Published in final edited form as:

Hum Psychopharmacol. 2009 August ; 24(6): 503–506. doi:10.1002/hup.1039.

Circadian patterns of *ad libitum* smoking by menstrual phase

Alicia M. Allen*, Marc Mooney, Rima Chakraborty, and Sharon S. Allen

Medical School, University of Minnesota, Minnesota, USA

Abstract

Objective—Recent research suggests nicotine metabolism may be influenced by sex hormones. Thus, we hypothesized that circadian smoking patterns would vary by menstrual phase.

Methods—Healthy female smokers ($n = 31$) between the ages of 18 and 40 with regular menstrual cycles, and not using hormones or psychotropic medications, were recruited for a randomized clinical study. Subjects recorded the time of each cigarette smoked and their menstrual phase with daily diaries prospectively for one complete menstrual cycle of *ad libitum* smoking. Analyses included Poisson regression to assess variations in the rate of smoking during waking hours (i.e., 6:00 a.m. and 12:00 midnight) and circadian smoking patterns by menstrual phase.

Results—Participants were 29.61 ± 5.44 years of age and smoked 16.93 ± 5.37 cigarettes per day. Participants had a lower rate of smoking during waking hours in the follicular phase as compared to the menses phase. There were no significant menstrual phase differences in the circadian smoking patterns.

Conclusions—These results offer further support for the influence of sex hormones on smoking behavior, but not on circadian patterns of smoking. Additional research is needed to study the direct relationship between nicotine metabolism, sex hormones, menstrual phase, and smoking behavior.

Keywords

women; smoking; menstrual cycle; circadian patterns

INTRODUCTION

Research indicates female smokers may be more likely to relapse after an attempt at smoking cessation compared to men (Bjornson *et al.*, 1995). Recent research has indicated that the menstrual cycle may play a role in undermining quit attempts (Carpenter *et al.*, 2006; Franklin *et al.*, 2004; Allen *et al.*, 2008; Allen *et al.*, 2009). Although the precise mechanism of this relationship remains unknown, it has been suggested that ovarian hormones alter nicotine metabolism. A recent study by Benowitz *et al.* (2006) indicated post-menopausal females and males had slower metabolism of nicotine compared to pre-menopausal females. Further, females using combined estrogen–progesterone contraceptive

*Correspondence to: A. M. Allen, Medical School, Department of Family Medicine and Community Health, University of Minnesota, 2701 University Avenue SE, Suite 201, Minneapolis, MN 55414. Tel: 612-627-1818; Fax: 612-627-4899, USA. alle0299@umn.edu.

pills had faster nicotine metabolism than females using progesterone-only contraceptives (Benowitz *et al.*, 2006). These findings suggest that sex hormones may effect smoking behavior across the menstrual cycle. However, the clinical literature on this topic is mixed. A number of studies have observed no differences in cigarettes smoked per day by menstrual phase (Allen *et al.*, 2009; Allen *et al.*, 1996; Allen *et al.*, 1999; Franklin *et al.*, 2004), whereas other studies have noted an increase in cigarettes smoked per day during the luteal phase (Craig *et al.*, 1992; Snively *et al.*, 2000; Marks *et al.*, 1994). All these studies are limited since their evaluation was on the total number of cigarettes smoked per 24 h day, without regard to the circadian patterns in which these cigarettes were smoked (e.g., the hourly rate of smoking over the 24 h day). Gender differences in smoking topography (Eissenberg *et al.*, 1999; Perkins, 1999) have been identified, suggesting sex hormones may play a role in smoking behavior on a more refined level than absolute number of cigarettes smoked per day.

To our knowledge, the present report is the first to longitudinally investigate *ad libitum* circadian smoking patterns by menstrual phase using a within subject design. The current study aims are to: (1) assess circadian patterns of smoking for the four menstrual phases: menses (M), follicular (F), luteal (L), and late luteal (LL), and (2) investigate the rate of smoking during waking hours (i.e., 6:00 a.m. to 12 midnight) for the same four menstrual phases. Numerous research studies in the last 30 years indicate that smokers show a characteristic steep rise in smoking upon waking, reflecting efforts to restore plasma nicotine levels depleted during sleep (e.g., Mooney *et al.*, 2006). We hypothesized this typical circadian pattern of smoking would differ by menstrual phase. Since estrogen is suspected to stimulate nicotine metabolism, we anticipated a steeper rise in the number of cigarettes smoked during the morning hours of F phase (when estradiol is at its peak) as compared to the other phases of the menstrual cycle. Further, we hypothesized that the rate of smoking during waking hours would not vary by menstrual phase, given previous work by our group which indicated no differences in total number of cigarettes smoked per 24 h day (Allen *et al.*, 1996; Allen *et al.*, 1999; Allen *et al.*, 2009).

