Marijuana Use, Strength Training, and Alcohol Consumption (MUSTAC) Study

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UF | Institutional Review Board
UNIVERSITY of FLORIDA

INFORMED CONSENT FORM
to Participate in Research, and

AUTHORIZATION
to Collect, Use, and Disclose Protected Health Information (PHI)

INTRODUCTION

Name of person seeking your consent:_____

Place of employment & position: _____

GENERAL INFORMATION ABOUT THIS STUDY

1. Name of Participant ("Study Subject")

_____

2. What is the Title of this research study (this "Research Study")?

Marijuana Use, Strength Training, and Alcohol Consumption (MUSTAC) Study

3. Whom do you call if you have questions about this Research Study (the "Study Team")?

Jeff Boissoneault, PhD, Principal Investigator (352-273-6147)
Erin Ferguson, MS, Co-Investigator (352-273-5220)
Michael Robinson, PhD, Co-Investigator (352-273-6617)

4. Who is paying for this Research Study?

The sponsors of this study are the University of Florida Center for Addiction Research and Education, the Research Society on Alcoholism, and the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

5. In general, what do you need to know about this Research Study?

Agreeing to become involved in any research is always voluntary. By signing this form, you are not waiving any of your legal rights. If you decide not to participate in this research, you will not be penalized in any way and you will not lose any benefits to which you are entitled. If you have questions about your rights as a research

subject, please call the University of Florida Institutional Review Board (IRB) office at (352) 273-9600.

You are being asked to be in the MUSTAC study because you are a healthy person older than 21 who regularly uses alcohol and marijuana and identifies as either White/Caucasian or Black/African-American. You should not participate in MUSTAC if any of the following apply to you:

- You have participated in exercises that involve the biceps in the past 6 months (e.g. bicep curls, pull-ups, Olympic weightlifting)
- You have had wrist/hand, elbow, or shoulder pain in the past 3 months
- You have a medical history including diabetes, kidney problems, muscle damage, major psychiatric disorder, high blood pressure, or chronic pain
- You have a medical marijuana prescription, recommendation, or card
- You consume marijuana using only non-inhalational methods (e.g. edibles, tinctures, or cannabidiol oil)
- You have not used alcohol and marijuana at least 2-3 times per week over the past 6 months
- You do not own a smartphone with a cellular/data plan
- You are pregnant, trying to become pregnant, or breastfeeding

a) In general, what is the purpose of the research, how long will you be involved?

The purpose of the MUSTAC study is to study the relationship between vigorous exercise and alcohol and marijuana consumption. Your participation will last approximately one week and involves two visits to our laboratory (including this one), as well as the completion of daily surveys.

b) What is involved with your participation, and what are the procedures to be followed in the research?

If you decide to participate in this study, you will complete a variety of questionnaires followed by brief computer-based tasks. You will then perform a series of biceps exercises and be scheduled for your second laboratory session. Participation in this study lasts approximately one week and involves two visits to our laboratory. The first visit will require about 2.5 hours. The second visit will require about 1 hour. Daily surveys will require approximately five minutes per day for one week.

c) What are the likely risks or discomforts to you?

This study collects information about your marijuana use, which is considered illegal if not done for medical reasons. Despite safeguards described below, there is a risk that information about your marijuana use may reach someone, who would use this information against you, e.g. by denying you employment. Performing the exercises in this study may result in soreness in your biceps muscles, and possibly swelling of the area around the biceps. There is a very small risk that you may get some other type of muscle damage from doing the exercise.

This risk can be reduced by drinking plenty of water before doing the exercises. Other potential risks are described in detail under Item 10.

d) What are the likely benefits to you or to others from the research?

There is no direct benefit to you for participating in this study.

e) What are the appropriate alternative procedures or courses of treatment, if any, that might be helpful to you?

Participating in this study is entirely optional. This is not a treatment study. If you are a faculty/staff member or student at the University of Florida, your decision whether to participate will have no impact on your employment or academic status.

Additional and more detailed information is provided within the remainder of this Informed Consent form, please read carefully before deciding if you wish to participate in this study.

WHAT CAN YOU EXPECT IF YOU PARTICIPATE IN THIS STUDY?

6. What will be done as part of your normal clinical care (even if you did not participate in this Research Study)?

Your normal clinical care will not be affected by participation in this study.

7. What will be done only because you are in this Research Study?

The MUSTAC study involves two visits to our laboratory. The first visit includes the following procedures:

a) After arriving at the Center for Pain Research and Behavioral Health (located on the ground floor of the UF Dental Tower in room DG-64), the Informed Consent form will be reviewed with you to make certain that you understand everything that is involved in the study procedures.

b) You will complete several questionnaires about your demographics (age, education, etc.), typical exercise, typical alcohol and marijuana use patterns, emotional state, personality, expectations about how alcohol and marijuana may affect you, medical history, and attitudes about pain.

c) You will complete brief computer-based tasks. In one task, you will decide how many alcoholic beverages you would consume at different prices, if they were available. In the other tasks, you will decide how much marijuana you would use at different prices if it were available. However, we do not actually provide alcoholic beverages or marijuana in this study.

d) We will test the strength of your biceps muscle using an exercise testing machine that you sit on. We are going to ask you to pull as hard as you can on a handle that is attached to the machine. Next, you will do some exercise with

your biceps muscles. You will be randomly assigned to either resist the machine pushing against you by pulling as hard as you can ("eccentric" exercise) or to complete several repetitions pulling against a resistance that is based on the results of your strength test ("concentric" exercise).

