Article Title: Effect of exogenous progesterone administration on cigarette smoking-related symptomology in oral contraceptive users who smoke

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ABSTRACT

Cigarette smoking-related symptomatology (e.g., craving; SRS) is linked to relapse after a quit attempt. SRS varies by menstrual phase, possibly due to variations in sex hormones (e.g., progesterone), though much of the research to-date has relied on observations from the menstrual cycle acting as a proxy for hormone levels. The goal of this study was to examine the effect of exogenous progesterone on SRS during ad libitum smoking and following overnight abstinence.

Oral contraceptive users who smoked completed two 9-day crossover testing periods (7 days of ad libitum smoking and 2 days following overnight abstinence) while taking double-blind active/ placebo exogenous progesterone. Participants completed questionnaires to measure SRS. The effect of exogenous progesterone and endogenous hormones (progesterone, estradiol, and progesterone-to-estradiol [P/E_2] ratio) on SRS was assessed with paired t-tests and linear mixed effect models.

Participants (n=53) were, on average, 24 years old and smoked 11 cigarettes per day. During ad libitum smoking, a doubling of the P/E_2 ratio was associated with 0.09 points lower anticipated relief from negative affect (95% confidence interval [CI]: 0.03-0.15 points lower; p=0.008) and 0.11 points lower psychological reward (95% CI: 0.03-0.18 points lower; p=0.006). After correction for multiple testing, these associations were not statistically significant: anticipated relief from negative effect (p=0.10) and psychological reward (p=0.09). No other significant associations were observed.

Although substantial previous literature indicates that progesterone influences SRS, exogenous progesterone administration did not alter SRS here. Additional research is needed to elucidate alternative mechanisms involved in menstrual phase effects on SRS.

Key Words
Sex Hormones, Progesterone, Women's Health, Cigarette Smoking-Related Symptomatology

Highlights

- Smoking-related symptomatology (SRS; e.g., craving) varies by menstrual phase.
- Progesterone is thought to influence SRS levels, this has not yet been tested.
- Using a cross-over design, we administered progesterone and measured SRS.
- Progesterone administration had no significant effects on SRS.

1. Introduction

Despite the negative health consequences of cigarette smoking and the advancements made in smoking cessation treatments over the last several decades, 13.6% of women in the US continue to smoke cigarettes (Phillips et al., 2017). Women experience cigarette smoking and cessation differently than men. For example, women report different barriers to successful cessation (Clark et al., 2006; Etter et al., 2002; Kalman 2002), respond less favorably to behavioral and pharmacotherapy treatments (Cepeda-Benito et al., 2004; Piper et al., 2010; Smith et al., 2017), are less likely to maintain long-term smoking abstinence (Piper et al., 2012; Smith et al., 2016), and are more vulnerable to the negative health consequences of smoking (Anderson et al., 2011; Huxley and Woodward 2011; Belani et al., 2007; Manchón et al., 2007; Papadopoulos et al., 2014). Understanding the mechanisms that underlie these sex/gender differences is an important step towards the development of sex-specific treatments.

The clinical literature suggests that menstrual phase may influence smoking-related symptoms (SRS). Specifically, withdrawal and, possibly, craving are higher during the luteal phase, as compared to the follicular phase, based on a recent meta-analysis (Weinberger et al., 2015). This may be related to neuroactive steroid sex hormones, notably progesterone and estrogen, which vary over the menstrual cycle. The molecular mechanism that reinforces the effects of nicotine are mediated by a nicotinic acetylcholine receptor, β_2*-nAChRs (Cosgrove et al., 2012). Cosgrove and colleagues (2012) using MRI and SPECT scans observed that higher progesterone levels were associated with lower β_2*-nAChRs availability in the cortex and cerebellum, suggesting that progesterone may diminish the effects of this nicotinic acetylcholine receptor. Other studies have made similar observations that progesterone interferes with the function of nicotinic receptors (Kudo et al., 2002; Takashima et al., 2002). Estrogen has been hypothesized to enhance the rewarding effects of nicotine and other drugs of abuse by facilitating the release of dopamine in the nucleus accumbens (O'Dell and Torres 2014). Taken together, there is strong neurobiological evidence for the role of hormones in tobacco use behavior in women.

