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Ibudilast Moderates the Effect of Mood on Alcohol Craving During Stress Exposure

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Abstract

Neuroinflammation is implicated in the development and maintenance of alcohol use disorder (AUD) and neuroimmune therapeutics show promise in treating AUD. Pro-inflammatory signaling contributes to progressive elevations in the dysfunction of mood and alcohol craving. The current study sought to examine potential biobehavioral mechanisms of neuroimmune modulation in AUD under experimental conditions. In a community sample of individuals with AUD who completed a placebo-controlled crossover trial of ibudilast, we tested the effect of ibudilast on the relationship between mood states and alcohol craving. Multilevel modeling analyses tested the hypothesis that ibudilast would moderate the effect of positive and negative mood states on alcohol craving during stress and cue exposures. Results revealed that after stress-induction, participants' feelings of depression and happiness were more strongly predictive of their craving for alcohol while taking ibudilast as compared with placebo (p's <.03). These results suggest that with neuroimmune modulation, positive and negative mood states may have a stronger influence on one's desire to drink, such that craving may be more mood dependent. No moderating effect of ibudilast on mood states and craving were observed after alcohol cue exposure. Given the potential of anti-inflammatory treatments to reduce depressive symptomatology, this strengthened relationship between mood and craving under ibudilast might reduce the likelihood of stress-related craving and subsequent drinking over time. Moreover, ibudilast may enhance the benefits of happiness, such that maintaining positive mood in the face of acute stress may attenuate craving. Future trials directly testing the clinical implications of these mechanistic findings are warranted.

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CRediT Authorship Contribution Statement

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Keywords

alcohol use disorder; neuroimmune; pharmacotherapy; mood; craving

Alcohol use disorder (AUD) is characterized by repeated alcohol use despite negative consequences, such as mood disturbance, cognitive impairment, alcohol craving, and liver disease (Sacks et al., 2015). As a result of neuroadaptations and psychological maintenance factors, AUD can be chronic in nature. Unfortunately, less than 8% of individuals with past-year AUD received treatment and many fewer received evidence-based care (SAMSHA, 2019). Even among those receiving front-line behavioral or pharmacological treatment, relapse is not uncommon, as existing therapies are only moderately effective (Heilig et al., 2019). Development of novel and more efficacious treatments for AUD is one aspect of a complex system that may lead to greater treatment utilization rates of evidence-based practices (Litten et al., 2012). In order to support individuals in reducing their drinking or achieving and maintaining abstinence, pharmacotherapies must target maintenance factors sustaining alcohol use. Accordingly, establishing a treatment's mechanisms of action by assessing intervention-based changes in these AUD-maintenance factors, is an imperative step in identifying predictors of good clinical response and furthering personalized medicine in addiction care.

An implicated phenotypic profile of AUD currently being explored is a sustained inflammatory state. Recent research supports the involvement of the neuroimmune system, especially innate immune responses, in the development and maintenance of alcohol and other substance use disorders (SUDs; (Crews et al., 2017; Walter & Crews, 2017). Neuroinflammation modulates neuronal function and is thought to maintain alcohol-seeking behavior and problematic use (Erickson et al., 2019; Robinson et al., 2014). In preclinical models, neuroinflammation induced by chronic alcohol use heightens motivation for alcohol intake, enhances alcohol-related reward, and may contribute to substance-related cognitive impairments and depression-like behavior (Alfonso-Loeches et al., 2010; Blednov et al., 2018; Breese et al., 2008; Briones & Woods, 2013; Frank et al., 2011). As a result, the neuroimmune system is now being tested as a potential treatment target for AUD (Ray et al., 2014). Given the rise in trials investigating pharmacological interventions that target immune signaling, more research concerning their biobehavioral effects is necessary to better understand their primary actions in treating AUD.

Literature depicts alcohol craving and mood as particularly relevant to an inflammatory state, as pro-inflammatory signaling contributes to progressive elevations in the dysfunction of mood and craving (Crews et al., 2017). Alcohol-related stimuli, such as the smell of wine or an image of beer, can provoke craving (i.e., cue-elicited craving) when conditioned associations develop between those stimuli and the pleasurable effects of alcohol (Monti et al., 1987; Schacht et al., 2013). Subjective craving, or a strong desire for alcohol, is an important predictor of alcohol consumption (Bujarski et al., 2018; McHugh et al., 2016), relapse (Schneekloth et al., 2012), and disorder severity (Hartwell & Ray, 2018). Alcohol-relevant cues are putatively associated with activation in neural regions involved in the reward pathway, including the anterior cingulate, ventral striatum, and prefrontal cortex

(Schacht et al., 2013). Craving is also implicated in neuroimmune theories of addiction, such that pro-inflammatory cytokines in the central nervous system modify craving processes for substances (Coleman & Crews, 2018). Moreover, among individuals with alcohol dependence, circulating levels of pro-inflammatory cytokines (e.g., interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α)) were shown to correlate with alcohol craving, severity, and mood symptomatology during early withdrawal (Heberlein et al., 2014). Taken together, these results highlight the importance of craving for alcohol as an important predictor of clinical outcomes and correlate of inflammatory processes in AUD.

Mood states are a central feature of addiction that influence substance use. Alcohol use has both positively and negatively reinforcing features, such that it can promote positive feelings and temporarily reduce negative feelings. Experimental manipulations, such as stress paradigms (Sinha, 2009; Sinha et al., 2000) are designed to modulate mood in the laboratory (Bujarski & Ray, 2016). Meta-analytic data suggests that these affective manipulations increase craving and alcohol consumption (Bresin et al., 2018). Negative mood in particular is consistently associated with poorer alcohol treatment outcomes and may also be linked to neuroinflammation induced by chronic substance use (Neupane, 2016). 'Sickness behavior', resembling symptoms of depression and anxiety, are connected to inflammatory states seen across a range of medical illnesses and psychiatric disorders (Miller & Raison, 2016). As such, interactions between neurocircuitry and the inflammatory pathways activated in depression, chronic disease, and addiction are hypothesized to contribute to these negative mood states (Coleman & Crews, 2018; Crews et al., 2017; Miller & Raison, 2016). Despite the shared neuroimmune correlates between negative affectivity and AUD, the specific behavioral mechanisms of neuroimmune signaling in this overlap remain elusive (Neupane, 2016) but with some initial preclinical support (Breese et al., 2008). Positive mood may also be involved in neuroimmune processes. Research from depression literature shows that positive affective response to acute stress may influence immune signaling and protect against depressive symptoms at follow-up (Aschbacher et al., 2012). Less is known about the role of positive mood in neuroinflammation in AUD. Together, these findings highlight the necessity of considering both affective states and craving for alcohol during experimental paradigms given their collective influence on alcohol consumption and maintenance of AUD.

