Understanding and targeting stress reactivity in women Veterans with alcohol misuse

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PI: Cathryn Holzhauer
Protocol Title: Stress, Emotion Regulation, and Alcohol in Women Veterans

1. **Principal Investigator:** Cathryn Holzhauer, Ph.D.

2. **Purpose:**

Women are the fastest growing segment of Veterans Health Administration users[1], expected to comprise 15% of the U.S. Veteran population by 2035[3]. The rate of alcohol misuse among women Veterans is also increasing [4], with lifetime Alcohol Use Disorder (AUD) at 27%, equal to rates for male Veterans[5]. Furthermore, posttraumatic stress disorder (PTSD) is common among women Veterans with alcohol misuse, with co-occurrence rates up to 62%[6]. Daily stress and acute stressors, including their physiological effects, are causally related to women's problem drinking [7-10]. Stress and negative emotion commonly act as triggers for drinking[11] and disrupt cognitive processes that are necessary for behavioral control[12]. Inhibitory control is one such cognitive process that reflects a person's ability to suppress ongoing or planned behavioral processes[13]. Stress-induced deficits in inhibitory control may prevent successful coping with alcohol triggers and cravings.

A previous study conducted by our lab targeted stress-induced craving and deficits in inhibitory control among women Veterans with alcohol misuse. Results show that use of an emotion regulation skill (cognitive reappraisal, CR) in the laboratory down-regulates not only stress, but also stress-induced alcohol craving. Additionally, use of CR proximally improves women's inhibitory control, particularly among women with more severe PTSD. This latter finding points to important person-level variability in the effects of CR on inhibitory control, suggesting that there may be key moderators, such as PTSD, that impact the efficacy of CR. The current study is a logical next step in this program of research and will build on that previous study by: (1) adding a physiological outcome measure of stress (Heart Rate Variability, HRV), in addition to the subjective (craving) and cognitive (inhibitory control) measures; (2) testing whether these laboratory findings extend to "real world" drinking behavior via daily longitudinal data collection; and (3) examining PTSD severity and hormonal context as moderators of CR's effects on inhibitory control, craving, HRV, and drinking. Research has shown that serum levels of the ovarian hormone progesterone, and its metabolite allopregnanolone (ALLO), are associated with lower stress reactivity[14, 15], less alcohol craving and use[16, 17], and better ability to regulate emotion[18]. Women with PTSD, however, exhibit a deficit in the conversion of progesterone to ALLO[15, 19]. This research suggests that women with low progesterone levels, within the context of menstrual cycle phase or co-occurring PTSD, may be particularly prone to higher stress reactivity and stress-induced drinking and may benefit from using effective emotion regulation skills.

Each woman (*n*=80) will be randomized to one of two conditions: a control condition (*n*=40) or a condition in which participants learn to use CR to regulate stress (*n*=40). Of the total 80 participants, up to 20 non-Veteran/Civilian women will be recruited for participation. Women in the CR condition will be asked to practice and use this skill over a 35-day period (to encompass an entire menstrual cycle) and will complete daily logs of alcohol use and stress. Each participant will come in for two experimental sessions, scheduled at the time of her peak and lowest progesterone levels, during which participants in the CR condition will use that skill in response to a personalized stress induction. Throughout these sessions, the effect of CR on the following variables will be assessed: (1) alcohol craving, (2) inhibitory control, and (3) HRV. These three variables, and (4) drinking during the 35-day period, will be the main study outcome variables.

Aim 1: Compare the effects of an emotion regulation skill (Cognitive Reappraisal, CR) to a control group (quiet sitting) on outcome variables. *Hypothesis 1a:* After a stress induction, use of CR in the laboratory will lead to greater improvement in alcohol craving, inhibitory control, and HRV,

compared to the control group. *Hypothesis 1b:* Women in the CR group will have significantly less stress-induced drinking over the 35-day assessment period compared to the control group.

Aim 2: Examine whether PTSD severity and progesterone levels moderate the effect of CR on alcohol craving and use, inhibitory control, and HRV. *Hypothesis 2a:* PTSD will moderate the association between condition and outcome measures, such that women with more severe PTSD will benefit more from CR. *Hypothesis 2b:* Progesterone will moderate the association between condition and laboratory outcome measures, such that women will benefit more from CR when progesterone levels are lowest. *Hypothesis 2c (Exploratory*): Explore the association between the two moderators, progesterone levels and PTSD severity, and their relative association with stress-induced drinking.

3. Background

Emotion dysregulation and daily stress are causally related to women's alcohol use: Chronic stress and acute trauma create a more influential pathway to substance misuse among women compared to men[25, 26]. For instance, among individuals with alcohol misuse, women are more likely than men to experience cravings in response to daily negative emotion and stress (e.g., arguments with loved ones) [7, 27-29]. This association between stress and drinking may be exacerbated among individuals with co-occurring alcohol misuse and PTSD. For example, in a sample of Veterans and civilians with PTSD and AUD, drinking to cope with negative emotion was associated with alcohol use for women but not men[30].

Emotion regulation is a general term that refers to the way in which an individual influences what emotions (including stress) she experiences, when emotions are experienced, or how emotions are expressed [29]. Drinking to cope with stress and negative emotion is common among individuals who tend to use maladaptive emotion regulation strategies, a tendency referred to as *emotion dysregulation*[29]. In other words, high emotion dysregulation may account for a person's – and particularly women Veterans' – tendency toward stress-induced drinking[31]. This idea has empirical support: among Veterans in residential substance use disorder (SUD) treatment, high emotion dysregulation (specifically: lack of access to emotion regulation skills, poor impulse control when distressed, and poor emotional awareness) was found to mediate (or explain) the relation between negative emotion and urges to engage in risky behaviors, including substance misuse[32].

Use of Cognitive Reappraisal (CR), an effective emotion regulation skill, may mitigate stress-induced drinking and improve behavioral control among women: While findings on stress and women's alcohol use have been widely research and established[33], the translation of these findings to treatment for women has been limited. Emotion regulation skills directly target stress and negative emotion states and are more often inherent in treatment of emotional disorders such as anxiety, depression, or borderline personality disorder[34]. Traditional alcohol treatments have generally viewed stress as a contextual factor that may increase the likelihood of a drinking episode or a relapse[11]. Thus, patients are often taught how to avoid drinking in response to stress/negative emotion[11], with less focus on teaching skills for directly mitigating the stress itself. Directly targeting stress and negative emotion may be a particularly important addition to alcohol treatment for women, to help them to avoid stress-induced drinking. Improved stress and emotion regulation as an endpoint in AUD treatment is slowly gaining traction[35, 36] as a valuable personalized medicine approach. This study will examine if, how, and for whom the strategy of directly targeting stress and emotion dysregulation works; specifically, if it reduces craving, arousal, and drinking, and improves inhibitory control, within a sample of women with alcohol misuse and varying levels of PTSD.

Cognitive Reappraisal of emotion (CR), the skill to be tested in this proposed study, is an *antecedent*-focused emotion regulation skill[40], which means that CR can be used *before* a behavioral response to a stressful stimulus is fully activated. Alternatively, a *response*-focused emotion regulation skill (e.g., distracting oneself, using relaxation skills) is an attempt at regulating emotion *after* the emotion is already underway[40]. This distinction is important, as use of antecedent-focused emotion regulation has been shown to more effectively decrease negative emotion states (including at the physiological level), more effectively reduce behavioral expression of emotion (e.g., fighting, yelling, drinking), and is less often taught in alcohol treatment compared to response-focused emotion regulation efforts[41]. There is little experimental research which manipulates use of effective emotion regulation skills in order to understand the utility of teaching these skills in treating alcohol misuse, and none among women Veterans.

