Official Title: Acute Effects of Alcohol Use on Chronic Orofacial Pain

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Protocol

1. Project Title:

Acute Effects of Alcohol Use on Chronic Orofacial Pain

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3. Abstract:

It has long been suggested that alcohol has analgesic properties. Data suggest that about 25% of chronic orofacial pain patients endorse the use of alcohol for pain management. However, the biopsychosocial mechanisms underlying this intuitive interaction are not well established. Studies of healthy individuals using quantitative sensory testing (QST) have shown that familial risk for alcoholism, as well as psychological characteristics like mood and personality, may act as critical factors modulating individuals' sensitivity to alcohol analgesia. However, to our knowledge, the acute pain-relieving effect of alcohol intake in individuals with chronic pain has never been systematically studied. This relationship is important to understand because alcohol analgesia may be associated with relief. Relief from pain may act as a potent negative reinforcer for alcohol intake, which, in turn, can have adverse health effects by increasing risk of developing an alcohol use disorder in people with chronic pain. Self-medication of pain with alcohol may also result in harmful drug interactions, risk of injury due to neurobehavioral impairment, and even development of painful alcohol neuropathy. The overall goal of this proposal is to test the analgesic effects of acute alcohol consumption in individuals with chronic pain and a comparison group of pain-free controls, and identify critical biopsychosocial modulators of alcohol analgesia. These efforts will inform research and clinical/translational efforts regarding modifiable and unmodifiable factors related to risk associated with self-medication of chronic pain using alcohol, and provide critical feasibility and effect size data for future proposals.

4. Background:

Introduction. While acute pain is an essential indicator of current or impending tissue damage, chronic pain is a maladaptive state with strong affective, biological, and psychological components. Chronic pain has strong negative effects on quality of life for the nearly 100 million American sufferers and is extremely costly, with associated expenditures reaching $635B per year in the United States alone (Institute of Medicine, 2011). Existing treatments for chronic pain, including opioid analgesics, are relatively ineffective, (Noble et al., 2010) rarely meet patients' own criteria for successful treatment (Robinson et al., 2005), and are associated with significant risk (i.e., the opioid epidemic; Volkow and Collins, 2017). Therefore, it is intuitive that patients may seek alternative and potentially maladaptive methods for pain relief. Nearly 25% of

individuals suffering from chronic orofacial pain endorse self-medicating their pain with alcohol (Riley and King, 2009). Alcohol interacts directly or indirectly with many neurotransmitter systems, including the serotonergic, glutamatergic, and opioidergic systems, providing a wide range of relevant pharmacologic targets that may affect pain sensation (Vengeliene et al., 2008). This behavior is concerning because harmful interactions may occur between alcohol and pain medications, self-medicating patients likely exceed moderate drinking guidelines, increasing risk of alcohol-related consequences, and alcohol withdrawal is associated with increased pain sensitivity (NIAAA, 2013). The health-related consequences of alcohol use and misuse are estimated at over $200B per year (Spanagel, 2009). Given that 25% of treatment seeking alcoholics report past-month pain, and 25% of chronic pain patients report heavy drinking (Zale et al., 2015), it is likely the adverse effects of self-medicating pain with alcohol are responsible for part of the cost associated with both conditions.

Mechanisms of Pain. Acute pain is a centrally mediated sensation driven by nociceptive input conducted by Aδ and C fibers responding to noxious stimulation or tissue injury in the periphery. An individual's experience of pain is modulated by the activity of a well-characterized set of neural structures involved in the contextualization and evaluation of the nociceptive stimulus, including those involved in sensory, limbic, and executive functions (Apkarian et al., 2005; Clarke and Lawrence, 2013; Craggs et al., 2007; Staud et al., 2008). In a minority of cases (~10-20%), pain persists even after the peripheral healing process is complete. The transition from acute to chronic pain is thought to be reflected by central sensitization (i.e., a generalized increase in pain associated with nociceptive input). Central sensitization is underpinned by marked change at multiple levels, including epigenetic modification of nociceptor-related genes (Bai et al., 2014), modulation of dorsal horn n-methyl d-aspartate receptors (NMDARs; Woolf and Salter, 2000), aberrations in functional measures of brain activity during pain (Hashmi et al., 2013), and psychological factors including anxiety, depression, fear, and catastrophizing (Williams, 2013). Therefore, it is likely that biopsychosocial mechanisms underlying alcohol analgesia as well at its efficacy may differ between individuals in acute pain vs. those with chronic pain conditions.

