 1).

Daily alcohol consumption was assessed using three items that asked participants to report the number of beer, wine, and liquor standard drinks that were consumed in the previous day. A daily alcohol consumption indicator was then created from these data to determine whether each day was a drinking day or an abstinence day. Drinking measures were only assessed via self-report and were not biologically verified.

Daily craving was assessed using four items adapted from the Penn Alcohol Craving Scale (PACS; Flannery et al., 1999) that asked participants to rate their past-day craving severity in terms of frequency, intensity, difficulty resisting drinking, and average craving over the last 24 hours. A fifth item from the original PACS that assessed the duration of alcohol craving was not included in the daily IVR assessment due to anticipation that it would be difficult for participants to differentiate craving duration from craving frequency when reporting on a 24-hour period via daily IVR assessment. Daily severity of negative affect was assessed using four items that asked participants to rate their past-day stress, anger, anxiety, and sadness. Likert-type scales for each rating ranged from 0 (no craving/no negative affect) to 8 (severe craving/most severe negative affect ever experienced). The four daily craving indices were highly correlated ($r=.81$ to $.90$), as were the four daily negative affect indices ($r=.57$ to $.75$), suggesting each set of items measured overlapping constructs reflecting negative affect or craving. The craving indices were also modestly correlated with the negative affect indices ($r=.31$ to $.38$), suggesting that the craving and negative affect items measured constructs that were likely theoretically distinct despite being correlated (associations between negative affect and craving have also been demonstrated in previous research; e.g., McCaul et al., 2017; Oslin et al., 2009). Of note, one IVR item assessed past-day boredom but this had substantially lower correlations with the other four negative affect items ($r=.34$ to $.48$); the boredom item was therefore excluded from the multivariate composite of daily negative affect (see Analytic Plan below).

Baseline and post-treatment craving and depression—Participants also completed the standard version of the PACS (Flannery et al., 1999) and the Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001) at the time of randomization (“baseline”) and after the 12-week treatment period (“post-treatment”). These provided secondary measures for evaluating changes in craving and depression (a construct that is separate from, but related to, negative affect). Most notably, these measures allowed us to describe the severity of baseline and post-treatment craving and depression at the beginning and end of

¹For the larger sample of 92 participants (i.e., retaining the 14 participants who were excluded from the present analysis due to a lack of enough daily IVR data to classify abstinence status), IVR data were available for a mean of 55.80 days (66.4% of all possible days, $SD=28.53$ days, range=0 to 83 days).

treatment using scales that are standardized, commonly used in clinical practice, and have good psychometric properties and normative reference values.

The PACS included five items assessing the frequency, intensity, and duration of craving, ability to resist drinking, and overall rating of craving during the past week. PACS scores can range from 0 (no craving) to 30 (most severe craving). The PHQ-9 included nine items assessing symptoms of depression; possible scores range from 0 (no depression symptoms) to 27 (severe depression symptoms), with scores of 10 or higher having good sensitivity and specificity in predicting a likely depression diagnosis. Both measures have good reliability, validity, and sensitivity to detecting change (Flannery et al., 1999; Kavanagh et al., 2013; Kroenke et al., 2001).

DSM-IV Diagnoses—Diagnostic eligibility criteria were assessed using sections of the Structured Clinical Interview for DSM-IV Disorders (First et al., 1995).

Baseline Drinking—PDA over the 90 days prior to baseline was assessed using the Form-90 (Miller & Del Boca, 1994).

Study Procedures

Participants were recruited using flyers, advertisements in local papers, Craigslist, and clinical referrals. Interested participants completed an in-person clinical screen to assess eligibility. Eligible participants returned for baseline appointments approximately one week later, at which time they completed baseline measures, were randomized to treatment condition, and received study medication. Participants were then given prazosin or placebo over a 12-week treatment period that included an initial two weeks of titration followed by ten weeks of stable dosing (4 mg in morning, 4 mg in evening, 8 mg at bedtime). Participants received brief medication management counseling once per week and routinely completed pill counts, urine testing, adverse event checks, and orthostatic vital sign checks with study staff during office visits.

