Effects of Progesterone and Alcohol on Impulsivity and Abuse Liability in Female Moderate Drinkers

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Abstract

The level of drinking in women is increasing steadily and past research has shown that alcohol increases impulsive behaviors in men, as well as women. Further, it has been suggested that elevated progesterone levels in the luteal phase of the menstrual cycle attenuate the positive subjective effects of stimulants and some behavioral measures of impulsivity. The purpose of this study was to determine if oral micronized progesterone alters the behavioral effects of alcohol, including measures of impulsivity and abuse liability, in “at risk” female drinkers (>7 drinks/week). 10 normally cycling women were tested in an outpatient setting for 2 blocks of testing sessions (total of 8 sessions) during the follicular phase over 2 consecutive menstrual cycles. Each testing block consisted of pretreatment with 300 mg of oral micronized progesterone or placebo, and administration of one of 3 doses of alcohol (0, 0.5, 0.75 g/kg), with the order of progesterone treatment counterbalanced across participants and alcohol dose order randomized within each block. Throughout each session, participants completed a range of tasks that assessed measures of impulsivity and risk-taking, abuse liability, cognitive performance, and mood. Alcohol produced a significant dose-dependent increase in Take Again and Drug Liking ratings and the peak crossover point in the Multiple Choice Procedure. However, there were no significant effects of alcohol dose, hormone pretreatment, or interaction effects across all impulsivity and risk-taking tasks. While these results are contrary to our original hypotheses, this was most likely related to inadequate power to detect effects. Regardless, they pave the way for extended research on the modulatory role of progesterone on impulsivity and abuse liability in female moderate drinkers.
Background

Previous research has supported the finding that alcohol misuse is widespread and is linked with health-related risks, including liver damage, brain disease, heart disease, and cancer (National Institute on Alcohol Abuse and Alcoholism (NIAAA; 2015). In addition, despite lower levels of alcohol use, women tend to ‘telescope’ or progress to problematic alcohol use and have greater and sooner adverse psychiatric and medical consequences than men (Piazza et al., 1989; Ross, 1989). Among the heaviest drinkers, female alcoholics have death rates 50 to 100 percent higher than those of male alcoholics, including death from alcohol-related accidents, suicides, heart disease, and liver cirrhosis (NIAAA, 2015). Further, a recent study suggests that heavy and binge drinking prevalence of all alcohol use measures, tended to increase more dramatically for women than men. As growing epidemiological data suggests that the level of drinking is increasing in women, the upsurge in alcohol consumption is concerning as it may further increase alcohol misuse and dependence in women (Dwyer-Lindgren et al., 2014). Despite this, there is little alcohol-related research in the field that evaluates the behavioral effects of alcohol exclusively in moderate to heavy drinking women, in a rigorously controlled setting.

One such factor that has been linked with the initiation and continuation of drug and alcohol use is impulsivity (Potenza & Wit, 2010). Impulsivity has been operationally defined as a “predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or others” (Potenza, 2007). Impulsivity is a complex and multifaceted behavioral construct, commonly consisting of at least two dimensions (Meda et al., 2009; Reynolds et al., 2006; Verdejo-Garcia, Lawrence, & Clark, 2008): choice impulsivity, as measured by temporal discounting, and response impulsivity, as measured by poor performance on tasks involving motor inhibition.
Given the complicated nature of impulsivity, researchers aim to understand how various facets of impulsivity fluctuate in response to alcohol and drug use.

Past clinical research suggests that alcohol impacts behavioral and self-reported measures of impulsivity differentially. For example, self-reported impulsivity was greater in heavy drinkers than controls (MacKillop et al., 2007; Reed, Levin, & Evans, 2012) and greater alcohol and cigarette use was correlated with higher self-report of impulsivity (Grano et al., 2004; Henges & Marczinski, 2012). In addition, past studies have demonstrated that alcohol administration increases behavioral measures of impulsivity on rapid-decision and continuous performance tasks in social drinkers (Dougherty et al., 2008; Henges & Marczinski, 2012). Further, impulsive responding on the Immediate and Delayed Memory Task and the Delayed Discounting Task was shown to be exacerbated by alcohol drinking among female heavy drinkers, but not consistently on the GoStop or Balloon Analogue Risk Taking Task (Reed, Levin, & Evans, 2012). Thus, these findings support the notion that a complex interaction exists between alcohol and impulsivity. In conjunction with previous studies, these data also suggest that impulsivity is not a unitary construct.

Moreover, prevailing clinical data suggests that healthy men and women differ on measures of impulsive behaviors, although results are largely mixed and vary as a function of task administered. For example, women and girls exhibit worse inhibition on stop signal tasks, which measure the time required to inhibit a response (Colzato et al., 2010; Morgan, Gray, & Snowden, 2011). Contrastingly, men demonstrate poorer inhibition on GoStop Tasks, which measure response inhibition failures (Hasson & Fine, 2012; Liu, Xiao, & Shi, 2013; Saunders et al., 2008). In addition, some studies have shown that during hypothetical or chance delayed discounting tasks, women discount more than men in procedures that use a die (Reynolds et al.,
2006; Smith & Hantula, 2008), whereas other studies have found that men discount more than women in procedures that use a lottery (Doi & Shinohara, 2015; Kirby & Marakovic, 1996). Overall, while sex differences exist, the direction of the differences varies across the multiple domains of impulsivity.

In addition, a few studies in the field have addressed the sex differences in impulsive behaviors across heavy drinkers. Initial data suggests that heavy, binge drinking women display greater inhibitory deficits on both stop signal and go/no-go tasks, in comparison to heavy drinking men and light drinkers (Nederkoorn et al., 2009; Townshend & Duka, 2005; Weafer, De Arcangelis, & de Wit, 2015). In addition, Bobova et al. (2009) showed that heavy drinking men discounted a hypothetical money reward more than heavy drinking women, although this sex difference was not limited to heavy drinkers. While existing evidence suggests that poor inhibitory control could be a risk factor specific to heavy drinking women, more research must be conducted to understand how other facets of impulsivity vary with alcohol use across male and female users. Further, the majority of studies that have indicated the trends between alcohol use and impulsivity have been conducted in men or mixed-gender samples, with a wide range of drinking patterns.

