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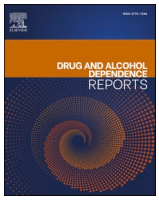

# Determinants of perceived pain relief from acute alcohol intake in a laboratory setting

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## HIGHLIGHTS

- Quantitative sensory testing measures were not predictive of pain relief ratings.
- Expectancy that alcohol relieves pain predicted greater pain relief.
- Subjective intoxication and positive stimulating effects predicted pain relief.

## ARTICLE INFO

*Keywords:*
Pain
Relief
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## ABSTRACT

*Background:* Studies of alcohol analgesia often assume that changes in pain sensitivity reflect the negative reinforcing effects of alcohol in pain self-management. However, factors that may influence perceived pain relief due to alcohol use remain incompletely characterized. Thus, the primary aim of this study was to identify which factors are most strongly related to self-reported pain relief in individuals with and without chronic pain after alcohol consumption.

*Methods:* This study combined data from two studies of alcohol analgesia in individuals who regularly consume alcohol with and without chronic pain. Alcohol analgesia expectancies were assessed during screening. In laboratory sessions, participants received an alcohol-containing (.08 g/dL target BrAC) or placebo beverage and rated subjective intoxication and subjective response (positive/negative aspects of stimulation/sedation). Participants underwent quantitative sensory testing to measure pain intensity, pain threshold, and relief. Paired sample t-tests determined effects of alcohol on pain measures. Hierarchical linear models determined factors associated with pain relief ratings in the alcohol condition.

*Results:* Pain relief and pain threshold were higher in the alcohol session relative to placebo, but pain intensity did not differ. In a 4-step hierarchical linear model, expectancy of pain relief, subjective intoxication, and high positive affect, but not pain threshold or pain intensity, were significantly and uniquely associated with perceived relief.

*Conclusions:* Taken together, results suggest the negative-reinforcing effects of alcohol for pain-management are not completely reflected by changes in pain sensitivity in a laboratory setting. Expectancies and subjective response may be important in determining an individual's evaluation of alcohol's efficacy for pain self-management.

## 1. Introduction

Pain is a national public health concern, affecting more than 100 million individuals with estimated expenditures of up to $635B in healthcare expenses and lost work productivity annually in the United States alone (Dahlhamer et al., 2018; Gaskin and Richard, 2012). Emerging empirical literature suggests that chronic pain and substance use often co-occur and it has been reported that approximately 25 % of individuals use alcohol to self-manage their pain symptoms (Ferguson et al., 2021; Riley and King, 2009). Pain self-management with alcohol

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may lead to chronic heavy drinking, increasing the risk developing or worsening pain and other adverse health outcomes, including cancer, cardiovascular disease, and liver disease (Ditre et al., 2019; Egli et al., 2012; Rehm, 2011).

Laboratory-based experimental studies consistently indicate analgesic effects of acute alcohol intake, as reflected by changes in pain threshold, intensity, and unpleasantness (Horn-Hofmann et al., 2015, Thompson et al., 2017, Vitus et al., 2022, Williams et al., 2021). Alcohol acts directly or indirectly on multiple neurotransmitter systems involved in pain processing (Boissoneault et al., 2023). For instance, GABA plays a significant role in mediating pain transmission and perception due to its widespread presence in the central nervous system (Enna and McCarson, 2006). Alcohol is a positive allosteric modulator at $GABA_A$ receptors, which may at least partially underlie its impact on pain perception and response (Boissoneault et al., 2023). In addition, preclinical studies suggest a critical role of mu and kappa opioid-mediated neurotransmission in alcohol analgesia (Neddenriep et al., 2019). Alcohol also disrupts functional activation in a number of regions related to pain processing, including anterior cingulate cortex, dorsolateral prefrontal cortex, and the basal ganglia (Boissoneault et al., 2023). Taken together,

Evidence suggests that alcohol's analgesic effects are similar in participants with and without chronic pain (Vitus et al., 2022). These findings, combined with those that approximately 25 % of pain patients report heavy drinking, suggest that the analgesic effects of alcohol may be a relevant motivator of alcohol use in people experiencing pain, whether that pain is acute or chronic (Lawton and Simpson, 2009, Vitus et al., 2022).

Despite consistent evidence of alcohol-induced reductions in pain intensity and increases in pain threshold, perception of pain relief itself is seldom measured. Instead, the negative reinforcing effects of alcohol in the context of pain are assumed to be reflected by changes in pain threshold/intensity. However, changes in pain sensitivity may not accurately capture alcohol's negative reinforcing effects. For example, Leknes et al. (2008) found that individuals' pain relief ratings following cessation of noxious heat stimuli were not correlated with pain intensity. Additionally, using pressure algometry, Vitus et al. (2022) found that the effect of alcohol on pain relief ratings was substantially larger than the effect of alcohol on pain threshold or pain intensity, emphasizing the importance of identifying biopsychosocial mechanisms underlying perception of pain relief above and beyond changes in pain threshold and/or intensity, *per se*. This implies that reductions in common QST metrics, specifically pain intensity, are not an accurate indicator of pain relief, and an individual's self-report of pain relief may be a better indicator of the negative-reinforcing effects of alcohol.

