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EXPLORING THE IMPACT OF GENDER AND REPRODUCTIVE STATUS ON OUTCOMES IN A RANDOMIZED CLINICAL TRIAL OF NALTREXONE AUGMENTATION OF NICOTINE PATCH

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Abstract

In a series of exploratory analyses, we examined the roles of gender, reproductive status and negative affect on smoking abstinence in subjects participating in a large (n=385) 6-week randomized clinical trial (RCT) of nicotine patch therapy, with varying doses of oral naltrexone (0 mg, 25 mg, 50 mg, 100 mg) treatment. Negative affect was assessed daily during the first post-quit week via telephone interactive voice response (IVR). Weight and adverse events were recorded weekly. In the intent to treat sample, the effects of dose on continuous abstinence were non-significant in the overall model for men and women. In the 295 study completers, there was a significant effect of dose on continuous abstinence in women only (F=8.53, p=0.04). In the 100 mg group, 71% of women were continuously abstinent compared to 41% in the placebo group (p<0.05). Women in the active naltrexone groups gained less weight (F=2.91, df=3, p=0.04). Women in the 100 mg versus placebo group were less adherent with medication (F=3.19, p<0.05). These effects were not significant in men. Naltrexone treatment condition (100 mg vs placebo, p=0.02, odds ratio (OR)=0.28), gender (OR=0.55 p=0.09), and IVR ratings of negative affect (OR 1.02, p=0.04) predicted abstinence at Week-1 in study completers. Menstrual cycle status on quit day had a modest affect on abstinence. These data suggest that naltrexone dose, gender, and negative affect play a role in smoking abstinence, particularly in the early stages of treatment. When used in conjunction with nicotine replacement therapy, naltrexone dose may be important in women.

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Keywords

NICOTINE; GENDER; MOOD; MENSTRUAL CYCLE; MENOPAUSE

1) INTRODUCTION

Despite increasing awareness of the adverse effects of cigarette smoking, 22% of women ages 18 or older in the United States smoke cigarettes, and nearly 30% of high school girls report having smoked within the previous month (U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau, 2003). Unfortunately, there is mounting evidence that women are overall less successful in quitting smoking (Bjornson et al., 1995; Royce, Corbett, Sorensen, & Ockene, 1997; Scharf & Shiffman, 2004; Swan, Jack, & Ward, 1997) and demonstrate diminished responsiveness to certain pharmacologic and/or behavioral treatment strategies (reviewed by Perkins, 2001).

While a number of possible explanations for gender-specific smoking recidivism have been explored, one of the most consistent findings has been the interplay between smoking and negative affect reduction (Benowitz & Hatsukami, 1998; Murphy et al., 2003) and/or nicotine withdrawal and increase in negative affect (Craig et al., 1992; Hogle & Curtin, 2006; Killen et al., 2003; O'Hara et al., 1989; Pomerleau et al., 1992; Shiffman et al., 1982; Svikis et al., 1986). Reduction in negative affect is a more frequent motivating factor for smoking in women than men and the presence of such motivation predicts poor prognosis with respect to smoking cessation (Ikard, 1973; Pomerleau et al., 1978). Comorbidity with depression is high in both male and female smokers (Glassman et al., 1990). However compared to men, women experience a greater increase in depressive symptoms during abstinence (Smith 2003), a strong predictor of smoking recidivism (Killen et al., 2003; Levine et al., 2003). This relationship holds true even with nicotine patch treatment and behavioral counseling (Pomerleau et al., 2001).

That the majority of women experience some degree of psychological and/or physical distress in the few days pre and post menses with symptoms peaking on the first day of menstrual flow (Ross et al., 2003) suggests that menstrual cycle and/or hormonal status may contribute to women's relative difficulty in quitting smoking. However, under ad lib conditions or with short-term abstinence (24 hours), menstrual cycle phase appears to have only a modest effect on smoking behavior (Snively et al., 2000; Allen et al., 1996; Pomerleau et al., 1992; 1994b; Steinberg & Cherek, 1989) and findings regarding the impact of menstrual cycle phase on the ability to quit on an assigned quit day or to maintain abstinence are conflicting. Several studies implicate the luteal/premenstrual phase when estradiol and progesterone are low (Perkins et al., 2000; Craig et al., 1992; Carpenter et al., 2008; Franklin et al., 2008) as a less desirable time for women to quit, perhaps because they are more likely to experience greater abstinence emergent withdrawal and depressive symptoms (Perkins et al., 2000), particularly if they have preexisting premenstrual dysphoria (Pomerleau et al., 1994a). The propensity for women to experience negative mood symptoms or physical discomfort along with the reported increase in withdrawal symptoms and enhanced craving for cigarettes during the luteal phase of the menstrual cycle (Craig et al., 1992; O'Hara et al., 1989; Pomerleau et al., 1992) may overwhelm women attempting to quit premenstrually. Although this argument is compelling, a recent study (Allen et al., 2008) found that women who quit smoking between days 4–6 of the menstrual cycle (follicular phase) versus those who quit between days 6–8 after ovulation (luteal phase) relapsed (7 slips in 7 days) more quickly after prolonged abstinence. While the timing of the quit day with respect to menstrual cycle may be important to abstinence, it remains unclear as to which menstrual cycle phase and/or hormonal milieu is preferable.

The relationship between nicotine addiction and weight appears to be particularly critical for women as women are more frequently concerned about weight gain after quitting (Pirie et al., 1991), experience more post-cessation weight gain (Williamson et al., 1991) and are more likely to cite weight gain as a reason for relapse (Swan et al., 1993). Concerns regarding weight gain have been the focus of interventions for smoking cessation (Perkins et al., 2001). Weight gain has been included as an outcome in pharmacologic trials for smoking cessation (O'Malley et al., 2006; Perkins et al., 2001; Toll et al., 2008), although it has not previously been examined by gender.