Pain is, by definition, aversive (International Association for the Study of Pain, 1979). Therefore, the cessation of pain is associated with relief. Although conceptually distinct from typical appetitive rewards like palatable food or drugs of abuse, substantial similarity between neurobehavioral responses to relief and appetitive rewards has been reported (Leknes et al., 2011; Seymour et al., 2005; Tanimoto et al., 2004; Ursu and Carter, 2005). Indeed, appetitive rewards are more reinforcing when simultaneously providing relief (Cabenac, 1979; Leknes et al., 2011). **This is likely due to a synergistic combination of positive and negative reinforcement, suggesting self-medication of pain using alcohol may represent a "double-hit" of reinforcement, increasing risk of developing an alcohol use disorder.**

Acute Alcohol Effects. Acute alcohol intake at legally intoxicating levels (i.e., BAC ≥ 0.08 g/dL) is associated with robust decrements in inhibitory control (Dougherty et al., 2008; Fillmore and Weafer, 2004; Loeber and Duka, 2009), psychomotor performance (Harrison and Fillmore, 2005), attentional function (Marczinski and Fillmore, 2006), and

working memory processes (Soderlund et al., 2005; Weissenborn and Duka, 2000). Even subintoxicating blood alcohol concentrations (BACs) can selectively disrupt neuropsychological processes critical for the processing of nociceptive stimuli, including sustained and/or divided attention, inhibitory control, and working memory (Boissoneault et al., 2014; Boissoneault et al., 2016; Breitmeier et al., 2007; de Wit et al., 2000; Friedman et al., 2011; Gilbertson et al., 2009; Holloway, 1994; Lloyd and Rogers, 1997). Numerous factors besides dose may modulate the effects of acute alcohol. Critically, expectations regarding the positive and negative effects of a given alcohol dose are important predictors of its neurobehavioral effects. Numerous studies indicate expectation of impairment is an important predictor of behavioral compromise following alcohol administration (Field et al., 2008; Fillmore et al., 1998; Marczinski and Fillmore, 2005) and almost certainly contributes to alcohol's analgesic effects as well. In addition, individuals with a family history of alcoholism (FH+) have atypical subjective responses to alcohol, with competing models describing either consistently lower levels of response to alcohol challenge, or increased stimulation on the ascending limb combined with decreased sedation on the descending limb (Morean and Corbin, 2010; Schuckit, 1994).

Studies of the neurophysical and functional correlates of alcohol-induced neurobehavioral compromise indicate disruption of functional activation and glucose utilization in brain structures including anterior cingulate gyrus, prefrontal cortex, medial frontal cortex, and the basal ganglia (Anderson et al., 2011; Marinkovic et al., 2012; Soderlund, et al., 2005, Volkow et al., 2006). Notably, these areas and the evaluative, limbic, and executive networks they form are implicated as modulators of acute and chronic pain*,* suggesting a common neural framework underlying both acute alcohol effects and the pain experience (Hashmi et al., 2013).

Alcohol Analgesia. Despite recent interest in the interaction between alcohol use/misuse and chronic pain (Apkarian et al., 2013; Egli et al., 2012; Zale et al., 2015) and data suggesting self-medication of pain with alcohol is widespread (Brennan et al., 2005; Riley and King, 2009), few systematic investigations of alcohol analgesia have been conducted. Early studies identified dose-dependent reductions in pain sensitivity from alcohol consumption, but major methodological limitations, including lack of placebo control and blinding, limit their usefulness (Mullin and Luckhardt, 1934; Wolff et al., 1941; Wolff et al., 1942; Cutter et al., 1976).