Alcohol acts directly and indirectly on a wide variety of neurotransmitter systems in the brain, suggesting its effects on pain processing are likely multifaceted (Spanagel, 2009). Concurrently, pain is a subjective experience, with discriminative, cognitive-evaluative, and affective components (Turk and Melzack, 2011). Alcohol-related changes in affect may be as or more reinforcing than changes in pain threshold or intensity. In addition, expectancy of pain relief has been associated with reductions in reported pain (Pollo and Benedetti, 2009) and expectations that alcohol will reduce pain have been linked to heavier drinking, suggesting that expectancies of alcohol analgesia may increase motivation to drink for individuals experiencing pain (Zale et al., 2015). However, the role of subjective response as a potential affective contributor to alcohol's analgesic effects remains largely uncharacterized.

Subjective response (SR) reflects an individual's differences in sensitivity to alcohol and is seen as a potential endophenotype for AUD risk, which can have a significant impact on drinking behavior (Morean and Corbin, 2010; Ray et al., 2016). These individual responses to alcohol are biphasic in nature, producing both stimulating and sedative effects, and each of which may have positive or negative facets (Morean et al., 2013). Evidence suggests that individual differences in SR predict AUD risk (King et al., 2014; Schuckit, 1994). As assessed using the Subjective Effects of Alcohol Scale (SEAS), high arousal positive subscale (HIGH+) includes feeling fun and lively, low arousal positive (LOW+) includes feeling mellow and relaxed; whereas high arousal negative (HIGH-) includes feeling aggressive or demanding, and low arousal negative (LOW-) includes feeling woozy or dizzy (Morean et al., 2013). Determining the role of SR in perceived relief from pain resulting from alcohol use may be instrumental for future research examining the relationship between alcohol and pain.

In this study, we tested that assumption that alcohol-induced changes in pain sensitivity reflect the perception of pain relief and the negative-reinforcing effects of alcohol by determining factors most strongly related to perceived pain relief in individuals with and without chronic pain. People with and without chronic pain were included because both groups engage in pain self-medication behavior. Given that perceived relief likely at least partially reflects the negative reinforcing effects of alcohol use in the context of pain, it is scientifically and clinically useful to determine whether chronic pain status is associated with that perception. Consistent with previous research, we hypothesized that participants' pain relief ratings would be significantly elevated following alcohol consumption relative to placebo. Additionally, we hypothesized that higher expectancy that alcohol would provide pain relief, subjective intoxication, and positive stimulating and sedating feelings after alcohol consumption would be associated with higher relief ratings.

**Table 1**
Demographic, affective, and alcohol use characteristics.

| | Pain (n=21) Mean (SD)/% | Control (n=142) Mean (SD)/% |
|---|---|---|
| Age (years) | 27.10 (5.73) | 26.41 (4.67) |
| Education (years) | 17.45 (2.08) | 17.26 (2.14) |
| Sex | | |
| Male | 14.29 % | 53.06 % |
| Female | 85.71 % | 46.94 % |
| Race | | |
| White | 66.67 % | 76.10 % |
| Black or African American | - | 3.5 % |
| Asian | 9.52 % | 11.3 % |
| Other or Multiple Races | 23.81 % | 7.7 % |
| Ethnicity | | |
| Hispanic/Latinx | 23.8 % | 24.8 % |
| QFI, oz. abs. EtOH/day | 0.47 (0.35) | 0.46 (0.31) |
| Alcohol Use Disorder Symptoms (AUDIT) | 4.24 (1.84) | 4.58 (1.74) |
| Depressive Symptomology (BDI-II) | 5.71 (5.41) | 2.65 (3.46) |
| STAI-Trait | 33.81 (14.09) | 29.25 (7.09) |
| Pain Anxiety (PASS−20) | 25.05 (16.60) | 21.91 (15.91) |
| Pain Catastrophizing Scale (PCS) | 13.71 (8.92) | 10.04 (8.08) |

## 2. Methods

The present study is a secondary analysis of combined data from two NIH-funded projects on the acute effects of alcohol intake in both adults with chronic pain as well as pain-free control participants (Project 1: R21AA026805, J. Boissoneault, PI, n=51; Project 2: R01AA025337, J. Boissoneault, PI, n=112). Both projects had similar designs involving completion of a single screening session and two laboratory sessions involving administration of an alcohol-containg beverage or placebo in counterbalanced order. The sample included in this analysis partially overlaps with that in several prior reports (Alexander et al., 2023; Vitus et al., 2022; Williams et al., 2021). The current study examined effects of alcohol intake on perceived pain relief compared to a placebo beverage, as well as associations between perceived pain relief and changes in pain sensitivity, expectancies, and subjective response after alcohol intake.