In order to enhance mechanistic understanding in the treatment of AUD, pharmacological interventions have been evaluated for their potential effects on craving and subjective feelings via experimental paradigms (Bujarski & Ray, 2016; Haass-Koffler et al., 2014). Despite the relevance of craving and mood to neuroinflammation in AUD, studies examining the pharmacological effects of neuroimmune modulators on both affective states and craving are limited (Crews et al., 2017; Ray et al., 2017). Our laboratory completed a randomized double-blind placebo-controlled crossover study of ibudilast, a neuroimmune modulator, to evaluate initial human efficacy at 50mg BID (i.e., twice daily; (Ray et al., 2017). Ibudilast is a selective phosphodiesterase (PDE) 3, 4, 10 and 11 inhibitor shown to reduce relapse and drinking in animal models of AUD (Bell et al., 2015; Gibson et al., 2006). In the aforementioned trial, 24 non-treatment seeking participants with AUD completed two 7-day outpatient protocols involving stress exposure and cue reactivity paradigms; state craving and aspects of mood were measured. As expected, the stress exposure paradigm increased

alcohol craving and negative mood as well as decreased positive mood (Ray et al., 2017). Ibudilast, compared with placebo, promoted a faster recovery of positive mood following the stress task. The cue reactivity task similarly increased alcohol craving but had less robust effects on positive and negative mood, although ibudilast had marginally significant effects on positive mood (Ray et al., 2017).

These findings highlight the potential for ibudilast to modulate craving and mood, important reinforcing features of AUD. Yet, the primary analyses from this trial did not examine how ibudilast impacts the relationship between mood and craving under experimental manipulation. Testing the impact of neuroimmune treatment on the relationship between mood and craving may be particularly relevant given the shared neuroimmune mechanisms between affective disorders and addiction as well as the relevance of mood-induced craving in AUD (Abulseoud et al., 2014; Bold et al., 2016; Wemm et al., 2019). To fill this gap in the literature, the present study was designed to further examine ibudilast's biobehavioral mechanisms of action by testing the impact of mood states on alcohol craving during two experimental psychopathology paradigms. This study serves as a secondary analysis of our laboratory's primary trial of ibudilast which enrolled non-treatment seeking individuals with AUD (Ray et al., 2017). We assess whether participants' positive and negative mood states predict craving for alcohol following stress and cue exposure paradigms and, moreover, whether ibudilast modulates these relationships. Specifically, we hypothesized that both one's positive and negative mood states would be associated with craving following the stress and cue exposures and that ibudilast, as compared with placebo, would moderate these effects.

MATERIALS AND METHOD

Participants

A non-treatment-seeking, community-based, sample of individuals with current DSM-5 AUD was recruited through print and online advertisements in the greater Los Angeles area. The study protocol and all procedures were approved by the Institutional Review Board of the University of California, Los Angeles [IRB#13–000744, Development of Ibudilast as a Novel Treatment for Alcoholism]. Full study procedures are detailed in the published primary trial manuscript (Ray et al., 2017). Study inclusion criteria were: (a) between 21 and 65 years of age; (b) meet current DSM-5 diagnostic criteria for AUD (First et al., 2015), as modified from DSM-IV criteria (First et al., 2002). Exclusion criteria were: (a) treatment seeking status, current treatment for alcohol problems, or received treatment in the 30 days before enrollment; (b) current DSM-IV diagnosis of dependence on psychoactive substances other than alcohol; (c) a lifetime DSM-IV diagnosis of schizophrenia, bipolar disorder, or any psychotic disorder; (d) current use of psychoactive drugs, other than cannabis or nicotine, verified by a urine toxicology screen; (e) clinically significant alcohol withdrawal symptoms as indicated by a score ≥ 10 on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar; (Sullivan et al., 1989); (f) if female: pregnancy, nursing, or a refusal to use reliable method of birth control; (g) medical condition that may interfere with safe study participation (e.g., unstable cardiac, renal, or liver disease, uncontrolled hypertension or diabetes); and (h) AST, ALT, or GGT ≥ 3 times upper normal limit.

A total of 138 individuals consented to participate in the initial screening visit. Of those, 62 individuals were clinically eligible and invited to complete a physical exam and laboratory tests for further screening. Participant exclusions were primarily attributed to either not meeting AUD diagnostic criteria or meeting criteria for an exclusionary DSM-IV diagnosis. Of the 62 eligible individuals from the initial screening visit, 47 elected to complete the physical exam visit and 38 were deemed medically eligible for randomization. A total of 32 participants were randomized to the first study medication, 28 of whom completed the first medication condition and 24 of whom completed the both medication conditions. The study protocol was registered in clinicaltrials.gov (NCT02025998). Included in the current analyses are the 28 participants who completed at least one medication condition.

Screening Procedures

Individuals interested in the study called the laboratory and completed a telephone-screening interview (see Figure 1). Eligible callers were then invited to the laboratory, and after receiving a full explanation of study procedures and providing written informed consent, completed the initial in-person screening visit. At the beginning of this visit, participants were required to have a breath alcohol concentration (BrAC) of 0.00g/dl and a urine toxicology test (10-panel) negative for all drugs excluding cannabis.