Finally, sex-specific factors related to pharmacologic and behavioral treatment and/or treatment emergent side effects have been purported to contribute to sex differences in rates of smoking abstinence (Perkins 2001). Pertinent to the parent RCT from which these data were extracted, there is a growing literature suggesting that relative to men naltrexone enhances smoking cessation in female samples (Byars et al., 2005; Covey et al, 1999; King et al., 2006), and reduces abstinence emergent withdrawal and negative affect (King et al., 2006). King and colleagues (2006) for example found that women who received nicotine patch with placebo naltrexone had lower quit rates than men (39% vs 67%), while their quit rates were comparable when they received active naltrexone in addition to nicotine patch (58% vs 62%). In the parent RCT, O'Malley and colleagues (2006) reported a significant effect of the naltrexone 100 mg/d dose versus placebo, 25 mg or 50 mg in study completers (N=295), but the effect of gender was not explored.

To understand the potential efficacy of naltrexone for smoking cessation among women, we examined the effects of naltrexone separately for women and men on the primary outcomes of smoking cessation and weight gain. Secondary outcomes examined included treatment adherence, adverse effects and naltrexone concentration. As gender, menstrual cycle status and negative affect have been implicated as potential factors influencing smoking behavior and/or abstinence in clinical trials, we examined the impact of these factors on Week-1 and Week-6 abstinence using daily reports of mood and withdrawal symptoms over the first post-quit week. Our primary expectations were that women would experience improvements in smoking cessation and reduced weight gain. Based on the literature, we anticipated that female smokers would experience more negative affect during the first post-quit week, negative affect would be associated with a reduction in abstinence at both time points and women who quit in the perimenstruum would be more likely to relapse during the first post-quit week.

2) METHODS

2.1) Participants

The original study was a 6-week RCT subjects that investigated the impact on abstinence of adding varying doses of oral naltrexone (placebo, 25 mg/d, 50 mg/d, or 100 mg/d) to 21mg/d nicotine patch (O'Malley et al., 2006). Written informed consent was obtained and 385 subjects (185 women, 200 men) comprised the intent-to-treat group. Only data from subjects in the intent-to-treat and completer groups (n=295) were considered in these analyses described herein. Briefly, subjects in the RCT were 18 years or older, spoke English, weighed more than 45kg, smoked ≥ 20 cigarettes daily for at least 1 year, and had an expired carbon monoxide (CO) level of 10 ppm or more. All subjects had at least one prior quit attempt. Subjects with current serious medical or neurological disorders, psychiatric disorder, dependence on alcohol or any use of opiates were grounds for exclusion. At intake participants completed a core battery with questions about demographics, smoking variables, mood, alcohol use and areas of daily functioning. Diagnostic information was obtained with the Fagerström Test for Nicotine Dependence (Heatherton et al., 1991), Alcohol Use Disorders Identification Test (Babor et al., 1992) and the Structured Clinical Interview for DSM-IV (Diagnostic and Statistics Manual of Mental Disorders, Fourth Edition) Research Version, Patient Edition (First et al., 1996) alcohol

and depression modules. Quit day was chosen according to the subject's preference. Subjects initiated the nicotine patch therapy on their quit day, while naltrexone 12.5 mg or placebo was started the following day. Naltrexone dose was titrated to 25, 50 or 100 mg over the 1st post-quit week according to group assignment. Study visits occurred weekly in order to monitor weight, expired CO levels, serum naltrexone/naltrexol levels and adverse symptoms. Weekly visits were also used to obtain behavioral ratings and information regarding daily tobacco and alcohol consumption.

We evaluated abstinence during the first week following the quit date and continuous 6-week abstinence from the quit date. Self-reported abstinence was confirmed with breath carbon monoxide tests less than or equal to 10 ppm (O'Malley et al., 2006). Participants who dropped out or missed multiple appointments were considered not abstinent. A single missed appointment was considered abstinent only if abstinence was biochemically verified at the appointments before and after the missed session.

2.2) Tracking of Menstrual Cycle and Determining Reproductive Status

Women (n=185) were interviewed at their screening appointment and physical examination regarding their menstrual and gynecologic history and use of estrogen and/or progesterone-containing substances. All women were asked to complete a 3-month retrospective menstrual cycle calendar and to maintain a prospective calendar of menstrual flow while participating in the RCT. For the purposes of this study, women with a uterus who reported having no menses for at least 12 months and women without a uterus who were older than 52 years were considered to be postmenopausal. Women who were in their 40s and reporting irregular menstrual cycles were excluded (n=30) from this analysis. These women were likely to be perimenopausal and their menstrual irregularity would have made it difficult to determine menstrual cycle phase or perimenstrual status with respect to their quit day. All other women were considered premenopausal.

For cycling women, follicular phase was considered to span from the first day of menstrual flow (Day 1) to ovulation, which occurs at approximately Day 14. Luteal phase was considered to be from Day 14 to the day before the next menstrual flow. As the hormonal milieu is highly variable across each phase of the menstrual cycle and 10%–48% of women have anovulatory or progesterone deficient luteal phases (Gandara et al., 2007; De Souza et al., 1998) we also characterized women as being either "perimenstrual" (± 4 days of their first day of menstrual flow) or "not perimenstrual" (all other days). Findings from epidemiologic and clinical samples suggest that unpleasant mood and physical symptoms are reliably elevated with varying degrees of severity during the perimenstrual period in up to 70% of women (Meaden et al., 2004; Ross et al., 2003; Bloch et al., 1997). In addition, the hormonal milieu during the perimenstrual period is relatively similar regardless of whether a woman ovulated that particular cycle (Gandara et al., 2007, Sherman & Korenman, 1975). Each woman set a quit date at her physical examination for the RCT, and we characterized participants according to the above menstrual cycle variables with respect to their quit date. The first day of the last menstrual period and menstrual cycle length were used to determine whether cycling women were in the follicular or luteal phase on their quit day.

When reproductive status (pre vs postmenopause) was considered, analyses were performed both with and without premenopausal women using steroid contraceptives (n=19, 24.6%) or postmenopausal women using hormone therapy (HT n=11; 12.6%). Premenopausal women who reported use of steroid contraceptives were excluded from analyses that included menstrual cycle phase (follicular or luteal) as a variable, but not those involving perimenstrual status (perimenstrual or not perimenstrual) as a variable.

2.3) Measurement of Negative Affect

As a requirement of the original investigation, all participants enrolled in the RCT were instructed to complete daily interactive voice response (IVR) ratings of mood and smoking behavior for the first week after their quit day. Participants were instructed to provide these ratings by calling a dedicated toll-free number first thing in the morning, at which time they responded to a brief series of questions about their smoking, alcohol consumption, mood, and nicotine withdrawal symptoms by touching numbers on their telephone keypad that corresponded to their answers (see Toll et al., 2005, 2008 detailed descriptions).