### 2.1. Participants

Social, non-problem drinkers between the ages of 21 and 45 (N=119) both with (n=21) and without (n=98) chronic jaw pain were recruited via flyers, print media, and word of mouth from the North Central Florida area, which includes a large university. Participants completed standard demographic and health history questionnaires to assess for exclusion criteria. Exclusion criteria included: (a) history of chronic pain, other than jaw pain (i.e., fibromyalgia, arthritis), (b) history of major psychiatric disorder, neurological disease, or other serious medical illness, (c) history of drug or alcohol dependence (assessed via single-item self report measures), (d) current use of opioid analgesics or prescription medication which contraindicate alcohol use, (e) being a current smoker, and (f) not consuming at least one alcoholic beverage, on average, per month over the past six months. All procedures were approved by the University of Florida Institutional Review Board and performed at the Center for Pain Research and Behavioral Health in Gainesville, FL. All participants provided written consent prior to participation in each project.

### 2.2. Screening session

During the screening session, participants completed questionnaires that included typical drinking behaviors (Alcohol Use Disorders Identification Test [AUDIT]; Saunders et al., 1993), alcohol use histories (Alcohol Use Questionnaire [AUQ]; Cahalan et al., 1969), anxiety about pain (Pain Anxiety Symptoms Scale [PASS-20]; Short Version; McCracken and Dhingra, 2002), catastrophic thinking related to pain (Pain Catastrophizing Scale [PCS]; Sullivan et al., 1995), alcohol analgesia expectancies (AE) using simple visual analogue scales (VAS), and demographics. Individuals with problematic alcohol use (AUDIT $\geq$ 8) or significant depression (*i.e.,* BDI-II $>$ 20) were excluded to avoid potential confounding effects of hazardous alcohol use or severe depression. Participants with chronic jaw pain were evaluated by a practicing orthodontist and orofacial pain expert in accordance with the published Research Diagnostic Criteria for TMD (Schiffman et al., 2014).

### 2.3. Measures

Alcohol Analgesia Expectancy Measure (AE). The first analgesia expectancy (AE) was measured as the strength of belief that the consumption of alcohol will provide pain relief using a 100 mm visual analog scale (VAS) with the prompt "When I'm experiencing pain, I expect alcohol will provide…", anchored from "no pain relief at all" to "complete pain relief" (Alexander et al., 2023; Vitus et al., 2022). The second AE was measured as the strength of belief that consumption of alcohol will decrease pain sensitivity using a 100 mm VAS with the prompt "When I drink, I expect my sensitivity to pain to be…", anchored from "strongly decreased" to "strongly increased".

Alcohol Use Disorder Identification Test (AUDIT). The AUDIT is a 10-item questionnaire used to screen individuals for hazardous and harmful alcohol consumption (Saunders et al., 1993).

Beck Depression Inventory-II (BDI-II). The BDI-II is a 21-question multiple choice inventory, used to assess existence and severity of symptoms of depression where higher scores indicate a higher severity of symptoms of depression (Beck et al., 1996).

Pain Anxiety Symptoms Scale-20 (PASS-20). The PASS-20 is a short, 20-item version of the original, 40-item Pain Anxiety Symptoms Scale (PASS). Similar to the original inventory, the PASS-20 measures anxiety and fear responses related to pain (McCracken, 2002).

Pain Catastrophizing Scale (PCS). The PCS is a 13-item self-report measure that assesses catastrophic thinking associated with pain according to 3 components: rumination, magnification, and helplessness; in which participants are asked to indicate to which degree they have experienced each of the items on a 5-point scale from 0 (not at all) to 4 (all the time) (Sullivan, 1995).

State-Trait Anxiety Inventory (STAI). The STAI is a 40-item self report inventory using a 4-point Likert scale that measures two types of anxiety – state and trait anxiety. Higher scores are indicative of higher levels of anxiety (Spielberger, 1983).

Subjective Intoxication. Subjective feelings of intoxication were measured prior to QST administration. Subjective intoxication was measured using a 100 mm visual analog scale (VAS) that asked participants to place a mark on a line anchored from "not at all intoxicated" to "most intoxicated imaginable."

Subjective Effects of Alcohol Scale. The Subjective Effects of Alcohol Scale (SEAS; Morean et al., 2013) is a self-report measure using an 11-point numeric rating scale anchored from "not at all" to "extremely" and is composed of 14 items categorized into 4 affective quadrants: high arousal positive (HIGH+; e.g., lively, high arousal negative (HIGH -; e.g., aggressive), low arousal positive (LOW +; e.g., calm) and low arousal negative (LOW -; e.g., wobbly). Participants completed the SEAS prior to QST administration.