Even though there is no approved effective pharmacological treatment for stimulant misuse, preclinical and human studies show that progesterone may alter the reinforcing effects of stimulants, specifically in females (Anker, Holtz, & Carroll, 2013; Evans & Foltin, 2006; Fox et al., 2013). For instance, animal studies have shown that responses to stimulants can be affected by sex differences, with female rodents being more sensitive than male rodents to the behavioral effects of stimulants (Roberts et al., 1989; Sell et al., 2000). Further, these sex-differences are related to fluctuating gonadal hormone levels in females (Lynch, Roth, & Carroll, 2002). In a
normally cycling female rat, estradiol levels are stable and progesterone are minimal during the estrus phase of the estrous cycle, while both hormones peak during proestrus. Many studies have suggested that the largest increase in locomotive and stereotypic behavioral response is observed when stimulants are administered to female rodents in the estrus phase (Diaz-Veliz et al., 1994; Quinones-Jenab et al., 1999; Sell et al., 2000); for example, rats demonstrate higher progressive ratio breakpoints for cocaine self-administration (Hecht et al., 1999; Roberts et al., 1989) and select the highest cocaine dose (Lynch, Arizzi, & Carroll; 2000). In addition, allopregnanolone, a metabolite of progesterone, decreased cocaine-primed reinstatement behavior exclusively in female rats (Anker et al., 2009; Anker & Carroll, 2010).

While conflicting data in preclinical literature suggests that the differential response to stimulants observed in male and female rodents may be a result of fluctuating estrogen levels, increasing evidence in laboratory animals also points to progesterone’s role in attenuating the effects of stimulants. For example, in Quinones-Jenab et al (2000), ovariectomized female rats pretreated with estrogen and progesterone exhibited a decrease in cocaine-induced locomotion in comparison to female rats pretreated with estrogen alone. Similarly, ovariectomized female rats pretreated with estradiol and progesterone, exhibited a decrease in cocaine-administration, while estradiol treatment this behavior, in females and not in males (Jackson, Robinson, Becker, 2006).

In addition, existing clinical research suggests that progesterone may alter the subjective response to other drugs of abuse, like cocaine, in women. For example, stress-induced and drug-induced cocaine craving were lower in women who had higher progesterone levels (Sinha et al., 2007). Further, research in women suggests that the positive subjective effects of stimulants, like cocaine, decreased during the luteal phase, and this may be a result of elevated progesterone levels (Evans & Foltin, 2006). Also, the administration of oral micronized progesterone
attenuated the subjective effects of cocaine (Evans & Foltin, 2006) in women during the follicular phase of the menstrual cycle. Although oral progesterone has been shown to attenuate subjective effects related to stress in men (Childs et al., 2010) and the cocaine-induced high in a mixed gender sample (Sofuoglu, Mitchell, Kosten, 2004), oral progesterone did not attenuate positive subjective effects of cocaine in men (Evans & Foltin, 2006) and did not lower cocaine use in men in a pilot treatment trial (Sofuoglu et al., 2007). These results demonstrate that fluctuations in endogenous progesterone levels may account for the sex differences between males and females, in response to stimulants.

In addition, past research has postulated that progesterone may serve to decrease the behavioral effects of impulsivity and abuse liability. For instance, in rats, progesterone decreased marble burying, a measure of impulsivity (Llaneza & Frye, 2009) and cocaine self-administration, a measure of abuse liability (Larson et al., 2007). Furthermore, progesterone, when co-administered with estradiol, in ovariectomized females, attenuated cocaine-seeking behavior, in comparison to ovariectomized rats that received only the estradiol pretreatment (Anker et al., 2007). In humans, oral doses of progesterone decreased in impulsivity, as measured by the Delayed Memory Task, in non-drug using females (Reed, Levin, & Evans, 2010). Furthermore, progesterone pretreatment, relative to placebo, attenuated drug liking ratings and enhanced suppression of smoking urges, when participants received intravenous doses of nicotine (Sofuoglu, Mitchell, & Mooney, 2009). While clinical studies indicate that progesterone attenuates stimulant-induced behaviors, we are unaware of any studies that directly investigate the effects of progesterone on impulsivity in moderate to heavy drinking women.

Therefore, the present study was designed to determine if progesterone would alter the behavioral effects, including abuse liability ratings and measures of impulsivity, of alcohol in “at
risk” female drinkers, without potential confounds of other risk factors (e.g. history of trauma, disease). Abuse liability was measured primarily through self-report questionnaires (the Drug Effect Questionnaire (DEQ), Biphasic Alcohol Effects Scale (BAES), and the Multiple Choice Procedure). The DEQ asked participants to rate “good effects,” “bad effects,” “strength of drug effect,” and “willingness to take the drug again.” In addition, the BAES was used to derive subscales measuring stimulant and sedative effects of alcohol. Lastly, the Multiple Choice Procedure assessed the reinforcing effects of alcohol, as participants made a series of discrete choices between drug dose administered and various amounts of money. We used the following self-report and behavioral tasks to measure impulsivity and risk-taking: Barratt Impulsiveness Scale (BIS), Immediate Memory Task/Delayed Memory Task (IMT/DMT), GoStop Task, Delayed Discounting Task (DDT) and Balloon Analogue Risk-Taking Task (BART). The BIS is a self-report questionnaire that computes scores on the attentional, motor, and non-planning facets of impulsivity. The following are computerized and written tasks that measure the behavioral impulsivity: IMT/DMT measures response initiation, the GoStop Task tracks response inhibition, the DDT quantifies temporal delayed gratification, and the BART assesses the level of potential risk-taking. In order to assess the effects of oral micronized progesterone without the confound of elevated progesterone levels during the luteal phase of the menstrual cycle, sessions were conducted during the follicular phase (days 3-10 after the onset of menstruation), when progesterone levels are minimal.

It was hypothesized that alcohol would produce dose-dependent increase measures of abuse liability and impulsivity, while progesterone would attenuate these effects.
Method

Participants

Research subjects were recruited through a Craig’s List advertisement and referrals. All potential participants were required to undergo a screening process prior to enrollment, which included a telephone interview, 2-3 in-person screenings, a physical examination, a meeting with a clinical interviewer, and an interview with the chief investigator of the study. In the initial telephone interview, participants were told that the purpose of the study was to determine the effects of progesterone and alcohol on mood, vital signs, and performance. In addition, all participants provided written informed consent before beginning the study and were paid $800-$1,200 upon completion the study.

Women between the ages of 21-35 years were enrolled. All women met the 2009 NIAAA guidelines for moderate to heavy (“at risk”) female drinkers, of consuming at least 7 drinks per week but no more than 20 drinks per week. According to the NIAAA, one standard drink includes 14 grams of alcohol, which is found in 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of hard liquor.