The proposed study will assess the effect of CR on alcohol craving, cognitive (inhibitory) control, physiological arousal (HRV), and drinking*:* Stress and strong emotion are associated with alcohol use and other impulsive behaviors via their subjective, cognitive, and physiological effects, yet there is considerable discrepancy between these three measures[42]. For instance, an individual may not report feeling stressed in response to a stimulus, however physiological measures indicate a stress reaction. Furthermore, behavior – such as attending to alcohol-related stimuli - is often initiated before conscious, aware deliberation; measures of physiological arousal are an indicator of pre-conscious reactivity to stimuli, particularly to stressors in our environment[42]. Thus, physiological measures are important indicators of emotion and craving states, as they reflect automatic processes or reactions to a stimulus (e.g. a stressor) that can drive behavior and affect cognitive control[42, 43].

As discussed above, emotion regulation skills can be used to reduce stress, and this stress reduction may then improve cognitive control and decrease stress-induced alcohol use. The experimental portion of the proposed study would examine the acute, immediate impact of an effective emotion regulation skill (CR) on subjective, cognitive, and physiological outcomes of stress/negative emotion. *Subjectively*, as described above, stress increases the likelihood of drinking by increasing alcohol craving, particularly among women[7, 28]. *Cognitively*, stress and strong emotion deplete inhibitory control[12], which may be another mechanism by which likelihood of alcohol misuse is increased under stressful conditions. Inhibitory control is one facet of impulsive behavior[44] that reflects the ability to suppress ongoing or planned cognitive or behavioral processes[13]. When an individual's inhibitory control is depleted (e.g., by stress), subsequent self-regulatory efforts (e.g., attempts to resist drinking) are more likely to fail[45]. *Physiologically,* stress decreases heart rate variability (HRV). HRV is an especially potent measure of factors that are automatic and occur outside our awareness, yet can impact our ability to respond effectively to situational demands[42, 43] – for example, a person's ability to cope with the situational demand of encountering an alcohol-related trigger (e.g., driving past a liquor store, being offered an alcoholic drink)[46]. HRV increases during successful use of emotion regulation skills[46, 47], and increased HRV and successful emotion regulation are both associated with increased blood flow in cerebral brain areas, which are important for behavioral control[43]. Thus, increased HRV may be an additional mechanism by which emotion regulation skills could decrease likelihood of stress-induced drinking. Indeed, resting HRV has been shown to associate with patients' severity of alcohol problems[48]. In sum, stress and strong negative emotion reduce HRV, deplete inhibitory control, and increase alcohol craving among individuals with alcohol misuse, all of which increase likelihood of impulsive, stress-induced alcohol use among women. The proposed study would examine whether patients' use of

cognitive reappraisal of negative emotion (CR) can acutely reverse these effects in the laboratory (Aim 1, Hypothesis 1a). We will also examine whether findings regarding the effect of CR on craving, inhibitory control, and HRV extend to actual drinking behavior over 35 days, given regular use and practice of those techniques (Aim 1, Hypothesis 1b).

PTSD and progesterone may moderate the effect of CR among women: Aim 2 of the proposed study will examine potential moderators of the impact of CR on our outcome variables (craving, inhibitory control, HRV, and drinking). Does CR work better or worse for some women, or based on contextual factors? This question is consistent with a contemporary theory of addiction, which conceptualizes alcohol use as a manifestation of self-regulation deficits (emotion dysregulation) which can be improved by intervention (use of emotion regulation skills), and are influenced by moderators or contextual factors which are specific to the patient[49]. In other words, while improved emotion regulation may be a mechanism leading to reduced alcohol use, the extent to which emotion regulation skills are used and whether they are effective depends on a number of dynamic, moderating factors. PTSD severity and progesterone levels are two such factors that impact women's stress reactivity[50, 51], emotion regulation[18, 52], and alcohol use[17, 53]. Attending to these two factors, given existing research and conceptual models suggesting their relevance described below, has important implications in personalizing treatment for women Veterans.

PTSD severity as a moderating factor of the effect of CR*:* The high co-occurrence between PTSD and alcohol misuse among women is notable, especially given research that shows worse substance use outcomes among treatment-seeking individuals with any co-occurring SUD and PTSD when compared to those with SUD alone[54, 55]. Women who have co-occurring alcohol misuse and PTSD may benefit from different interventions than women with alcohol misuse alone[56]. Emotion regulation skills may be one such therapeutic intervention that may work more or less well for women with alcohol misuse and PTSD[56]. Emotion dysregulation is a core component of PTSD, thought to give rise to a number of symptoms, and it can affect the symptomatology of multiple disorders[57] (i.e., can have "transdiagnostic" implications). Among individuals with SUD, those with co-occurring PTSD use more maladaptive emotion regulation strategies than those without PTSD[58], with ability to regulate emotion inversely associated with PTSD severity[59]. This role of emotion dysregulation in PTSD has also been found among Veterans specifically [52, 60]. Therefore, women Veterans with co-occurring PTSD and alcohol misuse might experience particular benefit from learning a new emotion regulation skill. In this way, PTSD severity may moderate the effect of CR on alcohol craving/use, inhibitory control, and physiological arousal (HRV). This would by signaled in the proposed study by a significant moderating effect of PTSD symptom severity on the impact of CR on the study's outcome variables (Aim 2, Hypothesis 2a).

Progesterone as a Moderating Factor: The ovarian hormone progesterone, and its metabolites, have been shown to be associated, in some cases causally, with women's stress reactivity[51], negative emotion[61], and emotion regulation[18]. Women's general stress reactivity (i.e., subjective feelings of stress, hypothalamic pituitary axis activity, and cortisol secretion in response to stressors) rises in the luteal (or post-ovulatory) phase of the menstrual cycle[62, 63], potentiated by fluctuating levels of progesterone. It is believed that low levels of progesterone, especially in the follicular and late luteal phase, may increase women's stress reactivity and decrease their well-being[64]. While the effect of progesterone on stress reactivity has been well researched, the extent to which this effect extends to behavior such as stress-induced alcohol use is less clear. However, it has been suggested that low levels of progesterone may increase the likelihood of use or relapse among women [28, 33, 65], and this may be the

case especially among women with co-occurring PTSD as they are prone to drinking to cope with stress/negative emotion[27, 66] and show irregularities in progesterone functioning[15, 19]. Alcohol craving and use fluctuate across the menstrual cycle[17, 67], as do coping motives for drinking[68] – specifically, craving, drinking, and coping motives appear to increase at times in the menstrual cycle when progesterone is low (i.e., the follicular or menstrual phase) or dropping (i.e., late luteal/premenstrual phase)[69, 70]. Additionally, research with women seeking treatment for AUD has found that negative affect and physical discomfort associated with fluctuating hormones across the menstrual cycle can act as a trigger for alcohol use[17]. Administration of exogenous progesterone during the early follicular phase (when endogenous progesterone levels are lowest) reduces substance cravings and use[71, 72] and reduces stress reactivity[14] among women with SUD. In a similar way, the effect of emotion regulation skills on alcohol craving and drinking – particularly stress-induced drinking – may be especially important during certain phases of the menstrual cycle (e.g., the follicular phase) when progesterone levels are low (Aim 2, Hypothesis 2b). Women may be at heightened risk of stress-induced drinking and relapse when their endogenous levels of progesterone are low.