Only IVR data from the first 5 days after quitting were utilized due to less than 70% participation on the sixth and seventh days (Toll et al., 2005). Participants rated several behavioral and mood measures from 0 (none) to 4 (severe) with regard to the past 24 hours. Affective state was measured using 10 items derived from mood adjectives in the circumplex model of mood experience (Larsen & Diener, 1992; Russell, 1980). A total negative mood score combining depressed mood, irritability, anxiety, and boredom ratings for each day was created in accordance with previous studies (Toll et al., 2007), and the mean score for each symptom across 5 days was used. Only scores of those participants who completed all 5 days were included in order to prevent bias from imputing scores. IVR data were available from 251 (73%) participants in the RCT: 134 males, 47 cycling females, and 69 menopausal females.

2.4) Weight Measurements, Adverse Effects of Treatment and Compliance

All subjects were weighed weekly. Adverse effects were recorded by a member of the research staff at each appointment using the SAFTEE (O'Malley et al., 2006). Adherence to oral naltrexone treatment was monitored with the eDEM caps, which recorded the time of bottle openings (APREX[ARRDEX USA], Union City CA). In addition, blood levels of naltrexone and 6-β-naltrexol, a metabolite of naltrexone were used as a marker of compliance at 1 and 4 weeks after abstinence and measured by high-performance liquid chromatography (HPLC) with electrochemical detection as modified from the literature (Meyer et al., 1984). Serum cotinine levels were measured on intake by HPLC (O'Malley et al., 2006).

2.5) Statistical Considerations

Our analytic strategy for examining outcomes was to conduct analyses parallel to the parent report (O'Malley et al., 2006) separately for men and women. Analyses including all enrolled participants (intent-to-treat or ITT analyses), as well as secondary analyses including only completers. For individual outcomes, each dose of naltrexone was compared to placebo within a single model. Because we previously reported an effect of naltrexone treatment condition on abstinence in treatment completers (O'Malley et al., 2006), we also examined treatment outcomes for this subsample.

Smoking abstinence outcomes were analyzed with logistic regression. The Wald criterion was used to evaluate the contribution of individual predictors (i.e. the three active naltrexone doses). Odds ratios with 95% confidence intervals are reported in the text.

Body weight was measured at baseline and at week 6. Weight gain, defined as change from baseline to week 6, was analyzed by one-way general linear model (GLM) with planned comparisons between each dose and placebo for the total sample, abstainers and treatment completers. Naltrexone and naltrexol concentrations were compared for the three active doses using GLM. For group comparisons with regard to negative affect, adverse events and compliance, χ^2 tests and analyses of variance (ANOVA) or GLM were used for categorical and continuous variables, respectively.

Negative affect ratings were not reported as part of the parent report. To explore the role of negative affect on treatment outcome, IVR ratings of negative affect in the first post-quit week, gender and naltrexone treatment condition were included as predictors of abstinence (Week 1 and continuous abstinence) in 226 subjects who completed 5 of the 7 days of IVR ratings and were also study completers (105 men, 121 women).

All tests are the two-tailed type. The initially specified significance level is 0.05. SAS (Version 9.1) and SPSS (Version 16) were used for statistical analyses.

3) RESULTS

3.1) Baseline Characteristics by Gender

As presented in Table 1 for the entire study sample, several baseline characteristics (% married, weight, BMI, cigarettes per day) were significantly different between women and men. While women reported smoking fewer cigarettes per day, there was no significant difference between genders with respect to CO and plasma cotinine levels or degree of nicotine dependence as measured using the Fagerström Test for Nicotine Dependence (FTND).

3.2) Smoking Abstinence by Gender

Table 2 presents treatment outcomes separately for men and women. There was no significant difference for continuous abstinence by treatment group for either women or men in the intent-to-treat sample. In the secondary population of 150 women who completed treatment, this analysis was statistically significant ($\chi^2 = 8.53$, df = 3, n = 150, p = .04). The comparison of the 100 mg dose to placebo was significant with 71.4% of the women in the 100 mg group abstaining for 6 weeks compared to 41.0% for the placebo group, (p=0.01, OR: 3.59, CI: 1.36–9.5). The effect of dose was not significant in the male subsample of completers.

3.3) Weight Gain by Gender

In continuously abstinent female participants (n =73), the overall test was significant (overall test: F=2.91, df=3, p=0.04). Weight gain was significantly less in the 25-mg group (0.6 kg ± 1.35, n =16, p<.05), marginally lower in the 50-mg group (0.8 ± 2.03, n = 17, p = .09), but not different in the 100mg group (1.7 ± 1.63 kg, n = 25, p = 0.75) compared to the placebo group (2.1 ± 1.95 kg, n =15). Findings regarding weight gain in the female group were similarly significant regardless of study completion or abstinence status. Weight gain did not significantly differ across doses for men (n = 84).

3.4) Treatment Exposure and Adverse Events by Gender

As presented in Table 2, the groups were similar on the percentage of participants who completed treatment, whether the analysis examined men or women. The percentage of days adherent with medications was significantly different between doses for women, with lower adherence in the 100 mg dose (66.0%) as compared to placebo (82.5%; F=3.19, $p < .05$). Although the overall test for the percentage of women who reported moderate to severe nausea was non-significant, higher rates of nausea among women in the 100 mg dose group could have contributed to this finding. There was no significant relationship between group assignment and nausea in men.

Analysis of variance comparing naltrexone and 6-beta naltrexol levels at week 4 for the three active doses within each gender revealed significant effects of dose. Visual inspection of the means suggested that women achieved higher concentrations. To follow-up on this observation, we compared men and women in a single model and found that mean naltrexone concentrations were higher at four weeks in women than in men across all dosages (F=5.73, $p = .02$; Table 2). Mean concentrations of naltrexone at 100 mg were 11.7 and 5.8 ng/mL for women and

men, respectively (F=4.17, p= 0.04). However, after controlling for weight or medication compliance or both, the difference reduced to a trend (p=.054, .069 or .095). Naltrexol levels were also higher in women than in men across all active doses (F=4.83, $p < 0.03$; Table 2).

