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Smoking- and menstrual-related symptomatology during short-term smoking abstinence by menstrual phase and depressive symptoms

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Abstract

Menstrual phase and depressive symptoms are known to minimize quit attempts in women. Therefore, the influence of these factors on smoking- and menstrual-related symptomatology during acute smoking cessation was investigated in a controlled cross-over lab-study. Participants (n=147) completed two six-day testing weeks during their menstrual cycle with testing order randomly assigned (follicular vs. luteal). The testing week consisted of two days of ad libitum smoking followed by four days of biochemically verified smoking abstinence. Daily symptomatology measures were collected. Out of the 11 total symptoms investigated, six were significantly associated with menstrual phase and nine were significantly associated with level of depressive symptoms. Two significant interactions were noted indicating that there may be a

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stronger association between depressive symptoms with negative affect and premenstrual pain during follicular phase compared to luteal phase. Overall, these observations suggest that during acute smoking abstinence in premenopausal smokers, there is an association between depressive symptoms and symptomatology whereas menstrual phase appears to have less of an effect. Further study is needed to determine the effect of these observations on smoking cessation outcomes, as well as to define the mechanism of menstrual phase and depressive symptoms on smoking-related symptomatology.

Keywords

Smoking cessation; menstrual cycle; depressive symptoms; withdrawal

Introduction

An estimated 44 million Americans smoke cigarettes, with a prevalence of 17% for women (Centers for Disease Control and Prevention [CDC], 2011). Research has shown that women may be less successful in quitting smoking compared to men (Perkins, 2001; King, et al., 2006; Scharf & Shiffman, 2004) and also experience significantly greater smoking-related morbidity and mortality (US Department of Health and Human Services [USDHHS], 2001).

While the bio-behavioral basis for this sex disparity is still evolving, sex hormones may play an important role, given the effect they have on the brain reward circuit (Lynch & Sofuoglu, 2010).

Preclinical data indicates that progesterone can decrease nicotine's reinforcing effects whereas estrogen may enhance motivation for nicotine (Carroll & Anker, 2010; Donny, et al., 2000; Lynch, 2009). The clinical literature, however, is less consistent due to differences in methodology and a lack of distinction between withdrawal symptoms and premenstrual symptoms (Carpenter, Upadhyaya, LaRowe, Saladin, & Brady, 2006). Two studies are available to date indicating that the luteal phase (low estradiol/high progesterone) is associated with improved smoking cessation outcomes when nicotine replacement therapy is not used (Allen, Bade, Center, Finstad, Hatsukami, 2008; Mazure, Toll, McKee, Wu, & O'Malley, 2011); whereas two other studies observed improved smoking cessation outcomes in the follicular phase (high estradiol/low progesterone) when nicotine replacement therapy was used (Franklin, et al., 2008; Carpenter, Saladin, Leinbach, LaRowe, & Upadhyaya, 2008). The reason for these seemingly conflicting results may be due to an interaction between nicotine, sex hormones and withdrawal symptoms. For instance, active nicotine patch (versus placebo patch) had the greatest effect in reducing both withdrawal and certain premenstrual symptoms in women during the late luteal phase versus follicular phase (Allen, Hatsukami, Christianson, & Brown, 2000).

Depression, a common comorbidity in smokers, may exacerbate the risk for smoking relapse in women and has been associated with sex hormones (Goletiani, Siegel, & Hudson, 2012; Michal, et al., 2013; Nakajima & al'Absi, 2012; Paperwalla, Levin, Weiner, & Saravay, 2004; Weinberger & McKee, 2011; Wewers, et al., 2012). The risk for experiencing depressive symptoms for women is high during periods associated with increased

fluctuations of sex hormones such as puberty (Deecher, Andree, Sloan, & Schechter, 2008), postpartum (Klier, et al., 2007) and the menopause transition (Ryan, et al., 2009). Some studies have shown that depression, depressive symptoms, or other negative moods are greater in the luteal phase (Allen, Hatsukami, Christianson, & Nelson, 1999; Harvey, Hitchcock, & Prior, 2009; Natale & Albertazzi, 2006). Female smokers with depressive symptoms during a smoking cessation attempt may experience more intensity and persistence of some withdrawal symptoms (Langdon, et al., 2013). Further, negative affect and somatic features of depression have been related to higher levels of nicotine withdrawal (Schnoll, Leone, & Hitsman, 2013) and increasing nicotine withdrawal severity has been associated with depression (Egervari, Csala, Dome, Faludi, & Lazary, 2012; Pergadia, et al., 2010). While extensive research has been done on smoking and Major Depressive Disorder (Dierker, Avenevoli, Stolar, & Merikangas, 2002; Holma, I., Holma, K., Melartine, Ketokivi, & Isometsä, 2013; Scarinci, Thomas, Brantley, & Jones, 2002; Wiesbeck, Kuhl, Yaldizli, & Wurstet, 2008), far less has focused specifically on depressive symptoms and smoking. This is of particular concern because subclinical depressive symptoms have been shown to adversely affect smoking cessation in the general population (Borrelli, et al., 1999; Niaura, et al., 2001; Weinberger & McKee, 2011).

