Addictive Behaviors 43 (2015) 50–53

Contents lists available at ScienceDirect

Addictive Behaviors

Short Communication

Subjective response to nicotine by menstrual phase

Alicia M. Allen [a,*], Scott Lunos [b], Stephen J. Heishman [c], Mustafa al'Absi [d], Dorothy Hatsukami [e], Sharon S. Allen [f]

[a] Department of Family Medicine & Community Health, Medical School, University of Minnesota, 717 Delaware Street SE, Room 422, Minneapolis, MN, USA 55414
[b] Biostatistical Design and Analysis Center, Clinical and Translational Science Institute, University of Minnesota, Minneapolis, MN 55414, USA
[c] Nicotine Psychopharmacology Section, National Institute on Drug Abuse Intramural Research Program, National Institutes of Health, Bethesda, MD 20892, USA
[d] Department of Behavioral Sciences, Medical School, University of Minnesota, DuluthDuluth, MN 55812, USA
[e] Department of Psychiatry, Medical School, University of Minnesota, Minneapolis, MN 55414, USA
[f] Department of Family Medicine & Community Health, Medical School, University of Minnesota, Minneapolis, MN 55414, USA

HIGHLIGHTS

- A cross-over study was used to explore nicotine response by menstrual phase.
- Luteal phase had greater changes in stimulation and urge to smoke.
- However, most menstrual phase differences were null.
- Subjective response to nicotine may not vary by menstrual phase.

ARTICLE INFO

Available online 16 December 2014

Keywords:
Addiction
Nicotine
Menstrual cycle
Smoking
Hormones

ABSTRACT

Introduction: The luteal menstrual phase might be a favorable time for smoking cessation when non-nicotine interventions (e.g. counseling, bupropion) are used, whereas the follicular menstrual phase appears favorable when nicotine interventions are used. Thus, there may be an interaction between menstrual phase and response to nicotine. We sought to examine the role of menstrual phase on response to nicotine during acute smoking abstinence.
Methods: In this controlled cross-over trial, women completed two identical experimental sessions (follicular [F] vs. luteal [L] phase) after four days of biochemically-verified smoking abstinence. During the sessions, nicotine nasal spray was administered, and participants provided a series of subjective assessments.
Results: Participants ($n = 140$) were 29.7 ± 6.6 years old and smoked 12.6 ± 5.8 cigarettes per day. Compared to the F phase, the L phase was associated with a greater increase in stimulation (7.2 ± 2.2 vs. 14.4 ± 2.3, $p = 0.01$, respectively) and greater decrease in urge to smoke (-13.6 ± 2.3 vs. -21.1 ± 2.5, $p = 0.02$, respectively) after the first dose of nicotine. No other significant differences were observed.
Conclusions: Out of 13 total measures examined at two different time points, we observed only two significant menstrual phase differences in the subjective response to nicotine. Therefore, these data do not provide strong evidence for a menstrual phase difference in the subjective response to nicotine. Additional research is needed to confirm this relationship and explore how non-nicotine smoking reinforcements (such as sensory sensations) may vary by menstrual phase.

1. Introduction

Women relapse to smoking at different rates and for different reasons compared to men (CDC, 2012; Nakajima & al'Absi, 2012; Perkins, 2001). Although research indicates women smoke more for non-nicotine reinforcers such as sensory effects and weight control (Perkins, 2001), women smokers are more sensitive to the effects of nicotine than men. Many studies using various forms of nicotine (nasal spray, oral, transdermal patch, and intravenous) have demonstrated that women have a greater subjective and physiological response to nicotine (Evans, Blank, Sams, Weaver, & Eissenberg, 2006; Myers, Taylor, Moolchan, & Heishman, 2008; Netter, Müller, Neumann, & Kamradik, 1994; Sofuoglu & Mooney, 2009). DeVito and colleagues, however, noted that men displayed a greater subjective response to intravenous nicotine, whereas women displayed a

* Corresponding author. Tel.: +1 612 624 0896.
E-mail address: alle0299@umn.edu (A.M. Allen).

http://dx.doi.org/10.1016/j.addbeh.2014.12.008
0306-4603/

greater physiological response (DeVito, Herman, Waters, Valentine, & Sofuoglu, 2014). Thus, sex hormones might play a role in response to nicotine.

Recent research has examined the role of menstrual phase (as a proxy for sex hormones) in smoking behavior and cessation (for additional information see the following review articles: Carpenter, Upadhyaya, LaRowe, Saladin, & Brady, 2006; Lynch & Sofuoglu, 2010). Overall, the follicular phase (low progesterone/estradiol [PE] ratio) seems favorable for smoking cessation when nicotine replacement therapy (NRT) is used (Carpenter, Saladin, Leinbach, Larowe, & Upadhyaya, 2008; Franklin et al., 2008). However, in the absence of NRT, the luteal phase (high PE ratio) may lead to more favorable outcomes (Allen, Bade, Center, Finstad, & Hatsukami, 2008; Mazure, Toll, McKee, Wu, & O'Malley, 2011). The specific mechanisms involved are unknown, but may be related to the biological response to nicotine at varying levels of sex hormones (Franklin & Allen, 2009). Understanding the effect of menstrual phase and sex hormones on response to nicotine will allow for the development of smoking cessation interventions tailored to the specific needs of premenopausal women.

