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Severity of Withdrawal Symptomatology in Follicular versus Luteal Quitters: The Combined Effects of Menstrual Phase and Withdrawal on Smoking Cessation Outcome

Alicia M. Allen^a, Sharon S. Allen^a, Scott Lunos^b, and Cynthia S. Pomerleau^c

^a Department of Family Medicine & Community Health, University of Minnesota, Medical School, 717 Delaware Street SE, Minneapolis, MN 55414

^b Biostatistical Design and Analysis Center, University of Minnesota, Clinical and Translational Science Institute, 717 Delaware Street SE, Minneapolis, MN 55414

^c Department of Psychiatry University of Michigan School of Medicine, Rachel Upjohn Building, Room 2137, Ann Arbor, MI 48105

Abstract

Women are at an increased risk of relapse after a smoking cessation attempt. While the reasons for this phenomenon are not fully understood, recent research indicates that both the menstrual cycle and negative symptomatology may play a role. The goal of this study was to describe the association between withdrawal symptoms during attempted smoking cessation, and to investigate the impact of these symptoms on smoking cessation outcomes as defined by 7-day point prevalence at 14 and 30 days. Negative symptoms associated with the premenstrual period were also assessed. Participants (n=202) were 29.8 (SD ± 6.6) years old and smoked 16.6 (SD ± 5.6) cigarettes per day. They were randomly assigned to quit smoking in the follicular (n=106) or luteal (n=96) menstrual phase. We observed several significantly more severe premenstrual and withdrawal symptoms in the luteal phase. Regardless of quit phase, most withdrawal symptoms were associated with an increased risk of relapse at 14 and 30 days post quit date. Participants attempting to quit smoking in the follicular phase who had higher levels of Anger and Craving were more likely to relapse to smoking at 14-days (OR=2.00, p-value=0.026; OR=2.63, p-value=0.006; respectively). These data suggest that the menstrual cycle may play a role in smoking cessation outcome, as well as in the symptomatology experienced during a cessation attempt.

Keywords

Smoking Cessation; Women; Menstrual Cycle; Withdrawal Symptoms; Premenstrual Symptoms

Corresponding Author: Alicia M. Allen, University of Minnesota, Department of Family Medicine and Community Health, 717 Delaware Street SE, Minneapolis, MN 55414, Phone: (612) 624-0896, Fax: (612) 626-4610, alle0299@umn.edu.

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1. Introduction

Despite the fact that women are at increased risk of premature morbidity and mortality associated with cigarette smoking as compared to men (USDHHS, 2001), women have lower rates of smoking cessation. A recent review (Perkins, 2001) indicates this sex disparity in smoking cessation may be due to concerns about weight gain, lack of social support, increased negative affect and/or increased susceptibility to social-environmental cues.

Another factor that may undermine a woman's ability to quit is the impact of the menstrual cycle. Premenstrual symptoms have been shown to have a moderate to high correlation with withdrawal symptoms, suggesting an additive effect that may jeopardize a quit attempt (Allen et al, 1996; Carpenter et al 2006; O'Hara et al, 1989; Pomerleau et al, 1992). Several studies have observed an increase in withdrawal and/or craving in the luteal phase under conditions of both ad libitum smoking and abstinence (Allen, et al 1996; Allen et al, 2009c; Franklin et al, 2004; O'Hara et al, 1989), suggesting that the luteal phase may be related to an increased risk of smoking relapse. Others, however, have failed to find this effect (De Bon, et al 1995; Marks, et al 1999; Masson & Gilbert, 1999).

The possible effects of menstrual phase on quitting are inferential in most of the above studies. A recent clinical trial by our group raised the possibility that the opposite may be true –a quit attempt in the follicular phase may be associated with a less favorable outcomes as women who attempted to quit in the follicular phase had fewer days to relapse (Allen et al, 2009b; Allen et al, 2009d). Further, our findings of significant increases in craving, withdrawal and smoking urges observed in the days preceding relapse to smoking regardless of menstrual phase, and a rapid abatement of symptoms following relapse (Allen, et al 2008) may indicate that phase effects are diminished or overpowered by emergent withdrawal symptomatology. We have also reported a possible impact of phase-related variability on success in quitting smoking (Allen et al, 2009c), such that women who experience greater phase-related variability in premenstrual symptoms and urge to smoke during ad libitum smoking were more likely to relapse after a quit attempt.