During the in-person screening visit, participants completed questionnaires on demographic information, substance use characteristics and history, and psychological functioning. Baseline questionnaires included the Beck Depression Inventory (BDI-II; (Beck et al., 1996) to capture levels of depressive symptomatology and the Beck Anxiety Inventory (BAI) to capture levels of anxiety symptomatology (Beck et al., 1988) as well as the Alcohol Use Disorders Identification Test (AUDIT; (Saunders et al., 1993) to measure alcohol problem severity. The following interviews were administered: (a) Timeline Follow-Back (TLFB) to capture alcohol use quantity and frequency over the 30 days prior to assessment (Sobell & Sobell, 1992; Sobell et al., 1986); (b) the CIWA-Ar (Sullivan et al., 1989) to assess for exclusionary and clinically significant alcohol withdrawal; and (c) the Structured Clinical Interview for DSM-IV (SCID-IV; (First et al., 2002) to assess criteria for alcohol abuse and dependence and to screen for exclusionary psychiatric diagnoses. In addition, the symptom of alcohol craving was added to the SCID-IV using an interview item from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; (Bucholz et al., 1994), thus allowing for diagnosing participants with mild to severe AUD according to DSM-5 criteria.

Participants deemed eligible following the in-person screening visit were again invited to the laboratory to complete a physical exam with the study physician. At the time of the physical exam, participants were required to have a negative urine toxicology screen for all drugs excluding cannabis and then completed clinical laboratory testing including a blood chemistry panel, liver profile, and an electrocardiogram (EKG).

Medication Administration and Intensive Outpatient Procedures—Medically eligible participants were then randomized to receive the first study medication. The study medication, ibudilast, and matched placebo were provided by MediciNova Inc. and

dispensed daily by the UCLA Health Pharmacy Investigational Drug Section, who managed the blind. Participants completed two separate 7-day intensive outpatient protocols at the UCLA Clinical and Translational Research Center (CTRC; see Figure 1). During the outpatient protocols, participants completed daily morning visits with a research nurse to take the study medication under observation as well as completed assessments of vital signs and medication side effects. At each daily visit the study nurse tested participants' BrAC and drug toxicology. Participants were asked to take PM medication doses at home. A riboflavin tracer (50mg) was utilized to verify medication compliance and all samples fluoresced during the trial.

Ibudilast was available in 10mg capsules and participants were titrated as follows: 20 mg (i.e., 2, 10mg capsules) BID during days 1–2, 50mg (i.e., 5, 10mg capsules) BID during days 3–6. Target medication dose of 50mg BID was selected based on safety considerations as well as preclinical and clinical data (Beardsley et al., 2010; Cho et al., 2010; Hutchinson et al., 2009; Worley et al., 2016). The maximally safe clinical dose was chosen based on data showing the efficacy of ibudilast to be dose-incremental- at least up to 80–100mg/day; this 50mg BID dose correlates with steady-state ~0.5 uM plasma and ~1.5 uM brain concentrations. Additionally, the half-life of ibudilast is approximately 19 hours, which supports BID dosing (Rolan et al., 2008). Matched placebo was provided, and medication order was randomized and counterbalanced. The AM medication doses and assessments took place at 8 am during days 1–6. Upon reaching a stable target dose of medication, participants completed a stress exposure paradigm (day 5; PM) and an alcohol cue exposure session (day 6; AM). The study met the minimum required 7-day washout period with an average washout timeframe of 16 days. As this was the first trial of ibudilast conducted in a sample of individuals with alcohol use disorder, investigators, in consultation with the pharmaceutical company providing the medication, instructed participants to refrain from alcohol consumption during the medication period for safety reasons; abstinence was verified daily by the study nurse via a breathalyzer. No positive breathalyzer readings were obtained in the study.

Experimental Procedures & Measures

The following well-validated experimental paradigms were implemented to examine medication effects on cue reactivity and stress reactivity (Bujarski & Ray, 2016; Mason & Higley, 2013). These exposure paradigms were conducted for each medication condition, such that participants served as their own controls.

Cue Exposure Paradigm—The study's crossover design is especially relevant to the cue exposure manipulation as research shows that not all individuals with AUD are cue reactive (Litt et al., 1990; Rohsenow et al., 1994; Rubonis et al., 1994). Cue exposure followed well-established procedures (Monti et al., 1987; Monti et al., 2001). Each session began with a 3-minute relaxation period. Participants were then asked to hold and smell a glass of water for three minutes to control for the potential effects of simple exposure to any potable liquid. Following, participants were asked to hold and smell a glass of their preferred alcoholic beverage for three 3-minute trials. Order was not counterbalanced because alcohol carryover effects that are known to occur (Monti et al., 1987). Participants identifying as cigarette

smokers were allowed a smoke break immediately prior to and after the cue reactivity assessment. Once after each exposure (water or alcohol cue), participants completed the Alcohol Urge Questionnaire (AUQ; (Bohn et al., 1995; MacKillop, 2006) as well as the short form of the Profile of Mood States (POMS-SF) survey (Curran et al., 1995; McNair et al., 1971). The AUQ is an eight-item measure that assesses participants' current desire or craving for alcohol on a 7-item Likert scale from 'Strongly Disagree' to 'Strongly Agree'. The POMS-SF is a standard, validated psychological rating scale that measures dimensions of transient affective states by asking participants to indicate how well each item describes their mood on a 5-point Likert scale from 'Not at All' to 'Extremely'.

Stress Exposure Paradigm—Personal information collected after randomization was used to generate personalized scripts for stressful conditions in line with standardized procedures (Sinha, 2009; Sinha et al., 2000; Sinha et al., 1992). Only stressful events rated ≥ 8 (on 0 – 10 point Likert scale, where 10 = most stressful) were used in script development; traumatic experiences were not included. The stress exposure consisted of playing 5-minute audio-recorded scripts recounting current and unresolved stressful events in the participants' lives that included cognitions and physical feelings. Participants completed the POMS-SF (Curran et al., 1995) to record current affective states as well as the AUQ (Bohn et al., 1995; MacKillop, 2006) to report on state alcohol craving at one pre-stress exposure timepoint and five post-stress exposure timepoints.

