A Pilot Daily Diary Study of Changes in Stress and Cannabis Use Quantity Across the Menstrual Cycle

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ABSTRACT

Menstrual cycle (MC) phase appears to influence changes in females' addictive behaviours (e.g., drinking, cigarette smoking). Few studies have examined cannabis use across the MC. We examined phase-specific changes in stress and cannabis use quantity across the MC in daily cannabis users. We hypothesized there would be an increase in self-reported stress and cannabis quantity premenstrually and menstrually versus other MC phases. Data were obtained prospectively, using a 32-day daily diary, from 14 normally-cycling, community-recruited, female cannabis users (Age: $M = 29.3$ years old, $SD = 4.9$). Participants completed measures pertaining to their daily stress levels (the General Stress Scale) and the quantity of cannabis used daily. A priori planned comparison t-tests and non-parametric Wilcoxon rank tests revealed MC phase effects on stress levels and cannabis quantity, respectively. In partial support of stress-response dampening (SRD) model and self-medication theory (SMT) predictions, stress levels were higher in the premenstrual versus the ovulatory phase, and a higher quantity of cannabis was used premenstrually versus the follicular and ovulatory phases. Findings suggest stress levels and cannabis use quantity are MC phase-sensitive. Results are consistent with SRD model and SMT predictions, where females learn to increase the quantity of cannabis used premenstrually to dampen their heightened stress response and negative affect. Female cannabis users of reproductive age could be trained to employ alternative strategies to cope with elevated stress premenstrually to prevent increased cannabis use.

Key words: cannabis use, menstrual cycle, stress, sex, females

Cannabis is the most commonly used illicit drug worldwide (United Nations Office on Drugs and Crime, 2016). Cannabis use disorders are highly comorbid with mental health disorders, such as depression, anxiety, and psychosis (Agrawal, Neale, Prescott, & Kendler, 2004; Casas, Roncero, Trasovares, Qureshi, & Bruguera, 2007; Connor et al., 2013; Hayley, Stough, & Downey, 2017; Robbins, Ehrman, Childress, & O'Brien, 1999). Research that has examined cannabis misuse suggests there are important sex differences in many aspects of cannabis use. Therefore, findings from substance use research among males may not generalize to

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female cannabis users (Green, 2006; Tuchman, 2010).

A female-specific factor that may be useful in understanding triggers for addictive behaviour is ovarian hormone variations across the menstrual cycle (MC; Carpenter, Upadhyaya, LaRowe, Saladin, & Brady, 2006; Franklin et al., 2004; Hudson & Stamp, 2011; Moran-Santa Maria, Flanagan, & Brady, 2014; Pearson & Schipper, 2013; Terner & de Wit, 2006). Examining the effects of ovarian hormone fluctuations across MC phase on substance use may allow for the development of sex-specific substance use treatments (Lynch, Roth, & Carroll, 2002).

The MC can be subdivided into five phases: menstrual (days one-five), follicular (days six-12), ovulatory (days 13-16), luteal (day 17 to the premenstrual phase), and premenstrual (five days prior to menstrual bleeding; Evans, Haney, Levin, Foltin, & Fischman, 1998; Johannes et al., 1995; Pastor & Evans, 2003). MC phases are characterized by rhythmic fluctuations in ovarian hormone concentrations (Feher, 2012; Griffin & Ojeda, 2004; Groome et al., 1996; Levy, Koeppen, & Stanton, 2000). The menstrual phase is characterized by low progesterone and estrogen concentrations (Griffin & Ojeda, 2004). Estrogen concentrations begin increasing during the follicular phase (Griffin & Ojeda, 2004). During ovulation, increases in follicle-stimulating hormone and luteinizing hormone concentrations are evident, resulting in a surge in progesterone and decline in estrogen concentrations (Feher, 2012; Groome et al., 1996; Levy et al., 2000). Estrogen concentrations remain stable during the luteal phase; however, progesterone concentrations increase and peak mid-phase (Griffin & Ojeda, 2004). In the absence of fertilization, estrogen and progesterone concentrations start to decline in the late luteal phase and continue to decrease premenstrually (Griffin & Ojeda, 2004). These fluctuations in ovarian hormones across MC phases have been implicated in variations in the addictive behaviour of reproductive-aged females, although findings have been mixed (see Joyce, Good, Tibbo, Brown, & Stewart, 2019; Moran-Santa Maria et al., 2014 for reviews).

To date, studies examining addictive behaviours across MC phase have predominantly examined changes in alcohol consumption or tobacco intake. Mixed findings surrounding alcohol consumption across MC phase are evident: levels of alcohol consumption have been variously shown to increase, decrease, or remain constant menstrually and premenstrually relative to other phases (Carroll, Lustyk, & Larimer, 2015). Most studies, however, show an increase in alcohol consumption premenstrually and menstrually (Carroll et al., 2015; Epstein et al., 2006). Joyce and colleagues (2018) further showed that increases in alcohol consumption menstrually are explained by increases in drinking to cope with negative mood. Further research examining self-administration of cocaine has shown an increase in cocaine craving in the late luteal phase, suggesting that women are at higher risk of drug craving and relapse when levels of estrogen and progesterone begin to decline during the late luteal phase and into the premenstrual phase (Moran-Santa Maria et al., 2014; Terner & de Wit, 2006). Additionally, research examining nicotine intake found that intake increases during the (pre-)menstrual phases (see review by Joyce et al., 2019a). Smoking relapse is often triggered by elevations in stress and/or associated negative affect (anxious/depressed affect), which further signifies the importance of examining associations between stress levels and addictive behaviours (Cohen & Lichtenstein, 1990).