In order to follow up on these findings and to elucidate factors that might contribute to menstrual phase differences in successful quitting, we studied 1) the severity of withdrawal symptomatology in women attempting to quit in either the follicular or luteal phase, and 2) the combined effects of withdrawal and menstrual phase on smoking cessation outcome. Smoking withdrawal symptoms (Craving, Anger, Anxiety, Concentration, Restlessness, Appetite/Weight Gain, Depression, Insomnia and Total Withdrawal) were assessed during the first six days of the cessation attempt. Premenstrual symptoms (Pain, Affect, Water and Total Premenstrual) were also queried. Smoking cessation outcome was defined as point prevalence abstinence at 14 and 30 days. We hypothesized that withdrawal symptomatology would be more severe in the luteal phase than in the follicular phase. We also expected the separate and combined effects of withdrawal symptomatology upon smoking cessation outcomes to vary by menstrual phase.

2. Methods

2.1 Protocol

Women aged 18-40 were recruited to participate in a randomized 26-week outpatient treatment trial designed to assess the effects of the menstrual phase on smoking relapse (Allen et al, 2009d). To be eligible, women had to smoke at least 10 cigarettes per day for the past year, have regular menstrual cycles for the past six months, and not be using any hormones or psychotropic medications. Women with a Shortened Premenstrual Assessment Form (PAF; Allen et al, 1991) score of 10 or less were excluded as this score indicates no premenstrual

symptoms. Candidates who appeared to be eligible attended a screening visit (arbitrarily scheduled with respect to menstrual phase) where informed consent was obtained and the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al, 1991) administered, along with other medical and smoking behavior forms. Those who enrolled were randomly assigned to a quit date in either the Follicular (F) phase (four to six days after the onset of menses) or the Luteal (L) phase (six to eight days after ovulation). Menstrual phase was determined by self-report and urine luteinizing hormone testing. Participants were provided with individualized behavioral counseling and self-help materials for smoking cessation. (For a detailed description of recruitment, inclusion/exclusion criteria, randomization and study protocol please see Allen et al, 2009d).

2.2 Measures

Participants completed the PAF, Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1998), Questionnaire of Smoking Urges (QSU; Tiffany & Drobes, 1991), a smoking diary, and a menstrual cycle diary daily during the first six days of a smoking cessation attempt beginning on their assigned quit date. The PAF is a 10-item subjective measure used to assess symptoms related to premenstrual syndrome. The total PAF score is an indicator of the overall severity of premenstrual symptoms (Total Premenstrual). The PAF is divided into three subscales: Water, Affect, and Pain. The MNWS is an 8-item scale used to assess nicotine withdrawal symptoms with an overall withdrawal symptomatology score (Total Withdrawal) and single item scores for Craving, Anger, Anxiety, Concentration, Restlessness, Appetite/Weight Gain, Depressed, and Insomnia. The QSU, a measure of smoking urges, consists of 32-items used to assess two factors. Factor 1 is a measure of primary intention and desire to smoke; Factor 2 is defined as an overwhelming desire to smoke to relieve withdrawal-associated negative affect. Smoking cessation outcomes were determined using seven-day point-prevalence smoking abstinence at 14 and 30 days after the participant's assigned quit date. Smoking abstinence was assessed via self-report, carbon monoxide levels (< 5ppm indicating abstinence) and saliva cotinine (< 15 ng/mL indicating abstinence).