However, this has not been substantiated in a meta-analysis on menstrual phase and smoking cessation outcomes (Weinberger et al., 2015), perhaps due the reliance of menstrual phase as a proxy for sex hormones. This imperfect proxy ultimately limits the ability to assess temporality and causal inferences of sex hormones on SRS due to the many other physiological changes that occur across the menstrual cycle (Strauss and Barbieri, 2014). In contrast, a series of papers published by Sofuoglu and colleagues (Sofuoglu et al., 2001; Sofuoglu et al., 2009; Sofuoglu et al., 2011) observed that exogenous progesterone administration was associated with decreased craving after overnight abstinence and urge to smoke after four days of abstinence. Further, two similar studies that administered exogenous progesterone (or placebo) to women for the prevention of postpartum smoking relapse observed lower craving in women randomized to exogenous progesterone compared to placebo (Allen et al., 2018a; Forray et al., 2017).
One possible explanation for this discordant findings is that the type of progesterone (endogenous versus natural exogenous versus synthetic exogenous, such as that in oral contraceptives) may have different effects. This study is unique in that it examines effects of

endogenous progesterone levels and natural exogenous progesterone administration in combination with synthetic progesterone administrations (e.g., oral contraceptives) on SRS.

The aim of this counterbalanced, double-blinded, placebo-controlled, crossover study was to examine the effect of progesterone (versus placebo) on SRS in women using combination oral contraceptives. The use of oral contraceptive provides a clinical model that standardizes the natural variability of endogenous sex hormones, allowing for a more controlled investigation of hormonal effects. Participants were randomized to testing order (active – 200 mg twice daily progesterone – followed by placebo, or vice versa) and completed measures of SRS under two different conditions (ad libitum smoking and after overnight abstinence). This allowed for testing differences in SRS based on (a) administration of exogenous progesterone (200mg twice daily) and (b) endogenous sex hormone (serum levels during the placebo period) including progesterone, estradiol, and the P/E_2 ratio. We hypothesized that active exogenous progesterone, higher endogenous progesterone levels, and a higher P/E_2 ratio would be associated with less severe SRS during both ad libitum smoking and following overnight abstinence.

2. Methods

2.1. Study participants

We enrolled women between the ages of 18 and 35 who were current users of a combination oral contraceptive, in line with current clinical recommendations (Curtis et al., 2016). Participants were recruited from local women's clinics and through social and mass media advertising. Inclusion criteria included: (1) smoked ≥5 cigarettes per day for at least the past year and not planning to change smoking behavior in next 3 months, (2) use of combination oral contraceptive pills for at least the past three months without complications and with willingness to switch to a study-supplied combination oral contraceptive, and (3) stable physical and mental health. Exclusionary criteria included: (1) current/recent (<3 months) use of psychotropic medications, (2) current/recent (<3 months) use of smoking cessation aids, other forms of nicotine/tobacco, or illicit drugs with the exception of marijuana two or fewer times per month, (3) contraindications to the use of combination oral contraceptives, exogenous progesterone, or nicotine nasal spray (the study medications), (4) intention of becoming pregnant during the study period, or (5) current/recent (<3 months) breastfeeding or pregnancy.

2.2. Study protocol

2.2.1 Screening

This study was approved by the University of Minnesota Institutional Review Board. Eligibility criteria was assessed by telephone interview and an in-person evaluation, which was scheduled during the week of inert pills of their current oral contraceptive. At the in-person evaluation prior to data collection, all participants provided informed consent and completed baseline

questionnaires on demographics, smoking behavior (including cigarettes per day [CPD]), and nicotine dependence (Fagerstrom Test of Nicotine Dependence; [FTND] (Heatherton et al., 1991)). Participants left with Tri-Sprintec, the study-supplied oral contraceptive, with instructions to begin after completing their current pack of oral contraceptive pills and a study visit schedule. Participants were also compensated for their time and participation at all visits.