Following completion of the first session, you will receive instructions related to completion of daily surveys about your use of alcohol and marijuana and any discomfort/pain you may have experienced due to your biceps exercise. Text messages with a link to a survey will be sent every night for one week and will begin the day of the first session.

The second visit will take place about 48 hours (2 days) after your first visit, and includes the following procedures:

a) You will complete several questionnaires about any discomfort or pain you may have experienced as a result of your biceps exercise, both at rest and with movement.

b) You will complete the same computer-based tasks about how many alcoholic beverages or how much marijuana you would consume at different prices, if available.

If you experience a physical or mental emergency during your screening or either laboratory session, we will request emergency services by dialing 911.

Once this research study is completed, any information that could identify you **might** be removed from any identifiable private information or identifiable biospecimens collected and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

If you have any questions now or at any time during this Research Study, please contact one of the Research Team members listed in question 3 of this form.

8. What identifiable health information will be collected about you and how will it be used?

The Research Team will collect the following protected health information (PHI) about you:

a) Your name, research record number, contact information, and dates associated with tests related to your participation.
b) Demographic and health status information
c) Responses to questionnaires
d) Results of the biceps exercise protocol
e) Social security number for the purposes of payment

This information will be gathered only through your self-report, participation in study procedures, or from your study visits or telephone calls.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You have been informed that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. That is, if you give written consent for the release of information, we cannot withhold that information and we cannot hold responsibility for how that person may use your information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances. If we learn about child abuse, elder abuse, or intent to harm yourself or others, we will report that information to appropriate authorities.

The Research Team listed in question 3 above will use or share your health information as described below to carry out this research study.

9. With whom will this health information be shared?

This health information may be shared with:

- the UF Department of Clinical and Health Psychology;
- United States governmental agencies which are responsible for overseeing research, such as the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections;
- The IRB that reviewed this Research Study and ensures your rights as a Study Subject are protected

Otherwise, your identifiable health information will not be shared without your permission unless required by law or a court order. Once your health information is shared with those listed above, it is possible that they could share it without your permission because it would no longer be protected by the federal privacy law.

10. How long will you be in this Research Study?

Participation in this study lasts approximately one week and involves two visits to our laboratory. The first visit will require about 2.5 hours. The second visit will require about 1 hour. Daily surveys will require approximately five minutes per day for one week.

This Authorization to use and share your health information expires at the end of the study, unless you revoke it (take it back) sooner.

11. How many people are expected to take part in this Research Study?

Our goal is for 56 people to complete this study.

WHAT ARE THE RISKS AND BENEFITS OF THIS STUDY AND WHAT ARE YOUR OPTIONS?

12. What are the possible discomforts and risks from taking part in this Research Study?

- You may feel uncomfortable answering questions about private topics during the screening session. However, you may choose not to answer any questions that make you feel uncomfortable.
- By performing the exercises in this study, you may get muscle soreness in your biceps muscles. It is also possible that the area around the biceps muscles will swell. There is a chance that this pain will limit how you move around for several days. There is a very small risk that you may get some other type of muscle damage from doing the exercise. This risk can be reduced by drinking plenty of water before doing the exercises. If you experience any severe and unusual symptoms, including vomiting or nausea, abdominal pain, confusion, dehydration, or fever, call 911 or seek care from a physician.
- There is a risk of spreading or contracting COVID-19 during participation in this study. We are taking the following steps to limit spread of COVID-19:
    - During laboratory visits, research staff will wear a disposable Level 1 surgical mask during all interactions with you or other staff members. Upon arrival for each session, you will be asked to wait outside of the Shands Dental Tower West Entrance, inform our staff of your arrival (352-273-5220), and wait for a research assistant to come outside and provide you with a disposable Level 1 surgical mask. You are required to wear the mask for the duration of all sessions.
        - If you are not willing to wear a mask, we ask that you do not participate in this study.
    - At the beginning of each study session, all consent material documents will be presented to you. You will be instructed when to flip to the next page, to reduce the number of times forms are passed between

people. Electronic devices (e.g. iPads) used to collect information will be designated for participants and thoroughly disinfected between study sessions. After the participant begins data collection procedures using the iPad, the device will not be passed back to research personnel until completion.

- All study equipment will be sanitized before and after each use with alcohol wipes. Study equipment includes, but is not limited to: tabletops, door knobs, writing utensils, and the Biodex machine used for musculoskeletal induction procedure. .
- The study personnel have acquired HEPA filtered air purifiers that will be placed in study rooms.

This Research Study may also include risks that are unknown at this time.

Please note that participating in more than one research study or project may further increase the risks to you. If you are already enrolled in a research study, please inform one of the Research Team members listed in question 3 of this form or the person reviewing this consent with you before enrolling in this or any other research study or project.

During the study, the Research Team will notify you of new information that may become available and might affect your decision to remain in the study.

The University of Florida is required by law to protect your health information. Your health information will be stored in locked filing cabinets or on computer servers with secure passwords, or encrypted electronic storage devices, as required by University policy. However, there is a slight risk that information about you could be released inappropriately or accidentally. Depending on the type of information, a release could upset or embarrass you, or possibly affect your ability to get insurance or a job.

If you wish to discuss the information above or any discomforts you may experience, please ask questions now or call one of the Research Team members listed in question 3 in this form.

13a. What are the potential benefits to you for taking part in this Research Study?

There is no direct benefit to you for participating in this study.

13b. How could others possibly benefit from this Research Study?

Improving understanding of the relationship between the effects of vigorous exercise and alcohol and marijuana use may benefit the scientific community.

13c. How could the Research Team members benefit from this Research Study?