### 2.4. Laboratory session

Upon arrival for each testing session, participants were asked to confirm their adherence to pre-testing criteria, including (a) fasting from food for at least 4 hours, (b) abstaining from alcohol consumption for at least 24 hours, and (c) from medications that may affect pain perception or interact with alcohol responses for at least 12 hours. Additionally, participants completed drug, pregnancy (if applicable), and baseline

**Table 2**
Subjective intoxication and Subjective Effects of Alcohol Scale (SEAS) outcomes by beverage conditions and pain status (N=163).

| Measure | Pain Alcohol Mean (SD) | Control Alcohol Mean (SD) | Pain Placebo Mean (SD) | Control Placebo Mean (SD) |
|---|---|---|---|---|
| Subjective Intoxication | 55.00 (21.18) | 44.47 (22.88) | 5.24 (12.86) | 7.85 (8.74) |
| SEAS High + | 18.52 (9.81) | 24.44 (9.44) | 10.05 (5.25) | 19.36 (8.95) |
| SEAS High - | 1.48 (3.57) | 1.27 (2.88) | 0.00 (0.00) | 0.29 (1.20) |
| SEAS Low + | 29.38 (7.36) | 29.17 (7.17) | 27.76 (7.41) | 29.50 (7.05) |
| SEAS Low - | 13.14 (7.14) | 9.40 (8.05) | 0.90 (3.06) | 1.84 (2.95) |

**Table 3**
Quantitative sensory testing outcomes by beverage condition and pain status.

| Variable | Pain Alcohol Mean (SD) | Pain Placebo Mean (SD) | Control Alcohol Mean (SD) | Control Placebo Mean (SD) |
|---|---|---|---|---|
| Pain Threshold | 0.30 (0.96) | −0.29 (0.79) | 0.32 (1.09) | 0.043 (1.02) |
| Pain Intensity | 34.47 (23.27) | 43.37 (19.28) | 25.42 (16.02) | 26.60 (16.31) |
| Pain Relief | 42.00 (29.20) | 9.14 (13.84) | 37.14 (23.57) | 12.65 (15.95) |

breath alcohol concentration (BrAC) testing. Once participant pre-testing criteria were confirmed, participants consumed a meal replacement bar (~200 kcal). One hour following the light meal, participants consumed the study beverage. Thirty minutes following beverage consumption, participants started the QST procedures.

### 2.5. Beverage administration

Participants completed two laboratory sessions in counterbalanced order in which they received either alcohol (target BrAC: 0.08 g/dL) or placebo (target BrAC: 0.00 g/dL) in a double-blinded fashion. Beverage condition order was counterbalanced across participants. Alcohol beverages were a mixture of 95 % United States Pharmacoepia-grade ethanol and cold, sugar-free lemon-lime soda in a 3:1 ratio, divided into two drinks (Boissoneault et al., 2014, Harrison et al., 2007). Doses of alcohol sufficient to produce a BrAC 0.08 g/dL were individually determined (Watson et al., 1981). Thus, total beverage volume differed between individuals. Placebo beverages consisted of sugar-free lemon-lime soda only. All beverages had a small amount of ethanol floated on the surface and on the rim of the glass and were misted with ethanol. Participants were asked to complete both drinks within five minutes.

BrAC was obtained every 10 min after bevrage consumption using a standard breathalyzer (CMI, Inc., Owensboro, KY, USA). In Project 2, salivary alcohol concentration (SAC) measurements (QED Saliva Alcohol Test, OraSure Technologies, Inc. Bethlehem, PA) were collected during quantitative sensory testing (QST) because they occurred in the high field magnetic resonance imaging (MRI) environment. Thus, estimated blood alcohol concentration (BAC) measures associated with QST for the combined study cohort are averaged from BrAC (Project 1) and SAC (Project 2) measurements. Participants were asked to rinse their mouth with water after beverage consumption. Participants were transported home using a HIPAA-compliant rideshare service when their BrAC was $\leq$ 0.02 g/dL.