2.2.2 Study medication and schedule

The study procedures occurred over two packs of the oral contraceptive Tri-Sprintec (manufactured by Barr Laboratories) with a 9-day testing period (7 days of ad libitum smoking followed by 2 days of overnight abstinence) beginning on day 21 of the oral contraceptive pack (i.e., the first day of inert pills). On pill day 1 to 20, doses included three weeks of increasing norgestimate (0.18mg, 0.215mg, and 0.25mg, respectively), with a steady dose of ethinyl estradiol (0.035mg). On pill day 21, participants discontinued the active pills and were randomly assigned to begin 200mg twice daily exogenous progesterone (manufactured by Teva Pharmaceuticals) or placebo for 9 days to correspond to a 9-day testing period. The dose of 200mg twice daily was chosen to provide a serum concentration comparable to that of the luteal phase of the menstrual cycle, 3 to 25 ng/mL (Sofuoglu et al., 2002; McAuley et al., 1996). Because this protocol adjusted the length of oral contraceptives from the typical 28-day cycle to a 30-day cycle, participants were asked to use additional non-hormonal contraceptive methods (i.e., condoms) throughout the study and pregnancy tests were completed at the beginning of each testing period.

2.2.3. 9-Day testing period

On day 1 of the first 9-day testing period, participants were randomized to testing order (i.e., active progesterone during the first 9-day testing period and then placebo during the next testing period, or vice versa). Medications were then prepared by the study pharmacist following double-blind procedures. Participants were provided instructions on the use of the study medication and the completion of the ecological momentary assessments. Abstinence data was collected via an in-clinic survey following overnight abstinence on the morning of day 9. Upon arrival at the clinic between the hours of 7:00 am and 10:00 am on day 9, overnight smoking abstinence (beginning at 6:00pm the previous evening) was confirmed by expired CO (CO ≤ 8 ppm indicative of acute abstinence (Marrone et al., 2010)). Hormones (progesterone, estradiol) were measured on day 1 (prior to progesterone administration) and on day 9 via serum samples. The clinic visit began with the measurement of vitals (including weight and expired carbon monoxide (CO), self-reported 7-day cigarette Timeline Follow Back-TLFB; (Brown et al., 1998), adverse events, SRS, and assessment of medication compliance (self-reported medication use and pill counts). Participants were allowed to miss up to 2 doses of medication on day 1 through day 7 of a testing period, however medication must have been taken on day 8 and day 9 due to the importance of adherence on the lab testing days.

2.2.4. Electronic momentary assessment (EMA) data collection

On days 1-7, participants completed EMA assessments to measure SRS during ad libitum smoking using a study-supplied device (Samsung Galaxy Exhibit™). Given changes in SRS throughout the day, these assessments were delivered in groups of 3 or 4 measures during blocks of time throughout the day: 8:00am to 12:00pm, 12:00pm to 4:00pm, and 4:00pm to 9:00pm. Participants were prompted to complete an assessment via an alarm on the electronic data capture device. A total of 18 assessments (3 times per day) were available beginning on day 2 through the end of the day 7 (ad libitum smoking period of the study). The EMA tool used for this project was developed with the assistance and support of MEI research and ran on PiLR Health™, a data management and analytic system.

2.2.5. Measures

SRS measures included data collected during ad libitum smoking via EMA and following overnight abstinence via in-clinic survey: Minnesota Nicotine Withdrawal Scale-MNWS; (Hughes and Hatsukami, 1998; Hughes and Hatsukami, 1986), Positive and Negative Affect Scale-PANAS; (Watson et al., 1988), Perceived Stress Scale-PSS; (Cohen et al., 1983), Modified Cigarette Evaluation Questionnaire (completed during ad libitum smoking only)-mCEQ (Cappelleri et al., 2007)), Brief Questionnaire of Smoking Urges-Brief-QSU; (Tiffany and Drobes 1991), and the Center for Epidemiologic Studies Depression Scale-CESD; (Radloff 1977).

The University of Southern California Endocrine Research Laboratory analyzed the serum hormone samples by radioimmunoassay with preceding organic solvent extraction and celite column partition chromatography. The sensitivity of the progesterone assay was 10pg/ml and the interassay coefficient of variation was 12% at 230pg/ml. For the estradiol assay, the sensitivity was 2pg/ml and the interassay coefficient of variation were 11%, 13%, and 12% at 15, 36, and 101pg/ml, respectively.