Subsequent studies have improved upon initial efforts using Widmark equations (Watson et al., 1981) to target specific BAC levels and by accounting for typical drinking pattern and history of alcoholism. Results of a double-blind, placebo controlled study in healthy young adults suggested pain relief was partially moderated by typical drinking pattern (Brown and Cutter, 1977). In a follow-up study, endorsement of alcohol use to increase confidence and reduce stress was associated with greater analgesic response (Cutter et al., 1979). Stewart and colleagues (1995) found that a legally intoxicating dose of alcohol (peak BAC ~0.09 g/dL) produced a reduction in pain ratings from electric shock that was significantly greater in individuals with an alcoholic parent. To minimize expectancy effects, several studies of alcohol analgesia using intravenous administration have been conducted. These studies lack ecological validity but provide

valuable insight into the pharmacological component of alcohol analgesia. James and colleagues (1978) found infusion of both 1.5 g/kg and .75 g/kg doses produced significant elevation in pressure pain thresholds. Similarly, BAC clamping at 0.10 g/dL produced significant increases in pain tolerance in healthy drinkers (Perrino et al., 2008). Follow-up analyses revealed that FH+ individuals with high neuroticism had a significantly greater analgesic response at 0.04 g/dL than FH negative or low neuroticism individuals, suggesting personality factors may interact with FH to determine analgesic responses to alcohol (Ralevski et al., 2010).

Summary. **To our knowledge, the analgesic effect of alcohol intake on clinical pain in a chronic pain population has never been studied despite strong biopsychosocial links between pain and risky alcohol use.** In addition, mechanisms and modulating factors underlying alcohol analgesia are poorly understood. Systematic study of alcohol analgesia is required to better understand these mechanisms and their implications for patient education, screening, care, and management. To maximize clinical relevance, we propose the use of a well-controlled, clinically-relevant pain induction (i.e., pressure algometry) in a population of patients with temporomandibular joint and muscle disorder (TMD) in this study.

5. Specific Aims:

Aim 1. Characterize the acute analgesic effects of alcohol in individuals with chronic temporomandibular joint and muscle disorder (TMD). Despite evidence that self-medication of pain with alcohol is common among people with TMD (Riley and King, 2009), quantitative data regarding the magnitude of this effect is largely lacking. Similarly, it is unclear whether the acute analgesic effects of alcohol may differ between individuals with and without chronic pain. We believe TMD is an ideal model with which to test the acute effects of alcohol intake on clinical pain because it is a relatively common condition (~5-12% of the general population; Goulet et al., 1995; Johansson et al., 2006), and clinically relevant pain can be reliably evoked in laboratory settings by applying pressure at the insertion of the masseter muscle (i.e., pressure algometry; Brown et al., 2000). **Hypothesis (H)1**. We hypothesize that consumption of a dose of alcohol sufficient to produce a breath alcohol concentration (BrAC) of ~ .08 g/dL will be associated with significant reduction in pain sensitivity compared to placebo in both TMD patients and healthy controls, and **H2.** acute alcohol will be associated with greater ratings of perceived relief than placebo following pain induction. Evidence from the animal literature suggests chronic pain may modulate the acute effects of opioid administration. Furthermore, chronic pain is associated with maladaptive plasticity in brain regions that underpin acute alcohol effects, including medial prefrontal cortex and nucleus accumbens (for review, see Egli et al., 2012). Thus, although it is likely that TMD patients may experience differential effects of alcohol use on pain sensation compared to healthy controls, the directionality of this effect is currently unclear. Thus, we predict **H3.** chronic pain status will moderate the magnitude of alcohol analgesia but ask as an empirical question **(E)1**. whether the effect of alcohol on pain sensitivity will be stronger or weaker in this group. Attenuated analgesic response in TMD patients would be consistent with rat studies suggesting neuropathic pain shifts opioid dose-response curves, increasing opioid self-administration (Egli et al., 2012). In contrast, an

exaggerated analgesic response would suggest alcohol use might be especially negatively reinforcing.