Studies have looked at links between depression and smoking (Weinberger & McKee, 2011; Wewers, et al., 2012), hormonal fluctuations and smoking (Allen, et al., 2008; Lynch, & Sofuoflu, 2010; Sofuoglu, Mouratidis, & Mooney, 2010) and hormonal fluctuations and depression (Allen, et al., 1999; Allen, et al., 2012; & Harvey, et al., 2009), but none have addressed the potential synergistic effects of sex hormones (as measured by the proxy menstrual phase) and depressive symptoms during smoking cessation. Given that the vast majority of premenopausal women relapse within the first few days of a quit attempt (Allen, et al., 2008), the present study was designed to examine the risk factors for smoking relapse within the first four days of abstinence. Specifically, we utilized a controlled cross-over study design to examine the effect of menstrual phase, depressive symptoms and the combined effect of menstrual phase and depressive symptoms on smoking- and menstrual-related symptomatology (referred henceforth as symptomatology) during acute smoking abstinence.

Our aims are to (1) determine the menstrual phase difference in symptomatology during acute smoking abstinence, (2) identify the association between depressive symptoms and symptomatology during acute smoking abstinence, and (3) examine menstrual phase as a potential effect modifier between depressive symptoms and symptomatology during acute smoking abstinence. We hypothesized that the luteal (L) phase, versus follicular (F) phase, would be associated with more severe symptomatology. We also expected to observe a positive correlation between severity of symptomatology and depressive symptoms and that the association between depressive symptoms and symptomatology would vary by menstrual phase.

Methods

Participants

Women 18–40 years of age were recruited for this study through local advertising, flyers, and social media. To be eligible, women had to smoke at least 5 cigarettes per day for the past year, have regular menstrual cycles every 24–36 days, experience premenstrual symptoms (as indicated by a score of 11 or higher on the Shortened Premenstrual Assessment form; PAF, Allen, McBride, & Pirie, 1991) and be in stable mental/physical health. Women were excluded if they were: obtaining nicotine from sources other than cigarettes (e.g., nicotine replacement, cigars, pipes, smokeless tobacco, etc.), recently (<3 months) pregnant or breast-feeding, or intending to become pregnant within 6 months, using exogenous hormones, had a recent (<6 months) episode of Major Depressive Disorder, had lifetime Premenstrual Dysphoric Disorder (PMDD), or currently receiving treatment for psychiatric or emotional disorders.

Study Protocol

Potentially eligible participants attended an in-person screening visit during the early F phase (days 2–7 of menstrual cycle). At this visit, after obtaining informed consent, study eligibility was confirmed by assessing psychiatric, medical, smoking, and menstrual cycle histories. We also attempted to stratify participants into two heterogeneous groups based on depressive symptoms status (no depressive symptoms versus depressive symptoms) per the results of the Composite International Diagnostic Interview based on the DSM-IV criteria (Wittchen, Kessler, & Ustun, 2001) along with the Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer, & Williams, 2001). However, while our initial goal was to compare these two distinct groups, ad hoc analyses showed that depressive symptoms (as measured by the Center for Epidemiologic Studies – Depression (CES-D; Radloff, 1977) for the two groups were not significantly different on the day before quit. Therefore, the two groups were collapsed and CES-D scores were used as a continuous variable in the analyses (details below). Participants were then randomized to testing order (e.g., F phase followed by L phase or vice versa). For additional details on the screening and randomization process, see Allen, A., Al'absi, Lando, Hatsukami, & Allen, S., 2013.

Each testing week consisted of six consecutive days. The F phase testing week occurred from days 2–7 (per self-report of onset of menses defined as day 1). The L phase testing week occurred 2–7 days post luteinizing hormone surge (per urinary luteinizing hormone testing).