Although individual differences in the subjective nicotine response have not been well studied, they are likely associated with the reinforcing effects of smoking (Stolerman & Jarvis, 1995). While it remains unknown as to whether subjective response may serve as an indicator of risk for smoking relapse (Pillitteri, Kozlowski, Sweeney, & Heatherton, 1997; Pomerleau, 1995), limited new research has begun exploring the effect of menstrual phase on nicotine response. Subjective nicotine response was greater during the follicular phase compared to the luteal phase in female smokers after overnight abstinence (DeVito et al., 2014). However, this relationship has not been examined in women who were abstinent for greater than 12 hours. The aim of this project was to determine if menstrual phase influenced the subjective response to nicotine during acute smoking abstinence. We hypothesized that the subjective response to nicotine would be greater in follicular compared to luteal phase.

2. Methods

2.1. Study sample

A sample of women were recruited for a study designed to explore the differences in smoking-related symptomatology by menstrual phase and depressive symptoms (Allen et al., 2014). Inclusion criteria included women between the ages of 18 and 40, smoking at least five cigarettes per day for at least the past year, regular menstrual cycles for at least the past six months, and stable physical and mental health. Exclusion criteria were recent (<3 months) pregnancy or breastfeeding, current premenstrual dysphoric disorder (PMDD), current major depressive disorder, and use of exogenous hormones (including hormonal contraceptives), psychotropic medication or any other forms of nicotine or smoking cessation aids.

2.2. Study procedures

All study procedures were approved by the Human Subject Protection Program at the University of Minnesota. To assess eligibility criteria, participants completed a telephone interview followed by an in-person screening visit, where informed consent was obtained and collection of baseline data was completed (e.g. demographics and smoking behavior including nicotine dependence via the Fagerstrom Test of Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991)). After study enrollment, participants were randomly assigned to complete the first testing week in Follicular (F; menstrual cycle days 2-7, with day 1 defined as the onset of menses) phase followed by the Luteal (L; 3−8 days after ovulation as determined by urine luteinizing hormone tests) phase, or vice versa. Serum hormone levels (progesterone and estradiol) were measured allowing for retrospective confirmation of menstrual phase. Additional detailed information on screening, randomization and protocol have been published elsewhere (Allen et al., 2014).

Each testing week consisted of two days of ad libitum smoking, followed by four days of smoking abstinence. During this six-day testing period, participants attended daily clinic visits to confirm smoking status (expired carbon monoxide < 5 ppm and salivary cotinine < 15 ng/mL on fourth day of smoking abstinence) (Benowitz, Bernert, Caraballo, Holiday, & Wang, 2009). On Day 6 (fourth day of smoking abstinence), participants completed a nicotine exposure laboratory session. During the session, participants were administered nicotine nasal spray (Nicotrol 2 mg) at Time 0 and 90 minutes, with assessment of subjective response measures at Time -30, 5, 10, 20, 30, 60, 95, 100, 110 and 120 minutes. Subjective response was assessed using two measures: (1) Subjective State Scale (SSS) (al'Absi, Hatsukami, & Davis, 2005; al'Absi, Hatsukami, Davis, & Wittmers, 2004) that contains 24-items yielding five subscales: Negative Affect, Positive Affect, Physical Symptoms (e.g. headache, hungry), Withdrawal and Craving, and (2) Visual Analog Scale (VAS) items that measured potentially rapid changes in negative or positive drug effects: *alert*, *dizzy*, *head rush*, *jittery*, *pleasant*, *relaxed*, *stimulated*, and *urge to smoke*. Participants responded on a 100-mm line ranging from 'not at all' to 'very much' (Jones, Garrett, & Griffiths, 1999). Blood pressure and heart rate were also measured at each time point to document physiological responses to nicotine (Allen, Allen, et al., 2013). At the completion of this laboratory session, participants resumed ad libitum smoking for approximately six weeks (1.5 menstrual cycles; a median of 46 days) and then completed identical data collection procedures in the alternate menstrual phase. Participants were compensated with cash (up to $910) for their time and efforts.

2.3. Statistical analyses

Descriptive statistics were calculated for demographics and baseline characteristics. Nicotine response was defined as the change from baseline (Time -30 minutes) to the first time point (Time 5 minutes) after the nicotine dose. Random-intercept models, adjusting for study design factors and potential confounders (e.g. sequence (carry-over), time effects, and depressive symptoms), were used to investigate the association of menstrual phase with nicotine response. Similar models were used to compare baseline measures. P-values less than 0.05 were deemed statistically significant. SAS V9.3 (SAS Institute, Cary, NC) was used for the analyses.

3. Results

3.1. Study sample

A total of 208 women were enrolled into the study. Of those, 61 participants were excluded from the analyses due to participant discontinuing study participation ($n = 51$), inability to achieve smoking abstinence ($n = 11$) or having hormone levels that were not consistent with menstrual phase of testing ($n = 6$). Therefore, the final sample size for this analysis was 140, including 72 who were randomized to the F-L order and 68 randomized to L-F order. Overall, women were 29.7 (S.D. ± 6.6) years old and smoked 12.6 (S.D. ± 5.8) cigarettes/day. Most (93%) had at least a high school education and were non-Hispanic White (54%) or Black (24%). Participants who were White non-Hispanic were more likely to be randomized to L-F phase testing order ($p = 0.04$), whereas participants who were Black non-Hispanic were more likely to be randomized to the F-L testing order ($p = 0.02$). There were no other statistically significant differences in study participants based by randomization (F-L vs. L-F) or by completion status (discontinued/excluded vs. completed).