In addition, all women were medically and psychiatrically healthy. Study physicians led a physical examination to assess medical history, vital signs, heart rhythms, clinical blood chemistries, and current medication (prescription and over the counter) use. In addition, participants had a structured clinical interview (SCID; First et al., 1995) conducted by a clinical interviewer, with a Master’s degree. The purpose of this interview was to rule out participants who met the criteria for current DSM-IV-TR (Diagnostic & Statistical Manual of Mental Disorders, fourth edition, text revision) Axis I psychiatric disorders (American Psychiatric Association, 2000) and psychoactive substance abuse or dependence (including alcohol and
stimulants), excluding nicotine; specific phobias (e.g., spiders) were not exclusionary. The Early Trauma Inventory (Bremner, Vermetten, & Mazure, 2000) was used to rule out any women suffering from a major history of trauma. All of the women were normally cycling, using a non-hormonal effective method of birth control, and were not pregnant, as confirmed by a urine blood test that was performed during screening and experimental sessions.

Women who were cigarette smokers or smoked marijuana occasionally were not excluded.

**Experimental Design**

Women participated in 8 outpatient laboratory sessions at the New York State Psychiatric Institute (Table 1). In order to assess the effects of oral micronized progesterone without the confound of elevated progesterone levels during the luteal phase of the menstrual cycle, all sessions occurred during the follicular phase (days 3-10 after the onset of menstruation), when progesterone levels are minimal. Though the follicular phase occurs days 1-14 after the onset of menstruation, the project time frame was restricted to 3-10 days for two reasons. First, previous data suggest that the initial days of the follicular phase are characterized by mood changes and uncomfortable physical symptoms. Further, on days 11-13 both estrogen and progesterone levels are increasing at a rapid rate. Estrogen levels effectively peak at the onset of ovulation (days 13-14), which is followed by a progesterone surge, seen in the luteal phase.

Sessions 1-4 and sessions 5-8 were scheduled during the follicular phases of 2 different menstrual cycles. In the first session, women were administered four placebo progesterone pills and a placebo beverage. The purpose of this session was to expose the participants to the mixed drink, hormone pretreatment capsules, and various computerized tasks and questionnaires that they would complete during the study. Data from this session were not used in final data
analyses. The testing phase included a total of 6 sessions (sessions 2-7). The order of assessing effects of alcohol and progesterone were counterbalanced, such that half of the women were pretreated with the placebo progesterone treatment first and the other half were pretreated with the 300 mg progesterone dose first. In addition, women received 1 of possible 3 doses of alcohol (placebo, 0.5, 0.75 g/kg) on each session. Alcohol dose was also randomized per phase. On each session, participants completed the Multiple Choice Procedure, a proxy for measuring abuse liability. In order to ensure reliable responding, a result from the Multiple Choice Procedure was implemented on the last session (session 8).

**Standard Experimental Session**

Table 2 depicts the standard experimental session timeline for sessions 1-8. As depicted in Table 2, upon arrival to the research center, each participant consumed a standard breakfast before drug administration. The same breakfast was provided on all of the following sessions because the bioavailability of micronized progesterone is enhanced twofold in the presence of food (Simon et al., 1993). In order to examine women in their normal state, caffeine consumers were permitted to consume a caffeinated beverage of their choice with the breakfast. In addition, cigarette smokers were allowed to take a smoke break briefly after their arrival and approximately 30 minutes prior to alcohol and hormone pretreatment administration. Further, they were not permitted to smoke 30 minutes before or during each assessment battery. These adjustments were made to the experimental design to counter the impact caffeine or nicotine withdrawal may have on mood or performance during the study.

Both prior to reporting to the laboratory and the evening of each experimental session, women were instructed to not drink alcoholic beverages or consume any medications. Thus, in the morning, each participant was also screened with a breathalyzer to monitor alcohol use and a
urine drug test to evaluate drug use. If a participant’s urine was positive for any drug other than marijuana (marijuana metabolites like tetrahydrocannabinol (THC) can remain in the body for many weeks) or the participant was intoxicated as indicated by the breath alcohol levels, the participant was sent home and the session was rescheduled. Prior to alcohol and progesterone administration, research assistants interviewed participants on any recent medication use, medical illnesses, and alcohol use since the last laboratory visit.

Women were required to complete a battery assessment at -40 minutes and then at multiple time points after alcohol and progesterone administration. The battery included a range of tasks that assessed measures of abuse liability, behavioral impulsivity, and mood. In addition, vital signs were measured prior to drug administration and multiple time points post drug administration. To ensure that women were tested in the follicular phase of their menstrual cycle, a blood test was conducted post progesterone dosing to measure hormone levels. This blood test was conducted two hours post progesterone administration because oral micronized progesterone peaks at this time point (de Lignieres, 1999). Results from the assay revealed whether or not participants were administered a placebo or progesterone treatment and what phase of the menstrual cycle they completed the session in. Further, urine pregnancy tests were performed weekly, to ensure that all women participating in the study were not pregnant. Exactly 3.5 hours after progesterone and alcohol dosing, participants were provided lunch that they selected from a menu. If the participants experienced adverse side effects that directly interfered with they study, a M.D. was called in immediately to assess the situation. If the participant was sent home, her session was either rescheduled or she was removed from the study protocol, depending on the circumstance.
At the end of each session, participants were only allowed to leave the laboratory after passing a field sobriety test and breath alcohol levels were \( \leq 0.02 \text{ mg/dl} \) (in accordance with NIAAA guidelines). However, if the participants were still impaired as indicated by increased vital signs, breath alcohol levels, or continued side effects, they were required to remain in the laboratory until the drug effect subsided. Further, at the end of each session, participants were not allowed to drive a car for the remainder of the day; instead, they were provided round-trip subway or taxi fare to go home.

During the study, participants were also required to complete Daily Rating Forms (DRFs; Evans et al., 1998) each evening. The responses of these questionnaires were used to prospectively track alcohol and drug use, the onset of menstruation, menstrual cycle length, and fluctuations in mood.

**Alcohol & Progesterone Dosing**

Since alcohol and progesterone treatments were administered in a significantly different way (capsule vs beverage), a double-dummy technique was implemented. During each session, participants orally ingested 4 capsules along with a beverage, assigned for their dosing sequence, within 5 minutes, under the direct supervision of a senior NYSPI staff member (Ph.D., M.D., or R.N.). Both staff and participants were blind to study medication.

Participants drank an alcohol beverage containing 0, 0.5, or 0.75 g/kg alcohol each session; alcohol content for each beverage was calculated based on the estimated body water of each participant (Evans & Levin, 2011; Watson et al., 1980). The highest dose of alcohol (0.75 g/kg) was enough to give a maximal breath alcohol concentration to reach the legal limit of intoxication: 0.08 mg/dl. This is approximately equivalent to having 3–4 standard drinks. All beverages were prepared similarly, with their volume held constant at 350 ml at no more than a
20 calorie difference. Drinks were prepared in a 3:1 tonic water and cranberry juice cocktail ratio. The alcohol beverage was built on the same mixture and supplemented with 100 proof Absolute vodka. In order to conceal the difference between the placebo and alcohol beverage, all drinks were topped with 1 ml of vodka and 1 drop of bitter tasting peppermint oil.