3.5) Impact of Gender/Reproductive Status and Negative Affect on Abstinence

Numerous studies have suggested that negative affect plays an important role in smoking abstinence. Table 3 presents the mean IVR negative affect ratings from the sample of 251 (65.2%) participants who completed the first 5 days of IVR ratings by gender and according to reproductive status in women. There were no significant differences for negative affect as assessed by mean IVR ratings for men and women. Mean IVR negative affect scores were higher for those women who were perimenstrual (5.7) or luteal (5.1) on their quit day, compared to all other groups (follicular [4.0], not perimenstrual [4.1], postmenopausal [4.3] and male [3.9]). However, the sample size was small and differences did not reach statistical significance.

We then explored the effect of negative affect over the course of the first post-quit week on our main outcomes, namely smoking abstinence at Week-1 and continuous abstinence. In an integrated analysis of the 226 subjects who completed 5 days of IVR ratings and also completed the study, gender, naltrexone dose and IVR negative affect ratings predicted Week-1 abstinence although the gender effect favoring men was at the level of a trend (Wald=2.95, p=0.09, OR=0.55, CI (95%)=0.28–1.09). The naltrexone condition (100 mg dose vs. placebo), *Wald*=5.60, p=0.02, OR=0.28, CI (95%)=0.10–0.81 and IVR negative affect ratings, *Wald*=4.15, p=0.04 OR=1.02, CI (95%)=1.00–1.05 were both statistically significant. Only dose predicted 6-week continuous abstinence rates.

We also examined the impact of reproductive status on abstinence outcomes. Considering the entire group of premenopausal women for whom perimenstrual status could be confirmed (n=75, one unclear), women who were not-perimenstrual (n=51) at the time of their quit day and were randomized to one of the three active naltrexone groups (n=37) versus the placebo (n=14) group were numerically more likely to have achieved continuous abstinence (49% vs. 21%) (χ^2 = 3.1, df=1, n=51, p=0.08). This difference in continuous abstinence between the drug (37%) and placebo (25%) groups was less pronounced for those women (n=24) who quit during the perimenstrual phase. Otherwise, the impact of reproductive status (pre vs. post menopause) or menstrual cycle phase (follicular vs. luteal) at time of quitting did not significantly affect abstinence outcomes. Overall, these comparisons are limited by the relatively small sample size, which occurs even in large RCTs once groups of women are subdivided by menstrual cycle phase and/or menopausal status.

4) DISCUSSION

As anticipated, gender was a moderating factor in several outcomes in this RCT of naltrexone augmentation of nicotine patch in the treatment of nicotine addiction. Among treatment completers, women in the 100 mg dose condition experienced higher smoking cessation rates compared to placebo and women in the two lower doses experienced less weight gain. These comparisons were not significant for men. In addition to these effects, women achieved higher concentrations of naltrexone than men did. Women but not men reported dose related differences in medication compliance. These data suggest that naltrexone exposure is important for abstinence in female smokers, but possibly less so in male smokers.

Women who were randomized to naltrexone 100 mg/d were significantly more likely to obtain and maintain abstinence than those women randomized to placebo among treatment completers, but this effect was not significant in men. These data are interesting in light of the growing literature suggesting gender differences in response to naltrexone treatment for nicotine addiction (Covey et al., 1999; King et al., 2006). Secondary analyses of RCTs indicate

that naltrexone enhances smoking cessation in female samples (Byars et al., 2005; Covey et al, 1999; King et al., 2006), and reduces urges to smoke to relieve negative affect and withdrawal to a greater degree in women than in men (King et al., 2006). Consistent with King et al., (2006), women receiving nicotine patch plus placebo naltrexone in our study had somewhat lower quit rates than men had (41.0% versus 55.6%); with naltrexone 100 mg their quit rates were similar (71.4% vs. 71.8%).

The better response to the highest naltrexone dose (100 mg) compared to placebo observed among women but not men, also suggested that gender related differences in drug exposure might have contributed to outcome. Women did indeed have significantly higher serum naltrexone and naltrexol concentrations than men. The significance of this difference was not altered when medication compliance was included in the statistical analysis. Women, however, received a higher weight adjusted dose. A two-way analysis that included weight weakened the independent association of naltrexone concentrations with gender although a trend persisted, suggesting that differences in drug exposure might be multi-factorial. We focused on concentrations of the parent compound, naltrexone, because a recent report indicated that in primates, naltrexone is approximately 100 times more active than its major metabolite, 6-beta naltrexol (Holden et al., 2006).

With respect to negative affect and abstinence, our failure to find gender differences in negative affect as assessed via IVR or smoking abstinence during the first five post-quit days is somewhat surprising as depression is more common in women and is a strong predictor of smoking recidivism (Borland, 1990). We did observe a greater degree of negative affect as measured by IVR in the first post-quit week in those women who were perimentrual versus not perimenstrual when they quit smoking. However, this relationship did not reach the level of significance and did not appear to impact abstinence outcomes in this small sample. A recent study suggests that women who currently smoke are twice as likely to experience PMS (both physical and mood symptoms) than nonsmokers (Bertone-Johnson et al., 2008), a phenomenon thought to contribute to reduced rates of smoking abstinence in those women quitting in the luteal phase of the menstrual cycle (Perkins et al., 2000; Carpenter et al., 2008; Franklin et al., 2008). These findings are consistent with data from a sub-group of subjects in this RCT who completed two months of daily ratings prior to their quit day suggesting greater negative affect in luteal phase women and heightened risk for relapse compared to men and follicular phase women (Epperson et al., 2005). Whether perimenstrual mood changes are an independent risk factor for smoking recidivism in women continues to be unclear, but of considerable interest.