Participants were asked to complete a 4–5 minute IVR call each day to report on drinking, craving, mood, and medication adherence via a toll-free phone number. Participants were reimbursed up to \$477 for completing all study visits and IVR calls. All procedures were approved by the VA Puget Sound Health Care System Institutional Review Board.

Analytic Plan

Statistical analyses aimed to model changes in craving and negative affect in relationship to initiating abstinence from alcohol. These analyses were conducted in a manner that is modeled after a previous study addressing a similar question using daily diary reports of drinking urges (Hallgren et al., 2016).

Daily craving and negative affect were modeled using multivariate growth curve models (MGCM), which were constructed within a multivariate multilevel modeling framework. The multilevel framework allowed models to account for nesting of repeated observations within participants; the multivariate framework allowed for the estimation of change over time for single multivariate composites that reflected the shared variance among the four

craving items or the four negative affect items. This allowed each set of correlated and theoretically overlapping craving or negative affect indices to be mapped into a single multivariate latent craving or latent negative affect construct and analyzed within a single model, rather than modeling, analyzing, and interpreting a series of separate models for each craving or negative affect indicator. This incurs several advantages (Snijders & Bosker, 2000); for example, reducing the number of models reduces type-I error rates and can provide greater theoretical parsimony (i.e., due to testing and drawing conclusions from a smaller number of statistical models), and the use of latent composites explicitly accounts for the shared variance among indicators and reduces error variance in latent composites, which can reduce type-II error rates.

Separate MGCMs were fit for each multivariate composite of daily craving and negative affect in each of the three drinking groups. For abstinence initiators, linear growth terms evaluated gradual changes in craving and negative affect over time before and after initiating abstinence, and a discontinuous growth term modeled any sudden change associated with the transition from drinking to abstinence. For already abstainers and continued drinkers, linear growth terms evaluated gradual change over the course of treatment (the effects of transitioning from drinking to abstinence could not be modeled in these subgroups). Growth terms were modeled using both fixed effects (representing mean rates of change) and random effects (representing variability between participants in rates of change). Time was centered at the point of abstinence initiation (for abstinence initiators) or the first day of treatment (for already abstainers and continued drinkers), and time was scaled such that a one unit change in time corresponded with a period of seven-days, allowing the growth term coefficients to reflect expected rates of change per week. All MGCMs were fit using daily data via the *nlme* package in R (Pinheiro et al., 2017) with an identity (Gaussian) link function and restricted maximum likelihood to reduce bias from missing data (Hallgren & Witkiewitz, 2013). Analyses of daily IVR measures covered an 84-day period that included up to 21 pre-abstinence days and 63 post-abstinence days for abstinence initiators, which constituted boundary points within which the majority of abstinence initiators had daily IVR data. An 84-day period was also used for already abstainers and continued drinkers.

Changes in PACS and PHQ-9 scores from baseline to post-treatment were evaluated within each drinking group using paired sample *t*-tests and Cohen's *d* effect sizes for evaluating within-group change. Approximately 35% of the sample ($n=27$) were missing follow-up PACS or PHQ-9 data; multiple imputation was therefore used to improve model accuracy when data were missing (van Buuren & Groothuis-Oudshoorn, 2011). Auxiliary variables for multiple imputation included demographic variables and baseline drinking, PACS, and PHQ-9 measures, and 20 imputation sets were modeled for the analysis.

There were no significant effects of prazosin or prazosin $\times$ time on any of the measures of craving (all $p > .49$), negative affect (all $p > .08$), or abstinence days (Simpson et al., under review). We therefore did not consider treatment condition to be a confounder and did not adjust for treatment condition in the statistical models.

Results

Changes in Daily Craving

MGCM results for craving are reported in Table 2. Intercept coefficients for each univariate craving indicator (Roman typeface) quantify the model-estimated mean levels of craving immediately prior to abstinence initiation (abstinence initiator group) or at the start of treatment (already abstainer and continued drinker groups). Growth term coefficients (bold typeface) quantify the rates of change per week or the degree of sudden change before versus after initiating abstinence for the multivariate craving composite. Fixed effect coefficient values reflect the mean intercept and growth term quantities for each group (e.g., mean rate of change over time) and random effect coefficients reflect the variability in these terms across participants (e.g., variability in rates of change over time).