300 mg of oral micronized progesterone was selected as the appropriate progesterone dose because it most accurately approximates the levels of progesterone seen in the normal luteal phase. For example, in a previous study that administered 300 mg/day micronized progesterone, mean progesterone levels were 8.2 ng/ml in the follicular phase in comparison to the 7.4 ng/ml produced naturally in the normal luteal phase (Evans & Foltin, 2006). The vehicle treatment was composed of olive oil and was prepared in a capsule identical to the packaging of the active progesterone treatment. The Women’s International Pharmacy (Madison, WI) provided 75 mg capsules of micronized progesterone and the matching placebo hormone pretreatment.

**Outcome Measures**

**Impulsivity.** One impulsivity self-report questionnaire, the Barratt Impulsiveness Scale, version 11 (BIS-11), was implemented during the screening process to measure baseline impulsivity. The BIS-11 is a 30-question survey that measures trait-related impulsivity. Each item on the questionnaire is rated on a 4-point Likert scale (rarely/never = 1, occasionally = 2, often = 3, almost always/always = 4) to generate a composite score ranging from 30 to 120. The instrument also generates subscale scores from the questionnaire that assess the motor, attentional, and non-planning aspects of impulsivity (Patton, Stanford, & Barratt, 1995).

During the experimental sessions, four tasks were administered to assess the behavioral measures of impulsivity: Immediate Memory Task/Delayed Memory Task (IMT/DMT), GoStop Task, Delayed Discounting Task (DDT), and Balloon Analogue Risk-Taking Task (BART).
Immediate and Delayed Memory Task. The IMT/DMT is a modified continuous performance task that assesses response initiation in impulsive behavior (Dougherty and Marsh, 2003; Dougherty et al., 2002, 2003a). The IMT/DMT were presented in one 5-minute block of the IMT that preceded a one 5-minute block of the DMT, with a 30 second resting period between the blocks. Both the IMT and DMT include randomly generated 5-digit numbers (e.g. 23765) displayed on a computer screen in black text on a white background. In the IMT, each 5-digit number (target stimulus) appeared successively on the screen for 500 ms, followed by a 500 ms inter-trial blank screen. Participants were required to click when the two identical target stimuli are presented in succession. In comparison, the DMT incorporated a distracter stimulus (e.g. 12345) that appeared 3 consecutive times between two target stimuli. Participants were instructed to ignore the distracter stimuli and only respond when the target stimuli spanning the distracter stimuli were identical. Responses to non-identical target stimuli were recorded as a commission error, if the number differed from the target by 1 digit, or a filler error, if the number differed from the the target by more than 1 digit. The primary dependent measure for each task was the ratio of commission errors to correct detections (Doughtery et al., 2002, 2008). The IMT/DMT was completed at baseline and 1, 2, and 4 hours post drug administration in each session.

GoStop Task. The GoStop Task was used to measure response inhibition or the ability to withhold initiated response when a stop cue is present (Dougherty et al., 2003b, 2005). In the GoStop Task, 5-digit numbers appear in rapid succession for 500 ms every 2 seconds (500 ms on, 1500 ms off). Matching numbers were presented on the “Go Trials” in black font for 500 ms. On the “Stop” trials, the 5-digit numbers change from black to red text during the following delays: 50, 150, 250, or 350 ms after target stimulus onset. Participants were instructed to
respond when two identical target stimuli are presented in series during the “Go” trials. The primary dependent measure was the 150 ms GoStop ratio, which detects the proportion of response inhibition failures at the 150 ms delay relative to the number of go responses, with higher ratios corresponding to greater response inhibition impulsivity (Dougherty et al., 2008). A 150 ms delay was analyzed because this time point provides the most representative distinction between high and impulsivity individuals (Marsh et al., 2002). The GoStop task was completed at baseline and 1, 2, and 4 hours post drug administration.

Delayed Discounting Task. The DDT is a paper-pencil questionnaire that assesses choice behaviors (Kirby & Marakovic, 1996; Kirby, Petry, & Bickel, 1999). Participants completed a 27 fixed-choice survey that asks participants to choose between an immediate smaller reward or delayed larger hypothetical reward (e.g. “Would you prefer $55 today or $75 in 61 days?). Amounts of money ranged from small ($25 to $35), medium ($50 to $60), and large ($75 to $85) and temporal delays ranged from 7 days to 6 months (Petry, Kirby, & Kranzler, 2002). The primary dependent measure was the k value, which determines the discount rate based on the hyperbolic discounting function, which takes into account the indifference value, fixed delayed reward, and length of delay (Mazur, 1987). Higher average k values indicate that rewards are being discounted more steeply; consequently, the participant is making a more impulsive choice as an immediate, smaller reward is valued over a higher, delayed reward. In order to promote conscientious responding, women were informed that on the last session, they would be given a 1 in 6 chance of receiving one of the rewards they chose on a particular session. On the final session, participants rolled a die and if they landed a 6, one question/response was selected from a pool containing all of the question/responses from each session. Women were then rewarded the cash amount corresponding to that question. Also, if they had selected a smaller, immediate
reward, they received the cash immediately. Alternatively, if they selected a larger, delayed reward, they received the cash amount after the corresponding time elapsed. The DDT was completed at baseline and 0.5, 1, 2, and 4 hours post drug administration.

*Balloon Analog Risk Taking Task.* The BART consisted of a computerized task through which participants virtually pumped a series of 15 balloons and each pump was accompanied with the reward of 5 cents (Lejuez et al., 2002). As the balloon expanded, participants’ earnings accumulated and they had the option to stop pumping at any time to save the rewards. However, upon reaching its breaking point of 64 pumps, the balloon explodes and all points associated with the trial were lost. The primary dependent measure was the average number of adjusted pumps on balloon trials without explosions, with more pumps corresponding to higher levels of risk-taking and impulsivity. Adjusted values were preferable to the absolute average number of pumps. According to the creators of the task, the absolute value number of pumps was constrained on balloons that exploded and limited between participants variability (Lejuez et al., 2002). The BART was completed at baseline and 0.5, 1, 2, and 4 hours post drug administration.

**Abuse Liability.** Abuse liability or abuse potential was assessed through the Biphasic Alcohol Effects Scale (BAES), Drug Effects Questionnaire (DEQ), and the Multiple Choice Procedure (MCP) during multiple time points throughout each session.