Stress can be defined by how overwhelming, unpredictable, and uncontrollable one finds a challenging situation to be (Cohen, Kamarck, & Mermelstein, 1983). The perception of stress is subjective; hence, stress responses differ substantially across individuals (Lazarus & Folkman, 1984). The stress-response dampening model (SRD; Levenson, Sher, Grossman, Newman, & Newlin, 1980) of substance misuse has two tenets: (1) substances dampen response to stress and (2) consequently, individuals learn to use substances in response to stress as a maladaptive coping strategy. Similarly, self-medication theory (SMT; Khantzian, 1997) explains how an individual, during periods of elevated negative affect, may use substances to cope with negative mood states (Joyce et al., 2018). Consistent these two theories, research shows positive associations between daily negative emotions and one's desire to drink alcohol, such that elevations in negative affect increase one's desire to consume alcohol (Backer-Fulghum, Patock-Peckham, King, Roufa, & Hagen, 2012). In fact, there is a concrete link

between experiencing negative affect and drinking alcohol in which increases in negative affect lead to an increase in alcohol consumption (Cooper, Russell, & George, 1988; Dermody, Cheong, & Manuck, 2013). Similar to alcohol, cannabis may also be used to dampen one's stress response and reduce negative affect, with cannabis users reporting coping with stress as the most common motivation behind their use (Hyman & Sinha, 2009). In fact, consistent with SRD model predictions, archival data examined in one study showed that self-reported stress levels were reduced by 58% following (vs. prior to) cannabis use (Cuttler, Spradlin, & McLaughlin, 2018).

Sex differences in several aspects of cannabis use have been reported (Sherman, Baker, & McRae-Clark, 2016). For example, males are more susceptible to: initiating cannabis use, using at greater intensity, and developing a lifetime cannabis use disorder (CUD; Sherman, Baker, & McRae-Clark, 2016). However, females exhibit a more rapid progression from first cannabis use to a CUD which may be explained by their greater sensitivity to cannabis dose (Cooper & Haney, 2014; Crocker & Tibbo, 2018). Females who are dependent on cannabis also exhibit more severe withdrawal than males, suggesting females may be less likely to respond to cannabis use interventions (Crocker & Tibbo, 2018). Sex differences in the neurobiological mechanisms of cannabis may contribute to sex differences in cannabis use behaviours and the substance's subjective effects (Calakos, Bhatt, Foster, & Cosgrove, 2017). One possible explanation for these unique responses to cannabis in women pertain to the female MC and its effect on stress.

Fluctuations in progesterone and estrogen are associated with phase-specific changes in the impact of psychosocial stressors (Albert, Pruessner, & Newhouse, 2015; Lahmeyer, Miller, & DeLeon-Jones, 1982; Richards, Rubinow, Daly, & Schmidt, 2006). For example, elevated estrogen concentrations during ovulation are believed to be associated with an increase in positive affect (Griffin & Ojeda, 2004; Richards et al., 2006). In contrast, elevations in stress and negative affect premenstually/menstrually are thought to be the result of low progesterone and estrogen concentrations (Angst, Sellaro, Stolar, Merikangas, & Endicott, 2001; Richards et al., 2006; Roney & Simmons, 2015). These elevations in stress and negative affect premenstrually/ menstrually suggest that females may increase their cannabis use at these phases, consistent with SRD and SMT predictions.

To date, two studies have examined cannabis use across the MC and findings have been mixed (Griffin, Mendelson, Mello, & Lex, 1986; Mello & Mendelson, 1985). In Mello and Mendelson's (1985) study, cannabis acquisition and use patterns were studied in twenty-one females during a 35-day in-laboratory conditioning task. Findings were mixed across participants: cannabis use increased premenstrually in some, decreased premenstrually in others, and remained constant across MC phase in yet another group (Mello & Mendelson, 1985). Consistent with the SRD and SMT predictions, females with increased negative affect and impaired social function (indicative of higher stress) premenstrually, simultaneously reported more cannabis use premenstrually (Mello & Mendelson, 1985). However, the Mello and Mendelson (1985) study was a laboratory-based experiment; thus, findings may not generalize to real-world settings, indicating the need for more externally valid studies examining cannabis use across MC phase.