Aim 2. Determine the influence of typical alcohol use and expectation of pain relief with alcohol use on magnitude of alcohol analgesia and associated feelings of relief. Studies of alcohol analgesia in healthy adults have indicated that individual patterns of typical alcohol use, motivation to drink, and personality factors may modulate alcohol analgesia, suggesting a critical role of conditioning and expectancies (Brown and Cutter, 1977; Cutter et al., 1979; Ralevski et al., 2010). However, this question has never been directly examined, either in healthy adults or those with chronic pain. **H4**. We predict individuals with stronger positive expectancies regarding alcohol analgesia will have significantly stronger analgesic responses to alcohol administration. **H5.** Based on previous research, we predict that individuals who endorse greater and more frequent alcohol consumption will experience a greater analgesic effect of alcohol, independent of the effect of expectancies. Finally, we ask as **E2**. whether chronic pain status will be associated with stronger expectancies of pain relief following alcohol consumption and **E3.** greater ratings of pain relief during pressure algometry after drinking.

6. Research Plan:

General Approach. For this study of current non-problem drinkers, we propose a repeated-measures, double blind placebo-controlled factorial design with chronic pain status (TMD vs. healthy control) as a between-subjects factor and alcohol administration (Alcohol Dose: placebo, 0.08 g/dL) as a within-subjects factor. The study will include both men and women. Study procedures will occur at the Center for Pain Research and Behavioral Health of the University of Florida under supervision of the PI (JB).

Methods

Participants. Individuals seeking care for temporomandibular joint and muscle disorder (TMD) (n=25) will be recruited for the study via flyers, word of mouth, internet/local radio advertisements, and Dr. Neubert's orthodontic clinic. A sample of healthy social drinkers without TMD (HC) will also be recruited as a comparison group (n=25). Individuals aged 21-45 years will be recruited to avoid any vulnerability to acute neurobehavioral effects of alcohol associated with older age (e.g., Boissoneault et al., 2016a). Because TMD is more prevalent in women than men (~2:1; Campbell et al., 2017), we anticipate the final sample will consist of approximately 2/3 women.

Selection Criteria. TMD diagnosis will be confirmed by Dr. John Neubert, a practicing orthodontist and orofacial pain expert, or a qualified dentist designated by Dr. Neubert in situations where he may not be available, based on published Research Diagnostic Criteria (Schiffman et al., 2014). As guided by the Research Diagnostic Criteria for TMD, TMD participants in the TMD group must report TMD-related orofacial pain over the 6 months preceding screening. Participants will be excluded if they have a history of a chronic pain condition other than TMD (e.g., osteo- or rheumatoid arthritis, fibromyalgia, complex regional pain syndrome); report use of opioid analgesics; current

major depression; history of any psychotic disorder; undercontrolled hypertension or diabetes (as reflected by self-report); neurological disease (e.g., multiple sclerosis, epilepsy, amyotrophic lateral sclerosis, Parkinson's disease); serious medical illness (e.g, hepatitis, HIV/AIDS); impaired cognitive function; or history of drug or alcohol dependence. Because chronic smoking is associated with adverse neurobehavioral changes (Boissoneault et al., 2011; Durazzo et al., 2013), participants must be non-smokers. Participants must also be current drinkers (i.e, consume at least 1 drink/month over the last 6 months). Alcohol abstinent or naïve individuals will be excluded. To avoid confounding effects of binge-drinking patterns, participants must score lower than an 8 on the AUDIT. To increase ecological validity and ensure feasibility of recruitment, use of prescription medications will be allowed provided they do not contraindicate alcohol use (Boissoneault et al., 2014; Gilbertson et al., 2009).