Using identical methods for both testing weeks, participants attended daily clinic visits to biochemically confirm smoking status and complete subjective questionnaires (details below). Participants smoked ad libitum for the first two days of the testing week followed by four days of abstinence. Smoking status was verified by carbon monoxide expired air (<5ppm indicating abstinence), salivary cotinine (<15ng/mL indicating abstinence on fourth day of smoking abstinence only) and, in a subset of the sample, plasma nicotine (<2ng/mL indicating abstinence on the fourth day of smoking abstinence only). Upon completion of the testing week, participants resumed ad libitum smoking for approximately six weeks

(depending on menstrual cycle length) and then completed the same procedures in the alternate menstrual phase. All study procedures were approved by the human subjects committee at the University of Minnesota.

Study Measures

Symptomatology was assessed daily using the following outcome measures (1) the Minnesota Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986; Hughes & Hatsukami, 1998), an 8-item scale measuring nicotine withdrawal symptoms and craving, (2) the Brief Questionnaire of Smoking Urges (QSU-Brief; Tiffany & Drobes, 1991), a 10-item questionnaire that consists of two sub-scales: desire to smoke (Factor 1) and anticipated relief from negative affect (Factor 2), (3) The Positive and Negative Affect Scale (PANAS; Watson, Clark, & Carey, 1988), a 20-item mood assessment scale using a five point Likert-type scale that results in two subscales: positive and negative affect, (4) the Perceived Stress Scale (PSS; Cohen, Kamarch, & Mermelstein, 1983), a 10-item measure assessing perceived stress, and (5) premenstrual symptoms were assessed using the Shortened Premenstrual Assessment Form (PAF; Allen, et al., 1991), a 10-item Likert-type scale with three subscales – affect, pain and water retention – as well as a total score.

Statistical Analyses

Descriptive statistics were calculated for demographics and baseline characteristics (mean and standard deviation for continuous variables, and count and percent for categorical variables). Symptomatology outcomes were defined two ways. The first was the average of the daily measures taken on abstinence days. We assumed peak symptomatology occurred on the second day of abstinence (i.e., day 4 of the testing week). Therefore, the second way was using change scores that were calculated by subtracting day 2 values (i.e., ad libitum smoking) from day 4 values (i.e., day 2 of abstinence). This was done to maximize symptomatology during abstinence and a possible phase effect. Random-intercept models with variables for sequence (carry-over) and time effects were used to investigate the association of menstrual phase and depressive symptoms with the symptomatology outcomes. Models were run with and without a menstrual phase by depressive symptoms interaction for each outcome separately. Results (means, standard errors, and p-values from type 3 tests for fixed effects) from these models are presented in the tables. P-values less than 0.05 were deemed statistically significant. SAS V9.3 (SAS Institute, Cary, NC) was used for the analyses.

Results

Study Sample

A total of 207 participants were enrolled into the study and randomized to testing order. Of these, 47 (22.7%) dropped out prior to starting the first testing week (most were lost to follow-up or had scheduling conflicts and were not able to participate). Nine (0.4%) were excluded given biochemical testing which indicated smoking during the abstinence period and four (0.2%) were excluded for having hormones levels inconsistent with their assigned menstrual phase.

Therefore, the final sample included 147 participants. Overall participants were mostly non-Hispanic White (56 %) with at least a high school diploma or equivalent (93%). The mean Fagerstrom Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) scores were 4.0 ± 2.1 , indicating low to moderate nicotine dependence. CES-D scores the day before quit were similar between those randomized to start in the F phase (10.4 ± 8.0) and the L phase (9.4 ± 8.6 ; $p=0.49$). Those who were randomized to test in the L phase first were significantly more likely to be non-Hispanic White (66%) compared to those who were randomized to test in the F phase first (46%, $p=0.02$). There were no other significant differences based on randomization order.

Symptomatology by Menstrual Phase during Smoking Abstinence—While during ad lib smoking no difference by phase was seen in withdrawal and perceived stress, during acute smoking abstinence, participants reported significantly higher average withdrawal and perceived stress in the L phase compared to the F phase (9.1 ± 0.4 vs. 8.0 ± 0.4 , $p=0.0090$; 23.2 ± 0.6 vs. 20.9 ± 0.6 , $p=0.0006$; respectively; Table 1). Further, for two premenstrual subscales (pain and water retention) as well as total premenstrual symptoms, the L phase had an increase in symptoms whereas the F phase had a decrease in symptoms, $p<0.0001$ (Table 2). However, the affect subscale although no difference by phase in ad lib smoking, had a greater increase during acute smoking abstinence when the L phase was compared to the F phase ($p=0.0353$). There were no other significant differences in either average or change in symptomatology by menstrual phase.