*Biphasic Alcohol Effects Scale.* The BAES (Martin et al., 1993) is a 14-item adjective-rating questionnaire that detects ethanol-induced stimulant and sedative effects. Past research demonstrates that the BAES has shown to yield higher stimulation scores during ascending blood alcohol concentrations (BACs) and higher sedation scores during descending BACs (Martin et al., 1993). Participants were instructed to indicate the extent to which they were feeling on a scale from “not at all” to “extremely.” The Stimulation scale was measured by adding scores for
adjectives elated, energized, excited, simulated, talkative, up, and vigorous. The Sedation scale was measured by adding scores for adjectives down, heavy head, difficulty concentrating, inactive, sedated, slow thoughts, and sluggish. The BAES was completed at baseline and 0.5, 1, 2, 3, 4, and 5 hours post drug administration.

*Drug Effects Questionnaire.* The DEQ asks participants to rate various different aspects of drug effects on a specific number line (Evans et al., 1994). Participants rated “drug liking” on a 9-point scale, on which -4 signified “dislike very much,” 0 signified “neutral or no drug effect,” and 4 signified “liked very much.” Women also ranked the “willingness to take the drug again” on a 5-point scale, ranging from 0, “not at all,” to 4, “very much.” In addition, participants ranked the “good effects” and “bad effects” of the drug on a 5-point scale, on which 0 signified “no effect” and 4 signified “very much.” Lastly, women ranked the “strength of the drug effect” from 0, “no effect at all,” to 4, “very strong effect.” The DEQ was completed at 0.5, 1, 2, 3, 4, and 5 hours post drug administration.

*Multiple Choice Procedure.* The MCP is used to detect a drug’s abuse potential (Griffiths, Rush, & Puhala, 1996). In sessions 2-7, the MCP was administered 4 times each session. Participants made a series of 9 choices between administered alcohol dose and varying amounts of money, with dollar value increasing from $0.25 to $64. During Session 8, participants randomly selected one of the previous choices from the MCP administered in sessions 2-7 via a lottery. Each chip in the lottery contained a number corresponding to a specific drug vs. money choice made within the duration of the study. After drawing a chip at random, the corresponding choice (money or drug) was administered. For example, if a participant picked chip that corresponded to a choice between the current drug or $15 in session 3, the participant’s selected answer (either the drug or $15) would be implemented. In essence, the purpose of
session 8 was to ensure that the drug vs. money selection was based on real world consequences. At lower amounts of money, it was anticipated that participants would select the drug. Data from this procedure were used to determine the cross-over point: the maximum dollar amount participants would assign to choose the drug over money (Reed, Levin, & Evans, 2012). The MCP was completed 0.5, 1, 2, and 4 hours post drug administration.

**Other measures.** Each assessment battery consisted of subjective-effects questionnaires and a variety of performance tasks. The Beck Depression Inventory II (BDI II; Beck et al., 1996) and the State Anxiety Inventory (STAI; Speilberger, Gorsuch, & Lushene, 1970) were completed at baseline and 2 and 4 hours post drug administration. The BDI II is a 21-item self-report questionnaire that measures characteristic symptoms of depression and the STAI is a 20-item component of the self-report questionnaire that assesses state anxiety levels.

The balance task (Evans & Levin, 2011) and Digit Symbol Substitution Task (DSST; McLeod, Griffiths, Bigelow, & Yingling, 1982) were administered at baseline and 0.5, 1, 2, 3, 4, and 5 hours post drug administration. The balance task assessed motor coordination by measuring each subject’s ability to stand upright for 30 seconds on each foot with both eyes closed. The primary dependent measure for the balance task was the total number of seconds each participant was able to balance. The DSST was a 3-minute task performed on a 3x3 computerized matrix. Each array was numbered 1-9 and during each trial, a randomly generated number appeared at the bottom of the screen, which indicated the pattern of arrays that should be created. Participants were required to replicate as many patterns as possible in the given time period. The primary dependent measure was the number of attempted and correct substitutions.
In addition, physiological measures, such as, blood pressure and heart rate were repeatedly measured at baseline and 0.5, 1, 2, 3, 4, and 5 hours post drug administration. Breath alcohol levels were also assessed upon participant arrival and departure.

**Statistical Analysis**

For all measures assessed during the six testing sessions, peak data will be analyzed. The direction of the peak effect (absolute value of the maximum or minimum) for each outcome measure will be determined from initial inspection of time-course data. Separate two-factor repeated measures within-subject ANOVA to determine the effects of hormonal pretreatment (progesterone vs. placebo) and alcohol dose (0, 0.5, 0.75 g/kg) and their interaction on each outcome measure.

**Results**

**Demographics**

Table 3 depicts the demographic characteristics of the research participants who successfully completed the study. Out of the 14 women who were originally enrolled in the study, 10 participants completed the study. On average, women were approximately 25 years old, with ovulatory menstrual cycles ranging from 27.75 to 37.50 days. Out of the 10 women who completed the study, 90% were binge drinkers, 80% were cigarette smokers, and 50% were marijuana users. In addition, Table 3 also reflects prospective alcohol consumption during the study, based on Daily Rating Forms. Participants consumed approximately 11.71 drinks/week and indulged in binge drinking on 35.44% of the days they drank alcohol.

**Hormone Levels**

Progesterone levels, when women were pretreated with oral micronized doses of progesterone, were significantly higher than in the placebo phase (16.86 ± 6.55 vs 0.57 ± 0.08
ng/mL, \( t(9) = -2.63, p = 0.027 \), Figure 1). The significantly low levels of progesterone during the placebo phase indicates that women were tested in the follicular phase of the menstrual cycle. However, estradiol levels in the progesterone-induced phase were not different than in the placebo phase, (55.80 ± 10.86 vs 52 ± 6.28 pg/mL, Figure 1).

**Breath Alcohol Levels and Cardiovascular Effects**

Figure 2 demonstrates time course data of mean breath alcohol levels plotted as a function of hormone pretreatment and alcohol dose. Peak breath alcohol levels were observed 1 hour after alcohol administration across all experimental conditions. Alcohol produced a significant dose-dependent increase in maximum breath alcohol levels (\( F(2,18) = 35.58, p<0.05 \)). Progesterone pretreatment did not significantly alter the breath alcohol levels within the intermediate and high dose of alcohol-treated women.

Peak systolic blood pressure, diastolic blood pressure, and heart rate are plotted as a function of hormone pretreatment and alcohol dose in Figure 3. There were no significant effects of alcohol dose, hormone pretreatment, or any interactions across all cardiovascular measures.

**Impulsivity and Risk-Taking**

Figure 4 reflects peak IMT ratio, DMT ratio, 150ms GoStop ratio, DDT overall \( k \) value, and BART adjusted average number of pumps graphed as a function of hormone pretreatment and alcohol dose. There were no significant effects of alcohol dose, hormone pretreatment, or any interactions across all impulsivity and risk-taking tasks.