**Table 4**
Hierarchical regression of predictors of perceived pain relief.

| Steps | Measurement | B | SE | β | *p* | *F* | $R^2$ | $\Delta R^2$ |
|---|---|---|---|---|---|---|---|---|
| 1 | - | - | - | - | - | 1.43 | 0.018 | - |
| | **(Intercept)** | **37.80** | **1.91** | **-** | **0.000** | - | - | - |
| | Chronic Pain Status | −.335 | 2.34 | −0.01 | 0.89 | - | - | - |
| | Project | 3.43 | 2.35 | 0.14 | 0.15 | - | - | - |
| 2 | - | - | - | - | - | 3.22 | 0.11 | 0.093 |
| | **(Intercept)** | **23.09** | **7.00** | **-** | **0.000** | | | |
| | Chronic Pain Status | −1.34 | 2.29 | −0.055 | 0.56 | - | - | - |
| | **Project** | **4.99** | **2.30** | **0.20** | **0.032** | - | - | - |
| | PASS−20 Score | **0.43** | **0.17** | **0.28** | **0.013** | - | - | - |
| | PCS Score | −0.25 | 0.34 | −0.09 | 0.45 | - | - | - |
| | **Expectancy of Relief** | **0.19** | **0.09** | **0.18** | **0.034** | - | - | - |
| | Expectancy of Pain Sensitivity Reduction | 0.006 | 0.12 | 0.004 | 0.96 | | | |
| 3 | - | - | - | - | - | 9.07 | 0.44 | 0.33 |
| | (Intercept) | −3.32 | 9.85 | - | .74 | - | - | - |
| | Chronic Pain Status | 2.23 | 1.99 | 0.09 | 0.26 | - | - | - |
| | Project | −2.94 | 2.14 | −0.12 | 0.17 | - | - | - |
| | PASS−20 Score | 0.25 | 0.14 | 0.16 | 0.09 | - | - | - |
| | PCS Score | −0.24 | 0.28 | −0.08 | 0.41 | | | |
| | **Expectancy of Relief** | **0.15** | **0.07** | **0.14** | **0.04** | - | - | - |
| | Expectancy of Pain Sensitivity Reduction | −0.03 | 0.10 | −0.02 | 0.73 | | | |
| | **Subjective Intoxication** | **0.54** | **0.10** | **0.51** | **0.000** | - | - | - |
| | Pain Threshold | 1.79 | 1.59 | 0.07 | 0.26 | - | - | - |
| | Pain Intensity | 0.08 | 0.10 | 0.05 | 0.42 | - | - | - |
| | **SEAS: High +** | **0.48** | **0.20** | **0.19** | **0.02** | | | |
| | SEAS: High - | −0.07 | 0.58 | −0.01 | 0.91 | | | |
| | SEAS: Low + | −0.22 | 0.25 | −0.07 | 0.38 | | | |
| | SEAS: Low - | 0.17 | 0.26 | 0.06 | 0.52 | | | |
| 4 | - | - | - | - | - | 8.065 | 0.45 | 0.01 |
| | (Intercept) | −2.68 | 9.89 | - | 0.79 | - | - | - |
| | Chronic Pain Status | 1.85 | 2.00 | 0.08 | 0.36 | - | - | - |
| | Project | −2.91 | 2.15 | −0.12 | 0.18 | - | - | - |
| | PASS−20 Score | 0.25 | 0.14 | 0.16 | 0.08 | - | - | - |
| | PCS Score | −0.26 | 0.29 | −0.09 | 0.36 | - | - | - |
| | Expectancy of Relief | 0.14 | 0.07 | 0.13 | 0.06 | - | - | - |
| | Expectancy of Pain Sensitivity Reduction | −0.06 | 0.10 | −0.04 | 0.56 | | | |
| | **Subjective Intoxication** | **0.56** | **0.10** | **0.53** | **0.000** | - | - | - |
| | Pain Threshold | 2.05 | 1.59 | 0.08 | 0.20 | - | - | - |
| | Pain Intensity | 0.09 | 0.10 | 0.07 | 0.33 | - | - | - |
| | SEAS: High + | 0.37 | 0.21 | 0.15 | 0.08 | - | - | - |
| | SEAS: High - | −0.15 | 0.58 | −0.02 | 0.79 | - | - | - |
| | SEAS: Low + | −0.16 | 0.26 | −0.05 | 0.54 | - | - | - |
| | SEAS: Low - | 0.20 | 0.26 | 0.07 | 0.43 | - | - | - |
| | Subjective Intoxication X Expectancy of Relief | 2.50 | 1.65 | 0.11 | 0.13 | | | |
| | SEAS: High + X Expectancy of Relief | −1.25 | 1.47 | −0.06 | 0.40 | | | |