Symptomatology and Depressive Symptoms during Smoking Abstinence—Several positive associations were noted between depressive symptoms and symptomatology. Specifically, higher level of depressive symptoms was significantly associated with higher levels of withdrawal, anticipated relief from negative affect (Factor 2), perceived stress, negative affect, premenstrual affect and total premenstrual symptoms ($p<0.05$; Table 1). Depressive symptoms also had a significant negative association with positive affect ($p=0.0046$). Further, in terms of the change in symptomatology during cessation, a higher level of depressive symptoms was significantly related to smaller change in levels of withdrawal, desire to smoke (Factor 1), perceived stress, negative affect, premenstrual affect, premenstrual pain, and total premenstrual symptoms ($p<0.05$). Greater levels of depressive symptoms were related to larger changes in PANAS positive affect (Table 2). Similar associations between depressive symptoms and symptomatology were seen during ad lib smoking (data not shown).

Symptomatology, Menstrual Phase and Depressive Symptoms during Smoking Abstinence—Menstrual phase was identified as a significant effect modifier between depressive symptoms and two items of symptomatology. First, we observed an interaction in the average of the premenstrual pain subscale such that there was a positive association between depressive symptoms and premenstrual pain seen in the F phase, but not in the L phase (β (SE)= $0.07(0.02)$ vs. β (SE)= $-0.02(0.03)$, $p=0.0126$; respectively). A second interaction was observed between menstrual phase and depressive symptoms on negative affect such that the association between negative affect and depressive symptoms

was stronger in the F phase compared to the L phase (β (SE)=0.27 (0.04) vs. β (SE)=0.14 (0.05), $p=0.0021$; respectively).

Discussion

The present study examined the role of menstrual phase and depressive symptoms in a controlled cross-over design with 147 premenopausal female smokers. Most measures of symptomatology did not significantly vary by menstrual phase as only the averages of withdrawal and perceived stress were greater in the L phase compared to the F phase during smoking abstinence. In contrast, several significant positive associations were observed between the level of depressive symptoms and symptomatology including withdrawal, anticipated relief from negative affect, perceived stress, negative affect, premenstrual affect, and total premenstrual symptoms. The only negative association was between depressive symptoms and positive affect. Two menstrual phase by depressive symptoms interactions were observed indicating that the association between depressive symptoms and negative affect, as well as premenstrual pain, were stronger in the follicular phase compared to the luteal phase.

The literature shows conflicting reports of the effect of menstrual phase on symptomatology. In the present study, while many symptoms were not significantly different by phase, we observed significantly higher levels of withdrawal and perceived stress during the luteal phase as compared to the follicular phase. While several studies have observed higher withdrawal during smoking abstinence in the luteal phase (Allen, et al., 2000; Allen, A., Allen, S., Lunos, & Pomerleau, 2010; Craig, Parrott, & Coomber, 1992; O'Hara, Portser, & Anderson, 1989; Perkins, et al., 2000), other studies have found no difference in withdrawal by phase (e.g., Allen, et al., 1999; Marks, Pomerleau, C., & Pomerleau, O., 1999; Masson, & Gilbert, 1999; Pomerleau, C., Garcia, Pomerleau, O., & Cameron, 1992; Pomerleau, C., Mehringer, Marks, Downey, & Pomerleau, O., 2000; Snively, Ahijevych, Bernhard, & Wewers, 2000; Allen et al., 2008). These conflicting reports may relate to differences in study design (e.g., cohort versus experimental trial and retrospective versus prospective), small sample sizes and the influence of selection bias (e.g., those who enroll in cessation trials may be different than those who enroll in lab-based studies), varying methods of defining menstrual phase (e.g., self-report vs. serum hormonal verification), and the strong correlation between premenstrual and withdrawal symptoms. For example, our present observation of greater withdrawal in luteal phase is consistent with a previous within subject outpatient lab study that used a similar protocol in which participants quit for two short-term periods during each phase (Allen, et al., 2000) whereas in our recent between subject smoking cessation trial we observed higher total withdrawal scores upon smoking abstinence (e.g., follicular phase: 10.35 ± 0.53 , luteal phase: 11.61 ± 0.54) but no menstrual phase difference (Allen, et al., 2010). These data suggest that a within subjects design may yield different results than a between subjects design. The present study also observed significantly higher but decreasing levels of premenstrual symptoms during follicular phase compared to luteal. This significant observation is likely attributable to the timing of the protocol as the follicular phase testing week started the day after the onset of menses, when premenstrual symptoms might still be present, whereas the luteal phase testing week started

two days after the surge of luteinizing hormones, when premenstrual symptoms may not be prominent.