Although there was no gender difference in the emergence of negative affect after quitting, the expected relationship between negative affect and abstinence was found in study completers. In this study, naltrexone treatment condition, gender and negative affect together contributed to abstinence, particularly early in the course of treatment. However, the effect of reproductive status (pre vs. post menopause) was not a factor and the impact of menstrual cycle phase/ menstrual status on outcome was relatively modest. Although negative affect and weight gain may vary by menstrual cycle stage, the relatively small sample size of women who could be characterized reliably as peri or not perimenstrual limited our ability to covary for these factors in our assessment of impact on abstinence. Interestingly, Allen and colleagues (2009) failed to find a relationship between short-term weight gain and phase of menstrual cycle during attempted smoking cessation. As is the case with the vast majority of RCTs, measurement of ovarian hormones, the gold standard for determining menstrual cycle phase, was not included in this study. Off setting this limitation, the female participants in this study provided the dates of their three menstrual periods prior to enrollment and prospectively reported their menstrual flow during the 6-week study. Without blood confirmation of ovulation, and thus luteal phase, we opted to include perimenstrual status as a more reliable dichotomous variable than menstrual cycle phase (follicular vs. luteal). It is the few days before and after onset of

menstrual flow that is most associated with negative physical and mood symptoms related to the menstrual cycle (Ross et al., 2003). Indeed, we found a trend for women who quit outside the perimenstrual period to have greater success in remaining abstinent throughout the entire study. There was no effect of menstrual cycle phase (follicular vs. luteal) on smoking outcomes.

Interestingly, a recent smoking cessation study using nicotine replacement therapy plus a behavioral intervention found a significant benefit of quitting during the follicular versus luteal phase with only 3 of 16 (19%) and 11 of 21 (52%) of subjects in each group, respectively, smoking at Day 3 post quit day (Franklin et al., 2008). However, Allen and colleagues (2008) using hormonally confirmed menstrual cycle phases found that women quitting without pharmacologic treatment or nicotine replacement in the early to mid-follicular phase when the estradiol/progesterone ratio was highest did not fair as well as those women who quit in the mid-luteal phase when the estradiol/progesterone ratio would be at its nadir. The authors suggest that their findings could be explained by estradiol's enhancement of nicotine metabolism (Benowitz et al., 2006) and/or the differential effects of estradiol and progesterone on the reinforcing effects of substances of abuse (Lynch et al., 2000; Roth et al., 2004; Sofuoglu et al., 2004). What role, if any, naltrexone addition to nicotine replacement therapy played in the disparity between our findings and those of Allen and colleagues is of interest.

In summary, this study provides additional evidence that gender may play a role in smoking cessation, and should be taken into consideration in large-scale RCTs. The results of this secondary analysis suggest that naltrexone augmentation of nicotine patch may be helpful to women trying to quit smoking. However, this study and all prior studies were not specifically designed to test this hypothesis and additional prospective research with adequate sample sizes is needed to test this hypothesis. Regardless of gender, our results suggest that negative affect in the days following the quit day can have a clinically meaningful impact on an individual's ability to obtain continuous abstinence. As each of the RCT study participants was screened for mood disorders using sections of the SCID (First et al., 1995), it is unlikely that these individuals met criteria for a major depressive episode and that it was negative affect, which emerges with smoking abstinence that was an important factor in abstinence in this study. PMS is more common in women with nicotine addiction, but rarely identified in RCTs due to the requirement of prospective screening for two menstrual cycles. Although limited by recall bias, retrospective ratings for menstrual cycle and mood would provide an assessment of PMS/PMDD at baseline. Prospective daily ratings for women throughout the RCT may shed light on the relationship between negative affect, menstrual cycle phase and smoking abstinence in women undergoing various treatment regimens. Finally, documentation of gonadal steroids on the quit day would provide a more accurate assessment of reproductive status and menstrual cycle phase.

References

Allen SS, Hatsukami D, Christianson D, Nelson D. Symptomatology and energy intake during the menstrual cycle in smoking women. J Substance Abuse 1996;8:303–319.

Allen SS, Allen AM, Mooney M, Bade T. Short-term weight gain by menstrual cycle phase following smoking cessation in women. Eating Behaviors 2009;10:52–55. [PubMed: 19171319]

Allen SS, Bade T, Center B, Finstad D, Hatsukami D. Menstrual phase effects on smoking relapse. Addiction 2008;103:809–821. [PubMed: 18412759]

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders Fourth ed. (DSM-IV). Washington, D.C: American Psychiatric Association; 1994.

Babor, TR.; de la Fuente, JR.; Saunders, J.; Grant, M. AUDIT: The Alcohol Use Disorders Identification Test: Guides for Use in Primary Health Care. Geneva, Switzerland: World Health Organization; 1992.

Baron JA, La Vecchia C, Levi F. The anti-estrogenic effect of cigarette smoking in women. Am J Obstet Gynecol 1990;162:502–514. [PubMed: 2178432]

Benowitz NL, Hatsukami D. Gender differences in the pharmacology of nicotine addiction. Addiction Biology 1998;3(4):383–404.

Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P 3rd. Female sex and oral contraceptive use accelerate nicotine metabolism. Clin Pharmacol Ther 2006;79:480–488. [PubMed: 16678549]

Bertone-Johnson ER, Hankinson SE, Johnson SR, Manson JE. Cigarette smoking and the development of premenstrual syndrome. American Journal of Epidemiology 2008;168(8):938–945. [PubMed: 18701443]

Bjornson W, Rand C, Connett JE, Lindrgen P, Nides M, Pope F, Buist AS, Hoppe-Ryan C, O'Hara P. Gender differences in smoking cessation after 3 years in the Lung Health Study. American Journal of Public Health 1995;85:223–230. [PubMed: 7856782]

Bloch M, Schmidt PJ, Rubinow DR. Premenstrual syndrome: Evidence for symptom stability across cycles. American Journal Psychiatry 1997;154:1741–1746.

Borland R. Slip-ups and relapse in attempts to quit smoking. Addictive Behav 1990;15:235–245.

Byars JA, Frost-Pineda K, Jacobs WS, Gold MS. Naltrexone augments the effects of nicotine replacement therapy in female smokers. Journal of Addictive Diseases 2005;24:49–60. [PubMed: 15784523]

Carpenter JM, Saladin Me, Leinbach AS, Larowe SD, Upadhyaya HP. Menstrual phase effects on smoking cessation: A pilot feasibility study. Journal of Women's Health 2008;17:293–301.

Connett JE, Murray RP, Buist AS, Wise RA, Bailey WC, Lindgren PG, Owens GR. Lung Health Study Research Group. Changes in smoking status affect women more than men: results of the lung health study. Am J Epidemiol 2003;157:973–979. [PubMed: 12777360]

Cooney NL, Litt MD, Cooney JL, Pilkey DT, Steinberg HR, Oncken C. Alcohol and tobacco cessation in alcohol dependent smokers: Analysis of real-time reports. Psychol Addict Behav. (in press).