4. Significance

Personalizing care: This study is consistent with the DVA 2018-2024 Strategic Plan, with regard to enhancing knowledge of at-risk groups of Veterans (women Veterans with mental health conditions) with Veteran-salient illnesses (PTSD and alcohol misuse) and advancing the fields of personalized medicine to improve effectiveness of treatment. A recent study found that 30% of VA Medical Centers provided female-segregated (e.g., non-mixed gender) substance treatment options[20], despite research showing that women, and especially women who have experienced trauma, often prefer female-segregated groups[38, 39]. Furthermore, research with civilian women has shown that such female-segregated treatments are most useful when female-specific programming is included[39]. Stress and emotion dysregulation are examples of antecedents to drinking that have greater relevance for women than men, as described above, and CR may be a specific relapse prevention strategy that therefore may be more relevant for women. Thus, the proposed study would provide much-needed empirical data to inform the development of personalized, female-specific treatment for women Veterans.

Understanding the role of progesterone in stress reactivity, emotion regulation, and alcohol use: Ultimately, interventions for alcohol misuse may be enhanced by indirectly or directly targeting fluctuations in, or low levels of, progesterone. For example, psychotherapy can help women develop coping skills to deal effectively with hormone fluctuations (e.g., by teaching them effective emotion regulation skills such as CR), and pharmacotherapy can consider the use of medications to regulate hormonal fluctuations (to the extent that such fluctuations impact stress reactivity, emotion regulation, and/or craving). Veterans may be at increased risk of stress-induced relapse, or may have more difficulty establishing abstinence from alcohol, during certain phases of their menstrual cycle. Similar findings have been made in the smoking literature[79].

Transdiagnostic implications: The proposed research will examine whether CR has its effects on several mechanisms (i.e., post-stressor craving, deficits in inhibitory control, and HRV/arousal). While we are measuring inhibitory control and HRV given their association with alcohol misuse, these are general measures related to self-regulation and therefore have transdiagnostic implications within this population (i.e., implications related to change across diagnostic conditions). For example, if CR improves inhibitory control and/or HRV after the stress induction, such a finding would suggest that using CR can reduce impulsivity and arousal more generally within this population – and perhaps more

or less effectively for women with co-occurring PTSD. Findings on the effect of CR on inhibitory control and HRV could have implications for improving other psychological symptoms[80] among women Veterans, such as anxiety or depression, or other impulsive behaviors such as suicidal behavior and non-suicidal self-injury[81]. Additionally, data on the moderating effect of progesterone on the impact of CR on physiological arousal and inhibitory control could have implications for women Veterans at certain life phases, e.g., for understanding and reducing impulsivity or anxiety among women post-partum[82]. Past research has linked suicidal behavior to low estradiol and progesterone levels among women[81].

5. Research Plan

Study methods and procedure. The proposed study will combine experimental, in-person sessions with daily self-report data from the women. Participation will take place across a period of at least 35 days, to encompass an entire menstrual cycle. All participants complete all sections of the study – the experimental sessions and the longitudinal (35-day) data collection. See Figure 3 for study flow and timing of sessions.

Participants will be recruited into one of two subgroups of 40 women (for *n*=80 total). **Subgroup 1** will comprise 40 women who meet restrictive inclusion/exclusion criteria ("strict criteria set") needed to examine Hypotheses 2b and 2c [excludes *(5) Peri- or postmenopausal; (6) Endocrine disorder; (7) Irregular menstrual cycle*]. Data from this "strict criteria set" of 40 participants will be used to examine hypotheses 2b and 2c, related to progesterone levels. Because there may be associations between progesterone and/or estradiol, stress reactivity, and alcohol use among non-normally cycling women, and because Study Aim 1 (Hypotheses 1a, 1b) and Hypothesis 2a do not require a sample of normally cycling women, **Subgroup 2** will comprise 40 women Veterans who may not meet the three, more restrictive, hormone-related exclusion criteria. All study procedures will be the same across subgroups, except that the timing of sessions may not be based on the participant's menstrual cycle if she does not have a menses. Additionally, they will not be asked questions about their menses, track ovulation, or provide information about their menstrual cycles, which is asked of participants in subgroup 1.

After establishing initial study eligibility over the phone, women will come in for **session 1 (intake session),** during which they will sign consent, complete baseline measures, and complete a clinical assessment [comprised of the Structured Clinical Interview for DSM-5 (SCID-5)] . At this time, participants in Subgroup 1 will also provide information about their past three menstrual cycles, which will be used to estimate their current menstrual phase and estimate the start date of their next cycle (as used in previous research[50]). Each participant will then be randomized to *start* the remaining study procedures in either the early Follicular Phase (eFP, when progesterone levels are lowest) or mid-Luteal Phase (mLP, when progesterone levels are highest), and the remaining sessions will be tentatively scheduled based on estimates of menstrual cycle phases (*note*: women will be urn randomized[92] to eFP or mLP based on use of hormonal contraception and severity of PTSD, AUD, and depression symptoms). Participants will begin the daily logs on either the 1st day of menses (if in eFP start group) or on the day of their luteinizing hormone (LH) surge (if in mLP start group). Participants who do not have regular menstrual cycles will be scheduled for session 1 and then will begin the 35-day period of completing daily logs any time after their initial session 1. During session 1, participants will also be educated on completing the electronic daily logs through REDCap and on using urine tests to estimate timing of LH surge (which indicates ovulation/start of luteal phase/when progesterone levels start to rise), and will schedule a regular day and time for weekly coaching/check in call.

COVID-19 accommodations for sessions 1, 2, and 5: Participants will be offered the option of completing sessions 1, 2, and 5 via telehealth/using VA Webex, if preferred. While sessions 3 and 4 of the study use biological assessments that require in-person attendance, these three sessions can feasibly be conducted virtually. Participants will be asked if they prefer virtual sessions (for 1,2, and 5) at the time of the phone screen, and the requirements to have virtual sessions (e.g., reliable internet connection in a private space, ability to download the Webex application, reliable mail service) will be explained at that time. All study procedures will occur remotely, with self-report questionnaires being completed by participant using remote control via the Webex application. See below for details regarding telehealth consent process. We expect this option will substantially reduce participant burden, will not deviate from typical VA telehealth care, and will allow participants with compromised health or increased responsibilities during this time (e.g., increased childcare responsibilities) the option of participating in this study. Any virtual sessions will follow guidelines that are used in routine VA telehealth care, including the following:

1. Communicating to the participant the importance of having private space to ensure their confidentiality during study sessions
2. Establishing an emergency contact, and the location/address of participant at the time of the study session
3. Using available elements of the video platform to ensure confidentiality (e.g., "locking" the virtual meeting room)