**Abuse Liability Measures**

In Figure 5, peak crossover point for choosing drug over money on the Multiple Choice Procedure, Take Again and Drug Liking ratings on the DEQ, and the Sedation and Stimulant subscale scores on the BAES are plotted as a function of hormone pretreatment and alcohol dose.
Alcohol produced a significant dose-dependent increase in Take Again (F(2, 18) = 3.83, p<0.05) and Drug Liking ratings (F(2,18) = 15.19, p<0.05), and peak crossover point on the Multiple Choice Procedure (F(2,18) = 4.18, p <0.05).

**Performance Tasks**

Peak correct array scores on the DSST and balance are plotted as a function of hormone pretreatment and alcohol dose in Figure 6. Alcohol produced a significant dose-dependent decrease on performance in the DSST (dose effect: F(2, 18) = 4.78, p<0.05). However, there were no significant effects of alcohol dose, hormone pretreatment, or any interactions on the DSST and balance task.

**Progesterone and Impulsivity Exploratory Analysis**

Figure 7 and 8 demonstrate peak IMT ratio and GoStop ratio graphed against progesterone levels, as a function of alcohol dose, for women in the progesterone-induced phase. Two participants were excluded as outliers in the correlation analyses, due to excessively elevated progesterone levels, which were greater than 2 standard deviations above the mean. There was a negative correlation between peak GoStop ratio and progesterone levels, for women who received a placebo dose of alcohol, in the progesterone-induced phase (r(8) = -0.79, p<0.05). There was no significant correlation between peak GoStop ratio and progesterone levels, for women who received an intermediate (r(8) = -0.63, p = 0.09) or high dose (r(8) = -0.45, p = 0.26) of alcohol, when women were pretreated with progesterone.

**Discussion**

This is one of the first studies to date to examine the effects of oral micronized progesterone on alcohol in normally cycling women. While previous laboratory studies have examined the effects of alcohol and drug use on impulsivity, many of these studies have been
conducted in men or mixed-gender samples (Dougherty et al., 2008; Stoops et al., 2008; Zacny, Walker, & Derus, 2008) with a wide range of drinking levels (Dougherty et al., 2008). However, a recent study, performed with an all female cohort of participants, showed that alcohol increases impulsivity in women, and this effect is heightened in female moderate drinkers, in comparison to female light drinkers (Reed, Levin, & Evans, 2012).

As anticipated, alcohol produced significant dose dependent increases in abuse liability, as indicated in the Take Again and Drug Liking ratings on the DEQ and the peak crossover point in the MCP. These results are consistent with findings from previous studies in the field (Evans & Levin, 2004); for example, in a recent study alcohol increased measures of abuse liability and the positive subjective effects of alcohol more strongly in female moderate drinkers, in comparison to female light drinkers (Brunelle, Barrett, & Pihl, 2007; King et al., 2011; Reed, Levin, & Evans, 2012). Combined, results from the previous and current WRC studies are clinically significant, as a previous study demonstrated that young adult moderate to heavy drinkers who experience increased stimulant and rewarding effects of alcohol are at greater risks for developing binge drinking habits over time, increasing overall alcohol consumption, and experiencing greater clinically relevant outcomes, like higher rates of DSM-IV-TR alcohol use disorders (King, de Wit, McNamara, & Cao, 2011; King et al., 2014).

Yet, contrary to expectations, progesterone did not alter the subjective effects of alcohol in the moderate drinkers. However, retrospective power analysis showed that if the sample size of the existing study was increased to 30 women, we would have adequate power to conclude that progesterone may significantly decrease the subjective effects of alcohol on the MCP (power *.80, minimal detectable difference of 14.79). Similarly, previous research has demonstrated that progesterone has attenuated the positive subjective effects of other drugs, primarily stimulants
such as cocaine (Evans & Foltin, 2006; Sofuoglu, Babb, & Hatsukami, 2002; Sofuoglu, Mitchell, & Kosten, 2004) and nicotine (Sofuoglu, Babb, & Hatsukami, 2001), in women and men. In addition, a past studied showed that during the follicular phase, estrogen enhanced the subjective responses to amphetamine; in contrast, during the luteal phase, the elevated progesterone levels attenuated the effects of estradiol on the subjective responses to amphetamine (Justice & de Wit, 1999).

In contrast to the original hypothesis, there were no significant effects of alcohol dose, hormone pretreatment, or interaction effects across impulsivity risk-taking tasks. These results are not supported by research in the field. In a study using a similar population (Reed, Levin, & Evans, 2012), alcohol increased impulsivity in women, and this effect was exacerbated amongst moderate drinkers, particularly on the IMT and GoStop Task, in comparison to light drinkers. In addition, high doses of alcohol further increased impulsive performance on the IMT and DMT in moderate drinkers (Reed, Levin, & Evans, 2012). Despite similar levels of breath alcohol levels and prospective alcohol consumption, our participants were less impulsive at baseline, as suggested by their scores on the self-report impulsivity questionnaires. Thus, these results are likely to pose as a conservative estimate of the changes in impulsive behavior across tasks that may be more pronounced amongst samples with higher impulsive traits at baseline (Reed, Levin, & Evans, 2012), like individuals with alcohol or drug dependence (Allen et al., 1998).

In addition, we did not detect any significant interactions between progesterone and alcohol across impulsivity and risk-taking tasks. Yet, based on reverse power calculations, a sample size of 24 women would have been necessary to observe an interaction between progesterone and alcohol on the DDT (power*.80, minimal detectable difference of 0.0015). Past pre-clinical data has shown that progesterone plays a role in decreasing the behavioral effects of
impulsivity; for example, in rats, progesterone effectively attenuated marble burying, an impulsive behavior (Llaneza & Frye, 2009). In addition, in humans, oral doses of micronized progesterone decreased response initiation on the DMT, in non-drug using females (Reed, Levin, & Evans, 2010). Alternatively, even with an expanded sample size, progesterone does not seem to significantly decrease performance on the DMT, in women, relative to the placebo dose of alcohol.

Alcohol decreased performance on the DSST, when women received the high dose of alcohol, but did not significantly alter performance on the balance task. Past studies have shown that alcohol does impair performance on the DSST (Holdstock & de Wit, 2000; Evans & Levin, 2011). In addition, a previous study showed that women with a family history of paternal alcoholism were less impaired by alcohol than women with no family history of alcoholism on the balance task; though, this effect was modest (Evans & Levin, 2011). This finding demonstrates that the response to alcohol on the balance task may be influenced differentially by a participant’s family history of alcohol consumption. Perhaps, in our study, alcohol did not significantly diminish performance on the balance task because our cohort of participants may have contained women who had a family history of paternal alcoholism.