Covey LS, Glassman AH, Stetner F. Naltrexone effects on short-term and long-term smoking cessation. Journal of Addictive Disease 1999;18:31–40.

Craig D, Parrott A, Coomber JA. Smoking cessation in women: Effects of the menstrual cycle. International Journal of Addictions 1992;27:697–706.

De Souza MJ, Miller BE, Loucks AB, Luciano AA, Pescatello LS, Campbell CG, Lasley BL. High frequency of luteal phase deficiency and anovulation in recreational women runners: Blunted elevation in follicular stimulating hormone observed during luteal-follicular transition. J Clin Endocrin & Met 1998;83:4220–4232.

Endicott, J. Daily Record of Severity of Problems Form. New York, NY: Department of Research Assessment and Training, NY State Psychiatric Institute; 1999.

Epperson, CN.; McKee, S.; Krishnan-Sarin, S.; Mazure, C.; O'Malley, S. Impact Of Negative Affect By Sex And Reproductive Status On Abstinence In A Controlled Clinical Trial for Nicotine Addiction; Oral presentation, Annual Meeting of College on Problems of Drug Dependence; San Juan, Puerto Rico. 2005.

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. Structured Clinical Interview for DSM-IV Axis I Disorders- Research Version, Patient Edition SCID-I/P. New York, NY: Biometrics Research, New York State Psychiatric Institute; 1996.

Franklin TR, Ehrman R, Lynch KG, Harper D, Sciortino N, O'Brien CP, Childress AR. Menstrual cycle phase at quit date predicts smoking status in an NRT treatment trial: A retrospective analysis. Journal of Women's Health 2008;17:287–292.

Gandara BK, Leresche L, Mancl L. Patterns of salivary estradiol and progesterone across the menstrual cycle. Ann N Y Acad Science 2007;1098:446–450.

Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, Loewy JW, Ehrich EW. Vivitrex Study Group. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A randomized controlled trial. JAMA 2005;293:1617–1625. [PubMed: 15811981]

Glassman AH, Helzer JE, Covey LS, Cottler LB, Stetner F, Tipp JE, Johnson J. Smoking, smoking cessation, and major depression. JAMA 1990;264(12):1546–1549. [PubMed: 2395194]

Glassman AH, Covey LS, Stetner F, Rivelli S. Smoking cessation and the course of major depression: A follow-up study. The Lancet 2001;357:1929–1933.

Hernandez-Avila CA, Song C, Kuo L, Tennen H, Armeli S, Kranzler HR. Targeted verses daily naltrexone, secondary analysis of effects on average daily drinking. Alchol Clin Exp Res 2006;30:860–865.

Hogle JM, Curtin JJ. Sex differences in negative affective response during nicotine withdrawal. Psychophysiology 2006;43:344–356. [PubMed: 16916430]

Holden MC, Divin MF, Lee H, Woods JH, Traynor JR. Differential iin Vivo Potencies of Naltrexone and 6β-Naltrexol in the Monkey. J Pharmacol Exper Ther 2006;316:772–779. [PubMed: 16258020]

Hornsby PP, Wilcox AJ, Weinburg CR. Cigarette smoking and disturbance of menstrual function. Epidemiology 1998;9(2):193–198. [PubMed: 9504290]

Ikard FF, Tomkins S. The experience of affect as a determinant of smoking behavior: A series of validity studies. J Abnorm Psychol 1973;81(2):172–181. [PubMed: 4697798]

Killen JD, Fortmann SP, Schatzberg A, Hayward C, Varady A. Onset of major depression during treatment for nicotine dependence. Addict Behav 2003;28:461–470. [PubMed: 12628619]

King A, de Wit H, Riley RC, Cao D, Niaura R, Hatsukami D. Efficacy of naltrexone in smoking cessation: A preliminary study and an examination of sex differences. Nicotine & Tobacco Research 2006;8:671–682. [PubMed: 17008194]

Larsen, RJ.; Diener, E. Promises and problems with the circumplex model of emotion. In: Clark, MS., editor. Emotion, Review of Personality and Social Psychology. Vol. Vol. 13. Newbury Park, CA: Sage Publications; 1992.

Levine MD, Marcus MD, Perkins KA. A history of depression and smokingcessation outcomes among women concerned about post-cessation weight gain. Nicotine Tob Res 2003;5:69–76. [PubMed: 12745508]

Lynch WJ, Roth ME, Mickelberg JL, Carroll ME. Role of estrogen in the acquisition of intravenously self-administered cocaine in female rats. Pharmacol Biochem Behav 2001;68:641–646. [PubMed: 11526960]

Mead PM, Harlage SA, Cook-Karr J. Timing and severity of symptoms associated with the menstrual cycle in a community-based sample in the Midwestern United States. Psychiatry Research 2005;134:27–36. [PubMed: 15808287]

Meyer MC, Straughn AB, Lo MW, Schary WL, Whitney CC. Bioequivalence, dose-proportionality, and pharmacokinetics of naltrexone after oral administration. J Clin Psychiatry 1984;45:15–19. [PubMed: 6469932]

McKinlay SM, Bifano NL, McKinlay JB. Smoking and age at menopause in women. Ann Intern Med 1985;103(3):350–356. [PubMed: 4026083]

Murphy JM, Horton NJ, Monson RR, Laird NM, Sobol AM, Leighton AH. Cigarette smoking in relation to depression: Historical trends from the stirling county study. Am J Psychiatry 2003;160:1663–1669. [PubMed: 12944343]

O'Hara P, Portser SA, Anderson BP. The influence of menstrual cycle changes on the tobacco withdrawal syndrome in women. Addict Behav 1989;14:595–600. [PubMed: 2618842]

O'Malley SS, Cooney JL, Krishnan-Sarin S, Dubin JA, McKee SA, Cooney NL, Blakeslee A, Meandzija B, Romano-Dahlgard D, Wu R, Makuch R, Jatlow P. A controlled trial of naltrexone augmentation of nicotine replacement therapy for smoking cessation. Arch Intern Med 2006;166:667–674. [PubMed: 16567607]