Statistical Analyses—All descriptive and statistical analyses were completed in SAS Version 9.4 on the sample of participants who completed the full protocol for at least one medication condition (n = 28). Three of the possible four POMS-SF subscales were utilized in these analyses: depression, happiness, and tension, to examine the effect of mood on craving; the vigor subscale was excluded, as a measure of energy or liveliness was not of a priori interest. For the primary analyses, multilevel mixed models with random intercepts were utilized to address the study's crossover design as well as data collection across the multiple timepoints of exposure paradigms. All models were fit in SAS using the MIXED procedure with residual maximum likelihood (REML) estimation. PROC MIXED with REML accounts for repeated measures data that is missing at random (Dickey, 2008) and for this reason, authors chose to include all randomized participants who completed at least one medication condition. Missing data exists for four participants who completed only one medication arm of the trial (i.e., 3 participants missing ibudilast data; 1 participant missing placebo data). To verify that mood states were associated with alcohol craving across medication conditions, three individual multilevel models were conducted to test the effect of each POMS subscale score (continuous predictor) on craving (continuous outcome) across the stress exposure timepoints. The same analytic method was utilized to verify an association between mood and alcohol craving following cue exposure. Additionally, three individual multilevel mixed models were conducted to test the effects of time, mood, medication (ibudilast vs. placebo), and a medication × mood interaction on alcohol craving for each POMS subscale during stress exposure. Consistently, three equivalent multilevel mixed models were run for the cue exposure paradigm to examine the effect of time (water vs. alcohol cue timepoint), mood, medication, and medication × mood interaction on craving. Notably, for the stress exposure paradigm, time was not a significant predictor of

alcohol craving for any models tested and, as such, was removed from the final models for the purpose of parsimony.

RESULTS

Participant Characteristics

The sample consisted of 28 non-treatment seeking participants with current AUD (75% male; average age 33 years) recruited from the community who completed at least one medication condition of the trial (see Table 1). The sample was racially and ethnically diverse with 39% identifying as Black, and 18% as each Latinx, Native American, and White. In the 30 days prior to their baseline visit, participants had on average 21 drinking days and 6.70 (SD = 4.22) drinks per drinking day.

Stress Exposure Paradigm

Effect of Mood States on Craving—All three mood states examined significantly predicted alcohol craving during the stress exposure paradigm (p's < .001; see Table 2). Specifically, ratings of depression and tension, in separate models, were positively associated with alcohol craving, such that higher levels of depression and tension were predictive of greater craving for alcohol during stress exposure across medication conditions. Contrastingly, ratings of happiness were negatively associated with alcohol craving, such that a more elevated state of happiness was predictive of less craving for alcohol.

Effect of Mood and Medication on Craving—One multilevel mixed model for each of the three POMS subscales tested (i.e., depression, happiness, and tension) was run to examine the effect of mood, medication condition, and a mood × medication interaction on alcohol craving during stress exposure (see Table 3).

Depression.: After accounting for other model terms, significant associations between craving (outcome) and depressed mood (p = .007), medication condition (p = .01), and their interaction (p = .029) were found (see Table 3). The interaction term was probed using a simple slopes approach to test the effect of participants' depressive state on alcohol craving for each medication condition (see Table 4). For both ibudilast and placebo, higher ratings of depression were associated with more craving for alcohol during stress exposure (p's < .05). However, when participants were randomized to ibudilast they displayed a stronger relationship between their depressive state and craving for alcohol (b = 0.79, SE = 0.12) than when randomized to placebo (b = 0.38, SE = 0.14; see Figure 2).

Happiness.: The relationship between happiness and craving was not significant (p = .535) after accounting for the other model terms. However, the relationship between medication and craving was significant (p = .01) and the medication × happiness interaction term was also significant (p = .002) after accounting for the other model terms. As such, the interaction term was probed using a simple slopes approach to test the effect of participants' happiness on alcohol craving for each medication condition (see Table 4). For ibudilast only, higher ratings of happiness were significantly associated with less craving for alcohol during stress exposure (p < .0001). When randomized to placebo, participants displayed a

marginally significant association between mood and craving ($p = .055$) and similarly with greater happiness predictive of less craving ($b = -0.07$, $SE = 0.11$); yet, this effect was stronger when taking ibudilast ($b = -0.58$, $SE = 0.11$; see Figure 2).

Tension.: After accounting for other model terms, a significant association between craving (outcome) and tension was found ($p < .0001$), with elevations in tension related to more craving for alcohol ($b = 0.80$, $SE = 0.14$; see Table 3) during stress exposure. However, neither the medication ($p = .96$) nor the medication × tension interaction ($p = .870$) terms were significant predictors of alcohol craving (see Figure 2). This suggests that participants displayed a similar relationship between tension and alcohol craving during stress exposure while receiving ibudilast or placebo.

Alcohol Cue Exposure Paradigm

Effect of Mood States on Craving—All three mood states examined significantly predicted alcohol craving following cue exposure (p's < .01; see Table 2). Again, ratings of depression and tension, in separate models, were positively associated with alcohol craving, such that higher levels of depression and tension were predictive of greater craving for alcohol following cue exposure across medication conditions. Ratings of happiness were negatively associated with alcohol craving, such that a more elevated state of happiness was predictive of less craving for alcohol.

Effect of Mood and Medication on Craving—One multilevel mixed model for each of the three POMS subscales tested (i.e., depression, happiness, and tension) was run to examine the effect of time (water vs. alcohol cue), mood, medication condition, and a mood × medication interaction on alcohol craving following cue exposure (see Table 5).

Depression.: After accounting for other model terms, significant associations between craving and depression ($p = .018$) as well as craving and cue type ($p = .003$) were found. Higher levels of depressed mood were related to more craving for alcohol following cue exposure ($b = 0.61$, $SE = 0.25$; see Table 5). Neither the medication ($p = .638$) nor the medication × depression interaction ($p = .587$) terms were predictive of alcohol craving (see Figure 2). This suggests that while receiving ibudilast or placebo, participants displayed a similar relationship between depressed mood and alcohol craving when exposed to an alcohol cue.