Participants who initiated abstinence had a model-implied mean craving composite of 3.95 three weeks prior to initiating abstinence, which was followed by marginally non-significant reductions over time during the period prior to initiating abstinence ($p=.056$). When these participants initiated abstinence, they experienced immediate reductions in craving that averaged 0.82 points on the nine-point Likert-type scale ($p<.001$, random effect $SD=1.06$), moving from a model-implied mean of 2.72 to 1.90 (both pooled random effect $SDs=1.61$). Cravings then continued to decline over time after this, decreasing by a mean of 0.21 points per week ($p=.001$, $SD=0.16$) until cravings were reported as being nearly absent by the end of the observation period.

Participants who were already abstinent had considerably lower mean levels of craving throughout the course of treatment. For these already abstainers, craving ratings were initially low at a mean of 0.91 (pooled $SD=0.94$) at the start of treatment, followed by small but significant reductions over time after that (mean decrease of 0.04 points per week, $p=.043$, $SD=0.08$).

Participants who continued to drink had considerably higher craving severity with small reductions over time throughout treatment. For these continued drinkers, cravings were initially high with a mean level of 4.69 (pooled $SD=1.43$) at the start of treatment, followed by small but significant reductions over time at a mean rate of 0.10 points per week ($p=.033$, $SD=0.28$).

Trajectories of craving over time are illustrated in Figure 1, which includes model-implied trajectories for the multivariate craving composite (straight black lines), observed daily means for each univariate craving index (color lines), and the number of participants providing IVR data for each day (black histograms below each line graph). This figure shows that craving was generally higher before abstinence was initiated compared to after it was initiated. For example, continued drinkers and abstinence initiators prior to quitting drinking had higher daily mean levels of craving on nearly all days (e.g., all mean daily craving indices > 2) compared to already abstainers and abstinence initiators after quitting drinking (e.g., most mean daily craving indices < 2). In addition, there was no evidence for systematic spiking or rebounding of craving in within the first several days after initiating abstinence (e.g., no sudden increases craving associated with quitting drinking).

Changes in Daily Negative Affect

MGCM results for daily negative affect are reported in Table 3. Participants who initiated abstinence had a model-implied mean negative affect composite of 1.71 three weeks prior to initiating abstinence and did not experience significant changes in negative affect over time prior to initiating abstinence. These participants also did not experience sudden changes in negative affect immediately after initiating abstinence, but they did experience significant, gradual reductions in negative affect over time after initiating abstinence. For these abstinence initiators, negative affect started at a model-implied mean of 1.80 (pooled $SD=2.02$) after abstinence was initiated and declined by a mean of 0.11 points per week ($p=.001$, $SD=0.12$) down to a model-implied mean of approximately 0.81 nine weeks later.

Participants who were already abstinent had considerably lower negative affect ratings throughout the course of treatment. For these already abstainers, negative affect was reported at mean of 1.03 (pooled $SD=1.19$) at the start of treatment and it did not change significantly over time after this (mean increase of 0.02 points per week, $p=.44$, $SD=0.09$).

Participants who continued to drink had higher negative affect ratings throughout the course of treatment. For these continued drinkers, negative affect was reported at a mean of 2.14 (pooled $SD=1.56$) at the start of treatment and it did not change significantly over time (mean increase of 0.01 points per week, $p=.50$, $SD=0.12$). These results are illustrated graphically in Figure 2.

Baseline to Post-Treatment Change in PACS and PHQ-9 Scores

PACS and PHQ-9 scores at baseline and post-treatment were evaluated to contextualize the overall degree of change in craving and depression using standardized measures. Baseline and post-treatment distributions of these measures are shown in Figure 3. The boxplots in Figure 3 illustrate the distributions of scores for each subgroup and time point, with the horizontal lines reflecting median scores, box intervals reflecting 25th and 75th percentile scores, and whisker intervals reflecting the full ranges of scores. Effect sizes and significance values for the degree of within-person change from baseline to post-treatment are displayed above each subgroup.