Perkins KA, Levine M, Marcus M, D'Amico D, Miller A, Keins A, Ashcom J, Broge M. Tobacco withdrawal in women and menstrual cycle phase. Journal of Consulting and Clinical Psychology 2000;68(1):176–180. [PubMed: 10710853]

Perkin KA. Smoking cessation in women special considerations. CNS Drugs 2001;15(5):391–411. [PubMed: 11475944]

Perkins KA, Marcus MD, Levine MD, D'Amico D, Miller A, Broge M, Ashcom J, Shiffman S. Cognitive-behavioral therapy to reduce weight concerns improves smoking cessation outcome in weight-concerned women. Journal of Consulting & Clinical Psychology 2001;69:604–613. [PubMed: 11550727]

Pomerleau CS, Garcia AW, Pomerleau OF, Cameron OG. The effects of menstrual phase and nicotine abstinence on nicotine intake and on biochemical and subjective measures in women smokers: A preliminary report. Psychoneuroendocrinology 1992;17(6):627–638. [PubMed: 1287682]

Pomerleau CS, Cole PA, Lumley MA, Marks JL, Pomerleau OF. Effects of menstrual phase on nicotine, alcohol, and caffeine intake in smokers. J Subst Abuse 1994a;6(2):227–234. [PubMed: 7804021]

Pomerleau CS, Teuscher F, Goeters S, Pomerleau OF. Effects of nicotine abstinence and menstrual phase on task performance. Addict Behav 1994b;19(4):357–362. [PubMed: 7992670]

Pomerleau CS, Brouwer RJ, Pomerleau OF. Emergence of depression during early abstinence in depressed and non-depressed women smokers. Journal of Addictive Diseases 2001;20(1):73–80. [PubMed: 11286432]

Pomerleau OF, Adkins D, Pertschuk M. Predictors of outcome and recidivism in smoking cessation treatment. Addict Behav 1978;3:65–70. [PubMed: 717094]

Prescott E, Hippe M, Schnohr P. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ 1998a;316:1043–1047. [PubMed: 9552903]

Prescott E, Osler M, Hein HO. Gender and smoking related risk of lung cancer. Epidemiology 1998b; 9:79–83. [PubMed: 9430273]

Ross C, Coleman G, Stojanovska C. Prospectively reported symptom change across the menstrual cycle in users and non-users of oral contraceptives. Journal of Psychosomatic Obs & Gyn 2003;23:15–29.

Roth ME, Cosgrove KP, Carroll ME. Sex differences in the vulnerability to drug abuse. A review of preclinical studies. Neurosci Biobehav Rev 2004;28:533–546. [PubMed: 15527861]

Royce JM, Corbett K, Sorensen G, Ockene J. Gender, social pressure, and smoking cessations: The Community Intervention Trial For Smoking Cessation (COMMIT) at baseline. Social Science and Medicine 1997;44:359–370. [PubMed: 9004370]

Russell JA. A circumplex model of affect. J Pers Soc Psychol 1980;39:1161–1178.

Satcher D, Thompson TG, Koplan JP. Women and smoking: A report of the Surgeon General. Nicotine Tob Res 2002;4(1):7–20. [PubMed: 11906680]

Scharf D, Shiffman S. Are there gender differences in smoking cessation, with and without bupropion? Pooled- and meta-analyses of clinical trials of bupropion SR. Addiction 2004;99:1462–1469. [PubMed: 15500599]

Sherman BM, Korenman SG. Hormonal characteristics of the menstrual cycle throughout reproductive life. Journal of Clinical Investigation 1975;55:699–706. [PubMed: 1120778]

Shiffman S. Relapse following smoking cessation: a situational analysis. J Consulting and Clinical Psychology 1982;50:71–86.

Smith SS, Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Jamerson B, Fiore MC, Baker TB. Targeting smokers at increased risk for relapse: Treating women and those with a history of depression. Nicotine Tob Res 2003;5:99–109. [PubMed: 12745511]

Snively TA, Ahijevych KL, Bernhard LA, Wewers ME. Smoking behavior, dysphoric states and the menstrual cycle: Results from single smoking sessions and the natural environment. Psychoneuroendocrinology 2000;25(7):677–691. [PubMed: 10938448]

Sofuoglu M, Mitchell E, Kosten TR. Effects of progesterone treatment on cocaine responses in male and female cocaine users. Pharmacol, Biochem Behav 2004;78:699–705. [PubMed: 15301924]

Steinberg JL, Cherek DR. Brief Report: Menstrual cycle and cigarette smoking behavior. Addict Behav 1989;14:173–179. [PubMed: 2728953]

Svikis DS, Hatsukami DK, Hughes JR, Carroll KM, Pickens RW. Sex differences in tobacco withdrawal symptoms. Addict Behav 1986;11(4):459–462. [PubMed: 3544698]

Swan GE, Jack LM, Ward MM. Subgroups of smokers with different success rates after use of transdermal nicotine. Addiction 1997;92:207–218. [PubMed: 9158232]

Toll BA, Cooney NL, McKee SA, O'Malley SS. Do daily interactive voice response reports of smoking behavior correspond with retrospective reports? Psychol Addict Behav 2005;19:291–295. [PubMed: 16187808]

Toll BA, Cooney JL, McKee SA, O'Malley SS, Cooney NL. Correspondence of Interactive Voice Response (IVR) reports of nicotine withdrawal, craving, and negative mood with questionnaire ratings. Nicotine & Tobacco Research 2008;10(6):1057–1064. [PubMed: 18584469]

Toll BA, Leary V, Wu R, Salovey P, Meandzija B, O'Malley SS. A preliminary investigation of naltrexone augmentation of bupropion to stop smoking with less weight gain. Addictive Behaviors 2008;33:173–179. [PubMed: 17587504]

Toll BA, Schepis T, O'Malley SS, McKee SA, Krishnan-Sarin S. Subjective reactivity to the first cigarette of the day as a predictor of smoking relapse. Drug Alcohol Depend 2007;89:302–305. [PubMed: 17320313]

Wilson K, Gibson N, Williams A. Effect of smoking cessation on mortality after myocardial infarction. Arch Intern Med 2000;160:939–944. [PubMed: 10761958]

Zang A, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. J Natl Cancer Inst 1996;88(3–4):183–192. [PubMed: 8632492]