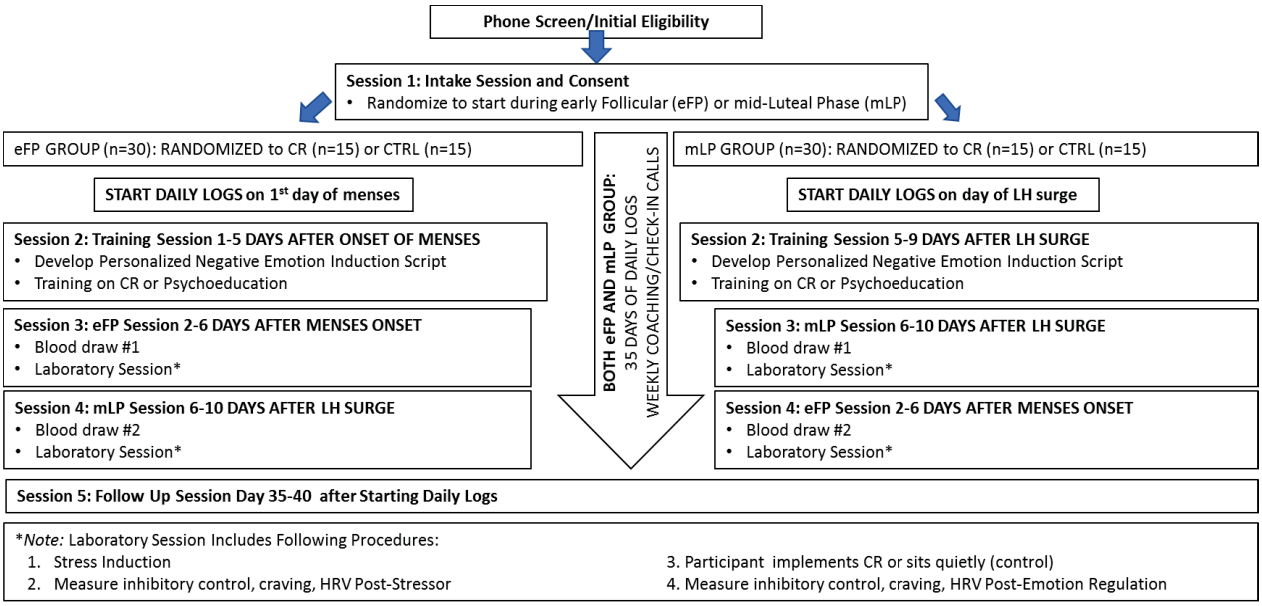

Figure 3. Methodology for Subgroup 1

eFP = early Follicular Phase; mLP = mid Luteal Phase; CR = Cognitive Reappraisal; CTRL= Control group; LH = luteinizing hormone (surge signals ovulation/start of luteal phase); HRV = heart rate variability

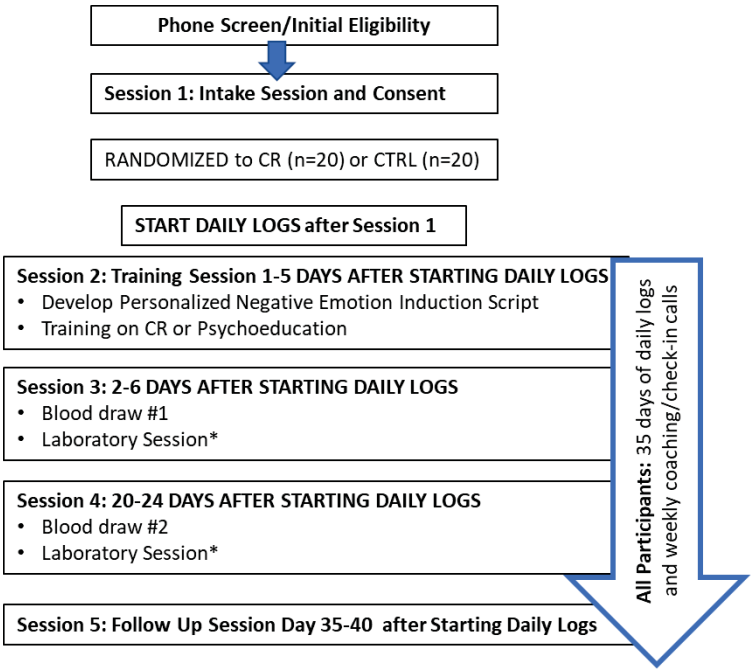

Figure 4. Methodology for Subgroup 2
Note: Laboratory Sessions follow same protocols as those outlined in Figure 3 for Subgroup 1

Details regarding consent process: Study staff will explain the project in detail, what the subjects should expect of the study, and what we do with their information. Study staff will also describe the purpose of the study to give subjects a broader scope of the researcher's intentions. It will be stressed to participants that their name will not be associated with any of the data that they provide for the study. The importance of the participant ID number is explained as well as the fact that their names/contact information will not be kept with the data.

Additionally, participants are informed that their participation is completely voluntary and that they can choose to withdraw from the study at any time. Also, if they choose not to answer a specific question, they have every right to refuse. The participants are encouraged to ask questions at multiple points during the consenting process. It is expected that all participants will speak English primarily. The consent form is written plainly to assist people with limited reading skills. Subjects also have the option of having the consent form read to them by a study team member or someone of their choosing.

The consent form will be reviewed with each participant and research staff providing information will check in at each section of the sheet to verbally ascertain whether the information was understood and to see if the participant has any questions. The participant will read the first paragraph of the informed consent form to verify their ability to read the consent form. The participant will be given time after review of the information sheet to read the form again and will again be asked if she has any questions. Any participants who are not cognitively capable of consenting will be excluded from the study, as outlined in the study's exclusion criteria.

After reviewing the consent form, study staff will explicitly reiterate that the participant may stop the study at any time, and it will not affect their usual care, and that they will be compensated for all portions of the study they complete.

Consent process for participants using virtual sessions: If, at the time of the phone screen, participants express a preference to have virtual sessions 1, 2, and 5, study staff will use Azure-

encrypted email or DocuSign to send them a study consent form and a HIPAA form. Study staff will also send participants an ovulation kit by mail. At virtual session 1, participants will be consented and sign HIPAA via DocuSign or Adobe PDF electronic signature and email the form back to the study staff. Alternatively, if they are unable to sign consent electronically, they may print the consent and HIPAA forms and provide a "wet" signature. Participants will be given three options on how to return the "wet" signed consent form and the HIPAA form: (1) take pictures of both forms with their phone and email the pictures to the study staff, (2) scan both forms and email them back to study staff, or (3) they will hold each signed page to the camera so that the study staff can take screenshots during session 1 . All electronically signed HIPAA and consent forms, scanned, or screenshots of the consent and HIPAA forms will be saved on the secure study drive. Since participants will be required to come in person for sessions 3 and 4, we will ask them to bring the signed forms to us in-person or return them by mail. However, in the case that a participant is lost to contact before session 3, we will have the documented consent via the picture taken.

On either first day of menses (eFP group) or day of LH surge (mLP group), in addition to starting daily logs, participants in Subgroup 1 will also be scheduled for **session 2 (training session).** Session 2 will be scheduled to occur within either 1-5 days after onset of menses (eFP group) or 5-9 days after the LH surge (mLP group) (see Figure 3). Those in Subgroup 2 will be scheduled for session 2 1-5 days after starting their daily logs. During session 2, participants will be engaged in the development of a personalized stress script[93], which asks them to describe the details of a recent, day-to-day stressful (but not traumatic) experience. This story is then developed into a six-minute script used in laboratory sessions 3 and 4 to induce stress. In session 2 participants also are again urn randomized (based on use of hormonal contraception, severity of PTSD, depression and AUD) to one of the two conditions – to receive the 50-minute cognitive reappraisal (CR condition) microintervention or psychoeducation on women's health (control condition) with a study therapist.

After session 2, **during the 35-day longitudinal period**, participants in the CR condition are instructed to use CR when experiencing stress or negative emotion until at least the end of their 35-day period (which started when she began her daily logs). Daily logs will be completed via REDCap, where two surveys per day will be sent via text message (using participants' phone number). Five homework assignments will be provided for participants to use for practice over the remaining weeks, and the day/time of the weekly coaching sessions will be confirmed. During the weekly coaching/check-in, the therapist will ask about daily log completion, answer questions, and – after the training session in which the microintervention is delivered – will provide coaching regarding use of CR (if not in control group). The methods used for the longitudinal period (e.g., coaching/check-in calls, participant compensation) are based on similar work by Dr. Simpson, study consultant[94]. The timing of the remaining laboratory sessions – 3 and 4 – will be scheduled based on each woman's onset of menses (in eFP group) or day of LH surge (in mLP).