To address some of the limitations of the Mello and Mendelson (1985) study, Griffin and colleagues (1986) examined cannabis use and mood [via the Moos Menstrual Distress Questionnaire (Moos, 1968)] in a daily diary study with 30 females across three consecutive MCs. Cannabis use did not vary across the MC and no association was found between cannabis use and negative affect across MC phase. However, there were several methodological issues with Griffin and colleagues' (1986) daily dairy study. First, females who were not normally-cycling, with MC lengths of up to 44 days, were included. In the present study, only normally-cycling females (i.e., MC lengths of 25-32 days) were included as per usual inclusion criteria in MC studies (e.g., Joyce et al., 2018). Second, no stress measure was included in Griffin and colleagues' (1986) study. Thus, a psychometrically-sound daily stress measure, the General Stress Scale (Bolger, Delongis, Kessler, & Schilling, 1989), was included in the present study. Third, participants were asked about negative affect and cannabis use simultaneously, which prevented the examination of whether earlier negative mood was associated

with subsequent cannabis use during different phases. In the current study, participants reported stress levels and cannabis use quantity at different time-points to examine whether effects of MC on stress earlier in the day showed similar patterns to effects of MC on cannabis use levels later in the day, consistent with SRD and SMT predictions (Khantzian, 1997; Levenson et al., 1980).

The present pilot study aimed to examine fluctuations in stress and cannabis use quantity across MC phase in reproductive-aged female cannabis users. Consistent with prior literature (Albert et al., 2015; Angst et al., 2001; Brugger, Milicevic, Regard, & Cook, 1993; Hastrup & Light, 1984; Woods, 1985), we hypothesized that stress levels would increase in the menstrual and premenstrual phases versus other MC phases (i.e., follicular, ovulatory, luteal). Based on SRD (Levenson et al., 1980) and SMT (Khantzian, 1997) predictions, we also hypothesized that cannabis use quantity (during the first consumption episode following the stress assessment) would similarly increase in the menstrual and premenstrual phases versus other MC phases.

METHOD

Participants

Participants were recruited through advertisements posted throughout the community and on social networking websites (e.g., Kijiji). A sample of 14 normally-cycling female cannabis users (Age: M = 29.3 years, SD = 4.9; 85.7% Caucasian, 14.3% mix race) were recruited. Sixty-four percent of participants were college/university graduates, 21.4% had completed some college/university, and 14.3% had completed some high school. On average, participants indicated using cannabis 25.7 days (SD = 8.4; 71.4% were daily users) during the prior 30 days on the Cannabis Timeline Followback (Robinson, Sobell, Sobell, & Leo, 2014). Participants reported experiencing an average cannabis use problem severity score of 12.7 (SD = 4.5) on the Cannabis Use Disorder Identification Test with 64.3% scoring above the cutpoint of 12 used to indicate the likely presence of a CUD (Adamson & Sellman, 2003).

To be included in the study, respondents were required to have used cannabis at least four times during the month prior to participation to increase the likelihood of participants using cannabis during the 32-day daily diary. All participants were required to meet a list of exclusion criteria. Females who were prescribed medicinal cannabis were excluded as medicinal users have a prescribed dose of cannabis (Maccallum & Russo, 2018). Participants could not be receiving treatment for a CUD and/or abstaining from or trying to abstain from cannabis use. Participants were required to be between the ages of 19 and 45 years-old, as 45 is the standard cut-off in MC research to exclude females undergoing menopause/perimenopause (Nelson, 2008). Additionally, respondents were excluded if they were diagnosed with a pain disorder to help ensure participants were not using cannabis to self-medicate chronic pain. Females with interferences to their MC causing changes in ovarian hormone concentrations were also excluded (i.e., recent/current pregnancy, current use of hormonal contraceptives, hormonal contraceptive use within the last three months, currently breastfeeding, past hysterectomy, current amenorrhea, or menopausal/ postmenopausal). All surveys were administered in English; therefore, participants were required to read and write efficiently in English. Finally, participants were required to own/have access to a smartphone (with a data and texting plan) to receive their daily diary surveys.

Procedure

Interested females responded to advertisements and completed a telephone screening to assess eligibility. Eligible participants were scheduled for their first in-laboratory session. During this session, eligibility was reconfirmed. Participants then provided consent to participate in the study and answered two standardized self-report questionnaires (i.e., Cannabis Timeline Followback and Cannabis Use Disorder Identification Test – Revised). Participants began the study at different periods of the MC (MC days one-seven or 18-24) to ensure that any fatigue or reactivity effects due to daily monitoring were distributed across MC phase. Over the course of 32 days following the initial session, the higher end of an average MC,

participants received text message surveys via smartphone daily at 10:30 am and 2:00 pm. The 10:30 am survey asked questions pertaining to stress levels and MC day, while the 2:00 pm survey asked participants about the quantity of cannabis used. During the 2:00 pm survey, participants were asked to begin the survey only when one or more of the following were true: they had already used cannabis that day; they were using cannabis in that moment; they were planning on using cannabis within the next hour (i.e., they would return to answer the survey when using cannabis); or they had not used cannabis that day and were now going to bed. A reminder to complete the 2:00 pm survey was sent to participants at 6:30 pm and participants were asked to complete the 2:00 pm survey regarding their first cannabis use occasion since the stress assessment at 10:30 am. Participants were debriefed and received their compensation at a final in-laboratory session. Compensation was based on the number of in-laboratory sessions attended and daily diary surveys completed, with a maximum compensation of $97.65 (CAN).