In general, presenting research results helps the career of a researcher. Therefore, the Research Team listed in question 3 of this form may benefit if the results of this Research Study are presented at scientific meetings or in scientific journals.

14. What other choices do you have if you do not want to be in this study?

Participating in this study is entirely optional. This is not a treatment study. If you are a faculty/staff member or student at the University of Florida, your decision whether to participate will have no impact on your employment or academic status.

15a. Can you withdraw from this study?

You may withdraw your consent and stop participating in this Research Study at any time. If you do withdraw your consent, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. If you decide to withdraw your consent to participate in this Research Study for any reason, please contact the Research Team listed in question 3 of this form. They will tell you how to safely stop your participation.

You can also change your mind and take back this Authorization at any time by sending a written notice to the Research Team listed in question 3 of this form to let them know your decision. If you take back this Authorization, the Research Team may only use and disclose your health information already collected for this research study. No additional health information about you will be collected or disclosed to the Research Team. However, if you take back this Authorization, you may not be able to continue in this study. Please discuss this with a member of the Research Team listed in question #3.

15b. Can the Principal Investigator withdraw you from this Research Study?

You may be withdrawn from this Research Study without your consent for the following reasons:

- If the Principal Investigator obtains information that participating in this study might cause you harm.
- For administrative reasons at the Principal Investigator's discretion.

WHAT ARE THE FINANCIAL ISSUES IF YOU PARTICIPATE?

16. If you choose to take part in this Research Study, will it cost you anything?

No. The Sponsor will provide all services and activities required as part of your participation in the study. There will be no cost to you. If you receive a bill related to this study, please contact Erin Ferguson, MS, at 352-273-5220.

17. Will you be paid for taking part in this Research Study?

Yes. You will receive $50 for the first session and $15 for the second, for a total amount of $65. If you do not qualify for the study after completing the screening questionnaires, you will be paid $15. For the daily surveys, compensation will be provided as a function of the number of surveys completed, with a maximum of $30 for participants who complete at least 5 out of 7 surveys. Additionally, if you refer an individual to the study that attends the screening session, you will also receive $20 per person referred. The people you refer will be responsible for contacting the study team in order to schedule the session. You will be eligible to refer participants regardless of whether you qualify to proceed with the study after screening procedures.

Your payment for participation in this research study is handled through the University of Florida's Research Participant Payments (RPP) Program. Your information which will include your name, address, date of birth, and SSN (depending on amount of money you are paid) is protected. Access to the (RPP) Program site is limited to certain staff with the assigned security role. You will be randomly assigned a specific identification (ID) number to protect your identity. If you have any problems regarding your payment contact the study coordinator.

If you are paid more than $199 for taking part in this study, your name and social security number will be reported to the appropriate University employees for purposes of making and recording the payment as required by law. You are responsible for paying income taxes on any payments provided by the study. Payments to ***nonresident aliens*** must be processed through the University of Florida Payroll and Tax Services department. If the payments total $600 or more in a calendar year, the University must report the amount you received to the Internal Revenue Service (IRS). The IRS is not provided with the study name or its purpose. If you have questions about the collection and use of your Social Security Number, please visit: http://privacy.ufl.edu/SSNPrivacy.html.

18. What if you are injured while in this Research Study?

If you are injured as a direct result of your participation in this study, the professional services that you receive from any University of Florida Health Science Center health care provider will be provided without charge. These healthcare providers include physicians, physician assistants, nurse practitioners, dentists or psychologists. Any other expenses, including Shands hospital expenses, will be billed to you or your insurance provider.

You will be responsible for any deductible, co-insurance, or co-payments. Some insurance companies may not cover costs associated with research studies. Please contact your insurance company for additional information.

The Principal Investigator will determine whether your injury is related to your participation in this study.

No additional compensation is routinely offered. The Principal Investigator and others involved in this study may be University of Florida employees. As employees of the

University, they are protected under state law, which limits financial recovery for negligence.

Please contact one of the research team members listed in question 3 of this form if you experience an injury or have questions about any discomforts that you experience while participating in this study.

Please contact one of the Research Team members listed in question 3 of this form if you experience an injury or have questions about any discomforts that you experience while participating in this Research Study.

SIGNATURES

As an investigator or the investigator's representative, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this Research Study; the alternative to being in the study; and how the participant's protected health information will be collected, used, and shared with others:

Signature of Person **Obtaining Consent** and Authorization	Date

You have been informed about this study's purpose, procedures, possible benefits, and risks; the alternatives to being in the study; and how your protected health information will be collected, used and shared with others. You have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask questions at any time.

You voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your protected health information as described above. By signing this form, you are not waiving any of your legal rights.

Signature of Person **Consenting** and Authorizing	Date

Protocol

1. Project Title:

Marijuana Use, Strength Training, and Alcohol Consumption (MUSTAC) Study

2. Investigator(s):

Jeff Boissoneault, PhD (PI)
Erin Ferguson, MS (Co-I)
Michael Robinson, PhD (Co-I)

3. Abstract:

A substantial body of research indicates that self-medication of pain with alcohol and marijuana (i.e. use to cope with and/or manage pain) is common among chronic pain patients, and epidemiological and observational studies suggest that pain can act as a potent motivator of substance use. Initial experimental evidence suggests that pain can increase urge and intention to consume alcohol, yet this relationship has not been replicated using clinically-relevant pain induction methods with greater ecological validity than typical experimental pain approaches. Further, despite similar pain-inhibitory effects and co-occurring use patterns of alcohol and marijuana, current research has not simultaneously examined the proximal effects of pain on alcohol and marijuana use. Thus, the proposed project will attempt to determine whether experimentally-induced musculoskeletal pain (i.e., delayed onset muscle soreness; DOMS) increases alcohol and marijuana demand among co-users. We will assess demand for alcohol and marijuana using well-validated behavioral economic measures before and after DOMS induction in the dominant elbow flexor muscle.