2.3 Analysis

Repeated measures models were used to test for group differences (F vs. L) in PAF (Water, Affect, Pain, and Total Premenstrual), MNWS (Craving, Anger, Anxiety, Concentration, Restlessness, Appetite/Weight Gain, Depressed, Insomnia, and Total Withdrawal), and QSU (Factor 1 and Factor 2) over the first six days of attempted abstinence (including quit day). The within-subject correlation of the repeated measures was modeled with an unstructured covariance matrix. The following covariates were included in each model as fixed effects: randomization phase (F vs. L), day of attempted cessation (0-5), number of cigarettes smoked on the corresponding day of attempted smoking cessation, and baseline FTND score. To assess whether the association between symptoms and smoking cessation outcome (seven-day point-prevalence at 14 and 30 days) varied by menstrual phase, logistic regression with randomization group, average symptom score over the first six days, and their interaction were included as covariates. P-values less than 0.05 were considered statistically significant. P-values for interactions were considered significant if less than 0.10. Statistical analysis was performed using SAS V9.1.3.

3. Results

3.1 Study Participants

A total of 1,611 women were assessed for study eligibility, 1,317 women were excluded for not meeting initial study criteria or being unwilling to participate. The remaining 294 women were randomized to F group (n=147) and L group (n=147). Of the 294 randomized participants, 202 (68.7%) reached their quit date and were included in our analyses. Participants who

withdrew from the study prior to their quit date had a significantly shorter duration of previous quit attempts, fewer years of education, and lower levels of income (see Allen, et al 2009d for details). The drop-out rate did not vary by randomization group ($\chi^2=1.58$, p -value=0.210).

Participants ($n=202$) were, on average, 29.8 ($SD \pm 6.6$) years old, completed 13.7 ($SD \pm 2.0$) years of education, and 82% were White. They smoked, on average, 16.6 ($SD \pm 5.6$) cigarettes per day and had an average FTND score of 4.1 ($SD \pm 2.0$). Compared to participants randomized to the L phase, participants randomized to the F phase reported smoking fewer cigarettes per day (17.5 ± 6.5 vs. 15.8 ± 4.7 , p -value=0.033, respectively) and had higher FTND scores (3.8 ± 2.1 vs. 4.4 ± 1.9 , p -value=0.031, respectively). There were no other significant differences in demographics or smoking behavior. See Allen et al, 2009d for a detailed description of the demographic and smoking status outcomes.

3.2 Premenstrual and Withdrawal Symptomatology by Menstrual Phase

Participants who attempted smoking cessation during the L phase had higher levels of the following symptoms (see Table 1) during the first six days of attempted abstinence: Water Subscale (5.55 ± 0.27 vs. 4.63 ± 0.28 , p -value=0.017), Pain Subscale (5.13 ± 0.23 vs. 4.31 ± 0.23 , p -value=0.011), Total Premenstrual Score (19.21 ± 0.73 vs. 17.17 ± 0.75 , p -value=0.047), and the item of Appetite/Weight Gain (2.02 ± 0.10 vs. 1.36 ± 0.10 , p -value<0.001). The L phase also had a higher level in the Total Withdrawal score but this did not reach statistical significance (L phase: 11.61 ± 0.54 , F Phase: 10.35 ± 0.53 , p -value=0.093). All participants, regardless of assigned menstrual phase quit date, reported significantly higher levels of several withdrawal and premenstrual symptomatology during the first two days of a quit attempt, compared to the sixth day, including the Affect Subscale, Total Premenstrual Score, Total Withdrawal Score, Factor 1 Subscale, Factor 2 Subscale and items of Craving, Anger, Anxiety, Concentration, and Restlessness in the MNWS (data not shown).

3.3 Associations between Premenstrual and Withdrawal Symptomatology and Smoking Cessation Outcomes

Regardless of quit phase, most withdrawal symptoms were significantly associated with smoking cessation outcome (see Table 2) with the exception of items of Appetite/Weight Gain (at 14- and 30-days, Restlessness (at 14-days) and Anger (at 30-days). No premenstrual symptoms were associated with smoking cessation outcome.

Among participants attempting to quit smoking in the F phase, those who had higher levels of Anger and Craving in the first six days of attempted abstinence were more likely to have relapsed to smoking at 14-days (Odds Ratio = 2.00, 95% Confidence Interval = 1.09-3.68, p -value = 0.026; Odds Ratio = 2.63, 95% Confidence Interval = 1.33-5.21, p -value = 0.006; respectively). These relationships were not significant at 30-days. No differences were observed for either time point among participants attempting to quit in the L phase. No other significant interactions were found between menstrual phase, symptoms, and smoking cessation outcomes (data not shown).