METHODS

Study participants

Thirty-three participants were enrolled in this study, 31 (93.9%) were included in these analyses and two (6.1%) were excluded due to lost-to follow-up after study enrollment. To be eligible for the study, participants had to be between the ages of 18 and 40, smoke at least 10 cigarettes per day for at least the past year, have regular menstrual cycles, not be using any hormones or psychotropic medications, and be motivated to quit smoking (see Allen *et al.*, 2008 for details on inclusion/exclusion criteria).

Study procedures

This study was approved by the University of Minnesota Institutional Review Board. Participants were recruited through local advertising. The screening process included assessment of study eligibility using self-reported medical, menstrual, and smoking histories, measurement of breath carbon monoxide (≥ 5 ppm indicative of current smoking),

and completion of demographic and smoking history forms, including the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton *et al.*, 1991). Informed consent was obtained before study enrollment and data collection.

Following screening, participants were instructed to prospectively record the time each cigarette was smoked on a daily paper diary provided to the participants at the screening visit. The diary included 20 blank lines for the subject to write down the time each cigarette was smoked. Subjects were instructed to carry the diary with them at all times. To discourage inaccurate retrospective reporting, they were told there was no penalty for missing forms. Participants attended weekly visits prior to their assigned quit date at which study staff collected completed smoking and menstrual diaries, verified smoking status (by CO levels), and encouraged participants to continue smoking at their baseline level until their assigned quit date. Participants were followed for one complete menstrual cycle of *ad libitum* smoking and one complete menstrual cycle of attempted smoking cessation (results of smoking intervention are reported elsewhere; Allen *et al.*, 2009). Study participants were compensated for participation.

To control for an order effect, participants were randomized to begin data collection during either the F phase (day 4–8) or the L phase (6–8 days after ovulation), with day 1 defined as the onset of menses. Menstrual cycle was monitored via menstrual calendars and urine luteinizing hormone (LH) testing (for further details see Allen *et al.*, 2008 for details). For the purposes of these analyses, menstrual phases were defined as follows: M phase includes the days of self-reported active bleeding (range of 3–8 days). L and LL phases are days 8–14 and 1–7, respectively, prior to the onset of the next self-reported menses. F phase was defined as the days between M and L phases up to a maximum of 10 days since the follicular phase (dependent on when the follicle starts to develop) has the most variability in the menstrual cycle.

Statistical analysis

All analyses were conducted using the statistical analysis system version 9.1.3 (SAS, 2008). Values of $p < 0.05$ were considered statistically significant, based on two-tailed tests. Seven of the 31 (22.5%) participants enrolled had one or more phases of missing data. Given these missing data, the sample size for each menstrual phase is as follows: M ($n = 24$), F ($n = 28$), L ($n = 29$), and LL ($n = 25$). Demographics and baseline smoking behavior was computed using data collected at the screening visit. Self-recorded smoking counts are summarized in 2 h intervals or bins (i.e., the day was divided into 12, 2 h bins; Frederiksen and Frazier, 1977). These bins were then used to describe the circadian pattern of smoking. Counts were analyzed with the GLIMMIX procedure. This mixed effects approach accommodates correlated data, induced by repeated observations of the same participants. More specifically, conditional upon the random effects (e.g., intercepts, slopes, quadratic terms, etc.), the outcome measure is Poisson distributed. A Poisson regression model was developed that included effects of menstrual phase, time of day during waking hours (from 6:00 a.m. to midnight), a quadratic term for time of day, and the interactions between phase and the two time of day terms.

RESULTS

Demographics and smoking behavior

Study participants ($n = 31$) were, on average, 29.61 (standard deviation [S.D.] ± 5.44) years of age with an average of 13.90 ± 1.85 years of education and 29% were non-white. They smoked a mean of 16.93 ± 5.37 cigarettes per day. Their average FTND score was 4.68 ± 2.08 .

Circadian smoking patterns by menstrual phase

Pattern of cigarette smoking across the 24 h day (averaged in 2 h bins) by menstrual phase are displayed in Figure 1. Because relatively little smoking occurred in the over night hours, analyses were restricted to the waking day (6:00 a.m. to midnight). Significant linear, $F(1, 31) = 6.71, p = 0.0145$, and quadratic $F(1, 835) = 5.55, p = 0.0187$ effects were observed, reflecting a steep rise in smoking rate in early morning hours, followed by stable rate of smoking across the balance of the day.