Moreover, contrary to the research hypothesis, progesterone did not alone impact performance, relative to the placebo hormone pretreatment dose, and it did not alter the effects of alcohol on both performance tasks, relative to the placebo dose of alcohol. These results are inconsistent with previous studies that demonstrate that progesterone alone decreased performance on the DSST (Reed, Evans, & Levin, 2010), as progesterone has shown to induce sedation (Freeman et al., 1992; van Broekhoven, Bäckström, Verkes, 2006) and impair performance on the DSST in non-drug using females (Freeman et al., 1992). Similarly, in a
previous study, progesterone alone decreased performance on the DSST, in women, relative to the placebo hormone pretreatment (Reed, Levin, & Evans, 2010).

In addition, there were no significant effects of alcohol dose, hormone pretreatment, or interaction effects across the following cardiovascular measures: systolic blood pressure, diastolic blood pressure, and heart rate. Consistent with the 2012 Reed, Levin, & Evans study, alcohol has shown to not produce significant increases in blood pressure, as a function of alcohol dose between light female drinkers and moderate heavy drinkers (Cushman, 2001; Cushman et al., 1998; Sesso et al., 2008). Similarly, another study noted that regular or light-to-moderate alcohol use may induce vasorelaxation, whereas chronic heavy alcohol consumption may increase blood pressure, significantly (Kudo et al., 2015). However, unlike the results of this present study, alcohol has been shown to increase heart rate, in a dose-dependent pattern (Reed, Levin, & Evans, 2012; Spaak et al., 2010). Interestingly, progesterone did not impact cardiovascular studies, confirming previous studies (Reed, Levin, & Evans, 2010; Sofuoglu, Babb, & Hatsukami, 2002 & 2001). However, other studies have shown that progesterone can attenuate the cocaine-related increases in cardiovascular measures (Evans & Foltin, 2006). Given the spectrum of findings, more research must be conducted to understand progesterone’s modulatory role on cardiovascular effects in alcohol users.

There were several strengths in this study, including the use of a within-subjects, dose-ranging, double dummy experimental design. Furthermore, a comprehensive assessment battery was used at multiple time points during each session to capture effects before alcohol administration and during the ascending limb, peak, and descending limb on the blood alcohol levels curve. In addition, since previous research has described impulsivity as a complex construct (Barratt & Patton, 1983), a variety of computerized tasks were implemented to measure
various facets of behavioral impulsivity. Also, as multiple studies have demonstrated that the
effects of alcohol (Evans & Levin, 2011; Lammers, Mainzer, & Breteler, 1995) and other drugs
like cocaine (Evans & Foltin, 2006; Sofuoglu et al., 1999) and nicotine (Marks et al., 1994;
Mello, Mendelson, & Palmieri, 1987) vary across the menstrual cycle, all women were tested in
the follicular phase of the menstrual cycle, to control for fluctuating progesterone and estradiol
levels. In addition, all women were given the same breakfast on each session, as the
bioavailability of micronized progesterone can be modified by food intake (Simon et al., 1993).
Further, participants in this study had significant experiences using alcohol; while it would be
expected that progesterone would have a stronger effect in heavy alcohol users, it could be
possible that the effects of progesterone vary between naïve or light drinking users and
experienced alcohol users. Lastly, females who met current DSM-IV-TR criteria, within the past
year, for Axis I psychiatric disorders were excluded from this study. Though this limited the
generalizability of our findings, as mental illnesses can increase the risk of substance misuse
(Khoury et al., 2010; Schuckit, Smith, & Kalmijn, 2013), the exclusion of such women allowed
us to control for confounding variables that may influence the interaction of progesterone and
alcohol in heavy drinking females.

In addition, confidence in the present findings are limited, due to a number of study
limitations. Due to the U.S.’s drinking age, we were unable to include younger female alcohol
users in our sample size; therefore, it is unclear whether the findings of this study may be
generalized to young adult female moderate drinkers. This is particularly important because
young adults between the ages of 18 to 20 years old are at the highest risk for developing alcohol
use disorders and heavy drinking patterns (Johnston, O’Malley, & Bachman, 2003; King et al.,
2011; Slutske et al., 2004). Further, sex-differences were not assessed, as men were not included
in the sample size. While this may be seen as a limitation, previous findings from both preclinical (Anker et al., 2009; Anker & Carroll, 2010) and laboratory research in humans indicate that the effects of progesterone are more pronounced in females compared to males (Evans & Foltin, 2006; Fox et al., 2013). Therefore, it seemed reasonable to limit this initial study to women.

As a result, a number of improvements could be made to the existing experimental design. Our small sample size of 10 women constrained our ability to detect statistically significant group differences or interaction effects. However, retrospective power analysis demonstrated that if our sample size had tripled, we would have had sufficient power to conclude that progesterone may be attenuating the effects of alcohol on the DDT and MCP. Furthermore, the suggested diminished ability for tasks, like the BART, to pick up subtle effects or group differences on various impulsivity measures was also another study limitation. Previous research studies using methodologies such as the BART to measure risk-taking amongst alcohol users have demonstrated inconsistent results. For example, risk-taking measured by the BART predicted greater substance use amongst college drinkers (Fernie et al., 2010). The variability in alcohol-related BART performance demonstrates that it may be limited to sense interaction effects within a specific group of interest (i.e “college drinkers”). Also, a study that included women from a similar demographic background as our women, observed no group differences in risk-taking, as measured by the BART, between low drinking females and moderate drinking females, as a function of alcohol dose (Reed, Levin, & Evans, 2012). Perhaps, the BART may not be an assessment that is sensitive to picking up group differences amongst the cohort of women in our study. In the future, this study, should be replicated with a larger sample size (n>30) and eliminate tasks like the BART from the research design. These changes may increase
our ability to better understand the interaction between progesterone and alcohol on the abuse
liability, impulsivity, and risk-taking tasks.