All three drinking subgroups had significant reductions in PACS scores (craving) from baseline to post-treatment, with the effect size being largest for abstinence initiators, lowest for continued drinkers, and intermediate for already abstainers. Baseline PACS scores were typically at levels that indicated substantial craving-related distress within all three subgroups (e.g., majority of participants scoring 12 or higher in each subgroup). However, post-treatment scores were often reduced to levels indicating much lower clinical distress, particularly for participants who were abstinence initiators (median post-treatment PACS score=5) or already abstainers (median post-treatment PACS score=2). In contrast, post-treatment PACS scores were often at levels that would indicate substantial craving-related distress among participants who continued to drink (median post-treatment PACS score=15).

Effect sizes for changes in PHQ-9 scores (depression) were substantially smaller for all drinking subgroups, and only the abstinence initiator group experienced significant reductions in PHQ-9 scores. In each of the three drinking groups, the majority of baseline

and post-treatment PHQ-9 scores were below the threshold that is commonly used to indicate a likely depressive disorder (i.e., median PHQ-9 scores were always below 10 for each group at each time point).

Discussion

There is growing interest in more precisely delineating how and when key clinical improvements occur during AUD treatment (Hallgren et al., in press; Huebner & Tonigan, 2007; Longabaugh et al., 2005; Magill et al., 2015). The present study evaluated the timing and magnitude of change in daily craving and negative affect in relationship to the initiation of abstinence from alcohol in the context of a trial of prazosin treatment for AUD. Participants who initiated abstinence during treatment experienced the largest reductions in standardized measures of craving and depression from baseline to post-treatment. Daily IVR measures more specifically indicated that, in addition to gradual reductions in craving over time in all three groups, participants who initiated abstinence experienced additional immediate reductions in craving immediately after initiating abstinence. Additionally, for abstinence initiators, negative affect gradually reduced over time after initiating abstinence, but not prior to or immediately after initiating abstinence. Several participants initiated abstinence prior to the start of treatment, which is consistent with prior research (Epstein et al., 2005; Stasiewicz et al., 2013), and these individuals also entered treatment with lower levels of daily craving and negative affect and had small reductions in craving, but not negative affect, over time. Participants who never initiated abstinence maintained higher levels of daily craving and negative affect, with small reductions in craving, but not negative affect, over time.

Several results were consistent with a prior study that examined changes in daily craving during cognitive-behavioral AUD treatment (Hallgren et al., 2016), including the immediate reductions in craving after initiating abstinence, gradual reductions in craving over time, and the lack of evidence for systematic “rebounding” in which craving was more severe after initiating abstinence compared to before. Also, consistent with the prior study, we found generally high levels of craving with a small degree of change over time among continued drinkers and generally lower levels of craving that further decreased over time among individuals who were abstinent at the start of treatment. The present study also extended the findings of Hallgren et al. (2016) by utilizing several methodological improvements (e.g., IVR data collection, multivariate measurements of craving and negative affect severity) and by examining changes in negative affect in relation to initiating abstinence. Regarding negative affect, the present study extends previous work by showing that negative affect only decreased gradually over time after initiating abstinence, without immediate reductions concurrent with initiating abstinence, and that daily negative affect did not significantly change among abstinence initiators and already abstainers. In addition, across groups, severity ratings for daily negative affect ratings were generally lower than the severity for daily craving ratings.

Behavioral and biological models of AUD often consider craving and negative affect to be bidirectionally related to alcohol consumption (Cohn et al., 2014; Law et al., 2016; Witkiewitz & Villaroel, 2009). While craving and negative affect often noticeably cue

drinking, continued drinking reinforces and maintains longer-term craving and negative affect through reinforcement learning and numerous changes in cognitive and biological systems (Berridge & Robinson, 2016; Köpetz et al., 2013; Koob et al., 2004; Sinha et al., 2009). Initiating abstinence from alcohol may reduce craving and negative affect by extinguishing learned associations of these variables with drinking, removing alcohol as a potent source for cuing craving and negative affect, and eliminating the altering effects of alcohol on cognitive and biological systems that help maintain craving and negative affect.

Many behavioral treatment models, including cognitive-behavioral therapies, have hypothesized that self-regulation skills for reducing and coping with craving and negative affect are mechanisms of behavioral change that are learned through cognitive-behavioral treatment and in turn facilitate longer-term positive drinking outcomes (Roos & Witkiewitz, 2017). However, it is also possible that the initiation of abstinence, even within the context of pharmacotherapy with no behavioral intervention, may itself help individuals achieve better regulation of craving and negative affect. By increasingly experimenting with new behavioral responses to craving and negative affect, it is possible that participants gradually strengthened their use of alternative, non-drinking approaches to cope with craving and to regulate negative affect, which may partly contribute to the gradual reductions in these uncomfortable subjective states over time. Of note, the role of self-regulation skills could not be tested in the present study; however, future research may evaluate changes in self-regulation in the context of medication-based AUD treatments.