It is notable that out of the eleven symptomatology measures we investigated, nine were significantly associated with the level of depressive symptoms. While all of these symptoms were significantly associated with level of depressive symptoms during ad libitum smoking (data not shown), eight remained statistically significant in the change score analyses. Previous research has indicated that depression (in general) plays an important role in all phases of smoking (Kassel, Stroud, & Paronis, 2003). This is particularly important for women who are more likely to report that smoking reduces negative affect (Cepeda-Benito, Reynoso, & Erath, 2000; Rundmo, Smedslund, & Gotestam, 1997; Weinberger & McKee, 2011). Further depressive symptoms may influence withdrawal symptoms and may be relevant to treatment of nicotine addiction (Egervari, et al., 2012; Langdon, et al., 2013). In one treatment study using nicotine patch, negative affect and somatic features of depression were related to higher levels of nicotine withdrawal (Schnoll, et al., 2013). Another study found baseline depression seemed to have a greater effect on quitting outcome by influencing withdrawal symptoms rather than the type of therapy, level of nicotine dependence or quantity of smoking (Egervari, et al., 2012).

One of our novel findings is the observation of menstrual phase as an effect modifier in the association between depressive symptoms and negative affect, as well as premenstrual pain. These associations were significantly stronger in the follicular phase than the luteal phase. The role of sex hormones in this interplay of depressive symptoms and withdrawal and smoking cessation is complex. While the mechanisms involved in these observations remain unknown, women with depressive symptoms who want to quit smoking may experience less severe symptoms of negative affect if they quit smoking during the luteal phase than during the follicular phase given that the association between depressive symptoms and symptomatology may be stronger during the follicular phase. Additional research is needed to explore this hypothesis.

In addition to the cross-over study design, which limits confounding, this study is also strengthened by its large, heterogeneous sample and the detailed measurement of menstrual phase, depressive symptoms, smoking status, and outcome symptomatology. However, a few limitations are noted. First, given the rigorous nature of the study, selection bias is present given many women were unable to participate due to schedule conflicts. Second, the impact of the observed associations on smoking cessation in the general population of premenopausal smokers is unknown given that those who enrolled knew they would return to smoking within a few days. Third, while we initially aimed to address the effect of menstrual phase on symptomatology within two groups (no depressive symptoms versus depressive symptoms) we were unable to identify two distinct groups. Finally, while the menstrual cycle is a proxy for sex hormones, it is fraught with problems of daily fluctuating levels of hormones. Improved methodology in defining phase and hormone variation may yield clearer results in the field as a whole.

In conclusion this study advances the current state of literature as it is the first to examine the independent and synergistic effects of menstrual phase and depressive symptoms on

smoking- and menstrual-related symptomatology in premenopausal women. We noted more significant associations during smoking abstinence between depressive symptoms and symptomatology versus menstrual phase and symptomatology. Also, the association between depressive symptoms with negative affect and premenstrual pain was stronger during follicular phase compared to luteal phase. Further study is needed to determine the effect of these observations on smoking cessation outcomes, as well as to define the mechanism of menstrual phase and depressive symptoms on smoking- and menstrual-related symptomatology.

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Highlights

- Associations were found between depressive symptoms and symptomatology (70).
- Withdrawal and perceived stress symptoms were higher in the luteal phase (72).
- Menstrual phase modified the effect between depressive symptoms and negative affect (83).
- Menstrual phase modified the effect between depressive symptoms and premenstrual pain (85).