Happiness.: After accounting for other model terms, significant associations between craving and happiness ($p = .037$) as well as craving and cue type ($p = .003$) were found. Higher levels of happy mood were related to less craving for alcohol following cue exposure ($b = -0.39$, $SE = 0.18$; see Table 5). Neither the medication ($p = .248$), nor the medication × happiness interaction ($p = .238$) terms were predictive of alcohol craving (see Figure 2). This suggests that while receiving ibudilast or placebo, participants displayed a similar relationship between happiness and alcohol craving when exposed to an alcohol cue.

Tension.: After accounting for other model terms, significant associations between craving and tension ($p < .0001$) as well as craving and cue type ($p = .004$) were found. Higher

states of tension were related to more craving for alcohol following cue exposure (b = 1.00, SE = 0.21; see Table 5). Neither the medication (p = .662), nor the medication × tension interaction (p = .632) terms were predictive of alcohol craving (see Figure 2). This suggests that, while receiving ibudilast or placebo, participants displayed a similar relationship between tension states and alcohol craving when exposed to an alcohol cue.

DISCUSSION

The current study sought to examine potential biobehavioral mechanisms of neuroimmune modulation in AUD by examining the impact of ibudilast on mood and alcohol craving under experimental conditions. Specifically, in a community sample of individuals with AUD who completed a placebo-controlled crossover trial of ibudilast, we tested the effect of ibudilast on the relationship between various mood states and craving during alcohol cue and stress exposure. The neuroimmune system's involvement in the development and maintenance of AUD is of growing interest to the field and, moreover, pro-inflammatory signaling is thought to contribute to progressive dysfunctions in both craving and mood states (Crews et al., 2017). In return, neuroimmune treatment for AUD may ameliorate these dysfunctions and potentially their interactive effects. The current study served to test the hypothesis that ibudilast would moderate the effect of one's mood state on phasic craving following exposure to an alcohol cue and a stressful imagery narrative. As a validation check, we confirmed that during both exposures, mood states were predictive of alcohol craving across medication conditions, such that increased depression and tension were associated with a greater desire to drink, while increased happiness was associated with a lesser desire to drink. Importantly, our hypothesis that ibudilast would moderate the effect of mood on craving was supported for the stress manipulation but not the cue exposure.

After listening to a personal script of a stressful event, participants' feelings of depression and happiness were more strongly predictive of their craving for alcohol while taking ibudilast as compared with placebo. These results suggest that with neuroimmune modulation, positive and negative mood states may have a stronger influence on one's desire to drink, such that craving may be more mood dependent. Chronic alcohol use blunts the body's natural biological stress system and, as a consequence, leaves individuals with AUD vulnerable to maladaptive stress coping and negative affect (Sinha, 2009). In return, stressful events induce negative mood-related craving (Koob, 2013; Wemm et al., 2019). Our findings show that ibudilast may manipulate this relationship, yet the clinical implications are unclear. Depression literature demonstrates that pro-inflammatory states contribute to negative mood symptomatology, which can be responsive to anti-inflammatory treatment (Kohler et al., 2016). Given the shared neuroimmune correlates between negative affectivity and AUD, one interpretation might be that ibudilast, through its anti-inflammatory properties, might diminish depressive states over time. As such, this potentially strengthened relationship between mood and craving under ibudilast might reduce the likelihood of stress-related craving and subsequent drinking. While speculative, this mechanism would be an important contribution to treatments for AUD, as no currently approved pharmacotherapies are thought to directly target stress-induced craving (Wemm et al., 2019). Results also suggest that ibudilast might enhance the benefits of positive mood, such that one's feelings of happiness in the face of acute stress might attenuate their urge

to drink, whereas under placebo, no such relationship between positive mood and craving was present. Unfortunately, the present study was primarily a safety trial and participants were not allowed to drink while in the study, rendering drinking outcomes unmeaningful. In this context, the study effectively captures a week of abstinence (i.e., early abstinence), during which period pronounced negative mood and stress-reactivity are likely (Heilig et al., 2010). This context may serve to reflect a relevant model of recovery, whereby individuals in early abstinence encounter a stressful situation, which challenges their abstinence or treatment goals (Blaine & Sinha, 2017; Breese et al., 2011; Heilig et al., 2010). For example, levels of negative mood and alcohol craving induced by laboratory stressors are shown to be predictive of relapse and drinking at follow-up (Breese et al., 2005; Sinha, 2009). Ibudilast did not moderate the effect of tension (i.e., feelings of unrest or anxiety) on one's urge for alcohol, indicating neuroimmune modulation could be less protective against the effect of stress-induced anxiety on craving for alcohol. As such, neuroimmune modulation may be less beneficial for individuals with AUD who experience a strong anxiety-like response to stress but future work on this topic is necessary.

To place these findings in the context of specific immunomodulatory and biological actions, ibudilast is as a selective PDE 3, 4, 10 and 11 inhibitor and these enzymes are known to regulate intracellular levels of cyclic adenosine monophosphate (cAMP), a potent regulator of immune cell function (Bender & Beavo, 2006; Wen et al., 2018). The cAMP signaling pathway is key to neural functioning and synaptic transmission in the central nervous system and chronic alcohol exposure attenuates this signaling in a brain-region specific manner (Wen et al., 2018). PDEs are expressed in brain regions involved in the reinforcing effects of alcohol (Pérez-Torres et al., 2000) and thereby ibudilast may exert its effects by restoring healthy neural signaling in these regions and in return, modulate AUD maintenance factors and reduce intake (Spanagel, 2009). Of relevance to the current findings, PDE4 is specifically involved in depressive- and anxiety-like behavior (Zhang et al., 2008). PDE downstream targets are also shown to serve as molecular substrates for negative mood-like behavior during alcohol abstinence (Pandey et al., 2003). Notably, another PDE4 inhibitor, rolipram, significantly attenuated abstinence-induced anxiety- and depressive-like behavior in rodents (e.g., via open-field test and forced-swim test), suggesting that PDE inhibitors may exert anxiolytic-like effects in models of AUD (Gong et al., 2017). Combined with our trial's findings, this suggests that PDE inhibitors may modulate emotional reactions to stress, particularly during early abstinence, by restoring healthy neural signaling (Li et al., 2009) to potentially reduce stress-induced craving and negatively reinforcing features of alcohol (Gong et al., 2017; Ray et al., 2017).