Screening Measure	Domain	Exclusionary Cutoff
BDI-II	Depressive Symptomology	≥ 20 (moderate depression)
STAI	State/Trait Anxiety	Not Exclusionary
AEQ	Alcohol Expectancies	Not Exclusionary
AUQ	Alcohol Use Pattern	Not Exclusionary
AUDIT	Alcohol Use Disorder Sx	≥ 8
PILL	Somatic preoccupation /neuroticism	Not Exclusionary
FTQ	FH Assessment	Not Exclusionary
PSQI	Sleep Quality	Not Exclusionary
BRS	Resilience to stressors	Not Exclusionary
DIS	Ability to tolerate physical discomfort	Not Exclusionary
EAA	Expectancies regarding pain relief from alcohol	Not Exclusionary
PCS	Pain catastrophizing	Not Exclusionary
PASS-20	Pain-related Anxiety	Not Exclusionary
IRI	Empathy	Not Exclusionary
OHIP-TMD	TMD Pain Severity and Interference	Not Exclusionary

Table 1. Screening Measures. BDI-II: Beck Depression Inventory (Beck et al., 1996); STAI: State-Trait Anxiety Inventory (Spielberger, 1983); AEQ: Alcohol Expectancies Questionnaire (Brown et al., 1987); AUQ: Alcohol Use Questionnaire (Cahalan et al., 1969); AUDIT: Alcohol Use Disorders Identification Test (Saunders et al., 1993); PILL: Pennebaker Inventory of Limbic Languidness; FTQ: Family Tree Questionnaire (Mann et al., 1985); *PSQI: Pittsburgh Sleep Quality Index (Buysse et al., 1989).* BRS: Brief Resilience Scale (Smith et al., 2008); DIS: Discomfort Intolerance Scale (Schmidt et al., 2006); EAA: Expectancies for Alcohol Analgesia Inventory (Ditre et al., 2018); PCS: Pain Catastrophizing Scale (Sullivan et al., 1995); PASS-20: Pain Anxiety Symptoms Scale (Short Version; McCracken and Dhingra, 2002); IRI: Interpersonal Reactivity Inventory (Davis, 1980), OHIP-TMD: Oral Health Impact Profile for TMDs (Durham et al., 2011).

Screening Procedure. Interested individuals contacting the Center for Pain Research and Behavioral Health via phone or email will be scheduled for a formal screening session. Dr. Neubert will also facilitate contact between potential TMD participants he encounters as a part of his orofacial pain practice and study staff. During screening, information regarding demographics, FH of drug and alcohol use (including nicotine),

typical drinking behavior, affective and personality, alcohol-related expectancies, and medical history will be collected (see Table 1). The PI will facilitate contact with clinical services if desired. Subjects endorsing suicidal intent will be withdrawn from the study. Dr. Robinson, a licensed clinical psychologist, will provide an appropriate referral. Baseline quantitative sensory testing (QST) measures of pain sensitivity and tolerance using pressure algometry at the insertion of the masseter muscle (described in detail below) will be taken after participants' eligibility and willingness to continue is confirmed. Participants will provide their own transportation to screening sessions. Participants will be paid $15 for completing screening, requiring ~1-2 hours.

Laboratory Sessions. Consistent with previous work (Boissoneault, et al., 2014; Lewis, et al., 2013), participants will be asked to fast for at least 4 hours prior to their scheduled session and abstain from alcohol consumption 24 hours before each of the two laboratory sessions. Use of non-steroidal anti-inflammatory drugs (NSAIDs) in the 12 hours prior to testing will also be restricted. Normal morning medications will be permitted, but OTC medications (including allergy medications and analgesics) will not be allowed. **A urine- based drug screen for tetrahydrocannabinol, cocaine, benzodiazepines, morphine, and methamphetamine (Innovacon, Inc., San Diego, CA) will be performed. Participants testing positive for any substance will be discontinued. A baseline breath alcohol concentration (BrAC) measure will be taken, which must be negative.** Women will complete a brief questionnaire regarding their menstrual cycle, including: 1) if they are currently menstruating or post-menopausal; 2) typical time between menstruation; 3) days elapsed since last menses; 4) typical menses length; and 5) use of any hormonal preparations (e.g., birth control). **Women of child bearing potential will be given a pregnancy test; positive tests will result in exclusion from the study with a recommendation to contact her physician.** Women who are currently breastfeeding will also be discontinued. All testing will be conducted in private rooms within the Center for Pain Research and Behavioral Health. Participants will be provided with a light breakfast one hour before alcohol administration (~200 kcal). Following breakfast, participants will repeat affective measures (BDI-II/STAI) as well as an Irritability Questionnaire (IRQ; Craig et al., 2008). Lunch will be provided following testing, as well as another light meal as needed. At the conclusion of their final laboratory session, individuals in the TMD group will also be asked whether and how frequently (never, sometimes, frequently, always) they have used alcohol to help control their TMD pain (Riley and King, 2009). For laboratory sessions, the PI or a research assistant will schedule a ride with Uber or Lyft to drive participants home after the completion of the session. Research assistants will use the GPS features of the rideshare app to ensure that participants make it home safely. If the rideshare app indicates that the participant was dropped off somewhere other than the vicinity of their home, the attending researcher will call the number left by the participant and speak with the participant. If the participant does not answer the phone, the researcher will contact the IRB to report the protocol deviation. Participants will be paid $50 for completing each of the two laboratory sessions. Laboratory sessions will be separated by at least 48 hours.