Overall, while the observed results did not reflect significant interaction effects between
alcohol and progesterone, this was most likely related to the small sample size and inadequate
power. Retrospective power analysis did show that our preliminary data do point to
progesterone’s role in attenuating the effects of alcohol on specific impulsivity and abuse
liability tasks, like the DDT and MCP. Further, the field is at a very early stage of addressing this
research question. Past research does show that progesterone can lower impulsivity and
subjective effects when interacting with other drugs of abuse, like nicotine and cocaine (Evans &
Foltin, 2006; Milivojevic et al., 2016; Sofuoglu, Babb, & Hatsukami, 2001). Overall, future work
should continue to reexamine these measures with a larger sample size of women to better
understand the interaction of progesterone and alcohol on impulsivity and abuse liability
amongst female moderate drinkers.
References


Dougherty, D. M., & Marsh, D. M. (2003). Immediate and Delayed Memory Tasks (IMT/DMT 2.0): A research tool for studying attention, memory, and impulsive behavior [Manual]. *Neurobehavioral Research Laboratory and Clinic, University of Texas Health Science Center at Houston, Houston, TX.*


Table 1: Experimental Study Design

<table>
<thead>
<tr>
<th>Session</th>
<th>Progesterone Treatment (mg)</th>
<th>Alcohol Dose (g/kg)</th>
<th>Menstrual Cycle Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Follicular Phase 1</td>
</tr>
<tr>
<td>2</td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Placebo</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Placebo</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 weeks later</td>
</tr>
<tr>
<td>5</td>
<td>300</td>
<td>0.75</td>
<td>Follicular Phase 2</td>
</tr>
<tr>
<td>6</td>
<td>300</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>300</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Multiple Choice Procedure Test</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Hormone pretreatment was counterbalanced such that half of the women received the placebo hormone pretreatment in the first four sessions, followed by the active progesterone dose in the following four sessions. The other half of the women received hormone pretreatment in the opposite order. Alcohol dose was also randomized per session.
Table 2: Standard Session Timeline

<table>
<thead>
<tr>
<th>Time (minutes relative to drug administration)</th>
<th>Scheduled Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>-75</td>
<td>Subject arrival, light breakfast, breathalyzer, urine sample, &amp; vitals</td>
</tr>
<tr>
<td>-40</td>
<td>Baseline assessment battery &amp; baseline impulsivity measures</td>
</tr>
<tr>
<td>0</td>
<td>Alcohol &amp; progesterone administration</td>
</tr>
<tr>
<td>15</td>
<td>Assessment battery, impulsivity measures, &amp; vitals</td>
</tr>
<tr>
<td>60</td>
<td>Assessment battery &amp; impulsivity measures</td>
</tr>
<tr>
<td>120</td>
<td>Assessment battery, impulsivity measures, &amp; blood hormone levels</td>
</tr>
<tr>
<td>180</td>
<td>Assessment battery</td>
</tr>
<tr>
<td>210</td>
<td>Lunch</td>
</tr>
<tr>
<td>240</td>
<td>Assessment battery &amp; impulsivity measures</td>
</tr>
<tr>
<td>360</td>
<td>Assessment battery</td>
</tr>
<tr>
<td>400</td>
<td>Field sobriety test, subject discharge</td>
</tr>
</tbody>
</table>
Table 3: Demographic Characteristics of Research Participants

<table>
<thead>
<tr>
<th>Demographic Category</th>
<th>Mean (+/- SD) n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>24.70 (1.13)</td>
</tr>
<tr>
<td>Race (Black/White/Hispanic/Other)</td>
<td>3/4/0/3</td>
</tr>
<tr>
<td>Education (years)*</td>
<td>15.30 (0.45)</td>
</tr>
<tr>
<td>Menstrual cycle length (days)*</td>
<td>30.77 (1.06)</td>
</tr>
<tr>
<td>Binge drinkers (n)</td>
<td>9</td>
</tr>
<tr>
<td>Cigarette smokers (n)</td>
<td>8</td>
</tr>
<tr>
<td>Marijuana smokers (n)</td>
<td>5</td>
</tr>
<tr>
<td><strong>Prospective alcohol consumption</strong></td>
<td></td>
</tr>
<tr>
<td>Alcohol (drinks/week)*</td>
<td>11.71 (1.22)</td>
</tr>
<tr>
<td>Absolute range (drinks/week)#</td>
<td>5.88 – 17</td>
</tr>
<tr>
<td>Drinking days (%)*</td>
<td>47.70 (3.49)</td>
</tr>
<tr>
<td>Drinks/drinking day*</td>
<td>3.51 (0.32)</td>
</tr>
<tr>
<td>Binge drinking days (%)*</td>
<td>35.44 (6.26)</td>
</tr>
<tr>
<td><strong>Self-Report Measures</strong></td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory*</td>
<td>3.59 (0.63)</td>
</tr>
<tr>
<td>Trait Anxiety Inventory*</td>
<td>28.70 (2.29)</td>
</tr>
<tr>
<td>State Anxiety Inventory*</td>
<td>27.70 (1.98)</td>
</tr>
<tr>
<td>Barratt Impulsiveness Scale (BIS-11)</td>
<td></td>
</tr>
<tr>
<td>Attentional*</td>
<td>13.60 (0.55)</td>
</tr>
<tr>
<td>Motor*</td>
<td>23.00 (1.17)</td>
</tr>
<tr>
<td>Non-Planning*</td>
<td>22.30 (1.67)</td>
</tr>
<tr>
<td>Total*</td>
<td>58.90 (2.17)</td>
</tr>
</tbody>
</table>

*The following demographics are presented as means +/- SD, unless otherwise noted.
#The participant who reported consuming 5.88 drinks/week on the DRFs, reported consuming 7 drinks/week at screening.
**Figure 1.** Mean progesterone and estradiol levels plotted as a function of hormone pretreatment (placebo or active progesterone dose). Error bars indicate standard errors of the mean. *p<0.05.
Figure 2. Time course of mean breath alcohol levels plotted as a function of hormone pretreatment and alcohol dose. Error bars indicate standard errors of the mean.
Figure 3. Peak Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate are plotted as a function of hormone pretreatment and alcohol dose. Error bars indicate standard errors of the mean.
Figure 4. Peak Immediate Memory Task (IMT) ratio, Delayed Memory Task (DMT) ratio, 150ms GoStop ratio, Delayed Discounting Task (DDT) overall $k$ value, and Balloon Analogue Risk Task (BART) adjusted average number of pumps are plotted as a function of hormone pretreatment and alcohol dose. Error bars indicate standard errors of the mean.
Figure 5. Peak crossover point for choosing drug over money on the Multiple Choice Procedure, Take Again and Drug Liking ratings on the Drug Effects Questionnaire (DEQ), and the Sedation and Stimulant subscale scores on the Biphasic Alcohol Effects Scale (BAES) are plotted as a function of hormone pretreatment and alcohol dose. Error bars indicate standard errors of the mean. * represents a significant difference compared to the 0 g/kg dose of alcohol after placebo hormone treatment.
Figure 6. Peak correct array scores on the Digit Symbol Substitution Test (DSST) and balance are plotted as a function of hormone pretreatment and alcohol dose. Error bars indicate standard errors of the mean.
Figure 7. Peak IMT Ratio are plotted against progesterone levels, as a function of alcohol dose, for women in the progesterone-induced phase.
Figure 8. Peak GoStop Ratio are plotted against progesterone levels, as a function of alcohol dose, for women in the progesterone-induced phase. There was a significant negative correlation between the peak GoStop Ratio and progesterone levels, when women received the placebo dose of alcohol in the progesterone pretreated phase.