Our finding that negative affect did not decrease over time in the already abstainer group was unexpected in light of the significant reduction in negative affect over time that abstinence initiators experienced after quitting drinking. It is unclear why this discrepancy was observed in the present study, but it is possible that this may be attributable to floor effects associated with the initially low ratings of negative affect and depression within the already abstainer group, as well as the nature of negative affect being influenced by numerous factors besides drinking.

Our finding that many participants initiated abstinence prior to starting treatment holds implications for research on mechanisms of behavioral change in AUD clinical trials. Previous research has shown that pre-treatment changes in drinking are common (Epstein et al., 2005; Stasiewicz et al., 2013). Yet, many clinical trials have few measurements (or no measurements at all) of hypothesized mechanisms of behavioral change (e.g., craving, negative affect) prior to the start of treatment. This limited pre-treatment assessment likely inhibits the ability to understand how and when pre-treatment changes in these mechanisms occur. As a result, much of the existing mechanisms of change research has focused on changes in mechanisms during treatment that may help *maintain* longer-term reductions in drinking, but there is substantially less work identifying mechanisms that help *initiate* behavioral change (e.g., initiation of abstinence). It is possible that the mechanisms that maintain behavioral change operate differently than those that initiate behavioral change (Hallgren et al., in press), and additional work identifying both types of mechanisms is warranted and may require more frequent observation prior to starting in treatment and early during the treatment process.

Clinical Implications

Craving and negative affect are distressing, commonly experienced, and clinically relevant targets in AUD treatment. Patients may often have limited insight regarding the extent and timing with which craving and negative affect are likely to improve during AUD treatment and in relation to initiating abstinence. Many patients, and even some clinicians, may assume that craving and negative affect must be adequately controlled in order to initially achieve abstinence from alcohol. In contrast to this assumption, the present study corroborates theoretical and empirical findings that continued drinking may help maintain craving and negative affect and suggests that, for many patients, craving and negative affect may be expected to decrease after initiating abstinence. The present study also provides greater precision regarding the timing and magnitude in which these changes occur and illustrates that these effects are present during a medication-based AUD treatment that had no corresponding behavioral intervention.

Treatment providers may reassure patients with AUDs that they are likely to experience reductions in craving during AUD treatment, particularly if they initiate abstinence from alcohol, and that they may expect these reductions to occur both immediately and gradually after quitting drinking. Providers may also reassure patients that negative affect is also likely to improve after initiating abstinence, although improvements in negative affect may occur more gradually over time rather than suddenly. Providers may discuss these expected courses of change with patients to help facilitate positive expectancies around AUD treatment and abstinence, which may help patients set more informed treatment goals, potentially instill positive expectancies around treatment and abstinence, and help patients understand how these experiences are interrelated with drinking behavior.

Importantly, these clinical implications should be interpreted with consideration of the three groups that were defined based on within-treatment drinking patterns. Patients with these different drinking patterns often have different courses of AUD treatment, with treatment goals and targets that change in correspondence to their drinking status – for example, targeting reduced drinking or initiation of abstinence for patients who are still drinking during treatment versus targeting broader coping skill development and relapse prevention for patients who have maintained reduced drinking or abstinence. Clinicians may therefore anticipate and discuss with patients how their craving and negative affect may be expected to change during treatment with respect to the individual patient's drinking status.