4. Background:

Chronic pain affects approximately 100 million adults and is one of the most common reasons for seeking medical treatment.[1] However, front-line treatments for chronic pain, including opioid medications, are often considered ineffective by patients and are associated with risk of harm (e.g. adverse side effects, diversion, abuse of opioids).[2-4] Growing evidence suggests that many individuals may report substance use, including alcohol and marijuana use, as an alternative means to manage pain-related symptoms and reduce distress.[5-8] Therefore, greater understanding of the causal pathway from pain to alcohol and marijuana use is warranted to inform prevention and intervention substance use approaches and achieve improved health outcomes for chronic pain patients.

Race and Sex Differences in Coping with Pain

Compared to White individuals, African Americans are disproportionately burdened by chronic pain and associated outcomes, including greater pain severity, functional limitations, and disability.[9-12] African Americans have been found to report higher levels

of pain catastrophizing,[13] lower perceived ability to effectively cope with pain,[14] and overall greater use of maladaptive coping strategies (i.e., passive, emotion-focused),[13-16] all of which have been linked to poorer chronic pain outcomes. Similarly, research consistently suggests that women report greater pain prevalence and severity.[16-17] catastrophize more frequently about pain,[18-20] and use emotion-focused coping strategies relative to men.[21-22] Interestingly, epidemiological studies suggest that White individuals and men are more likely to use alcohol to cope with pain, which may reflect differences in alcohol use patterns among the general population and/or the influence of sociocultural factors.[6] Nevertheless, identifying demographic correlates of self-medication behaviors of pain with alcohol and marijuana may provide clarity for a relatively discrepant literature on pain-coping and self-medication, as well as inform targeted interventions for pain management and substance use.

Alcohol and Marijuana Use to Cope with Pain

Alcohol and marijuana use are highly prevalent among US adults, with 65.7% and 15% reporting past year use respectively.[23] While there are several overlapping reasons for use (e.g. enhancement, relaxation), coping with pain and distress is often cited as a motive of use for both substances.[5] Previous studies suggest that alcohol drinkers report consuming alcohol to self-medicate their physical pain.[6, 24-26] Further, 64% of medical marijuana users endorse use to cope with pain, and marijuana use rates are higher among chronic pain patients than in the general population.[7,27] Of most concern with such behaviors is the possibility of adverse interactions between alcohol and pain medication, as well as increased risk for alcohol and cannabis use disorders. For example, young adults with chronic pain were more likely to endorse heavier patterns of marijuana consumption (e.g. extensive histories of regular use, higher quantities of marijuana per use episode) than users without chronic pain, which have been associated with increased risk of cannabis use disorder (CUD).[28] Theoretical models for reciprocal alcohol-pain interactions suggest that self-medicating patients may escalate consumption over time, consequently creating a feed-forward cycle of greater risk of AUD in individuals with chronic pain and vice versa.[5,29]

Co-Use of Alcohol and Marijuana

Co-use (concurrent or simultaneous) of alcohol and marijuana is common among individuals with chronic pain. Medical marijuana users with chronic pain have higher rates of hazardous drinking than non-users, [30-31] and hazardous drinking has been associated with reduced pain severity and disability.[30] Findings that hazardous drinking is related to lower pain severity underscore the likelihood of alcohol use to manage pain among this population.[8, 30] Overall, co-use of alcohol and marijuana is associated with a range of deleterious consequences beyond those associated with use of a single substance, including increased rates of comorbid substance use and mental health disorders, poorer treatment outcomes, and greater social and behavioral consequences (e.g. driving under the influence). [32-34] Prevalence estimates for alcohol and marijuana co-use among those with chronic pain (~60%) are similar to those in the general population.[30-31, 35] However, co-users with chronic pain may be even more susceptible to heavier consumption over time for pain-coping purposes, [5] thereby resulting in

greater risk of adverse consequences. Improved understanding of the proximal, causal role of pain on alcohol and marijuana co-use is urgently needed to clarify unique risks of co-users with pain and the temporality of the pain-substance use relationship.

Pain as an Antecedent of Alcohol and Marijuana Use

Emerging literature suggests that pain can act as a motivator for substance use, such that chronic pain may be associated with increased substance use.[5] Marijuana users use greater amounts of marijuana when they are experiencing increased pain levels, and chronic pain remains one of the most common reasons patients seek medical marijuana.[36-37] To this point, pain relief has been documented as the most important motivation for marijuana use for users with chronic pain.[28] With regard to alcohol use, higher ratings of pain unpleasantness have been associated with greater motivation to consume alcohol among chronic pain patients.[38] Moreover, individuals with co-occurring AUD and chronic pain report that pain significantly contributes to their alcohol use, with many also identifying pain as their initial reason for alcohol misuse.[24,39] Findings from experimental research indicate that both alcohol and marijuana use can produce acute pain-inhibitory effects, highlighting the potential for negative reinforcing effects of marijuana and alcohol for those using to cope with pain.[40-41] To the authors' knowledge, only one empirical study has examined pain as a causal determinant of alcohol use, concluding that thermal pain induction in a laboratory setting increased urge and intention to consume alcohol.[42] Despite similar analgesic properties of alcohol and marijuana, existing literature has not concurrently investigated chronic pain as an antecedent to alcohol and marijuana co-use.