Ibudilast did not moderate the effect of mood on alcohol craving following cue exposure. Craving is a multifaceted construct and therefore, stress and alcohol cue exposure likely induce different psychobiological craving states (Fox et al., 2007), which may not be impacted by neuroimmune modulation in the same manner. Relatedly, a previous study using personalized stress imagery and alcohol cue imagery scripts found dissociable relations between alcohol craving and mood states following these stress and cue exposures (Fox et al., 2007). Moreover, a recent study found that stress and alcohol cue-elicited craving were associated with different peripheral cytokine immune responses, such that stress exposure was associated with dampened TNFα levels and alcohol exposure was

associated with dampened TNF receptor 1 levels (Fox et al., 2017). Together these findings demonstrate variation in the two exposures' psychological and immunological effects and support our divergent results. Alternatively, the cue paradigm involved a brief exposure to an alcohol cue (i.e., smell of an alcoholic beverage) and perhaps may have been less effective at manipulating mood states than the stress exposure paradigm, which required participants to listen to an imagery script covering a highly stressful and unresolved personal situation. This is consistent with findings from this trial's initial findings showing that cue exposure had less robust effects on mood (Ray et al., 2017).

We interpret these intriguing results in light of the study's strengths and weaknesses. The strengths included a rigorous experimental design including a randomized placebo-controlled double-bind crossover trial of ibudilast and two well-established experimental psychopathology laboratory paradigms to screen medication biobehavioral effects. This crossover design reduces error variance, as participants serve as their own controls and the human laboratory paradigms are uniquely suited for study hypotheses, as they are consistently shown to manipulate both mood states and alcohol craving. Additionally, the diverse community sample included individuals who met current mild to severe DSM-5 criteria for AUD and had a range of alcohol use severity. The study includes a novel neuroimmune medication, ibudilast, that has strong preclinical data and is currently being tested in several clinical trials of alcohol and other SUDs. As reported in the primary trial manuscript, no severe adverse events were reported in the trial and there were no study dropouts or dose reductions directly related to ibudilast (see (Ray et al., 2017) for full list of side effects). Limitations of the current study include a modest sample size, which restricts statistical power, inclusion of non-treatment seeking participants, which may limit the findings' generalizability to treatment-seeking or patient samples of AUD, and lack of medication blind assessment. While this trial's within-subjects design prioritized a repeated assessment of a stress exposure response, the stress paradigm did not include a neutral script condition to further account for the effect of stress exposure beyond exposure to a control script. However, this paradigm is well-validated and shown to increase craving and negative mood in alcohol-abstinent individuals beyond levels induced by a control condition (Fox et al., 2007; Sinha, 2009; Sinha et al., 2009). Further, since this experimental medicine trial involved a 7-day human laboratory protocol, longer dosing of ibudilast is warranted to examine its impact on long-term clinical outcomes in a naturalistic setting, similar to a recently completed Phase II clinical trial of ibudilast for the treatment of methamphetamine use disorder (Heinzerling et al., 2020). The analyses did not examine drinking outcomes and thus the clinical implications of these findings should be interpreted with caution. Similarly, as participants were not allowed to drink during the trial for safety reasons, results might differ under normal drinking conditions as opposed to a period of early abstinence. The directionality of the relationship between mood and craving under these experimental conditions cannot be definitely determined. Finally, stress-induced craving and drinking may play a particularly central role in the maintenance of AUD for women (Peltier et al., 2019). Yet, this modest sample was 75% male, which precludes a powered examination of sex differences.

In conclusion, this is an exploratory analysis of the first trial of ibudilast in a human sample of AUD that contributes to the literature on neuroimmune treatment for addiction.

We examined ibudilast's effects on maintenance factors of AUD, namely mood states and craving. Results suggest that ibudilast strengthens the influence of positive and negative mood states on alcohol craving in the face of psychological stress. We did not find support for a moderating effect of ibudilast on mood and craving following alcohol cue exposure. While these results provide only initial support for ibudilast's effects, they serve to translate preclinical data that demonstrates this medication's ability to reduce drinking in models of AUD. To effectively probe the clinical significance of the current project's findings, ongoing studies from our group will focus on the direct implications of ibudilast's effects on mood, as determined by within-person drinking and recovery-related outcomes. Finally, future trials of ibudilast and other neuroimmune modulators should extend these findings to treatment-seeking samples and examine the impact of mood-dependent craving on drinking outcomes in naturalistic settings.

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Public Significance Statement

Neuroimmune therapies show promise in treating alcohol use disorder (AUD), yet their mechanisms of action remain elusive. Results from a placebo-controlled crossover trial of AUD show that ibudilast, a neuroimmune modulator, strengthens the association between mood states and alcohol craving during stress exposure. Given the potential of anti-inflammatory treatments to reduce depressive symptomatology, this potentially strengthened relationship between mood and craving under ibudilast might reduce the likelihood of stress-related craving and subsequent drinking over time.