Alcohol Administration. Alcohol administration procedures are consistent with our previous work and NIAAA guidelines for the safe and ethical administration of alcohol in

experimental settings (Brown et al., 2014). Participants will complete two laboratory sessions in which they will be administered one of two beverages: placebo (0.00 g/dL target BrAC) or active alcohol (0.08 g/dL target BrAC). Session order will be counterbalanced across participants. For laboratory sessions in which a participant will be given the active dose, the quantity of medical/United States Pharmacopeia grade alcohol (100% or 95% ethanol) needed to achieve 0.08 g/dL (i.e., approximately 3-4 standard drinks) will be calculated using a modification of the Widmark formula. This formula utilizes age and weight measures for men and height and weight measures for women (Watson, et al., 1981; Widmark, 1932). For example, a 30-year old man who is 183 cm tall and weighs 75 kg would receive 55.3 ml of absolute ethanol, or ~.58 g/kg. In order to maintain the study's double blind, a researcher not involved in QST will be responsible for calculating alcohol doses and mixing drinks, and the dose calculation and mixing procedure confirmed by a second research assistant. Pre-calculated dose lookup tables indexing height and weight for women and age and weight for men will be used to avoid dosing errors. Alcohol will be mixed with cold sugar- free lemon-lime soda in a 1:3 ratio and split into two servings (Boissoneault, et al., 2014; Gilbertson, et al., 2009; Harrison et al., 2007). Placebo beverages will consist of only soda. Participants will consume both servings within 5 minutes. **Both active and placebo drinks will be misted with alcohol to enhance placebo effectiveness. A small amount of alcohol will be placed on the rim of the glass and floated on the surface of the beverage to further mask the study condition.** Participants will rinse their mouths thoroughly with water once their beverage has been consumed. No suggestion regarding the potential pain-relieving effects of alcohol will be provided before or after beverage administration to avoid influencing expectations. All study staff over the age of 21 designated as "Interacts or intervenes directly with study subjects" on the myIRB smart form will be trained by the PI how to use the lookup tables and mix beverages and may serve in this capacity depending on availability for a given laboratory session.

BrAC Assessment. Following beverage administration, breath alcohol concentration (BrAC) measures will be obtained every 10 minutes, as well as immediately prior to and after QST, using standard a handheld breath analysis device (e.g., Intoxylizer 400PA, CMI, Inc., Owensboro, KY). Breath measures will be taken periodically until the participant's BrAC is ≤ 0.02 (Brown et al., 2014). They will then be transported home.

Subjective Intoxication and Placebo Effectiveness. Participants will complete brief visual analog scales (VAS) assessing their subjective intoxication (anchored from 'not at all intoxicated' to 'most intoxicated imaginable'; Harrison, et al., 2007). These assessments will be administered concurrently with BrAC assessments and before/after QST. To assess the contribution of subjective stimulatory/depressant effects to alcohol analgesia, the Subjective Effects of Alcohol Scale (SEAS; Morean et al., 2013) will be administered immediately prior to QST. The SEAS measures both positive and negative aspects of stimulation and sedation (i.e., HIGH+/- and LOW+/-). After testing, participants will indicate whether they believe they received an alcoholic beverage; those who do not believe they received a beverage will be asked when they made that determination.