Measures

Initial In-Laboratory Session

Cannabis timeline followback (CTLFB). The CTLFB was a 30-day retrospective calendar, which examined past-month cannabis use (Robinson et al., 2014). The CTLFB examined a number of cannabis use parameters (e.g., type of cannabis intake, amount of money spent on cannabis). The CTLFB was used in this study to confirm eligibility (past month cannabis use frequency) and for participant demographics. The CTLFB has high test-retest reliability over a 30-day period, with test-retest reliabilities ranging from 0.75 to 0.96 (Robinson et al., 2014).

Cannabis Use Disorder Identification Test – Revised (CUDIT-R). The CUDIT-R was an eight-item measure used to screen for problematic cannabis use by assessing cannabis use levels, problems, and dependence (Adamson & Sellman, 2003). The CUDIT-R demonstrates good internal consistency ($\alpha = 0.91$; Adamson et al., 2010) and was used to describe the sample in terms of their problematic cannabis use levels.

Daily Diary Surveys

Menstrual cycle day. Participants responded to a single question to determine their current MC day. This question was asked once daily during the 10:30 am survey. If participants were unsure of their MC day, they were provided with the option of responding "unknown" until menstruation began (at which time day one was indicated). Reporting MC day, as opposed to whether menstruation is occurring (yes/no) accounts for variable MC lengths and reduces errors when determining day one of menstruation (Joyce et al., 2018).

General Stress Scale (GSS). The GSS (Bolger et al., 1989) was a three-item measure used to assess daily stress levels. The first question asked participants to choose from a list of situational stressors that may be troublesome for them that day (e.g., family demands, argument with someone). The second question asked participants to select their most troublesome stressor that day from the list of situational stressors. The third question asked participants to rate the amount of stress currently experienced as a result of their most troublesome stressor using a visual analogue scale (VAS) ranging from "not at all stressful" (scored as zero) to "extremely stressful" (scored as 100; Bolger et al., 1989). Participants were instructed to respond by placing a mark on a point between the anchors "not at all stressful" to "extremely stressful", scored as zero to 100 respectively for data analysis purposes.

Cannabis use. The cannabis use measure in the daily diary was an adapted version of a question on the CTLFB used to assess daily cannabis use prospectively (rather than retrospectively; Robinson et al., 2014). For this study, the quantity of cannabis used during the first consumption episode since the 10:30 am stress assessment (in standard joint equivalents) was assessed. Participants were informed that a standard joint referred to 0.50 grams of cannabis, five bong or pipe hits, or ten puffs (Zeisser et al., 2012). The first cannabis-using occasion was examined as this occasion was the most temporally proximal to the daily stress assessment.

Data Analysis

Daily diary data was divided into the following five MC phase designations: menstrual (days one-five), follicular (days six-12), ovulatory (days 13-16), luteal (days 17 to the premenstrual phase), and premenstrual (five days prior to menstrual bleeding; Joyce et al., 2019a). Phase designation was determined using MC data obtained from the daily question pertaining to MC day. In the case of an unknown menstrual cycle day, an alternative method (i.e., a count forward-backward method from the first day of menstruation) was used to retrospectively determine MC day for each survey (see Joyce et al., 2018).

Following phase designation, the average stress level per MC phase and average quantity of cannabis used per MC phase were determined. The average stress level per MC phase was calculated by summing the stress VAS scores for each day of a specific MC phase and dividing the sum by the number of days within each MC phase (Joyce et al., 2019b). The quantity of cannabis used per MC phase was calculated by dividing the total number of standard joints consumed across each MC day within a specific phase by the number of cannabis-using days in that MC phase.

Once average stress level and cannabis use quantity per MC phase was determined, multiple imputations were used to account for missing data at the phase-level (i.e., for participants failing to answer the cannabis use question or GSS survey for an entire phase). Multiple imputations used an expectation maximization algorithm in SPSS (Version 24). The average stress level and cannabis used per MC phase was calculated for a total of 70 phases (i.e., 14 participants across 5 phases). Of the 70 averages calculated, multiple imputations were used to account for a total of five missing phases on both variables (i.e. stress level and quantity of cannabis used).