Delayed Onset Muscle Soreness (DOMS)

Delayed onset muscle soreness (DOMS) is a sensation of muscular pain and soreness that often follows engagement in unfamiliar, strenuous exercises, particularly those involving eccentric muscle contractions.[43-46] Pain from DOMS peaks in intensity 36-48 hours after exercise and typically resolves within a week.[43,,47] Unlike laboratory pain induction methods, DOMS provides an analogous paradigm for musculoskeletal pain as an antecedent of alcohol and marijuana use because it produces elevated pain intensity for several days, functional impairment, initiation of self-care behaviors, and pain-associated negative affect,[48-52] thereby more effectively mimicking clinical pain conditions. Use of DOMS induction also allows for experimental control over intensity, duration, and localization of pain that cannot be obtained when recruiting patients with clinical pain conditions. Given that musculoskeletal pain is the most common form of chronic pain, [1, 53] DOMS associated changes in alcohol and marijuana demand will have strong ecological validity, particularly compared to other experimental pain induction techniques. Thus, we propose inducing DOMS in the dominant elbow flexor muscles to model musculoskeletal pain as a determinant of alcohol and marijuana demand.

Alcohol and Marijuana Purchase Tasks

Behavioral economics approaches provide a valuable theoretical framework for measuring the relative value of a substance, as they propose that overvaluation of a substance relative to other rewards serves as a determinant of substance misuse.[54-55]

Prior research suggests that substance use demand, which refers to the quantitative relationship between drug consumption and its cost, may provide a meaningful complement to other measures of substance use motivation by denoting potential for abuse liability.[56] In contrast to direct measurement of demand with operant procedures,[57-59] hypothetical purchase tasks offer a more parsimonious, rapid assessment of demand that reflects the relative reinforcing efficacy of a substance.[60-62] Demand for alcohol and marijuana can be efficiently measured using the Alcohol Purchase Task (APT) and Marijuana Purchase Task (MPT), which have demonstrated good psychometric validity, test-retest reliability, and correspondence with actual substance use consumption and other markers of addiction.[60-61,63-65] A single study measuring alcohol demand with the APT among co-users of alcohol and marijuana suggests that co-use is associated with higher demand for alcohol and overvaluation of alcohol rewards compared to alcohol only users.[66] However, current research has not yet attempted to disentangle the economic relationships between alcohol and marijuana among this population. By using both the MPT and APT, this study is designed to assess DOMS-related changes in alcohol and marijuana demand, thereby allowing for characterization of the relationship between the substances.

Conclusions

Current evidence and theoretical models suggest that pain often motivates use of alcohol and marijuana, and co-use of these substances is common. Notably, self-medication of pain with alcohol and marijuana use may increase risk for heavier substance use, substance use disorders, and may even worsen pain symptomatology over time. Previous studies are limited by laboratory pain induction methods with restricted ecology validity and clinical relevance. Use of a DOMS based approach in this study overcomes these limitations by producing time-limited, robust musculoskeletal pain and associated impairment, which we believe will provide data relevant to those with clinical pain conditions, such as chronic pain.

5. Specific Aims:

The overall aim of this project is to provide clinically-relevant data regarding musculoskeletal pain as an antecedent to alcohol and marijuana co-use and identify potential psychosocial moderators of this association. This study has two specific aims.

Aim 1. Determine impact of DOMS pain on demand for alcohol and marijuana and examine race and sex as moderators of this relationship.

We predict that those who undergo the DOMS induction paradigm will show greater increases in alcohol and marijuana demand than participants in the sham DOMS control group. We also predict an interactive effect of race and sex on DOMS-related changes in alcohol and marijuana demand, such that increases may be greater in White men than Black women and men, as well as White women.

Aim 2. Identify psychosocial factors associated with change in demand for alcohol and marijuana after DOMS induction.

Consistent with current evidence, [42, 67] we predict that pain-related negative affect will mediate the association between DOMS-related pain and increased demand for alcohol and marijuana. We also predict that greater expectancy of analgesia from marijuana or alcohol use, higher negative urgency, and history of self-medication behaviors will predict greater change in alcohol and marijuana demand.

6. Research Plan:

Participants

We will recruit participants aged 21 years and older who are regular co-users of alcohol and marijuana (i.e., concurrent or simultaneous use at least 2-3 times per week over the past 6 months). Extent of co-use will be determined using the Alcohol Use Disorders Identification Test (AUDIT) and Cannabis Use Disorder Identification Test, Revised (CUDIT-R). A research team member will inform participants of inclusion and exclusion criteria via email or the phone. If an individual believes they meet all study criteria, they will be scheduled for the first study session (see Phone and Email Scripts for details). We will review all inclusion and exclusion criteria one additional time with participants before initiating the Informed Consent process.

Inclusion/Exclusion Criteria

Detailed inclusion/exclusion criteria are provided in Table 1.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria

- Aged 21-65 years;
- English-speaking
- Self-identify as White/Caucasian or Black/African American
- Own a smartphone with cellular/data plan
- Regularly co-use alcohol and smoked marijuana as indicated by scores of ≥3 on item 1 of the CUDIT-R and AUDIT.
- Willing and able to give informed consent

Exclusion Criteria

- Participation in exercises that involve the biceps in the past 6 months*
- Self-reported wrist/hand, elbow, or shoulder pain the past 3 months
- Chronic medical condition that may affect pain perception (e.g. diabetes, fibromyalgia, headaches)
- Self-reported kidney dysfunction, muscle damage, or major psychiatric disorder
- Medical marijuana prescription, recommendation, or card
- Consumption of marijuana using only non-inhalational methods (e.g. edibles, tinctures, or cannabidiol oil)
- Women who are pregnant, trying to become pregnant, or breastfeeding

*Examples include bicep curls, pull-ups, olympic weightlifting, etc.