Limitations and Strengths

The present study has noteworthy limitations. The sample size was relatively small which limited our ability to test between-group differences and person-level variables, such as withdrawal status and gender, which could potentially moderate changes in craving and negative affect during treatment (Hallgren et al., 2016; Petit et al., 2017). The inability to randomly assign participants to drinking classes also resulted in unequal numbers of participants between classes, potentially limiting power within smaller classes (e.g., abstinence initiators) relative to larger classes (e.g., continued drinkers). The lack of random assignment also limited the extent to which results could be interpreted with causal explanations, and it is possible that unmeasured variables could account for the

corresponding changes in drinking, craving, and negative affect. Therefore, results should be interpreted as correlational (i.e., changes that typically co-occur when abstinence is initiated) rather than causal (i.e., changes that are caused by initiating abstinence). Participants were asked to rate their cravings and negative affect from the previous 24 hours during IVR calls, and it is possible that these ratings were influenced by their success in not drinking during the same period; thus, real-time assessment of craving and negative affect in future studies would further help remove this potential source of bias. Drinking groups were defined based on the presence of 14 days of continuous abstinence, which was consistent with the abstinence goal of the treatment studied here, but other methods for classifying participants based on moderate drinking outcomes were not tested (e.g., Witkiewitz et al., 2017). Drinking data were not biologically verified and there was a non-trivial degree of missing daily IVR data (22.9% on average) with the possibility that drinking was more common on days with missing data.

The present study also has several strengths. Measures of daily craving and negative affect were collected using IVR methods and assessed multiple facets of craving and negative affect. The daily IVR data included a high density of repeated measurements, providing numerous data points suitable for analyses that focused on within-person change over time. The sample was likely representative of individuals seeking pharmacotherapy for AUD and had a relatively high proportion of African Americans, who are often under-represented in clinical AUD research. The treatment contained minimal behavioral intervention with no formal psychoeducation around the relationships between craving and negative affect, which may have minimized the potential for the observed changes in craving and negative affect to be primed by expectations set by discussions with treatment providers.

Conclusions

The relationships between drinking, craving, and negative affect are likely dynamic and bidirectional, and patients in AUD treatment may have little understanding of whether and how craving and negative affect are expected to change during treatment and in relation to initiating abstinence. Patients and treatment providers may benefit from evidence-based knowledge that initiating abstinence from alcohol is likely to correspond with immediate reductions in craving followed by gradual reductions in both craving and negative affect. Discussing these expected improvements could facilitate more informed discussion of treatment goals and expectancies around initiating abstinence.

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Figure 1.

Changes in craving over time. Color lines indicate observed mean values for each craving index; solid black lines indicate MGCM-represented change for the multivariate craving composite. Black histograms below each line graph indicate the number of participants providing valid craving data on each day.

Figure 2.

Changes in negative affect over time. Color lines indicate observed mean values for each negative affect index; solid black lines indicate MGCM-represented change for the multivariate craving composite. Black histograms below each line graph indicate the number of participants providing valid negative affect data on each day.

Figure 3.

Baseline and post-treatment distributions of standardized craving and depression measures. Horizontal lines indicate median values for each outcome variable for each drinking group, box boundaries indicate 25th and 75th percentiles, and whisker boundaries indicate maximum and minimum values. P -values indicate significance of differences from baseline to post-treatment within each drinking group based on paired sample t -tests estimated with multiple imputation. Cohen's d effect sizes reflect the magnitudes of change from baseline to post-treatment within each subgroup, standardized by dividing that difference by the standard deviation of each baseline measure observed across all three subgroups.

Table 1**Participant Demographics and Percentages of Days Abstinent (PDA)**

	Full Sample (<i>N</i> = 72)	Abstinence Initiators (<i>n</i> = 17)	Already Abstainers (<i>n</i> = 20)	Continued Drinkers (<i>n</i> = 41)
	M (SD)	M (SD)	M (SD)	M (SD)
Male, <i>N</i> (%)	63 (80.8%)	11 (64.7%)	18 (90.0%)	34 (82.9%)
Caucasian, <i>N</i> (%)	44 (57.1%)	10 (58.8%)	13 (65.0%)	21 (52.5%)
African American, <i>N</i> (%)	24 (31.2%)	6 (35.3%)	5 (25.0%)	13 (32.5%)
Other Race, <i>N</i> (%)	9 (11.7%)	1 (5.9%)	2 (10.0%)	6 (15.0%)
Veteran, <i>N</i> (%)	17 (21.8%)	7 (41.2%) ^b	6 (30.0%)	4 (9.8%) ^b
Age	48.49 (10.02)	47.82 (11.19)	50.20 (10.69)	47.93 (9.31)
Days employed (out of past 90)	17.33 (23.76)	14.94 (22.83)	11.11 (16.62)	21.30 (26.58)
Baseline PDA	23.28 (25.08)	20.85 (21.82) ^a	43.39 (29.70) ^{ac}	14.47 (17.82) ^c
Within-Treatment PDA	59.05 (37.72)	84.09 (9.22) ^{ab}	99.49 (1.35) ^{ac}	28.93 (26.27) ^{bc}
Number of IVR Observations	64.77 (20.54)	69.12 (14.57)	69.80 (15.57)	60.51 (23.93)