Pain Induction Procedure. QST testing will occur in a private room within the Center for Pain Research and Behavioral Health using an approach developed by our research group (Brown et al., 2000). Pain induction will involve application of manual pressure to the insertion of the masseter muscle, 1 cm superior and anterior to the angle of the mandible. This location will be marked with ink to ensure a consistent stimulation site. For participants with TMD, pressure will be applied to the most affected (i.e., sensitive) side of the face, as determined during Dr. Neubert's examination. For control participants, the side of the face to be stimulated will be randomly determined. Dr. Neubert will train the PI and all research assistants (RAs) to ensure consistent localization of this point across participants. Pressure will be increased over a 1s duration and maintained for 2s using a Wagner Force One pressure algometer (Wagner Instruments, Greenwich, CT). VAS pain intensity and unpleasantness ratings (anchored from "no pain at all"/"not at all unpleasant" to "most intense/unpleasant imaginable") will be collected. Ratings will be collected at 4, 5, and 6 foot pounds per square inch (fpsi). Pain ratings will also be collected 15 and 30 seconds after algometer removal to assess aftersensation. This procedure will be repeated three times, with pressures alternated in pseudorandom order. Mean pain ratings at each stimulation level will be used to calculate individualized slopes (representing discriminability between pressure stimuli) and intercepts (representing response bias) for each participant and treatment condition (i.e., active alcohol vs. placebo) (Brown et al., 2000). Pain threshold will also be assessed by increasing pressure on the masseter insertion at a rate of .5 fpsi/s. Participants will indicate when the sensation first becomes painful and provide a VAS rating of pain intensity at the threshold pressure. This procedure will also be repeated three times and threshold and pain intensity measures will be calculated as the mean of the three trials. Following each QST measure, participants will be provided with a 10 cm VAS assessing perceived relief from pain resulting from beverage consumption (anchored from "No relief at all" to "Most profound relief imaginable"). QST procedures will require approximately 15 minutes. During laboratory sessions, QST procedures will begin approximately 15 minutes after beverage consumption to allow for absorption of alcohol (Boissoneault et al., 2014).

Data Analysis Strategy. Data will be analyzed using SPSS 24 (IBM Corp., Armonk, NY).

Aim 1. **Determine the effect of chronic pain status on magnitude of alcohol analgesia and associated feelings of relief**. To assess hypotheses and empirical questions related to Aim 1, chronic pain status will be included as an independent variable in repeated measures general linear models analyses (rmGLM; SPSS GLM procedure; repeated: dose), with QST measures, associated relief ratings, and SEAS measures as dependent variables. Demographic, personality/affective (i.e., BDI/STAI/IRQ/BFI), substance use-related (recent alcohol use/alcohol use disorder symptomatology), pain-related (TMD severity), and biological (i.e., approximated menstrual phase for female participants) variables will be included as covariates should any correlate significantly with magnitude of alcohol analgesia or relief ratings.

Aim 2. **Determine the influence of typical alcohol use, and alcohol analgesia-related expectancies on magnitude of alcohol analgesia and associated feelings of relief.** A combination of approaches will be used to address Aim 2. Simultaneous multiple regression of alcohol analgesia expectancy and typical alcohol consumption

(estimated in ounces of absolute ethanol consumed per day derived from the AUQ) on QST measures will be used to evaluate H4 and H5. As in Aim 1, rmGLM will be used to assess E2 and E3.