Prior to running any data analyses, the skewness and kurtosis of each variable (stress levels and cannabis use quantity) were analyzed to determine whether parametric or non-parametric statistical methods should be used given the study's small sample size. Findings suggested that self-reported stress levels were normally distributed with a skewness of 0.417 (*SE* = 0.132) and kurtosis of -1.00 (*SE* = 0.264), suggesting that parametric tests could be used (Hair, Black, Babin, & Anderson, 2010). Cannabis use quantity was not normally distributed, with the data showing positive skew (γ_1 =1.19; *SE* = 0.136) and significant kurtosis (γ_2 = 1.76; *SE* = 0.271; Hair et al., 2010). Since parametric data analytic methods rely on normal distributions and are influenced by outliers, such analyses could not be performed within the present pilot study for the cannabis use quantity data. Therefore, parametric planned comparisons were used to analyse the stress level data across MC phase, whereas planned comparisons in the form of non-parametric Wilcoxon rank tests were used to analyse cannabis use quantity data across MC phase. One-tailed *t*-tests were used to assess hypothesis one, as a directional hypothesis was made *a priori* based on predictions of the SRD model and previous research suggesting stress levels are highest premenstrually/menstrually (Albert et al., 2015; Angst et al., 2001; Levenson et al., 1980). One-tailed tests were also used for cannabis use quantity across the MC. Stress levels and cannabis use quantity premenstrually were compared sequentially to levels/use during all other phases except menstrual. Similarly, stress levels and cannabis use quantity menstrually were compared sequentially to levels/use during all other phases except premenstrual.

RESULTS

A set of within-subjects planned paired comparison *t*-tests were conducted, with MC phase as the independent variable (see Table 1). Partially consistent with hypothesis one, findings revealed that stress levels were significantly higher premenstrually (*M* = 39.16; *SD* = 26.04) than at the ovulatory phase (*M* = 28.99; *SD* = 22.71; *p* = 0.039); this effect was of medium magnitude (*d* = 0.520; Figure 1; Table 1).

Partially consistent with hypothesis two, the quantity of cannabis used differed by MC phase. Results suggested that females used more cannabis premenstrually (Mdn = 1.58; Range = 3.17) relative to the follicular (Mdn = 1.00; Range = 2.61; *p* = 0.003) and ovulatory phases (Mdn = 1.21; Range = 2.11; *p* = 0.018; Figure 2; Table 2); these effects were both large (*r* = .730 and *r* = .560, respectively); *r* is a correlation coefficient or the standardized measure of effect size for non-

Table 1. *Planned Comparisons for Stress Levels across MC Phase Pairs.*

	MC Phase Pair	*M*	*SE*	*95% CI*	*t*	*d*	*df*	*p*
General Stress	Premenstrual-Follicular	.100	3.08	[-6.56, 6.76]	.032	.009	13	.488
	Premenstrual-Ovulatory	**10.176**	**5.29**	**[-1.25, 21.60]**	**1.924**	**0.520**	**13**	**.039***
	Premenstrual-Luteal	7.168	4.65	[-2.88, 17.22]	1.541	.414	13	.074
	Follicular-Menstrual	1.449	4.56	[-11.31, 8.41]	.317	.087	13	.378
	Menstrual-Ovulatory	8.628	4.90	[-1.97, 19.22]	1.760	.493	13	.051
	Menstrual-Luteal	5.620	5.04	[-5.28, 16.52]	1.114	.305	13	.143

Note. All significant results are represented in bold. Directionality of each effect is shown in the 'MC phase pair' column, with the highest value presented first. An asterisk (*) indicates significant difference in stress levels between MC phase pairs at the $p < 0.05$ level (one-tailed tests). M = mean difference in stress levels between the MC phase pairs.