In addition, participants who indicate they have consumed of any drugs (e.g., alcohol, theophylline, tranquilizers, over-the-counter and prescription pain medications, including NSAIDs and opioids) that may affect pain perception or hydration status 24 hours before participation in a testing session or used caffeine 4 or less hours before testing session will be discontinued or rescheduled at the PI's discretion. Additionally, participants who report that they have used any tobacco products less than 1 hour before participation in a testing session will be discontinued or rescheduled at the PI's discretion.

Screening Procedure

Screening assessment procedures will take place in a private exam room within the Center for Pain Research and Behavioral Health. Participants will be given a choice of completing the informed consent process with paper documents or electronically via REDCap. The consent process will take place in person, regardless whether it is documented on paper or electronically After providing informed consent, participants will complete a series of surveys as part of the assessment on a secured laptop computer or tablet, using REDCap. These measures are intended to both address study aims and characterize the sample. All participants will be provided with a pamphlet containing information about local mental health services; if desired, the PI or research assistant will facilitate contact with clinical services. The Patient Health Questionnaire-9 is a well-validated and widely used measure of depressive symptomatology, including suicidal ideation/intent. Responses on the Patient Health Questionnaire-9 regarding suicidal intent will be reviewed by the study team prior to the participant leaving the sight of the study team. Any subjects endorsing suicidal intent during screening will be withdrawn from the study. Dr. Robinson, who is a licensed clinical psychologist, will then provide appropriate referral (e.g. Crisis Hot Line referral, or direct referral to clinical services if deemed appropriate). Women of childbearing potential will also be given a pregnancy test. A positive result will be exclusionary and if desired, the investigative team will facilitate referral for medical care.

Screening Measures

Participants will provide demographics and medical history information, including racial identity and whether they are pregnant, trying to become pregnant, or breastfeeding. They will also complete questionnaires related to mood (Patient Health Questionnaire-9,[68] Generalized Anxiety Disorder 7-item scale[69]), attitudes about pain (Pain Anxiety Symptoms Scale,[70] Pain Catastrophizing Scale,[71] Fear of Pain Questionnaire,[72] Discomfort Intolerance Scale[73]), somatization (Pennebaker Inventory of Limbic Languidness[74]), and recovery from difficult life events (Brief Resilience Scale[75]).

Negative Urgency will be assessed using the Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale.[76] Participants will complete visual analog scale (VAS) questions related to spontaneous pain and pain with movement, with each line being anchored with 'none' on the left and 'worst imaginable' on the right.[77] Additionally, participants will complete several pain experience visual analog scales (PEVAS); the PEVAS includes seven 10-cm lines that measure a different component of the pain experience (i.e. depression, anxiety,

frustration, fear, anger, pain intensity, pain unpleasantness) with a written description of 'none' on the left and 'worst imaginable' on the right. The PEVAS will measure pain-related negative affect, and participants will provide their rating by placing a mark along each line. Expectancies of muscle soreness from the exercises involved in this study will be assessed with a VAS-style question anchored by 'no muscle soreness' and 'most intense muscle soreness imaginable.' In addition, expectancies of analgesia from alcohol and marijuana, as well as urge to consume alcohol and marijuana, will also be measured using VAS-style questions, with lines being anchored by 'no pain relief at all' and 'complete pain relief' for expectancies of analgesia and lines being anchored by 'no urge' and 'very strong urge' for urge-related questions. History of self-medication behaviors will be assessed using separate VAS-style questions measuring likelihood of using alcohol or marijuana when experiencing pain in the past. Each line will be anchored by 'none of the time' and 'all of the time'. Other measures will assess alcohol use patterns (Alcohol Use Disorders Identification Test, [78] Alcohol Use Questionnaire[79]), marijuana use patterns (Cannabis Use Disorder Identification Test, Revised, [80] Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory[81]), and use of other substances (NIDA Modified Alcohol, Smoking and Substance Involvement Screening Test,[82] Fagerstrom Test for Nicotine Dependence[83]). Finally, a single-item question will measure frequency of simultaneous alcohol and marijuana use behaviors over the past 12 months.[84]

Participants who continue to qualify following completion of screening procedures and agree to proceed will be assigned to either the *DOMS* or *Sham DOMS* group. Assignments will be made according to a participant's unique subject identifier using a spreadsheet listing group assignment in pseudo-random order using the Excel random number function.

Participants will then complete the Alcohol Purchase Task (APT), Marijuana Purchase Tasks, (MPT), and DOMS or sham DOMS induction procedures. They will also be will be scheduled for a second lab session 48 hours later so that potential changes in DOMS-associated alcohol and marijuana demand can be investigated. Participants who complete the screening but either do not qualify or decide not to proceed will be paid $15 via gift card. Those who do qualify and proceed with the study will be paid $50 at the end of the first lab visit and $15 at the end of the second lab visit. For the daily surveys, compensation was provided as a function of the number of surveys completed, with a maximum of $30 for participants who completed 5/7 or more of their assessments (see "Daily Measures" section for additional information). We will also ask whether their DOMS (if any) has resolved with the daily measures. Additionally, participants who refer an individual to the study that attends the screening session will also receive $20 per person referred. The referee(s) will be responsible for contacting the study team via phone or email in order to schedule the session. The referrer will receive the $20 bonus once the person they refer attends their screening session, whether or not they eventually decide to participate. All participants who provide informed consent will be eligible to refer participants to the study regardless of whether they qualify to proceed after screening procedures.