### 2.6. Quantitative sensory testing (QST)

QST was conducted in a private exam room. Thirty minutes after beverage administration, participants completed QST in the form of either pressure algometry at the insertion of the masseter muscle (n=51; Project 1) (Wagner Instruments, Greenwich, CT) or a thermal stimulus applied to the glabrous skin of the foot using a computer-controlled Q-Sense device (Medoc, Ramat Yishai, Israel; n=112; Project 2). In three blocks of testing, pressure increased at a rate of.5 lbf/s or thermode temperature increased from 32°C to a maximum of 50°C until participants indicated the moment (i.e., temperature or pressure) when the sensation transitioned from pressure to pain or heat to pain (pain threshold). To evaluate pain intensity, the painful stimuli was increased over a 1 s duration and maintained at 4-,5-, and 6- lbf for 2 s each (target pressures; three repetitions per pressure level; Project 1) or thermal stimuli (44° - 49° C) individually calibrated to produce pain intensity ratings of approximately 50/100 on a 100 mm VAS (Project 2). After each stimulus, participants rated pain intensity using a 100 mm VAS anchored from "no pain" to "most intense pain imaginable". Additionally, following cessation of each stimulus (Project 1) or each block of 7 stimuli (Project 2), participants rated perceived relief using a VAS with the prompt, "Please place a mark on the line below indicating the degree of relief from pain you feel as a result of consuming your beverage", anchored from "no relief at all" to "most profound relief imaginable". Pain thresholds, intensity ratings, and relief ratings were averaged across repetitions for analysis purposes.

### 2.7. Analysis strategy

Data were analyzed using SPSS Statistics Version 29.0 (IBM Corp., Armonk, NY). Effects of alcohol on pain relief, pain threshold, and pain intensity compared to placebo were determined using paired sample t-tests. Pain threshold was standardized (i.e., z-transformed) due to the differing pain stimuli, and thus threshold units (lbf vs. °C) used between the two studies. Pain relief ratings, pain intensity ratings, and pain threshold were combined across studies for analyses. This decision was made a) to maximize statistical power to detect associations between QST measures (pain threshold and intensity) and relief; and b) because we did not have *a priori* hypotheses that these associations might differ as between QST modalities.

Hierarchical linear regression was used to determine the association of pain intensity, pain threshold, subjective intoxication, AE, and SEAS dimensions with perceived relief in the alcohol condition. Pain intensity, pain threshold, chronic pain status, project group, and those demographic and psychosocial factors with significant bivariate correlations with pain relief ratings were included in hierarchical linear models. Additional potential covariates were screened for inclusion in the hierarchical regression by determining which variables correlated significantly with pain relief rating, with only PCS (r=.17, p=.03) and PASS-20 scores meeting criteria (r=.23, p=.003). Model 1 included chronic pain status to test potential differences in perceived pain relief between groups before other potential explanatory variables were added. It also included study because we wanted to evaluate the influence of trait-like psychological factors (Model 2) and session-specific subjective responses (Model 3) above and beyond potential confounding effects of study cohort. Model 2 included trait-like psychological factors (AE relief VAS, PASS-20, PCS) to control for baseline psychological differences first before examining session-specific subjective responses in Model 3, including pain threshold; pain intensity; High+, High-, Low+, and Low- SEAS dimensions; and subjective intoxication ratings. As an exploratory step, Model 4, we included interaction terms of the AE relief VAS with subjective intoxication and High+ to test the possibility that these subjective response factors may be more strongly related with perceived pain relief among individuals with strong relief expectancies. We examined change in $R^2$ ($\Delta R^2$) at each step to assess relative contributions of each set of variables to the observed variance in pain relief ratings.

## 3. Results

### 3.1. Participant characteristics

Participants included 163 adults, both with (n=21; 85.7 % female) and without (n=142; 51.4 % female) chronic jaw pain. Chronic pain participants averaged 27.10 years of age (SD= 5.73) and 17.31 years of education (SD= 1.76); pain-free controls averaged 26.41 years of age (SD= 4.67) and 17.53 years of education (SD= 2.45). In chronic pain participants, a total of 66.7 % identified as white, 9.5 % identified as Asian, and 23.8 % identified as another race or multiple races. In pain-free controls, 76.1 % of participants identified as white, 3.5 % identified as Black, 11.3 % identified as Asian, and 7.7 % identified as another race or multiple races. Additionally, 23.8 % of chronic pain participants and 24.8 % of pain-free controls identified as Hispanic or Latinx. See Table 1 for detailed demographic and affective information.

### 3.2. Typical drinking habits, alcohol disorder symptomology, and subjective response

Individuals with chronic pain reported an average daily consumption of 0.47 oz. (SD=0.35) of absolute ethanol over the past 6 months (quantity-frequency index [QFI]; ~.78 standard drinks); pain-free controls reported an average daily consumption of 0.46 oz. (SD=0.31). The average AUDIT score for chronic pain participants was 4.24 (SD=1.84), whereas the average was 4.58 (SD=1.74) for pain-free controls (see Table 1).