The personalized negative emotion script[73] asks participants to tell the details of a recent, day-to-day stressful (but not too stressful) experience. This story told by the participants is then developed by study staff into a six-minute script that is used in sessions 3 and 4. This script development procedure has been used in several studies in the past, and Dr. Holzhauer received training on this manualized script development procedure from Dr. Rajita Sinha at the Yale Stress Center. (See below for details on reducing potential risk associated with the negative emotion induction procedure).

All **sessions 3 and 4 (experimental sessions)** will follow similar protocol: (1) participants will provide a blood sample to assay ovarian hormone levels (progesterone and estradiol); (2) baseline

salivary cortisol, progesterone, and estradiol; (3) resting baseline period; (4) 2nd baseline cortisol; (5) undergo the negative emotion/stress induction (listening to the personalized script that was developed in training session 2); (6) assess outcome variables (inhibitory control, alcohol craving, cortisol) in stressed state; (7) Implementation/use of CR, or sit quietly for a matched period of time (if in control group); (8) assess outcome variables post-CR use. HRV will be measured throughout the sessions. Sessions 3 and 4 will be conducted by study staff, who will have minimal, scripted interaction and study-related conversation with the participant. To control for diurnal hormonal fluctuations and physiological spikes, laboratory sessions 3-4 will be scheduled between 12:00pm and 4:30pm; participants will be asked to abstain from nicotine and caffeine for 1 and 4 hours prior to session, respectively, and to abstain from eating 2-3 hours before visits.

Within 5 days of the end of the 35-day period, women will be asked to return for **session 5 (follow-up session)** in which they will turn in remaining daily logs, complete the Alcohol Timeline Follow-Back (TLFB), complete end of study self-reports, and receive a full study de-briefing. Although women will be tracking whether or not they consumed alcohol on the daily surveys, the TLFB will be used at all laboratory sessions to fill in any potentially missing data and ask for details regarding number of drinks; this is a technique used in our team's past research to maximize data collection.

All sessions will be audio recorded and labeled only with the study ID number. These recordings will be kept on the VA network and will be accessible by study staff only. The audio recordings will be used by study staff for training and rating the integrity of microintervention delivery and clinical interviews in session 1.

Recruitment: Research participants will be recruited from clinics at VACWM (Central Western Massachusetts) at the Leeds campus, and the Springfield and Worcester Outpatient Clinics as well as the clinics at VA Bedford Healthcare System and VACHS at the West Haven campus. We will also recruit women Veterans from community programs in the Central Western Massachusetts region that specialize in care and services to Veterans. Dr. Holzhauer or study staff will meet with health providers and clinic managers and provide information about this research project. Study Staff will provide them with a study flyer. Participants will be recruited using the following procedures:

1) health providers from above-mentioned clinics and programs give their patients who may qualify a handout with study and ask the patients to contact the research team directly or if the patient would like the team to contact them (in which case the veteran's information will be conveyed to the research team who will then call the veteran for a phone screen), and 2) Flyers posted in the above-mentioned clinics and community programs. In addition to the clinical and community-based service settings, study staff will hang flyers in general community gathering spaces in CWM. 3) A study website which has basic study information and a place to contact study staff to request further information or an eligibility screen (seraresearchgroup.com). 4) Study staff will also use medical record reviews to identify potentially eligible participants (i.e., women Veterans with AUDIT-C scores of 3 or higher). Upon identifying a woman who may be eligible, we will extend an invitation to participate in our study by sending her a generic letter in the mail. The letter will be sufficiently generic so that if someone other than the intended recipient was to read the letter (e.g., a family member), there would be no

information that would convey information about the Veteran's health. In cases where 3 letters have been sent with no reply, the same message will be sent via email using the email address listed in the recipient's medical chart. Once participants contact us to indicate their interest in participating, we will conduct an eligibility screen either over the phone (or in person, if she preferred). Once initial eligibility is established, we will schedule session one. 4) Study participants will be eligible to refer up to two other women to us. If their referral completes our phone screen the referring woman will receive $15 in gift cards, regardless of whether or not the referred individual is found to be eligible for the study.

Up to 20 non-Veteran (Civilian) women will also be recruited from the community, via flyers in community settings (e.g., transportation hubs, coffee shops, local Universities/Colleges, hospitals).

All 80 women who participate in the proposed CDA-2 study will be assessed for eligibility based on the following:

Inclusion Criteria: (1) Age 18 and older; (2) Current alcohol misuse, defined as scoring 3 or higher on the AUDIT-C; (3) If using other illicit substances, alcohol is their primary substance of use; (4) Alcohol use in the past 45 days; (5) Able to write and speak in English; (7) Willing to provide blood samples at laboratory sessions to assay hormone levels and take urine ovulation tests at home. All inclusion criteria will be established via participant self-report during the phone screen and confirmed at session 1. All inclusion criteria are the same for women in Subgroups 1 and 2.

Exclusion Criteria: (1) Psychotic symptoms or uncontrolled Bipolar Disorder (screened for during session 1 using SCID-5 screening modules); (2) Brain damage or were in an accident that affects ability to complete the computerized task; (3) Current (past 3 months) active suicidal ideation or intent;(4) Current pregnancy; (5) Currently receiving treatment for alcohol use; Subjects will *not* be asked to discontinue clinically indicated medications to qualify for the study. Exclusion criteria 1-5 apply to participants in Subgroups 1 and 2.

Subgroup 1 has four additional exclusion criteria: (7) Peri- or postmenopausal; (8) Endocrine disorder; (9) Irregular menstrual cycle (i.e., cycle length outside of 25 to 35 days, recurrent history of missed periods, or vaginal bleeding between periods); (10) Use of benzodiazepines and opiates (unless very infrequent use or use for a discrete medical event such as dental work) and medications known to influence the neuroactive steroids of interest (progesterone & estradiol), including hormonal contraceptives; (11) Made a medication change in the past 2 months. All women will be screened for these criteria during the phone screen; those who meet exclusion criteria 7-11 in addition to those above will be included in the study as participants in Subgroup 1.

All exclusion criteria will be established via participant self-report during the phone screen and confirmed during the clinical screen via interview at session 1. Medical records will also be reviewed prior to session 1, with participant's verbal consent.

Participant Compensation. Participants will be compensated for all steps of the study, consistent with previous research[94], to encourage completion of all sessions and daily logs. Participants will receive

gift cards for participating in sessions 1-5 ($25 for sessions 1, 2, and 5, and $30 for in-person/experimental sessions 3 and 4). Additionally, they will receive $4 per day/ $2 for each of the two surveys for each of the 35 days they complete a daily log (for a total possible of $140) and a $25 "bonus" for completing all laboratory sessions. Thus, total compensation for completing all elements of the study is $300. Additionally, if a participant must drive 20 miles or more to get to the Leeds, Springfield, or Worcester Campus for sessions three and four, we will compensate them in the form of gas gift cards based on gas mileage up to 150 miles (75 miles one way) total. We will pay in increments of $5 at a rate of $0.13 per mile, based on the average price of gas and gas mileage. This compensation is applicable to participants driving a personal automobile to sessions.

Measures

Clinical Intake Interviews. Master's or doctoral-level study staff will administer the Structured Clinical Interview for DSM-5 (SCID-5) to assess clinical diagnoses at session 1.

Measures of Dependent Variables. The *Alcohol Craving Questionnaire*[96] will be used to assess alcohol craving, and the *Alcohol Timeline Follow Back*[97] (TLFB) will assess frequency/quantity of drinking over the 45 days prior to study enrollment, and during the study period as described above. *Daily Logs* will be sent to participant's mobile phones, via REDCap, for every morning and mid-day (10:00am and 2:00pm) for 35 days. Participants will complete the daily logs electronically each of the 35 days during the longitudinal period. The 35-day period will begin on the first day of a participant's menstrual cycle (if in the eFP group) or on the day of ovulation (if in the mLP group) in Subgroup 1, and any day after Session 1 for Subgroup 2. The morning survey will track: any alcohol use for the previous day, frequency and intensity of alcohol cravings, ovulation status, and stress level over the past 24 hours. The mid-day survey will track momentary stress level and contain the 10 item *Positive Affect/ Negative Affect Scale (PANAS)* to track emotions. To encourage completion of the daily logs, participants will be compensated $4 for each day of logs completed.