Note. Values with identical superscript letters indicate there were significant differences between groups. Differences for continuous variables were evaluated using Fisher exact tests; differences for continuous variables were evaluated using *t*-tests. PDA = percentage of days abstinent, IVR = interactive voice response.

Table 2

Changes in Daily Craving During Treatment

	Fixed Effect Estimate	(SE)	<i>p</i>	Random Effect (SD)
Abstinence Initiators				
Thinking of Drinking	2.78	(0.41)	< 0.001	1.65
Peak Craving	2.73	(0.39)	< 0.001	1.53
Difficulty Resisting	2.63	(0.36)	< 0.001	1.42
Average Craving	2.73	(0.45)	< 0.001	1.79
Pre-Abstinence Change Over Time	-0.41	(0.22)	0.056	0.78
Post-Abstinence Immediate Change	-0.82	(0.28)	0.004	1.06
Post-Abstinence Change Over Time	-0.21	(0.04)	< 0.001	0.16
Already Abstainers				
Thinking of Drinking	0.92	(0.22)	< 0.001	0.98
Peak Craving	0.89	(0.21)	< 0.001	0.92
Difficulty Resisting	0.86	(0.21)	< 0.001	0.92
Average Craving	0.98	(0.22)	< 0.001	0.95
Change Over Time	-0.04	(0.02)	0.043	0.08
Continued Drinkers				
Thinking of Drinking	4.50	(0.24)	< 0.001	1.49
Peak Craving	4.70	(0.22)	< 0.001	1.41
Difficulty Resisting	4.96	(0.22)	< 0.001	1.39
Average Craving	4.61	(0.23)	< 0.001	1.46
Change Over Time	-0.10	(0.05)	0.033	0.28

Note. Terms reflecting within-person change over time are in bold font. Estimates reflect fixed effect estimates from multivariate growth curve models. Random *SDs* indicate participant-level variability in these estimates estimated via random effect terms. Significance levels were computed via *t*-test statistic, computed as estimate divided by SE, and are not shown here.

Table 3

Changes in Daily Negative Affect During Treatment

	Fixed Effect Estimate	(SE)	<i>p</i>	Random Effect (SD)
Abstinence Initiators				
Stress	2.52	(0.51)	< 0.001	2.07
Anger	1.64	(0.41)	< 0.001	1.65
Anxiety	2.26	(0.52)	< 0.001	2.09
Sadness	2.47	(0.55)	< 0.001	2.21
Pre-Abstinence Change Over Time	0.17	(0.20)	0.394	0.77
Post-Abstinence Immediate Change	-0.42	(0.31)	0.168	1.18
Post-Abstinence Change Over Time	-0.11	(0.03)	0.001	0.12
Already Abstainers				
Stress	1.38	(0.27)	< 0.001	1.21
Anger	0.55	(0.17)	0.001	0.73
Anxiety	1.29	(0.34)	< 0.001	1.49
Sadness	0.90	(0.27)	0.001	1.19
Change Over Time	0.02	(0.02)	0.435	0.09
Continued Drinkers				
Stress	2.57	(0.25)	< 0.001	1.60
Anger	1.63	(0.23)	< 0.001	1.45
Anxiety	2.43	(0.26)	< 0.001	1.64
Sadness	1.94	(0.24)	< 0.001	1.54
Change Over Time	0.01	(0.02)	0.500	0.12

Note. Terms reflecting within-person change over time are in bold font. Estimates reflect fixed effect estimates from multivariate growth curve models. Random *SDs* indicate participant-level variability in these estimates estimated via random effect terms. Significance levels were computed via *t*-test statistic, computed as estimate divided by SE, and are not shown here.