4. Conclusion

As expected, women who attempted smoking cessation during the luteal phase had significantly more severe premenstrual symptomatology as seen in the water subscale, pain subscale, and total premenstrual score (but not affect subscale) compared to women who attempted smoking cessation in the follicular phase.

We also observed a higher score on the appetite/weight gain item on the withdrawal symptom checklist among women attempting to quit in the luteal phase—possibly because increased

appetite during the luteal phase has also been identified as a premenstrual effect independent of smoking or smoking abstinence (Dickerson et al, 2003).

Most withdrawal symptoms were significantly associated with point prevalence at both 14 and 30 days. No premenstrual symptom was significantly related to smoking cessation outcome.

Finally, we observed significant menstrual phase differences in the association between smoking cessation outcomes and four symptoms (craving item, anger item, affect subscale, and total premenstrual score). Higher levels of craving and anger were associated with increased risk of relapse, but only for those who attempted to quit in the follicular phase, suggesting that menstrual phase may moderate the relationship between these symptoms and smoking cessation outcome. Possibly, for example, women who attempt smoking cessation in the follicular phase may be more susceptible to unexpected negative symptomatology, which may, in turn, lead to smoking relapse.

The results of this study extend our previous findings in the same participants that higher levels of craving during ad libitum smoking are associated with smoking relapse among women who quit in the follicular phase (Allen et al, 2009a) and that quitting in follicular phase is associated with poorer smoking cessation outcomes (Allen et al, 2009b; Allen et al, 2009d). We have also shown in our earlier work that symptoms of withdrawal, craving and smoking urges peaked on the days immediately prior to smoking relapse, then quickly subsided (Allen et al, 2008).

Animal studies have shown that higher levels of estrogen (as seen in the follicular phase) are associated with more reinforcing effects of addictive drugs, whereas higher levels of progesterone (as seen in the luteal phase) are associated with less reinforcing effects (e.g. Lynch et al, 2001; Mello et al, 2007). While the precise mechanisms underlying these observations have yet to be explained, it is likely that sex hormones mediate the observed phase-specific association between withdrawal symptoms and smoking cessation outcome.

Although the overlap of withdrawal and premenstrual symptomatology complicates interpretation of all studies of smoking across the menstrual cycle, inclusion of the variable craving (*not* a premenstrual symptom) helps to offset this concern. Some additional limitations of this study should also be acknowledged: 1) the study relied heavily on self-report; 2) many candidates were either ineligible or chose not to participate in the study, limiting the generalizability of our findings; and 3) normal fluctuations in hormonal levels may have influenced daily ratings and thus limited our ability to detect phase effects.

Despite these limitations, our hypotheses were largely confirmed. Differences in severity of withdrawal symptoms were observed based on the menstrual phase of an abstinence attempt. Moreover, menstrual phase and severity of withdrawal symptomatology had a combined effect on the likelihood of successful quitting. Further research will be needed to elucidate the mechanisms underlying our observations, to resolve discrepancies in the literature regarding the effects of menstrual phase on outcome (see Franklin & Allen, 2009, for the possible contribution of methodological differences), and to guide the development of cessation strategies that take into account the influence of menstrual phase on withdrawal discomfort and ability to abstain.