Inhibitory Control, our main outcome measure which is a measure of behavioral impulsivity[44] (see conceptual model, Figure 1), will be assessed with a computerized task (a stop-signal task, *STOP-IT*[98]). The STOP-IT presents a horizontal block arrow and requires participants to hit a button on the keyboard corresponding to the arrow's direction. On 25% of trials, the arrow suddenly turns blue, representing a "stop" signal that is presented at varying times. When this stop signal is presented, participants must withhold their learned response of pressing the key in response to arrows. Participants' stop signal reaction time (SSRT) reflects varying levels of inhibitory control (lower SSRT reflects better inhibitory control) [98]. Heart rate variability (HRV), our main outcome measure which is a physiological measure of arousal and shown to be a measure of stress reactivity [43] and impacted by successful emotion regulation [46, 47](see conceptual model, Figure 1), will be assessed with a Biopac MP160 data acquisition unit with an ECG amplifier that allows for the measurement of HRV. Biopac software *AcqKnowledge* assists with analysis and calculation of HRV.

Salivary Cortisol, *Progesterone, and Estradiol* will be collected via passive drool and kept in a -20º freezer. This assessment procedure is minimally invasive. Participants will be given instructions in passive drool collection, and be directed to use disinfectant wipes to wipe down the outside of the tubes, place the tubes in a small clear specimen bag. Study staff will send the specimens using shipping materials and directions provided by Salimetrics. Analysis of all three hormone levels will be conducted at Salimetrics, LLC (https://salimetrics.com), an FDA-Registered company that provides salivary bioscience testing. Salimetrics provides all saliva collection materials and provides analyses of hormone levels. All analyses will be completed without identifying information, with samples labeled only with a bar code that corresponds to our own tracking of participant ID number and date/time of sample collection.

Measures for Randomization and Moderating Factors: Depression and PTSD symptom severity will be assessed via *Beck Depression Inventory*[101] and the PTSD Checklist for DSM-5 with Life Events checklist and Criterion A (*PCL-5*)[102], respectively. The Adverse Childhood Experiences (ACE) Questionnaire will provide information pertinent to PTSD diagnosis and provide important descriptive information about the sample[123]. Addition of VA's MST (military sexual trauma) screening questions will serve the same purpose – to provide a comprehensive overview of participants' trauma exposure, and to investigate whether MST is associated with outcomes. Severity of AUD will be measured with the *Alcohol Use Disorder Identification Test (AUDIT[103])*, of which the first three questions represent the *AUDIT-C* which is used for study inclusion. The SCID PTSD, AUD, and Depression modules will also provide clinical interview data on the diagnostics and severity of these conditions. The other moderator, progesterone level, will be assessed via VA laboratory blood sample. Participants will provide a blood sample at the VACWM laboratory, where samples will be taken by trained phlebotomists. The samples are refrigerated and sent to a nearby outside lab (Quest Diagnostics, Florence MA) for analysis. To help estimate menstrual cycle phase, participants will also take at-home daily urine tests which indicate the LH (luteinizing hormone) surge indicative of ovulation (i.e., transition to luteal phase of cycle) and will record the results on the daily log; lastly, participants will indicate on the logs if they have their menses each day.

Baseline Measures/Assessing Independent Variables: Use of CR skills at baseline and during the study will be measured by the *Emotion Regulation Questionnaire[104]*.

Cognitive Reappraisal (CR) Microintervention and Control Group (Behavioral Intervention): The CR microintervention (session 1) is drawn from Dr. David Barlow's empirically supported treatment for emotional disorders (the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders[70]). The microintervention lasts 45-60 minutes and consist of four sections: (1) Introduction to cognitive appraisal; (2) Introducing the idea of "thinking traps" that prevent reappraisal and maintain negative emotion; (3) Describing CR as a strategy that can help the participant "get out" of such thinking traps; (4) Providing an example of this process (situation→ negative appraisal→ negative emotion→ thinking trap→ opportunity for CR) and have participants provide a personalized example.

The manualized psychoeducational control microintervention, serving as an attentional control, is derived from two sources: 1. The first session of the Women's Health Education Manual[71], which provides psychoeducation about the basic body systems and their function, with focus on components of the immune system and 2. Fact sheets published by the American College of Obstetricians and Gynecologists(ACOG)[72], providing female-specific facts about cancer and heart health. None of this psychoeducation discusses potential relevancy of alcohol use, nor will any behavior changes be suggested during the control microintervention. This psychoeducational microintervention also lasts 45-60 minutes and provides the participant with information about women's health.

Debriefing/minimizing risk associated with emotion induction during experimental session (3 & 4): Dr. Holzhauer was trained by Dr. Rajita Sinha at the Yale Stress Center, who developed the Imagery Script Development emotion induction technique that will be used in this study (Sinha & Tuit, 2012). Dr. Holzhauer was trained on the emotion induction procedures, including debriefing procedures for participants after the inducement of negative emotion and/or craving states. Dr. Sinha has used these procedures in multiple studies, including individuals with substance use disorders, co-occurring mental health conditions, and including PTSD. This methodology has also been used by other research groups with Veteran populations at the VA Connecticut Healthcare System[74] – using both stress (negative emotion) and trauma scripts. The manualized procedure uses specific methodological strategies to minimize the risk for extreme discomfort. One strategy is that, when developing the personalized negative emotion script, participants are asked to provide an example that is stressful but not overly stressful. Participants are asked to use a negative emotion situation that is "highly stressful, but day-to-day events that are fairly common in today's world". Any potentially traumatic experiences (i.e., experiences that are not experienced on a regular, day-to-day basis) are not allowed. Examples of not allowable events include any assault, interpersonal violence, serious car accident, military trauma, etc. If a participant begins to describe a potentially traumatic situation (again, defined as any situation that is not a typical, day-to-day experience), the manual indicates that the researcher should stop the participant and re-state the goal of the procedure – to describe an event that is day-to-day and fairly common in today's world, and re-directs the participant to think of a situation that is less intense. This minimizes the likelihood that a participant would become overwhelmed with discomfort. A second strategy outlined in the manualized procedure is the debriefing that is conducted at the end of the session, to ensure that the participant feels comfortable proceeding with their day and is not in emotional distress. This strategy involves giving the participant 10 minutes, with instructions to relax and focus on deep breathing. After this time has passed, we will re-administer the PANAS (see attached self-reports) and compare to their baseline state to assess whether the participant has returned to a baseline emotional state. In addition, the researcher will ask the participant about their emotional state, and provide the option of additional relaxation/debriefing. If the participant is still feeling distressed or would like the additional relaxation, we will use the relaxation training from Sinha & Tuit's manual (see attached), which will be recorded and walk the participant through progressive muscle relaxation (PMR).