### 3.3. Effects of alcohol administration on BAC, subjective intoxication, and SEAS dimensions

BAC during QST in the alcohol condition was.076 g/dL (SD=0.16). Subjective intoxication ratings were significantly greater in the alcohol than placebo condition $t(162)=20.53$, $p<.001$, Cohen's d = 1.61 ($M_{alcohol}=45.83$, SD= 22.88; $M_{placebo}=7.52$, SD = 9.36). Similarly, SEAS HIGH+ $t(162)=8.28$, $p<.001$, Cohen's d = 0.65 ($M_{alcohol}=23.67$, SD= 9.67; $M_{placebo}=17.82$, SD=8.91), HIGH- $t(162)=4.31$, $p<.001$, Cohen's d=0.34 ($M_{alcohol}=1.29$, SD=2.96; $M_{placebo}=0.25$, SD=1.05), and LOW- $t(162)=13.19$, $p<.001$, Cohen's d = 1.03 ($M_{alcohol}=9.88$, SD=8.02; $M_{placebo}=1.60$, SD=2.87) ratings were significantly greater in the alcohol than placebo condition. No significant effect of alcohol on LOW+ ratings was noted $t(162)=0.12$, p=.90, Cohen's d = 0.01 ($M_{alcohol}=29.20$, SD=7.17; $M_{placebo}=29.12$, SD=7.45). Detailed participant subjective intoxication and SEAS data by pain group and beverage condition can be found in Table 2.

### 3.4. Effects of alcohol administration on pain relief, threshold, and intensity

Participants reported significantly greater pain relief ratings in the alcohol condition than the placebo condition $t(161) = 13.25$, $p<.001$ ($M_{alcohol} = 37.77$, SD= 24.32; $M_{placebo}=12.27$, SD = 15.72; Cohen's dz=1.04) (Table 3). Additionally, pain threshold was signifcantly greater in the alcohol condition compared to placebo $t(162) = 4.00$, $p<.001$ ($M_{alcohol} =.315$, SD = 1.07; $M_{placebo} = 0.00$, SD = 1.00; Cohen's dz=.31). The difference in pain intensity between the two beverage

conditions approached, but did not achieve, significance $t(162) = 1.91$, p=0.058 ($M_{alcohol}$ = 26.58, SD = 17.30; $M_{placebo}$ =28.76, SD = 17.58, Cohen's dz=.15). Detailed quantitative sensory testing data by pain group and beverage condition can be found in Table 3.

### 3.5. Hierarchical linear models

At Step 1, chronic pain status and project were non-significant predictors of pain relief ratings, and the overall model was non-significant. Addition of PCS score, PASS score, and AE relief and sensitivity reduction measures at Step 2 accounted for 11.1 % of the variance in pain relief ratings ($\Delta R^2 = 0.093$; F(4155)=4.06, p=.004). At Step 3, addition of pain threshold, pain intensity, subjective intoxication, and the four SEAS affective domains accounted for 44.3 % of the variance in relief ratings ($\Delta R^2 = 0.33$; F(7148)=12.63, p<.001). In Step 4, addition of the interaction terms of AE relief ratings with subjective intoxication and the High+ SEAS dimension resulted in a non-significant increase in $R^2$ ($\Delta R^2 = 0.01$; F(2146)=1.30, p=.28).

In the final model (Step 3), higher ratings of subjective intoxication ($\beta$=.51, p<.001), stronger expectancies that alcohol will provide pain relief ($\beta$=.14, p=.045), and higher scores on the HIGH+ domain of the SEAS ($\beta$=.19, p=.018), were each uniquely and positively associated with higher pain relief ratings upon alcohol consumption. Detailed results are displayed in Table 4.

## 4. Discussion

Consistent with hypotheses and prior reports (Vitus et al., 2022; Williams et al., 2021), analyses indicated that individuals perceived greater pain relief from consuming their beverage in the alcohol condition relative to the placebo condition. As predicted, individuals also had a higher pain threshold after alcohol consumption compared to placebo. Chronic pain status was not associated with pain relief, suggesting that the negative reinforcing effects of alcohol intake in the context of pain may not differ meaningfully between people with and without chronic pain. Contrary to our expectations and previous studies (Horn-Hofmann et al., 2015; Thompson et al., 2017; Vitus et al., 2022), pain intensity ratings did not differ significantly between the two beverage conditions. It is unclear why we did not identify a significant reduction in pain intensity after alcohol administration, although methodological differences in QST procedures between this study and prior work, including use of a calibration procedure to standardize pain perception in Project 2, may have contributed (Thompson et al., 2017). Nevertheless, the fact that alcohol intake resulted in statistically large increases in pain relief compared to placebo but did not significantly affect pain intensity provides additional evidence that the perception of pain relief reflects negative reinforcing processes that are not fully captured by changes in psychophysical tests in laboratory settings.