Power Analysis. Power analyses for the proposed work are based on effect sizes derived from our initial feasibility study (see attached grant application for details) and were performed assuming two-tailed hypothesis tests with alpha=.05. Effect sizes are reported as Cohen's d, Pearson's r, or R2 (Cohen, 1988). Analyses indicated N=50 would provide excellent (98%) power to detect analgesic effects of alcohol administration on QST measures (Cohen's d > .58) and correlations between VAS ratings of relief and alcohol analgesia (r = .64). Critically, this sample size will also provide 80% power to detect small-to-medium sized effects (d > .40; r > .37; R^2 > .14) for which prior estimates are not available (e.g., the effect of chronic pain status on alcohol analgesia and subject alcohol affects). *We will recruit a total of 60 qualified subjects over the course of the project to account for 10% anticipated participant dropout before completing all study visits.*

7. Possible Discomforts and Risks:

Psychological Discomforts and Risks. Some aspects of the questionnaires utilized in this proposal may make study participants uncomfortable, especially those dealing with affect or medical history. To ameliorate this possibility, participants will be informed they can withdraw from the study at any time or skip individual questions that may be upsetting to them.

Acute Alcohol Intake. Alcohol intake may result in dizziness, nausea, and vomiting should a participant tolerate the active dose of alcohol poorly. The risk of these as well as more serious consequences may increase if a participant uses medications that contraindicate the use of alcohol (e.g. benzodiazepines/opioid analgesics). Should a participant experience any of these symptoms, they will be allowed to rest until symptoms subside and will be allowed to withdrawal from the study if desired. We have attempted to minimize this risk by recruiting only those who are regular moderate drinkers and excluding those regularly taking prescription medications that contraindicate the use of alcohol. Ss will be rescheduled if they report having taken prescription or over-the-counter medications that contraindicate alcohol use on the day of testing.

Pregnancy: Alcohol intake is an unacceptable risk in pregnancy. Therefore, anyone of childbearing potential will be tested for pregnancy on the morning of the laboratory session. Positive pregnancy tests will result in exclusion from study and lab staff will assist in making a referral as appropriate. Finally, any documents associated with a participant testing positive for pregnancy will be destroyed without reference to a specific cause.

Breath Analyzer Testing: Breath analyzer testing may result in dizziness or lightheadedness for some individuals. However, the PI has administered many of these tests and never observed a significant negative consequence. Staff will be trained to recognize discomfort resulting from breath analyzer testing and will assist participants in

ameliorating symptoms should they occur (eg., discontinue testing, place head between knees, etc.).

QST Discomfort and Risks. QST, by definition, will induce pain in participants. However, risk of harm as a result of QST procedures is minimal for the following reasons: 1) the pain is transient in nature and generally subsides immediately after the procedure; 2) participants are instructed that they may stop any procedure at any time with no adverse consequences; and 3) although pain sensation may continue after pressure algometer removal (at discretion of the participant), this is not expected to last longer than 90 seconds. Furthermore, because pressure applied to the masseter will not exceed 8 foot pounds per square inch (fpsi) the risk of contusion is very slight. Should a participant suffer continued pain 24 hours after pressure algometry, an adverse event will be reported to the IRB.

Participant Confidentiality Risks. The investigative team places a high priority on protection of patient confidentiality and will use the following procedures to protect patients. Unique participant identifiers will be generated in order to collect protected health information (i.e., from questionnaires) for research purposes. Paper questionnaires and forms will be stored in a locked storage space, digital information will be stored in encrypted, password protected files on secure servers, and the data that links the participants to their unique identifiers will be stored in a separate location. When the study is completed and all raw data is entered electronically, participant identifiers will be destroyed. Despite these efforts, it is possible that participant confidentiality may be breached. If a breach occurs, it will be reported to NIH and the IRB and appropriate measures will be taken. These measures include but are not limited to informing affected participants of the breach and assisting with protective measures once the breach is detected.

Data and Safety Monitoring Plan

Because the proposed study does not comprise a clinical trial, a formal Data and Safety Monitoring Board has not been planned. The investigative team, including Drs. Boissoneault, Robinson, and Neubert, will meet quarterly to discuss data and safety monitoring issues. Any issues identified during these meetings will be handled in a manner consistent with the policies of the NIH and University of Florida.

8. Possible Benefits:

There are no potential benefits to participants in this study.

9. Conflict of Interest:

There is no conflict of interest involved with this study beyond the professional benefit from academic publication or presentation of the results.

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