Waking smoking rate by menstrual phase

Significant differences in smoking rate (cigarettes/2 h bin) as a function of phase were observed: M ($M = 1.61, SE = 0.08$), F ($M = 1.45, SE = 0.07$), L ($M = 1.51, SE = 0.07$), and LL ($M = 1.54, SE = 0.07$; $F(3, 835) = 5.44, p = 0.0010$). *Post hoc* comparisons, using a Tukey-Kramer adjustment to maintain Type I error rate, showed a lower rate of smoking occurred in the F phase as compared to the M phase during the waking day ($t(835) = 4.02, p = 0.0004$).

DISCUSSION

The results of the current study indicate the overall circadian pattern of smoking did not vary by menstrual phase. As expected, we observed a sharp rise in number of cigarettes smoked in the early morning, followed by a stable smoking pattern during the remainder of the day. Contrary to our hypothesis, we also observed a lower rate of smoking during waking hours in the follicular phase as compared to the menses phase.

This study raises a number of questions with regards to the impact of sex hormones on smoking behavior. Our results suggest that sex hormones may not play a role in the circadian smoking patterns. This agrees with previous results (Mooney *et al.*, 2006), which showed no gender differences in smoking patterns. However, gender differences and role of sex hormones may present as differences in nicotine withdrawal symptomatology, rather than changes in smoking behavior as hypothesized. Differences in withdrawal by menstrual phase have been observed (Allen *et al.*, 1996; De Bon *et al.*, 1995), where withdrawal during *ad libitum* smoking has been observed to be higher in the late luteal and menses phases compared to the follicular and ovulatory phases. A confounding issue here might be premenstrual symptoms which are prevalent in the late luteal phase and correlate with withdrawal symptoms (Allen *et al.*, 1996). Research is mixed on gender differences of craving and withdrawal symptoms. Some studies (Pomerleau *et al.*, 2005; Svikis *et al.*, 1986) show no gender difference while others indicate women experience greater

withdrawal during smoking cessation than men (Leventhal *et al.*, 2007; Hogle and Curtin, 2006).

When examining the rate of smoking during waking hours we observed significant phase effects; specifically, the follicular phase was associated with a lower rate than menses phase. Albeit the magnitude of this difference is small and the clinical importance may not be significant. Since by nature the follicular phase is the most variable in length, perhaps a tighter window for follicular phase i.e., 4–5 days right before ovulation when estradiol is higher, might provide more information about the role of estrogen. Further, daily estradiol measurements are needed to determine if this hormone effects the metabolism of nicotine and hence the smoking rate. Lastly, the accuracy of paper records is limiting, although we did not have electronic data collection at the time of the study.

While this study has several strengths, including its prospective nature and randomized design, there are several study limitations. These limitations include a relatively small and homogenous study sample, the collection of self-reported data using paper diaries, and no measurement of sex hormones.

CONCLUSION

Our results indicate that while the menstrual phase does not appear to play a role in circadian smoking patterns, there may be a relationship between menstrual phase and *ad libitum* rate of smoking during waking hours which varied by phase (i.e., lower in follicular compared to menses). Additional studies should include a larger, more diverse study sample, pharmacokinetic measurements of sex hormones and nicotine levels, as well as electronic capture of smoking patterns. This would help define the relationship between smoking patterns and sex hormones which could lead to the development of more effective smoking cessation interventions for women.

ACKNOWLEDGEMENTS

This work was funded by NIDA Grant 2-R01-DA08075. Dr Marc Mooney is supported by NIDA Career Development Award K01-DA-019446. Rima Chakraborty was supported by grants from the Multicultural Summer Research Opportunity Program and the University of Minnesota Undergraduate Research Opportunity Grant. We also thank our research staff—Tracy Bade, Jennifer Widenmier, and Roshan Paudel—for help with study management, participant recruitment, data measurement, and data entry.