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Table 1
Premenstrual and Withdrawal Symptoms by Menstrual Cycle Phase during Attempted Smoking Cessation (n=202)

	F Phase * (n=106) mean ± SE	L Phase * (n=96) mean ± SE	Coefficient	p-value
Premenstrual Symptoms (PAF)				
Water Subscale	4.63 ± 0.28	5.55 ± 0.27	-0.91	0.017
Affect Subscale	8.13 ± 0.41	8.74 ± 0.40	-0.61	0.287
Pain Subscale	4.31 ± 0.23	5.13 ± 0.23	-0.82	0.011
Total Premenstrual	17.17 ± 0.75	19.21 ± 0.73	-2.04	0.047
Smoking Withdrawal Symptoms				
Craving (MNWS)	2.78 ± 0.08	2.79 ± 0.08	-0.01	0.910
Anger (MNWS)	2.04 ± 0.10	2.03 ± 0.10	0.02	0.912
Anxiety (MNWS)	1.74 ± 0.10	1.75 ± 0.10	-0.01	0.955
Concentration (MNWS)	1.50 ± 0.10	1.67 ± 0.10	-0.16	0.249
Restlessness (MNWS)	1.60 ± 0.10	1.78 ± 0.10	-0.18	0.201
Appetite/Weight Gain (MNWS)	1.36 ± 0.10	2.02 ± 0.10	-0.66	<0.001
Depressed (MNWS)	1.13 ± 0.09	1.19 ± 0.09	-0.06	0.621
Insomnia (MNWS)	1.06 ± 0.10	1.14 ± 0.10	-0.08	0.571
Total Withdrawal (MNWS)	10.35 ± 0.53	11.61 ± 0.54	-1.27	0.093
Factor 1 (QSU)	3.97 ± 0.09	4.00 ± 0.09	-0.03	0.823
Factor 2 (QSU)	3.31 ± 0.12	3.42 ± 0.13	-0.11	0.539

* The least square means for the main effect of symptom within the randomly assigned Follicular (F) or Luteal (L) phase.

Table 2
Premenstrual and Withdrawal Symptoms by Smoking Cessation Outcomes (n=202)[†]

	14-Day Point Prevalence Odds Ratio (95% Confidence Interval)	30-Day Point Prevalence Odds Ratio (95% Confidence Interval)
Premenstrual Symptoms (PAF)		
Water Subscale	1.00 (0.90-1.13)	0.96 (0.86-1.07)
Affect Subscale	Luteal: 1.00 (0.90-1.11) Follicular: 1.20 (1.00 -1.43)	1.07 (0.98-1.18)
Pain Subscale	1.01 (0.88-1.16)	0.96 (0.84-1.10)
Total Premenstrual	Luteal: 0.99 (0.94-1.04) Follicular: 1.11 (0.99 -1.24)	Luteal: 0.98 (0.94-1.03) Follicular: 1.10 (0.98 -1.23)
Smoking Withdrawal Symptoms		
Craving (MNWS)	Luteal: 1.25 (0.73-2.14) Follicular: 2.63 (1.33 -5.21) [*]	1.67 (1.09-2.56) [*]
Anger (MNWS)	Luteal: 0.98 (0.64 -1.51) Follicular: 2.00 (1.09-3.68) [*]	1.26 (0.89-1.78)
Anxiety (MNWS)	1.57 (1.11-2.22) [*]	1.59 (1.12-2.25) [*]
Concentration (MNWS)	1.73 (1.22-2.45) [*]	2.11 (1.44-3.08) [*]
Restlessness (MNWS)	1.40 (1.00-1.98)	1.43 (1.01-2.02) [*]
Appetite/Weight Gain (MNWS)	1.27 (0.90-1.79)	1.25 (0.88-1.77)
Depressed (MNWS)	2.01 (1.32-3.05) [*]	1.78 (1.19-2.68) [*]
Insomnia (MNWS)	1.63 (1.13-2.35) [*]	1.76 (1.20-2.59) [*]
Total Withdrawal (MNWS)	1.11 (1.04-1.19) [*]	1.12 (1.04-1.20) [*]
Factor 1 (QSU)	1.88 (1.32-2.68) [*]	1.92 (1.33-2.76) [*]
Factor 2 (QSU)	1.78 (1.31-2.41) [*]	1.62 (1.19-2.19) [*]

[†] Main effect for symptom from a logistic regression model with symptom and menstrual phase as covariates. If the interaction between menstrual phase and symptom was significant at 0.10, the odds ratio for symptom was estimated within each menstrual phase. A non-significant interaction means that the symptom effect on the smoking cessation outcome did not differ between menstrual phases.

^{*} p < 0.05