As suggested, these debriefing strategies have been used in previous studies from Dr. Sinha's lab that evoke emotion or craving states. Extensive research using the emotion induction methodology that

will be used in this study[73] has used these same techniques for debriefing among participants with substance use disorders[75] after a stress/negative emotion induction. Additionally, our previous study with 38 women Veterans has been using this induction technique without any clinical issues arising. Neither Dr. Sinha nor our own study have reported significant clinical issues resulting from the emotion/craving induction across their various studies. We would also like to note that half of the participants (i.e., those in the experimental condition) will receive an emotion regulation strategy microintervention (i.e., CR) that is known to down-regulate distress and discomfort at both sessions. In the case that a participant has gone through the full debriefing procedure and is still reporting distress (via PANAS and/or self-report), or in the event that a participant reports any suicidal intent during her participation in the study, Dr. Holzhauer will take the following steps to ensure participant safety: 1. Contact Dr. Holzhauer to notify the study PI of the situation; 2. Walk the participant to the Walk-in Mental Health Clinic; 3. In the case this Clinic is unavailable, Dr. Holzhauer will contact Dr. Henry Rivera, the Program Manager for Outpatient Mental Health for clinical consultation. In the case of a health care emergency, participants will be walked to the Urgent Care Clinic for evaluation.

Power Analysis. See Table 1 for the effect sizes and required sample sizes, for all hypotheses. Note that the full sample (*n*=80, including participants from Subgroup 1 and 2) will be evaluable for Hypotheses 1a, 1b, and 2a. Data from participants in Subgroup 1 (*n*=40) will be used to examined hypotheses 2b and 2c.

Hypothesis 1a. Past studies which have examined the effects of CR on participants' cognitive control (specifically, attentional bias, which is highly associated with inhibitory control)[113], cigarette craving[107], and physiological reactivity (specifically, electromyography and skin conductance)[74], to a control group, are used to guide the study's power analysis. While these effect sizes ranged between .09 and .51, the high correlation between repeated measures and use of multiple measurements (2 groups tested across 3 measurement time points) provided estimated required samples between 4 and 12 participants, to have sufficient power to answer Hypothesis 1a.

Hypothesis 1b: This hypothesis examines the effects of CR and EA on drinking behavior over the course of 35 days. Table 1 shows effect sizes from a previous study[94] by study consultant Dr. Simpson, which informed the proposed study's methodology; the effect sizes shown in Table 1 reflect the effect of CR on percent days abstinent during a longitudinal period.

Hypothesis 2a. While there is no research to guide our power analyses about the moderating effect of PTSD symptom severity on the efficacy of CR and EA, data from my VISN 1 pilot project provided estimated effect sizes of the interaction/moderation term (condition – CR/control – by PTSD symptom severity on craving and inhibitory control). Again, while these effect sizes were small, the high correlation between repeated measures and use of multiple measurements provided estimated required samples between 36 and 48 participants.

Hypothesis 2b: A previous study[114] examined inhibitory control (stop signal reaction time/SSRT on the stop signal task, the same outcome as in the proposed study) across the follicular, luteal, and menstrual phases, finding longer SSRT or poorer inhibitory control in the follicular phase compared to the other phases. Hypothesis 2b focuses on the moderating effect of progesterone on CR, comparing reactivity in two phases of the menstrual cycle (eFP and mLP). The estimated effect size, shown in Table 1, yielded a required sample of 10 women to obtain sufficient power. An additional study[115] examined reactivity to stress and cigarette cues across the menstrual cycle among women; although estimated effect sizes were not provided, their total sample size was 37.

Hypothesis 2c. There is a lack of research that examines the association between progesterone levels and PTSD symptom severity, and their relative association with any of our outcome variables. Therefore, this hypothesis is exploratory and will provide data for future power analyses.

Table 1. Power Table, by Aim & Hypothesis

Aim & Cited Study Providing Effect Size for each outcome measure	*Estimated Effect Size*	*Required n power=.80*
Aim 1		
1a. Main Effect of Condition on:		
Inhibitory Control[113]	η^2_p =.11	12
Craving[107]	η^2_p =.09	8
HRV[74]	η^2_p =.51	4
1b. Main effect of condition on longitudinal alcohol use[94]	*d* = .78	10
Aim 2		
2a. Interaction Effect of Condition * PTSD on:		
Inhibitory Control (VISN 1 CDA Pilot Data)	η^2_p =.025	48
Craving (VISN 1 CDA Pilot Data)	η^2_p =.017	36
2b. Inhibitory Control in mLP v. eFP[114]	η^2_p = .19	10

Note: η^2_p = Partial eta squared; d = Cohen's d; Condition = Cognitive Reappraisal versus Control Group Effects; mLP = mid-luteal phase; eFP = early follicular phase

In sum, as can be seen in Table 1, the largest required sample size would be to examine the moderating effect of PTSD symptom severity on the effect of the emotion regulation strategies on inhibitory control (Hypothesis 2a). The required sample sizes for this hypothesis were generated with alpha at .05, two groups and three time points, for a repeated measures ANOVA testing within (time) x between (condition) interaction, and the estimated effect size of the interaction term on the inhibitory control/SSRT outcome measure. The analysis indicated the **required total sample size was 48**, providing actual power of 0.80. Study consultant Dr. Pineles completed a study with similar methods[19], with women across the menstrual cycle; of the 62 women who consented to the study, 51 completed study procedures (completion rate = 82%). **We will consent 80 women**, across Subgroups 1 and 2, to account for attrition or other difficulties related to the study procedures. 40 women will provide sufficient power to examine Hypotheses 2b and explore 2c.

Data Collection, Storage, and Security

Each participant will be assigned a subject number upon entry into the study, and all measures/records will be tracked using only this number. Most data (with the exception of inhibitory control task/STOP-IT performance, HRV/physiology measures, and REDCap Daily Log Surveys) will be collected via hard copy and will be promptly entered into a Microsoft excel electronic database. Data from the inhibitory control task, as well as data collected from the BIOPAC physiology monitor, will be temporarily stored on the PI's laptop computer, which has been approved and secured by the VA, as the task records results directly onto the hard drive of the computer. This data that is temporarily stored on the hard drive is NOT identified by any personally identifiable information, however, and only by participant study ID number. At the end of the day, this data from the inhibitory control task and

physiological data will be transferred to the Research drive with the rest of the data and compiled into a Microsoft Excel electronic database. The data from this task is via computer, so the original data form is electronic. Progesterone and Estradiol levels collected by the VACWM laboratory will be entered into the patients' medical records as clinical data. The hormone level values will be entered into the data spreadsheet on the VA network by study staff after looking them up in medical records.

Cardiac activity is collected from a BIOPAC EKG monitor and BIOPAC's software, Acqknowledge, is used to generate Heart Rate Variability (HRV) values. The cardiac data that is collected is identified only by a study ID number, with no identifying information (e.g. no participant age, name, initials, date of birth, etc.) "attached" or indicated. The cardiac data is fully deidentified by the assignation of a separate HRV ID number. The HRV ID and study ID number will be paired only in a database that is password protected. The output data file from BIOPAC is an EKG waveform datafile, which is then used by software to generate output values such as HRV. These de-identified data files will be analyzed by a non-VA collaborator, Dr. Nnamdi Pole, at Smith College (Northampton, MA). Dr. Pole is a Professor of Psychology and IRB committee Chair there in 2022-2023. He is an expert in trauma and psychophysiological response to stress. He is collaborating with our VA team to clean, analyze, and publish physiological data from the current study. The files sent to him for analysis, again, are completely de-identified. Furthermore, the files will be saved on private USB drives and can only be viewed in combination with the BIOPAC-provided USB "key". Dr. Pole's lab will use the BIOPAC USB key and de-identified EKG files to clean and analyze data, generate output variables, and return to our lab. The data will then be uploaded to the VA network and entered into our master database.