Alcohol Purchase Task (APT) and Marijuana Purchase Tasks (MPT)

Both the APT and MPT will be administered on REDCap during the first lab session prior to DOMS induction and during the second lab session (48 hours post DOMS induction). In the APT, participants are provided with a set of instructions, including a definition of a standard drink, and asked how many standard drinks they would consume at 21 prices, ranging from free to $30/drink (e.g. “How many drinks would you consume if they were $1.00 each?”). Procedures for the MPT are virtually identical, except a standard definition of the number of hits of marijuana in one joint is provided, and participants are asked how many hits of marijuana they would take at a series of escalating price points ranging from free to $10/hit. Participants will also complete an adapted form of the MPT that allows for differences in preference for various marijuana-based products and modes of administration. From these data, the following indices of alcohol and marijuana demand will be generated: intensity (consumption of hits/drinks when free); breakpoint (the first price at which consumption was zero); O_{max} (maximum expenditure on alcohol and marijuana hits); P_{max} (price where demand becomes elastic); elasticity (rate of change in consumption with changes in price). Studies have demonstrated that these indices can be reduced to two latent factors: persistence (maintaining consumption despite increasing price) and amplitude (maximum consumption and price levels). Persistence is composed of elasticity, P_{max}, breakpoint, and O_{max}, while amplitude is composed of intensity and O_{max}.[85-86]

Isometric Strength Testing and DOMS Induction

Figure 1. Biodex setup for isometric strength and DOMS.

Maximum voluntary contraction (MVC) of elbow flexion strength will be tested using a Biodex System Isokinetic Dynamometer (Biodex Medical Systems, Shirley, NY), and torque values obtained from this testing will be used to inform exercise protocols. The participant will first be seated within the testing apparatus with a stabilizing strap attached proximal to the elbow joint. The participant will then move through their available range of motion in the elbow flexion and extension. The device will be locked at 90 degrees of elbow flexion, and the participant will be instructed to build maximal flexion force while holding onto the grip handle of the machine. Once peak effort is achieved, the participant will be instructed to relax, the device will be released, and the subject will be returned to a neutral position.

DOMS-inducing exercise protocol. To perform the dynamic fatiguing exercise bout, the participant will be seated in the Biodex machine in order to isolate elbow flexion. The participant will perform the isometric strength test (described above). Following 60 seconds of rest after the isometric test, participants will complete an exercise protocol consisting of eccentric (elbow straightening/biceps lengthening) exercises designed to induce DOMS at the biceps. **Participants in the DOMS group will perform 3 sets of 15 repetitions at a speed of 60$^{o/s}$. Participants in the Sham DOMS group will complete one set of 15 concentric (elbow flexion/biceps shortening) repetitions at**

a resistance set to 30% of their maximum voluntary contraction, which is unlikely to induce significant DOMS.

DOMS-related Pain Measures

Upon arriving in the laboratory for their second study session, participants will complete several measures regarding pain associated with the exercise protocol.

1. Pain Experience*:* Pain experience visual analog scales (PEVAS) include seven 10-cm lines that measure a different component of the pain experience (i.e. depression, anxiety, frustration, fear, anger, pain intensity, pain unpleasantness) with a written description of 'none' on the left and 'worst imaginable' on the right. The PEVAS will measure pain-related negative affect, and participants will provide their rating by placing a mark along each line.

2. Pain with Movement: Participants will also rate pain during elbow extension and elbow flexion using the same scale. This will give ratings of both spontaneous pain and pain with movement.

Daily Measures

Participants will receive instructions related to the daily electronic diary following DOMS induction. These measures will primarily be used evaluate the pain associated with DOMS and assess alcohol and marijuana use following the exercise protocol. Participants will receive a text message with a link to the REDCap survey every night for one week, and text messages will begin the day of the first lab visit. The daily assessment will be personalized, such that participants will inform study staff of preferences for when they receive the survey each night before bed. Prior to leaving lab session 1, participants will be sent a practice text message to ensure that they receive it. Individuals who fail to complete their daily diary will be prompted via a reminder text or telephone call. Participants will provide daily reports of 1) Pain Experience VASs, 2) VAS questions related to spontaneous pain and pain with movement, 3) the number of standard alcoholic drinks they have consumed, 4) route of administration (ROA) of marijuana use and number of hits taken according to route of administration (in checklist form to allow for endorsement of multiple ROAs of marijuana use), and 5) number of hours "high." If a participant endorses marijuana use by a non-inhalational ROA (e.g. edibles, tinctures, topicals), they will be prompted with a free-response question to describe the quantity of their marijuana use in as much detail as possible. A single yes/no item will inquire about whether alcohol and marijuana were used simultaneously, such that their effects overlapped, and participants will also report the intensity of their "high" from marijuana via a VAS-style question with 'not at all high' on the left and 'extremely high' on the right. Additionally, participants will report whether or not other substances (e.g. tobacco, cocaine, hallucinogens) or over-the-counter and prescription pain medications were used. They will also indicate the extent to which pain interfered with several domains (e.g. general activity, walking ability, enjoyment of life, sleep) over the past 24 hours.

Study Design

The overall design of the study is detailed in Figure 2.