Table 1

Average (Days 3–6) of Smoking and Menstrual Symptomatology during Smoking Abstinence by Menstrual Phase and Depressive Symptoms (n=147)

	Menstrual Phase *			Depressive Symptoms *		Phase by CESD Interaction	
	F Phase Mean $\pm$ SE)	L Phase (Mean $\pm$ SE)	Phase Difference (L-F; Mean $\pm$ SE)	p-value	CES-D (β $\pm$ SE)	p-value	p-value
Smoking-Specific							
Withdrawal (MNWS)	8.0 $\pm$ 0.4	9.1 $\pm$ 0.4	-1.1 $\pm$ 0.4	0.0090	0.23 $\pm$ 0.04	<0.0001	n.s.
Craving (MNWS)	2.9 $\pm$ 0.1	3.0 $\pm$ 0.1	-0.1 $\pm$ 0.1	n.s.	0.01 $\pm$ 0.01	n.s.	n.s.
QSU Factor 1 (QSU)	24.6 $\pm$ 0.7	25.0 $\pm$ 0.7	-0.4 $\pm$ 0.6	n.s.	0.09 $\pm$ 0.06	n.s.	n.s.
QSU Factor 2 (QSU)	16. $\pm$ 0.7	17.6 $\pm$ 0.7	-0.9 $\pm$ 0.6	n.s.	0.14 $\pm$ 0.05	0.0088	n.s.
Mood							
Perceived Stress (PSS)	20.9 $\pm$ 0.6	23.2 $\pm$ 0.6	-2.3 $\pm$ 0.6	0.0006	0.39 $\pm$ 0.05	<0.0001	n.s.
Positive Affect (PANAS)	26.8 $\pm$ 0.7	25.9 $\pm$ 0.8	0.9 $\pm$ 0.5	n.s.	-0.16 $\pm$ 0.06	0.0046	n.s.
Negative Affect (PANAS)	15.0 $\pm$ 0.4	15.6 $\pm$ 0.4	-0.6 $\pm$ 0.4	n.s.	0.15 $\pm$ 0.06	<0.0001	0.0021
Premenstrual Symptoms							
Affect (PAF)	7.1 $\pm$ 0.3	7.5 $\pm$ 0.3	-0.4 $\pm$ 0.3	n.s.	0.15 $\pm$ 0.02	<0001	n.s.
Pain (PAF)	4.4 $\pm$ 0.2	4.3 $\pm$ 0.2	0.1 $\pm$ 0.2	n.s.	0.02 $\pm$ 0.02	n.s.	0.0126
Water (PAF)	4.7 $\pm$ 0.2	4.5 $\pm$ 0.2	0.2 $\pm$ 0.3	n.s.	0.02 $\pm$ 0.02	n.s.	n.s.
Total (PAF)	16.2 $\pm$ 0.5	16.3 $\pm$ 0.6	-0.2 $\pm$ 0.6	n.s.	0.19 $\pm$ 0.05	0.0003	n.s.

* Results are from the main effects models

Change Scores (Day 4-Day 2) of Smoking and Menstrual Symptomatology during Smoking Abstinence by Menstrual Phase and Depressive Symptoms (n=147)

Table 2

	Menstrual Phase*		Depressive Symptoms*		Phase by CES-D Interaction	
	F Phase (Mean ±SE)	L Phase (Mean ±SE)	Phase Difference (L-F; Mean ±SE)	p-value	CES-D (β ±SE)	p-value
Smoking-Specific						
Withdrawal (MNWS)	3.8±0.5	4.3±0.5	-0.6±0.7	n.s.	-0.12±0.04	n.s.
Craving (MNWS)	1.2±0.1	1.3±0.1	-0.1±0.1	n.s.	-0.02±0.01	n.s.
QSU Factor 1 (QSU)	9.0±0.8	8.5±0.9	0.5±1.1	n.s.	-0.23±0.08	n.s.
QSU Factor 2 (QSU)	6.8±0.7	8.1±0.8	-1.2±0.9	n.s.	-0.09±0.07	n.s.
Mood						
Perceived Stress (PSS)	2.1±0.6	3.8±0.7	-1.7±0.9	n.s.	-0.33±0.06	<0.0001
Positive Affect (PANAS)	-1.3±0.6	-2.1±0.7	0.8±0.9	n.s.	0.29±0.06	<0.0001
Negative Affect (PANAS)	1.5±0.5	2.1±0.6	-0.6±0.7	n.s.	-0.23±0.05	<0.0001
Premenstrual Symptoms						
Affect (PAF)	0.1±0.3	0.9±0.3	-0.8±0.4	0.0353	-0.13±0.03	<0.0001
Pain (PAF)	-1.1±0.2	0.1±0.2	-1.3±0.3	<0.0001	-0.05±0.02	0.0074
Water (PAF)	-1.2±0.2	0.2±0.2	-1.4±0.3	<0.0001	-0.03±0.02	n.s.
Total (PAF)	-2.3±0.5	1.2±0.6	-3.5±0.7	<0.0001	-0.21±0.05	<0.0001

* Results are from the main effects models