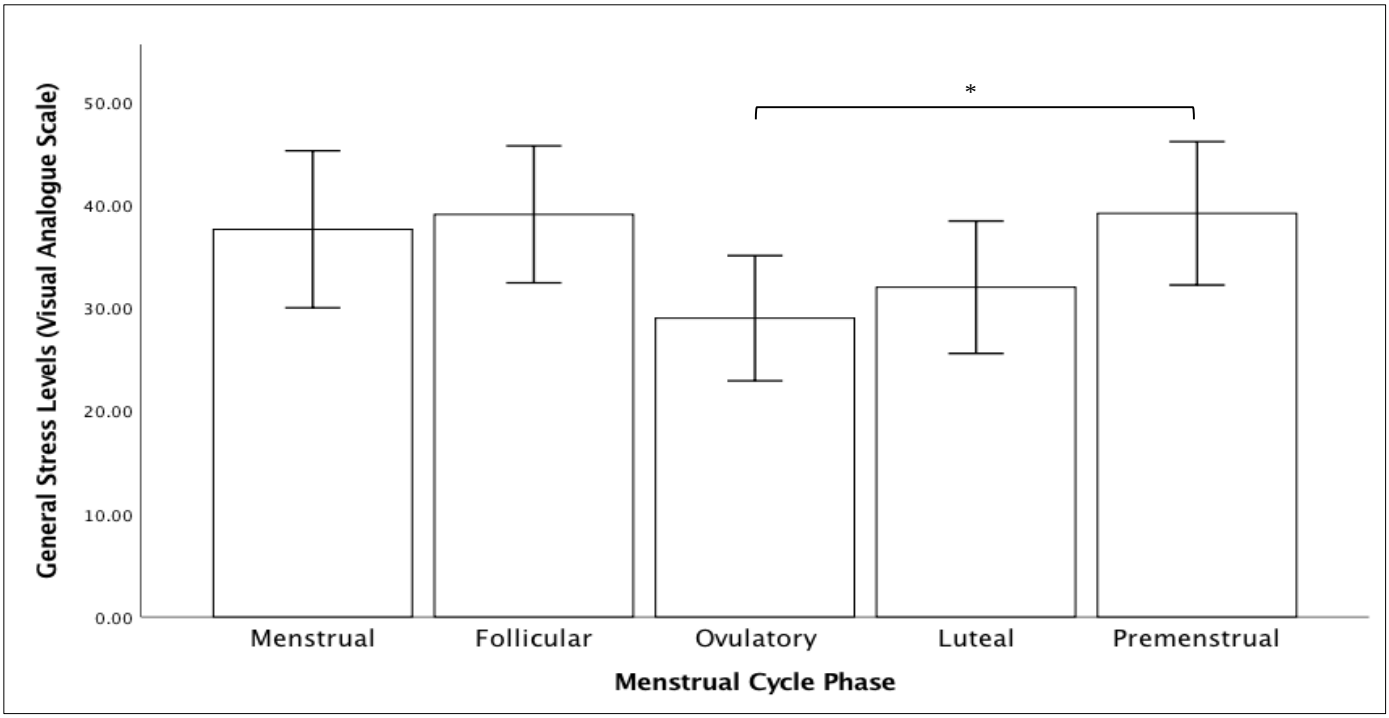

Figure 1. Mean levels of stress endorsed by menstrual cycle phase. The error bars represent standard errors. Significant differences (one-tailed tests) between premenstrual phase and other phases are indicated with asterisks. *Significant at the $p < 0.05$ level.

parametric tests. When a non-parametric test is conducted, two menstrual cycle phases are being compared. Each r value indicates the relationship between the two menstrual cycle phases analyzed (see Rosenthal, 1994 for more information). Effects were identical if parametric statistics were to be used: females used more cannabis premenstrually (M = 1.75; SD = 0.87) relative to the follicular (M = 1.21; SD = 0.91; t = 3.695; p = 0.002; d = 0.989) and ovulatory phases (M = 1.24; SD = 0.75; t = 2.468; p = 0.014; d = 0.667)

Table 2. *Summary of Wilcoxon Rank Tests of Cannabis Use Quantity across Menstrual Cycle Phase Pairs*

Variable	*MC Phase Pair*	*Z*	*p*	*r*
Cannabis Use Quantity	Menstrual-Follicular	1.293	.196	.346
	Menstrual-Ovulatory	1.138	.255	.304
	Menstrual-Luteal	.315	.753	.084
	Premenstrual-Follicular	**2.732**	**.003***	**.730**
	Premenstrual-Ovulatory	**2.097**	**.018***	**.560**
	Premenstrual-Luteal	1.381	.167	.369

Note. All significant results are represented in bold. Directionality of each effect is shown in the 'MC phase pair' column, with the highest value presented first. An asterisk (*) indicates significant differences between MC phase pair at the p<0.05 level. The column "*r*" refers to the effect size of each phase comparison conducted (small effect size = 0.1; medium effect size = 0.3; large effect size = 0.5).