In order to confidentially send the daily questionnaires to participants' phones, we will use the secure REDCap account of our academic affiliate, University of Massachusetts Medical School, to collect data. The participant's cell phone number will be entered into REDCap in order to send them the links to the surveys, however the actual surveys will not collect any identifying information. Additionally, when the database of collected data is generated, their cell phone numbers will not be included – therefore, that identifying information of their phone number will not be associated with their data (which is all numerical anyway; i.e., meaningless to anyone who does not have the survey questions and survey response labels). Participants will be assigned a separate ID number for their REDCap data, that will be merged later, within the VA network, to their other non REDCap data. No other personally identifying information will be collected via REDCap. Mobile devices will be used by participants to self-report on urge to drink, mood, and stress level. If participants lose their smartphone, they will be at no excess risk of their identity or highly sensitive information being revealed to individuals outside of the study. (In other words, because they are not completing hard-copy surveys and only completing surveys through a survey link, their answers to survey questions are only accessible to the study team with access to REDCap). Also, mobile surveys will use a multiple-choice format and participants will not be asked to enter any responses as free text. This eliminates the participant's ability to enter any responses that could be used to identify them. For example, participants will be asked to respond to how much they are craving from 0 – not at all to 7- extremely and data will be recorded only as a numerical response.

Personal identifiers (name & phone number) will be obtained at study screening, however this information will be kept in a separate electronic folder from the participants' other information (e.g.,

their self-report measures/clinical interviews) which will only be identified by their participant number. All electronic data will be kept on the secure VA research network (\\R04NHMNAS21.v01.med.va.gov\Research\Other PI Projects\Holzhauer\). The hard copy data (identified by participant number only) will be kept in locked drawers which will be in locked, secure offices within Building 12, Room 112 at the Northampton VA. Hard-copy consent and HIPAA forms with participant signatures (and without study ID number) will also be kept in the team's offices in locked drawers, separate from the de-identified study data which will be labeled only with study ID number. A suspected or confirmed loss of VA information will immediately be reported via email to the Study Investigators, Privacy Officer, Information System Security Officer, IRB and the VACWM research office.

A copy of all research records will be retained at VACWM research department according to VA policies and procedures. Research data will be destroyed 6 years after the end of the FY in which the study is completed as required by VHA regulations and RCS-10-1.

In order to reduce travel burden on participants that live further away from our main site on the Leeds or Worcester VACWM campus, we will provide the option for participants who choose to complete sessions in-person to complete their study sessions at one additional VACWM CBOCs (Springfield). This is offered as an alternative to at-home or virtual sessions. The study staff who run the session will transport session data (i.e., hard copy self-reports and interviews) that participants complete back to Northampton so it can be stored with all the other study data in the research study office. Forms that are collected and transported will only have a participant study identification number on them, with the exception of the study consent form and HIPAA for session 1 (which will not have their study ID on them). Thus, documents with sensitive personal information will only be labeled with a study ID number and no participant personally identifiable information such as name or personal address. An inventory of the documents will be made before the transport is initiated. The consent and HIPAA forms will be transported in a bank bag in the trunk of a locked vehicle. The documents will be kept with the staff at all times during transport from Worcester to Leeds and immediately placed in locked cabinets after transport.

Data analyses by hypothesis

We will first conduct descriptive analyses and examine the distributions of all outcome variables, to identify any non-normal variables or other issues related to distribution. Numeric transformations will be performed on continuous variables to symmetrize distributions as needed. Missing data will also be identified and accounted for (see below).

Hypothesis 1a. Effect of Cognitive Reappraisal (CR) versus control (psychoeducation) on alcohol craving, inhibitory control, and HRV in experimental sessions: Repeated Measures ANOVA will be conducted to examine the effect of CR versus control on these outcomes. Given that women will be urn randomized into either the CR or control condition, we do not anticipate significant differences between groups in terms of alcohol use, AUD severity, or PTSD severity (or other relevant variables). However, we will test for equivalence between groups on baseline measures prior to analyses and control for any

differences that may be found. The RM ANOVA will test the between-person main effects of condition (CR v. control) and within-person change in our outcome variables which are continuous variables (craving, inhibitory control, and HRV) across the three study time points (baseline, after the stressor, and after using CR or sitting quietly) during the lab session. For these analyses, we will use laboratory data from the eFP/Session 1 session, controlling for randomization to "start group" (eFP v. mLP start group). If a condition by time effect is found, post-hoc tests will be conducted to examine the time period(s) at which significant differences occur.

Hypothesis 1b. Effect of CR versus control on daily alcohol use: This hypothesis will be tested using mixed effects or multilevel modeling (MLM) to examine within-person effects, between-person effects, and interactions of within- and between-person effects on stress-induced alcohol use across the 35-day daily log portion of the study. These effects will be assessed according to the following MLM equations:

- Within-person effects (Level 1):

$Drinking_{ij} = \beta_0 + \beta_1 * stress$

- Between-person effects (Level 2):

$\beta_0 = \gamma_{00} + \gamma_{01} * CR_j + u_0$

$\beta_1 = \gamma_{10} + \gamma_{11} * CR_j + u_1$

In these multi-level equations, within-person effects of stress on drinking are modeled at level 1 across the 35 days. At level 2, between-person differences in daily drinking are modeled in the β_0 equation, where u_0 represents variability in daily drinking, γ_{00} represents daily drinking for the control group, and γ_{01} represents the difference in daily drinking for the CR group. The β_1 equation tests the association between stress and drinking. Here, u_1 models the variability in the stress-drinking association across participants, γ_{10} represents the strength of this association for the control group, and γ_{11} represents the difference in this association for the intervention (CR) group. Our hypothesis is that the CR microintervention group will have a significantly lower stress-drinking association than the control group.

Drinking will be operationalized in two ways: (1) the above model will be tested using a binary outcome reflecting drinking vs. not drinking on each day, using a binomial (Bernoulli) distribution MLM; (2) drinking will also be modeled as a count outcome, using a negative binomial or Poisson MLM, depending on the distributional properties found in drinks per day variable and testing for potential over-dispersion.

Hypothesis 2a. PTSD will moderate the association between condition and outcome measures: The moderating effect of PTSD on the effect of CR will be examined using experimental session data as well as longitudinal drinking data. To examine whether PTSD moderates the effect of CR on alcohol craving, inhibitory control, and/or HRV in the lab, we will conduct the RM ANOVA as described for Hypothesis 1a; however, we will enter a dichotomized PTSD variable as a third factor, and an interaction term of condition (CR/control) by PTSD to examine the moderating effect. Similarly, PTSD severity will be entered as an additional, Level 2 between-person main effect in the MLM equation described in Hypothesis 1b, along with the interaction of PTSD and treatment condition.

Hypothesis 2b. Progesterone will moderate the association between condition and outcome measures: Whether progesterone levels moderate the effect of CR on alcohol craving, inhibitory control, and HRV in the experimental sessions will be assessed, given that hormone assays will occur at the time of these in-person sessions. Progesterone level will be added to the RM ANOVA models described in Hypothesis 1a, and the interaction of progesterone level (low/high) and condition (CR/Control) will be tested to determine whether CR more effectively regulates stress-modulated craving, inhibitory control, and/or HRV when progesterone levels are low.

Hypothesis 2c (Exploratory). Explore the association between the two moderators, progesterone levels and PTSD severity, and their relative association with stress-induced drinking: Given that this hypothesis is exploratory, we will first use simple statistical analyses to examine the correlation between PTSD severity and progesterone levels during the eFP and mLP of the menstrual cycle. We will additionally conduct regression analyses to compare the relative strength of statistical prediction of each of these two variables, entered within the same regression equations, on the change in craving, inhibitory control, and HRV in response to stress in the lab. These analyses will provide initial data on whether PTSD severity and progesterone levels are associated, and the extent to which they may have separate or interactive effects on alcohol-related outcomes and behavioral control.

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