REFERENCES

- Allen SS, Allen AM, Pomerleau CS. Influence of phase-related variability in premenstrual symptomatology, mood, smoking withdrawal, and smoking behavior during ad libitum smoking, on smoking cessation outcome. *Addict Behav.* 2009; 34:107–111. [PubMed: 18818024]
- Allen SS, Bade T, Center B, Finstand D, Hatsukami D. Menstrual phase effects on smoking relapse. *Addiction.* 2008; 103:809–821. [PubMed: 18412759]
- Allen S, Hatsukami D, Christianson D, Nelson D. Symptomatology and energy intake during the menstrual cycle in smoking women. *J Subst Abuse.* 1996; 8:303–319. [PubMed: 8934436]
- Allen SS, Hatsukami DK, Christianson D, Nelson D. Withdrawal and pre-menstrual symptomatology during the menstrual cycle in short-term smoking abstinence: effects of menstrual cycle on smoking abstinence. *Nicotine Tob Res.* 1999; 1:129–142. [PubMed: 11072394]

- Benowitz NL, Lessov-Schlaggar CN, Swan GE, Peyton J 3rd. Female sex and oral contraceptive use accelerate nicotine metabolism. *Clin Pharmacol*. 2006; 79:480–488.
- Bjornson W, Rand C, Connett JE, Lindgreen P, Nides M, Pope F, et al. Gender differences in smoking cessation after three years in the lung health study. *Am J Public Health*. 1995; 85:223–230. [PubMed: 7856782]
- Carpenter MJ, Upadhyaya HP, LaRowe SD, Saladin ME, Brady KT. Menstrual cycle phase effects on nicotine withdrawal and cigarette craving: a review. *Nicotine Tob Res*. 2006; 8:627–638. [PubMed: 17008190]
- Craig D, Parrott A, Coomber J. Smoking cessation in women: effects of the menstrual cycle. *Int J Addict*. 1992; 27:697–706. [PubMed: 1612821]
- DeBon M, Klesges RC, Klesges LM. Symptomatology across the menstrual cycle in smoking and nonsmoking women. *Addict Behav*. 1995; 3:335–343. [PubMed: 7653315]
- Eissenberg T, Adams C, Riggins EC 3rd, Likness M. Smokers' sex and the effects of tobacco cigarettes: subject-rated and physiological measures. *Nicotine Tob Res*. 1999; 4:317–324. [PubMed: 11072428]
- Franklin TR, Napier K, Ehrman R, Gariti P, O'Brien CP, Childress AR. Retrospective study: influence of menstrual cycle on cue-induced cigarette craving. *Nicotine Tob Res*. 2004; 6:171–175. [PubMed: 14982700]
- Frederiksen LW, Frazier M. Temporal distribution of smoking. *Addict Behav*. 1977; 2:187–194. [PubMed: 607790]
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The fagerstrom test for nicotine dependence: a revision of the fagerstrom tolerance questionnaire. *Br J Addict*. 1991; 86:1119–1127. [PubMed: 1932883]
- Hogle JM, Curtin JJ. Sex differences in negative affective response during nicotine withdrawal. *Psychophysiology*. 2006; 4:344–356. [PubMed: 16916430]
- Leventhal AM, Waters AJ, Boyd S, et al. Associations between Cloninger's temperament dimensions and acute tobacco withdrawal. *Addict Behav*. 2007; 12:2976–2989. [PubMed: 17624682]
- Marks J, Hair C, Klock S, Ginsburg B, Pomerleau C. Effects of menstrual phase on intake of nicotine, caffeine, and alcohol and non-prescribed drugs in women with late luteal phase dysphoric disorder. *J Subst Abuse*. 1994; 6:235–243. [PubMed: 7804022]
- Mooney M, Green C, Hatsukami D. Nicotine self-administration: cigarette versus nicotine gum diurnal topography. *Hum Psychopharmacol*. 2006; 21:539–548. [PubMed: 17066490]
- Perkins KA. Nicotine self-administration. *Nicotine Tob Res*. 1999; 1:S133–S137. [PubMed: 11768171]
- Pomerleau OF, Pomerleau CS, Mehninger AM, Snedecor SM, Ninowski R, Sen A. Nicotine dependence, depression and gender: characterizing phenotypes based on withdrawal discomfort, response to smoking and ability to abstain. *Nicotine & Tobacco Research*. 2005; 7:91–102. [PubMed: 15804681]
- Svikis DS, Hatsukami DK, Hughest JR, Carrol KM, Pickens RW. Sex differences in tobacco withdrawal syndrome. *Addictive Behaviors*. 1986; 11:459–462. [PubMed: 3544698]
- Snively T, Ahijevych K, Bernhard L, Wewers M. Smoking behavior, dysphoric states and the menstrual cycle: results from the single smoking sessions and the natural environment. *Psychoneuroendocrinology*. 2000; 25:677–691. [PubMed: 10938448]

Figure 1.
Circadian pattern of smoking by menstrual phase