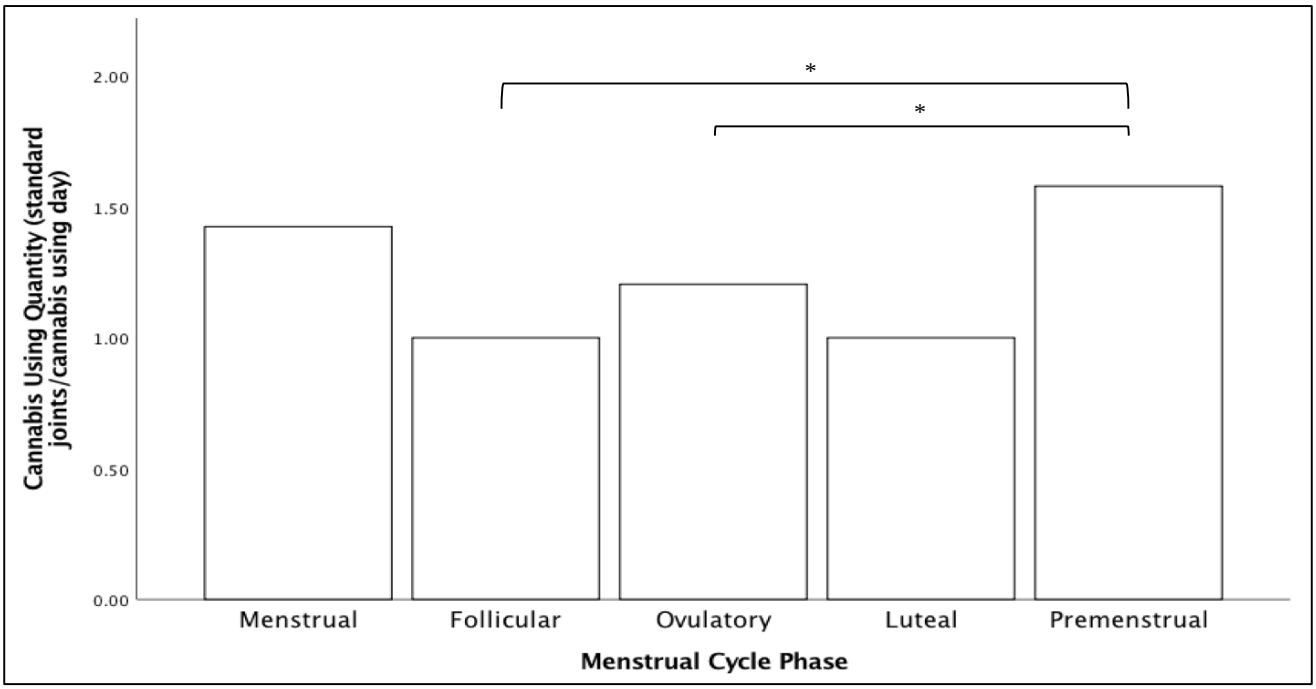

Figure 2. Median quantity of cannabis use (standard joints/cannabis-using day) by menstrual cycle phase. Significant differences (one-tailed tests) between premenstrual phase and other phases are indicated with asterisks. *Significant at the $p < 0.05$ level.

DISCUSSION

The results of this 32-day daily diary study expand upon previous literature examining changes in cannabis use across the MC (Griffin et al., 1986; Mello & Mendelson, 1985). The current study is the first to simultaneously assess MC phase-related changes in stress levels and MC phase-related changes in subsequent cannabis use quantity.

Based on prior research examining stress across the MC (Albert et al., 2015; Angst et al., 2001; Brugger et al., 1993; Hastrup & Light, 1984; Woods, 1985), stress levels were predicted to be higher premenstrually/menstrually versus the other MC phases. Findings provided partial support for hypothesis, in that stress levels were significantly higher premenstrually than in the ovulatory phase – a difference of moderate magnitude. Findings from this study are thus partially consistent with prior research

suggesting females are most reactive to psychosocial stressors premenstrually/ menstrually, when estrogen and progesterone concentrations are low versus other MC phases (Albert et al., 2015; Ossewaarde et al., 2010).

Based on SRD and SMT models of substance use (Levenson et al., 1980), it was also predicted that cannabis use quantity would increase premensturally/menstrually versus other MC phases. Findings again provided partial support for SRD and SMT predictions, in that cannabis use quantity was higher premenstrually relative to both the ovulatory and follicular phases; these effects were both large in magnitude, respectively. As was the case for changes in stress, increases in cannabis use quantity during the premenstrual phase may be attributable to fluctuations in ovarian hormone concentrations, specifically progesterone and estrogen.

The premenstrual phase is characterized by a precipitous decline in progesterone and estrogen concentrations (Griffin & Ojeda, 2004). Since our results exhibited an elevation in both stress and cannabis use quantity premenstrually, but not menstrually, it may be the precipitous decline in estrogen and progesterone premenstrually (rather than low estrogen and progesterone concentrations menstrually; Griffin & Ojeda, 2004) which explains the observed increases in stress levels and cannabis use premenstrually. Moreover, the fact that the difference in stress and cannabis use levels reported premenstrually were both relative to the ovulatory phase (and to the follicular phase in the case of cannabis use), points specifically toward the involvement of estrogen since it is estrogen that: begins increasing during the follicular phase, is highest during ovulation, and declines sharply during the premenstrual phase (Feher, 2012; Groome et al., 1996; Levy et al., 2000). Additionally, a surge in estrogen concentration, occurring during ovulation, is associated with an increase in positive affect (Richards et al., 2006). Increases in positive affect during ovulation may be related to the reported decrease in cannabis use quantity during the ovulatory phase (relative to cannabis use quantities premenstrually), as females may be less likely to use cannabis to cope during the ovulatory phase relative to the premenstrual phase given their stress levels are relatively lower during the ovulatory phase. Overall, this pattern of findings points more toward the likely involvement of estrogen than progesterone.

The exhibited fluctuations in cannabis use quantity were quite similar across MC phase to those seen for stress levels across MC phase. Specifically, stress levels and cannabis use quantity were both significantly higher premenstrually than during the ovulatory phase. Moreover, our study involved a temporal lag between the assessment of stress and the quantity of cannabis used during a subsequent cannabis use occasion later that day. SRD model and SMT predictions have two tenets: (1) cannabis reduces an individual's response to stress/stressors and/or negative affect, respectively; and (2) people learn to use cannabis when experiencing stress/stressors and/or negative affect. Recent findings indicate that using cannabis substantially alleviates self-reported stress, consistent with predictions of the first tenet of the SRD model (Cuttler et al., 2018). The present findings are consistent with the second tenet of the SRD model (Levenson et al., 1980), in that increases in earlier day stress levels were seen premenstrually as were increases in subsequent daily cannabis use quantity during the first cannabis-using occasion following the stress assessment. Results are consistent with the possibility that the increase in cannabis quantity premenstrually may be used functionally to dampen a heightened response to stress premenstrually.