TABLE 1

Subject Baseline Characteristics By Gender For 385 subjects participating in a placebo-controlled Randomized Control Trial of natrexone augmentation of nicotine patch therapy

Baseline Measures	Women N=185	Men N=200	p value
Age (M ± SD)	46.7 ± 11.1	45.2 ± 11.2	0.19
Weight (kg)	71.1 ±14.4	87.9 ± 14.1	<.0001
BMI	26.9 ± 5.3	28.5 ± 4.5	0.002
# Cigarettes/day	24.7 ± 6.8	28.7 ± 10.9	<.0001
CO level (ppm)	24.9 ± 10.5	24.9 ± 9.3	0.98
FTND Scores	4.9 ± 1.5	5.2 ± 1.6	0.15
CESD Scale Scores	13.6 ± 5.4	13 ± 5.8	0.33
Mean Plasma Cotinine Level (ng/ml)	297.8 ± 116.9	312.1 ± 133.6	0.28
Married (%)	49.5%	65.0%	0.002
White	87.0%	87.5%	0.89
Heavy Drinkers	23.8%	27.0%	0.47
NIAAA Heavy Drinkers	24.9%	29.0%	0.36

FTND= Fagerström Test for Nicotine Dependence; CESD= Center for Epidemiologic Studies Depression Scale

Table 2

Treatment outcome in males and females as a function of naltrexone dosage.

Outcome measures	Male						Female					
	Placebo	25 mg	50 mg	100 mg	Chisq/F	P	Placebo	25 mg	50 mg	100 mg	Chisq / F	P
Smoking abstinence												
Continuous abstinence[a]	20 (43.5%)	22 (45.8%)	16 (32.0%)	28 (50.0%)	3.75	0.29	16 (34.0%)	16 (35.6%)	18 (39.1%)	25 (53.2%)	4.45	0.217
Continuous abstinence, completers[a]	20 (55.6%)	22 (56.4%)	16 (51.6%)	28 (71.8%)	3.63	0.305	16 (41.0%)	16 (44.4%)	18 (45.0%)	25 (71.4%) *	8.53	0.036
Weight change												
Weight change[b]	2.0 ± 1.71	0.9 ± 2.3S	1.0 ± 1.79	1.2 ± 2.16	1.97	0.121	1.6 ± 1.73	0.6 ± 1.43**	0.8 ± 1.84	1.6 ± 1.48	4	0.009
Weight change, abstinent subjects[b]	1.8 ± 1.42	0.9 ± 2.45	1.3 ± 1.87	1.39 ± 2.29	0.69	0.561	2.1 ± 1.95	0.6 ± 1.35*	0.8 ± 2.03	1.7 ± 1.63	2.91	0.041
Weight change, completers[b]	2.1 ± 1.69	0.9 ± 2.38	1.1 ± 1.77	1.2 ± 2.16	2.1	0.103	1.6 ± 1.73	0.6 ± 1.43*	0.9 ± 1.88	1.6 ± 1.48	3.77	0.012
Adherence												
Completed study[a]	36 (78.3%)	39 (81.3%)	31 (62.0%)	39 (69.6%)	5.6	0.133	39 (83.0%)	36 (80.0%)	40 (87.0%)	35 (74.5%)	2.52	0.472
% medication taken[b]	77.9 ± 28.01	75.7 ± 30.25	69.2 ± 33.38	70.4 ± 34.80	0.84	0.475	82.5 ± 24.28	75.9 ±31.62	81.9 ± 23.73	66.0 ± 35.98*	3.19	0.025
Adverse events												
Any moderate to severe side effect[a]	24 (54.6%)	25 (54.4%)	26 (54.2%)	32(61.5%)	0.795	0.851	33(71.7%)	24 (55.8%)	28 (62.2%)	31 (68.9%)	2.95	0.399
Any moderate to severe nausea[a]	4 (9.1%)	4 (8.7%)	5 (10.4%)	9 (17.3%)	2.37	0.499	5 (10.9%)	9 (20.9%)	10 (22.2%)	14 (31.1%) *	5.61	0.132
Drug plasma levels												
Naltrexone concentration, week 4 (ng/ml,n=221)[c]	0	1.2 ± 2.4	3.3 ± 4.5	5,8 ± 9.1##	4.98	0.01	0	1,5 ± 2.7	5.5 ± 9.1	11.7 ± 15.7^ ##	7,74	0.001
Naltrexol concentration, week 4 (ng/ml, n=221)[c]	0	13.3 ± 11.91	33.5 ±27,96++	59.4 ± 41.24^^ ##	22.26	<.0001	0	15.8 ± 19.49	42.1 ± 31.11++	78.2 ± 55.25^^ ##	26.08	<.0001

[a] Logistic regression analyses are conducted separately for men and women, overall Chi-Square and p values are reported.

[b] General Linear Models are used separately for men and women, overall F and p values are reported.

[c] General Linear Models are used separately for men and women, overall F and p values are reported for active doses.

Each active dose comparing to placebo: *p <.05, ** p <.01.

100mg dose comparing to 50mg dose: ^ $p < .05$, ^^ $p < .01$.

100mg dose comparing to 25mg dose: # $p < .05$, ## $p < .01$.

50mg dose comparing to25mg dose: $^{+}$ $p < .05$, $^{++}$ $p < .01$.

TABLE 3

MEAN IVR RATINGS FOR 250 SUBJECTS ACROSS SEX, REPRODUCTIVE STATUS, MENSTRUAL CYCLE PHASE AND ORAL CONTRACEPTIVE USE

STATUS	MENSTRUAL CYCLE PHASE	MEAN IVR	SD
Cycling Females n=47**		4.6	3.3
	Follicular n=16	4.0	3.4
	Luteal n=20	5.1	3.4
	Perimenstrual n=14	5.7	3.7
	Not Perimenstrual n=32	4.1	3.4
	Oral Contraceptives n=10	4.5	3.4
	No Oral Contraceptives n=37	4.7	3.4
Menopausal Females n=69	N/A	4.3	3.1
All Females n=116	N/A	4.3	3.1
Males n=134	N/A	3.9	2.6

Legend: Women on oral contraceptives were not classified with regards to menstrual cycle phase. The menstrual cycle phase of one cycling female is unknown.

** Phase and Perimenstrual status could not be confirmed in 1 woman.