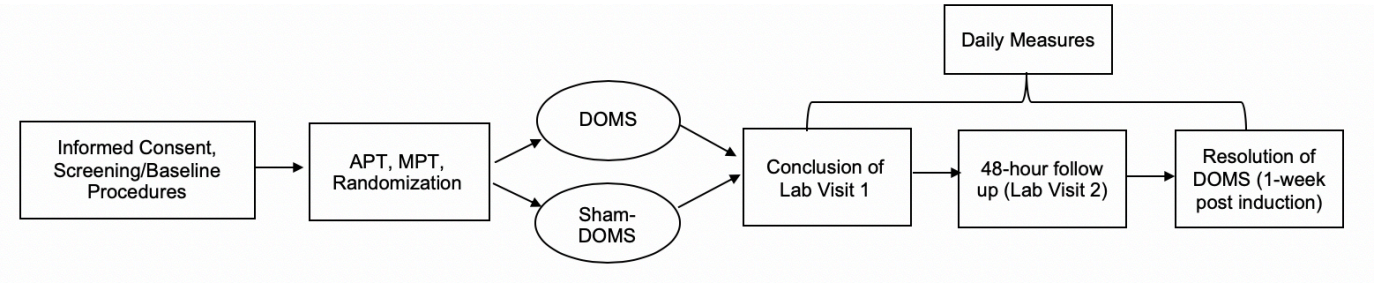

Figure 2. Study design flowchart.

Data Analysis Strategy

Data will be collected in a Research Electronic Data Capture (REDCap) database and analyzed using IBM SPSS 25.

Aim 1: Determine impact of DOMS pain on demand for alcohol and marijuana and examine race and sex as moderators of this relationship.
Hypotheses for DOMS-related changes in alcohol and marijuana demand indices (persistence and amplitutde) will be assessed using separate 2 (group: DOMS vs. sham DOMS) x 2 (sex: men vs. women) x 2 (race: White vs. Black) x 2 (time: visit 1 vs. visit 2) repeated measures analysis of variance (ANOVA). Identical ANOVAs will examine changes in marijuana demand indices.

Aim 2: Identify psychosocial factors associated with change in demand for alcohol and marijuana after DOMS induction.

To test the hypothesis that negative affect mediates the relationship between DOMS pain and increased alcohol and marijuana demand, Pearson correlations will be conducted to examine continuous relationships between measures of pain, pain-related negative affect (e.g. pain experience VASs), and change in alcohol and marijuana demand. A series of linear regressions will then be conducted to examine 1) the effect of group (DOMS vs. sham DOMS) on change in alcohol and marijuana demand, and 2) the effect of group and pain-related negative affect on change in alcohol and marijuana demand. We will test the significance of indirect effects of pain-related negative affect using PROCESS, a custom macro in SPSS.

To examine the hypothesis that greater expectancy of analgesia from marijuana or alcohol use, higher negative urgency, and history of self-medication behaviors will predict greater change in demand, a simultaneous multiple linear regression analysis will be conducted with these variables as predictors in the model.

Power Analysis

Effect size estimates for this study were derived from an interim analysis of data from an ongoing pilot project that examined the effect of DOMS on alcohol demand (N=40). In our pilot work, alcohol demand was assessed using the Alcohol Purchase Task (APT) before and after DOMS induction. Amplitude and persistence were derived from APT data using principal components analysis,[83-84] and these factors explained approximately 89% of the variance in alcohol demand metrics. Changes in amplitude and persistence were examined using separate 2 (group: sham vs. DOMS) x 2 (time: time 1 vs. time 2) x 2 (sex: men vs. women) repeated measures ANOVAs. Results indicated sex x group x time interactions for both factors, such that DOMS tended to increase amplitude in men and decrease amplitude in women, $F(1,36)=3.13$, $p=.09$, partial eta squared=.08. A similar pattern of effects was found for persistence where DOMS decreased persistence in women and increased persistence in men, $F(1, 36) = 14.55$, $p=.001$, partial eta squared=.29. With power analyses conducted in G*Power ($\alpha=.05$, power=.80, correlation between repeated measures=0.5), we expect that a proposed sample size of 56 participants will be sufficient to achieve the objectives of the proposed research and have adequate sensitivity to detect medium between-group and interactive effects for which we do not have preliminary data.

7. Possible Discomforts and Risks:

Psychological Discomforts and Risks. Participants may be reminded of unpleasant emotions or experience negative thoughts or bodily sensations while reporting aspects of their current psychosocial functioning or medical history. To mitigate this risk, all participants will be informed they can withdraw from the study at any time or skip individual questions that may be upsetting to them.

Induction of Muscle Pain using Exercise: There is a low risk that exertional rhabdomyolysis (breakdown of muscle tissue due to damage) and myoglobinuria (a large amount of muscle proteins in the urine) may occur following eccentric exercise. However, research suggests that this occurs primarily if a person had not consumed enough fluids before multiple muscle groups are exercised eccentrically.[87-88] We will address this risk by instructing participants to remain well-hydrated 24 hours prior to DOMS induction.

Participant Confidentiality Risks. The research team places a high priority on protection of participant confidentiality and will do so using the following procedures. Unique participant identifiers will be generated in order to collect protected health information (i.e., from questionnaires) for research purposes. All data will be stored in encrypted, password-protected files on a secure server, and access to the data will be restricted to research staff. The devices used to collect self-report data will be double-encrypted: the devices and REDCap software used to collect and store the information will be both password-protected and stored in a locked room. Data that links the participant to their unique identifiers will be stored in a separate location. When the study is completed and all data is in an electronic database, participant identifiers will be destroyed. Any

adverse events will be reported to the University of Florida IRB and study sponsors as appropriate. Despite these procedures, it is possible that participant confidentiality may be breached. If a breach occurs, it will be reported to 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.

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.

10. Data Safety Monitoring Plan: Because the study does not comprise a clinical trial, a formal Data and Safety Monitoring Board has not been planned. The investigative team will meet quarterly to discuss data and safety monitoring issues. Any issues identified during the course of these meetings will be handled in a manner consistent with the University of Florida's policies.

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