Limitations

Results should be interpreted with four limitations in mind. First, participants' self-reported MC day was not validated via biological means (e.g., progesterone assays). However, self-reports of menstrual cycle day have been validated in prior work using progesterone assays as a form of biological verification (Andreano, Arjomandi, & Cahill, 2008; Andreano & Cahill, 2010). In fact, data using an identical protocol with normally-cycling female drinkers and gamblers indicated that self-report MC phase could be validated via progesterone assays (Joyce et al., 2018; Joyce et al., 2019b). Second, the small sample size within this pilot study (n = 14) may have reduced power to detect smaller magnitude effects. As an example, we had predicted that stress levels would be higher in the menstrual

phase relative to other MC phases. While we did not observe a significant difference, stress levels menstrually were marginally higher relative to the ovulatory phase (p = .051) – an effect which was small-to-moderate in magnitude. This effect might have proved statistically significant if the sample size had been larger and thus adequately powered to detect smaller effects. The small sample size of this pilot study did not allow us to run a multilevel model; therefore, we were not able to test relations between earlier stress levels and later cannabis use and whether these relations varied by menstrual cycle phase. A larger sample size would permit analyses of these kind which could be used to further test predictions of the SRD and SMT models.

Third, we took steps to maximize variability in cannabis use quantity by excluding medical cannabis users (who would be using cannabis daily and/or at consistent doses). Despite these efforts, we nonetheless recruited a sample that was predominantly daily cannabis users. Additionally, the CUDIT-R suggests that many of our participants (64.3%) likely had a CUD. As a result, these findings may not be generalizable to non-problem cannabis users. However, the results may well benefit treatments for reproductive aged females with CUDs. While daily users and those with cannabis problems would be the most-clinically relevant samples of participants to examine, future studies should examine whether there are more marked changes in cannabis use quantity across the MC in females with various patterns of cannabis use (e.g., those who do not use cannabis daily). Perhaps in such cases, it may be that the frequency (rather than the quantity) of cannabis use varies significantly across MC phase.

Finally, information pertaining to the type of cannabis used was not obtained. For example, Sativa is a type of cannabis used to produce a euphoric effect, whereas Indica is used for its relaxing and calming effects (Piomelli & Russo, 2016). Identified differences in the effect of cannabis type suggests the strain of cannabis used may vary across MC phase. This research may be easier to conduct in Canada or in certain US states now that cannabis is legalized. As such, participants will have more information on the content of the cannabis they are using. Thus, future daily diary studies should ask participants to specify the type of cannabis used on each occasion.

Future Research and Implications

Future research should employ more rigorous statistical analyses (e.g., multilevel modeling or time-varying effect models; Snijders & Bosker, 2012; Tan, Shiyko, Li, Li, & Dierker, 2012) to determine whether earlier stress predicts later cannabis use quantity, particularly in the premenstrual phase. Our findings provide preliminary evidence to suggest that both stress levels and cannabis use quantity increase in the premenstrual (versus ovulatory) phase, however, these more rigorous statistical analyses will allow us to determine if daily stress levels predict the quantity of cannabis used at a daily level across the MC. For instance, the implementation of time varying effects models would allow us to determine whether increases in stress levels premenstrually explain the subsequent increase in cannabis use quantity observed premenstrually in this study (see Joyce et al., 2018 for an example). Furthermore, such analyses along with appropriately timed cannabis use and stress assessments would allow for the additional examination of whether cannabis use subsequently reduces stress, as predicted by the SRD and SMT models (see Battista et al., 2015 for a similar daily diary study in the alcohol area; N = 132).

Further, future research should examine whether changes in cannabis use across the MC are mediated by changes in motives for use, specifically: enhancement, conformity, expansion, coping, and/or social motives (Simons, Correia, Carey, & Borsari, 1998). Findings by Joyce and colleagues (2018) indicated that coping and social motives are associated with increases in alcohol consumption menstrually and mid-cycle, respectively. SRD and SMT predictions (Levenson et al., 1980) would suggest coping motives explain increased cannabis use premenstrually and coping motives, in particular, should therefore be assessed in future studies on cannabis use across the menstrual cycle.

Future research should also examine whether MC phase-related links exist between negative affect (depressed and/or anxious affect) and cannabis use quantity. Perhaps changes in depressed and/or anxious affect across the MC

may better explain changes in cannabis use quantity across the MC than changes in daily stress levels examined here. Alternatively, depressed and/or anxious affect may mediate the hypothesized relation of stress to cannabis use in the premenstrual phase.

Conclusions

Findings indicated phase-related increases in both stress and cannabis use across the MC, specifically premenstrually (relative to at least one other MC phase) which may be useful when developing cannabis interventions options for reproductive-aged females. For example, quit attempts may be more efficacious if a quit date is set during an MC phase associated with decreased stress and decreased cannabis use levels (e.g., during ovulation rather than premenstrually). Similar methods have been employed in smoking cessation interventions across the MC (Franklin et al., 2008). Additionally, given that the premenstrual phase appears to be associated with both increased stress levels and increased cannabis use quantity, implementing strategies to better cope with stress premenstrually may reduce the likelihood of females engaging in excessive cannabis use, thereby reducing cannabis-related risk.

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