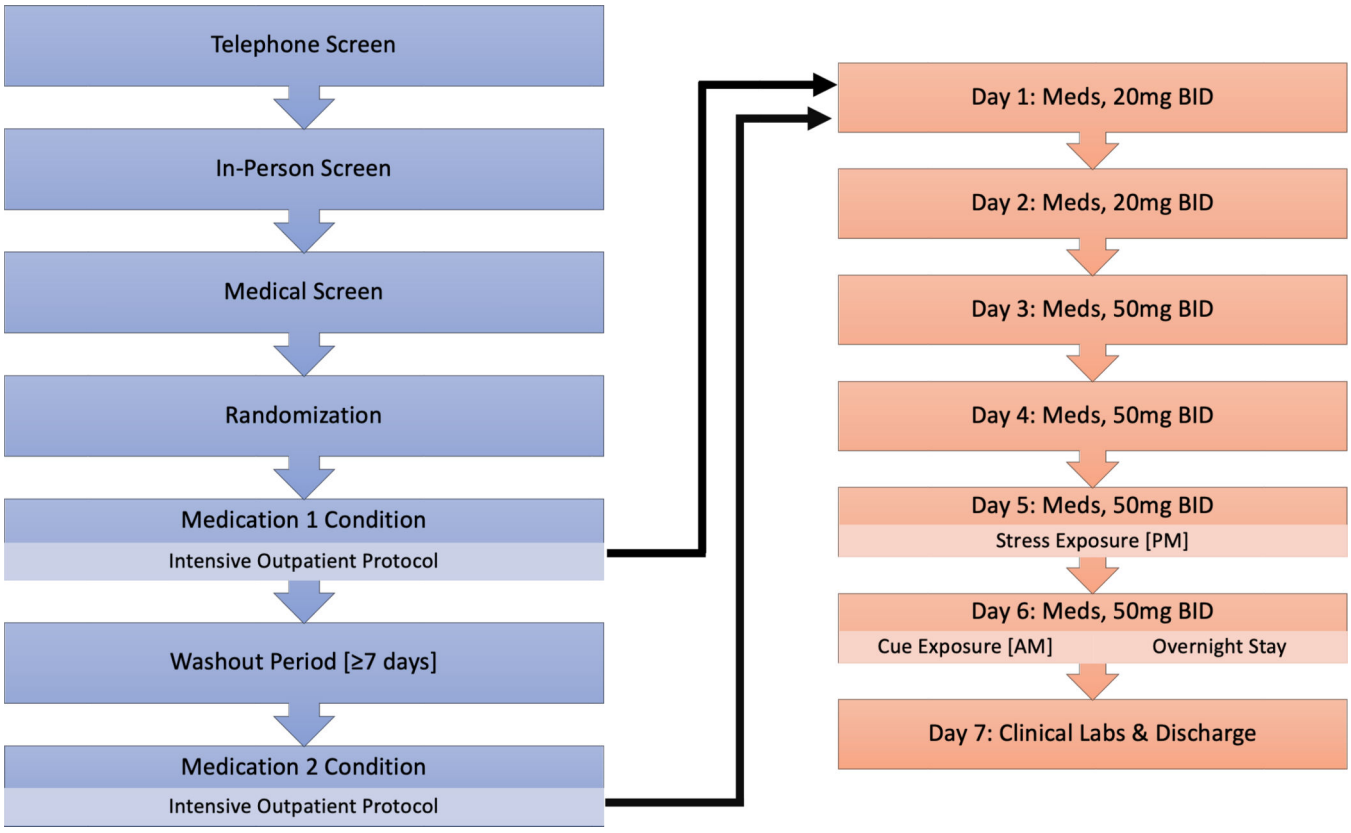

Figure 1.

Procedure Flowchart for Randomized Double-Blind Placebo-Controlled Crossover Trial of Ibudilast

Note. BID = twice daily; medication order was randomized and counterbalanced

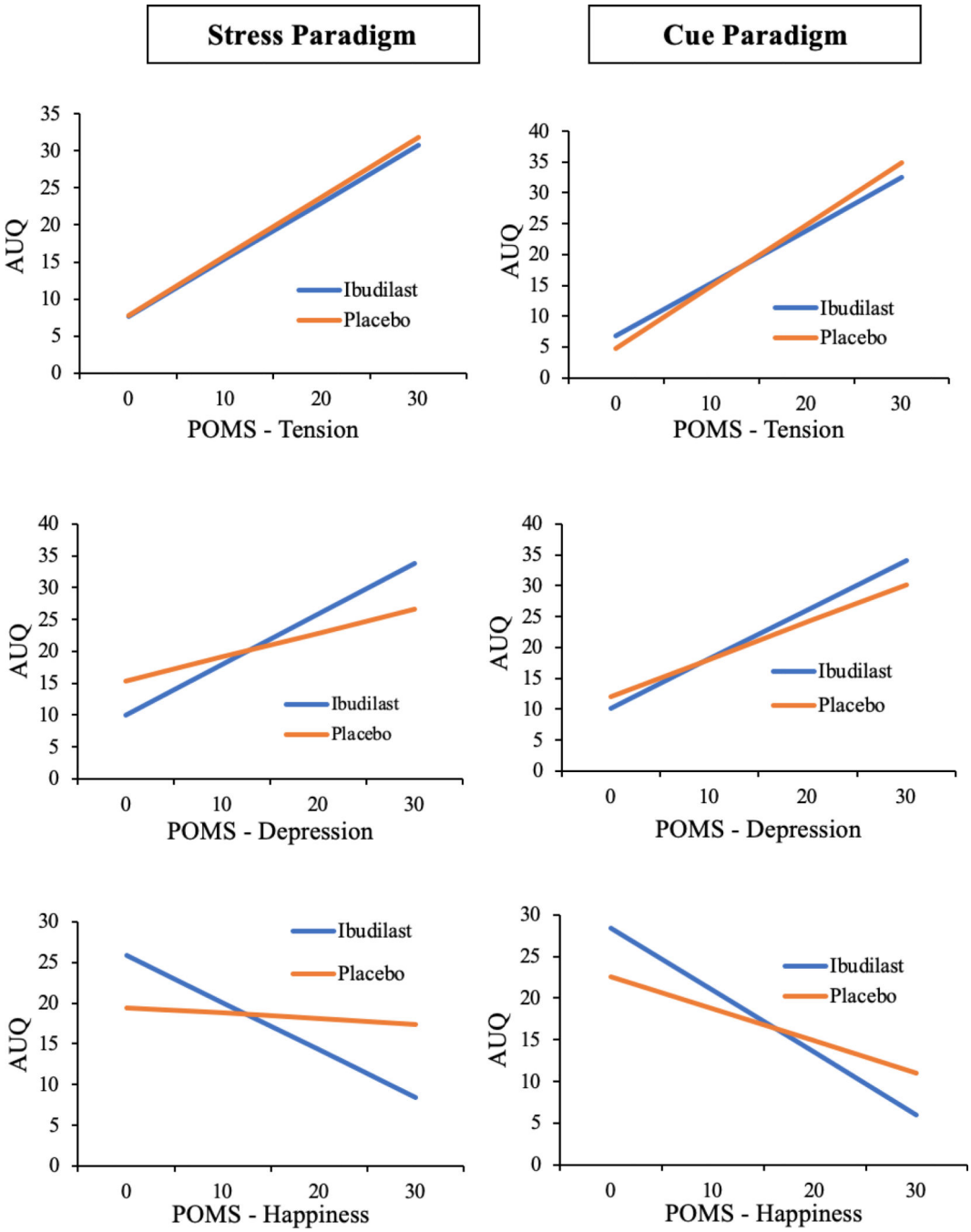

Figure 2.