As hypothesized, our analysis indicated a significant positive association between the expectancy of alcohol providing pain relief and ratings of pain relief. However, the expectancy that alcohol would reduce pain sensitivity was not significantly associated with ratings of pain relief, suggesting that these expectancy measures may index distinct beliefs regarding the effects of alcohol on pain. To the best of our knowledge, this is the first study to examine the relationship between expectancy of relief from alcohol consumption and self-reported pain relief ratings. Existing literature indicates that expectancies are significantly associated with changes in pain perception and that alcohol users have been shown to hold substance-specific, pain-related outcome expectancies (Atlas and Wager, 2012; Ditre et al., 2019; Zale et al., 2015). Given positive alcohol outcome expectancies are correlated with greater quantity and frequency of alcohol consumption, these expectancies may lead to increased risk for alcohol-related consequences (Ditre et al., 2019, Jones et al., 2001a,2021b; LaRowe et al., 2022). Thus, future studies should also consider the role of expectancies in determining the negative reinforcing effects of alcohol intake in the context of pain. A better understanding of this relationship could impact research and treatment approaches for individuals with co-occurring pain and AUD by providing novel intervention targets (e.g., challenging expectancies for substance-related pain relief or teaching adaptive pain-coping strategies; Ditre et al., 2019).

Additionally, consistent with our hypothesis, subjective intoxication was significantly and strongly associated with perception of pain relief such that participants who reported higher levels of intoxication indicated higher ratings of relief. Furthermore, HIGH+ scores on the SEAS were positively associated with perceived relief ratings, whereas SEAS dimensions were not. In other words, individuals who reported stronger feelings of arousal with positive valence after alcohol consumption also tended to have higher ratings pain relief. Given that the positive simulating effects of alcohol tends to predominate on the ascending limb of the BAC curve (Morean et al., 2013) and that positive affect predicts greater likelihood of engaging in drinking (e.g., Duif et al., 2020), these results suggest that individuals engaging in pain self-management using alcohol may be more likely to consume greater amounts of alcohol over longer periods to maximize alcohol's negative reinforcing effects in the context of pain (i.e., perceived relief). It is unclear why other facets of subjective response were not also predictive of relief ratings, although we note that very low HIGH- and very high LOW+ ratings may be suggestive that their lack of significance may be driven by floor and ceiling effects, respectively. That both subjective intoxication and HIGH+ subjective response were independently predictive of relief ratings suggests that subjective intoxication may capture aspects of subjective response not fully captured by the SEAS, including changes in interoceptive function (Leganes-Fonteneau et al., 2021). It is interesting to note that the association of subjective intixocation and High+ response with relief was not moderated by expectancy that alcohol provides pain relief. This lack of moderation suggests alcohol may produce pain relief via changes in subjective intoxication and mood even in the absence of strong *a priori* beliefs regarding alcohol's efficacy as a pain reliever. Overall, our findings are consistent with the multifaceted nature of SR and highlight the potential importance of examining SR to improve understanding of pain-self management behaviors following alcohol consumption in individuals with pain.

### 4.1. Limitations

Although the present study's findings demonstrate an important step in understanding mechanisms underlying alcohol consumption for pain self-management, they are not without limitations and findings should be considered within the context of the limitations. Most notably, data for this secondary analysis were obtained by combining two projects by the same investigative team with nearly identical methods. Although project was a factor in analyses and pain threshold was standardized to account for differences in units, it is possible that this may have influenced present findings. Second, although gender was not significantly associated with perceived pain relief, a majority of the individuals in the chronic pain group self-identified as female (consistent with typical epidemiological patterns associated with TMD) and a more balanced sample may be beneficial for future studies. Additionally, this study did not measure ratings of perceived pain intensity reduction after alcohol consumption. It is possible that if perceived intensity reduction were used as the dependent variable, perceived intensity would be significantly associated with perceived reduction due to the similar language. Further, the study sample was highly educated and had limited racial diversity, which may limit generalizability. Lastly, it is important to note that experimental pain is not equivalent to clinical pain with regard to psychological and physiological components (Moskal et al., 2018; Thompson et al., 2017). Clinical pain can worsen existing mood disorders as well as lead to changes in mood (Institute of Medicine, 2011), and although experimental pain induction can advance the understanding of pain mechanisms, studies of the effects of alcohol on clinical pain are needed. Future studies may benefit from using experimental

pain models that simulate characteristics of clinical pain (Thompson et al., 2017).

### 4.2. Conclusions

In summary, results provide additional evidence that changes in pain sensitivity assessed through quantitative sensory testing may not adequately capture perceptions of relief resulting from alcohol use and highlight the importance of alcohol-related outcome expectancies, subjective intoxication, and subjective response in forming perceptions of pain relief.

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## CRediT authorship contribution statement

**Sharmagh Aghabeigi:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. **Nicholas Bush:** Writing – review & editing, Writing – original draft, Validation, Formal analysis. **Jeff Boissoneault:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

## Declaration of Competing Interest

The authors declare no conflict of interest.

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