Visualization of the Effect of Mood on Alcohol Craving by Medication Condition for Stress and Cue Exposure Paradigms

Note. AUQ = Alcohol Urge Questionnaire; POMS = Profile of Mood States; a significant moderating effect ($p < .05$) of medication on mood state (depression and happiness) and alcohol craving was found during the stress exposure paradigm

Table 1

Baseline Participant Characteristics (N = 28)

	Mean	Standard Deviation
Age	32.50	8.87
Sex (% male)	75.0%	-
Cigarette (% smoker)	25.0%	-
Cannabis (% user)	28.6%	-
Ethnicity		
Black	39.3%	-
White	17.9%	-
Latinx	17.9%	-
Native American	17.9%	-
Asian American	7.1%	-
Timeline Follow-Back		
Drinking days	21.21	6.03
Drinks per day	4.80	3.51
Drinks per drinking day	6.70	4.22
AUDIT Total	20.57	6.31
Mood Symptomatology		
Beck Depression Inventory (BDI-II) Total	9.18	10.06
Beck Anxiety Inventory (BAI) Total	5.21	6.58

Note. Timeline Follow-Back data includes the 30 days prior to baseline; AUDIT = Alcohol Use Disorders Identification Test

Table 2

Effect of Mood on Alcohol Craving during Stress and Cue Exposure Paradigms

Fixed Effect				
	b	**SE**	**t-value**	**p-value**
Stress Exposure				
Depression	0.59	0.10	6.20	<.0001***
Happiness	−0.30	0.08	−3.79	<.001***
Tension	0.78	0.09	8.48	<.0001***
Cue Exposure				
Depression	0.71	0.18	3.94	.0001***
Happiness	−0.51	0.15	−3.37	.001**
Tension	0.96	0.16	6.18	<.0001***

Note.

*** $p < .001$

** $p < .01$

measures of mood are Profile of Mood States short form (POMS-SF) subscales scores; measure of alcohol craving is the Alcohol Urge Questionnaire (AUQ) total score

Table 3

Stress Exposure Paradigm: Effect of Medication and Mood on Alcohol Craving

Fixed Effect				
	b	**SE**	**t-value**	**p-value**
Depression Model				
Intercept	15.31	1.49	10.27	--
Medication *(Ibudilast vs. Placebo)*	−5.34	2.15	−2.48	0.01*
Depression	0.38	0.14	2.69	0.007**
Med × Depression	0.42	0.19	2.19	0.029*
Happiness Model				
Intercept	19.44	1.61	12.10	--
Medication *(Ibudilast vs. Placebo)*	6.37	2.47	2.58	0.01*
Happiness	−0.07	0.11	−0.62	0.535
Med × Happiness	−0.51	0.16	−3.20	0.002**
Tension Model				
Intercept	7.79	2.10	3.71	--
Medication *(Ibudilast vs. Placebo)*	−0.15	2.77	−0.05	0.960
Tension	0.80	0.14	5.59	<.0001***
Med × Tension	−0.03	0.19	−0.16	0.87

Note.

*** $p < .001$

** $p < .01$

* $p < .05$

measures of mood are Profile of Mood States short form (POMS-SF) subscales scores; measure of alcohol craving is the Alcohol Urge Questionnaire (AUQ) total score

Table 4

Stress Exposure Paradigm: Simple Effect of Mood on Alcohol Craving for Medication Conditions

Fixed Effects				
	b	**SE**	**t-value**	**p-value**
Ibudilast				
Depression	0.79	0.12	6.37	<.0001***
Happiness	−0.58	0.11	−5.07	<.0001***
Placebo				
Depression	0.38	0.14	2.60	.010*
Happiness	−0.07	0.11	−0.61	.055

Note.

*** $p < .001$

* $p < .05$

significant ($p < .05$) med × mood interactions were probed for simple effects; measures of mood are Profile of Mood States short form (POMS-SF) subscales scores; measure of alcohol craving is the Alcohol Urge Questionnaire (AUQ) total score

Table 5

Cue Exposure Paradigm: Effect of Medication and Mood on Alcohol Craving

Fixed Effects				
	b	**SE**	**t-value**	**p-value**
Depression Model				
Intercept	19.09	2.97	6.43	--
Medication *(Ibudilast vs. Placebo)*	−1.83	3.88	−0.47	.638
Depression	0.61	0.25	2.41	.018*
Time *(Cue vs. Water)*	−7.13	2.32	−3.07	.003**
Med × Depression	0.19	0.35	0.54	.587
Happiness Model				
Intercept	29.87	3.24	9.23	--
Medication *(Ibudilast vs. Placebo)*	5.80	4.99	1.16	.248
Happiness	−0.39	0.18	−2.11	.037*
Time *(Cue vs. Water)*	−7.30	2.36	−3.10	.003**
Med × Happiness	−0.36	0.30	−1.19	.238
Tension Model				
Intercept	11.13	3.26	3.41	--
Medication *(Ibudilast vs. Placebo)*	1.95	4.45	0.44	.662
Tension	1.00	0.21	4.89	<.0001***
Time *(Cue vs. Water)*	−6.35	2.14	−2.97	.004**
Med × Tension	−0.15	0.30	−0.48	.632

Note.

*** $p < .001$

** $p < .01$

* $p < .05$

measures of mood are Profile of Mood States short form (POMS-SF) subscales scores; measure of alcohol craving is the Alcohol Urge Questionnaire (AUQ) total score