2.3. Statistical methods

Descriptive statistics were used to summarize the baseline characteristics of the study sample. Categorical variables were summarized using counts and percentages, while continuous variables were summarized with means and standard deviations (SDs). Hormone levels were log transformed prior to analysis. SRS measures collected during the ad libitum period (days 1-7) were averaged prior to analysis.

To examine the relationship between administration of exogenous progesterone and the SRS measures, we used paired t-tests to test for differences in SRS by week (exogenous progesterone vs. placebo). This was done for both the ad libitum period and abstinence period. To test for an association between endogenous levels of progesterone, estradiol, and the P/E_2 ratio and the SRS measures, we fit linear mixed effect models. The outcome was the SRS measure and the log hormone level was the predictor, while controlling for cigarettes per day (CPD) at the screening visit and the log hormone level on day 1. A random intercept was used to account for the correlation of SRS outcomes measured on the same women during the different testing weeks. We fit separate models for the ad libitum and acute abstinence periods.

To correct for multiple testing, we applied Holm's method to produce corrected p-values (Aickin and Gensler, 1996). Specifically, the p-values were corrected to control the family-wise error rate at 0.05 for the testing of the various SRS outcomes for each combination of predictor (exogenous progesterone vs. placebo, progesterone level, estradiol level, P/E_2 ratio) and testing condition (ad libitum smoking, overnight abstinence). All statistical analyses were performed using R version 3.4.1.

3. Results

3.1. Sample Description

There were a total of 496 participants that completed the telephone screening and, of these, 276 were invited to an in-person assessment, including 115 who completed the screening process. A total of 70 participants were enrolled into the study. There was no evidence that first randomization to progesterone or placebo influenced retention in the protocol. Fifty-three women completed at least one testing week and 43 women completed both weeks. Participant data was excluded from the analysis for the following reasons: non-compliance with the overnight abstinence or medication protocol and missing data due to missed visit, lost to follow-up, or a participant discontinuation. Therefore, the final data used for this analysis included 53 women who completed at least one testing week and 37 women who completed both weeks.

Of the participants who completed at least one testing period (n=53), the mean age was 24.1 (SD: 4.5) years old and most were White (75%). The races of the other participants were Black (5.7%), American Indian or Alaskan Native (3.8%), Asian (1.9%), Native Hawaiian or Pacific Islander (1.9%), and multiple races (11%). The majority had completed some college (74%), while the remainder had a high school diploma (21%) or less (5.7%). Almost all of the participants had never been married (89%), a few had been divorced or separated (9.4%), and even fewer were currently married (1.9%). The participants smoked 11.1 (SD: 4.4) CPD on average. The average age of becoming a regular smoker was 17.5 (SD: 3.1) years old. The mean FTND score was 3.5 (SD: 1.8). There were no differences in baseline factors by randomization to testing order.

3.2. SRS measures

Table 1 summarizes each SRS measure collected.

3.3. Hormone levels

Progesterone levels and P/E_2 ratios were significantly higher during the active progesterone week compared to their placebo week. Specifically, the median progesterone level was 6.7 ng/ml (1^{st} quartile [Q1]: 3.8, 3^{rd} quartile [Q3]: 13.2) during the active progesterone week and 1.1 ng/ml (Q1: 0.76, Q3: 3.0) during the placebo week ($p<0.001$). The median P/E_2 ratio was 94.7

(Q1: 47.5, Q3: 185.7) during the active progesterone week and 15.2 (Q1: 9.1, Q3: 37.4) during the placebo week ($p<0.001$). There was no difference in estradiol between the active progesterone and placebo weeks; median estradiol level was 0.070 ng/ml (Q1: 0.056, Q3: 0.090) during the exogenous progesterone week and 0.081 ng/ml (Q1: 0.063, Q3: 0.114) during the placebo week ($p = 0.45$).

3.4. Within-individual changes between exogenous progesterone and placebo administration and SRS during ad libitum smoking and acute abstinence

In Figure 1, we summarize the within-individual changes in SRS between the active progesterone week and placebo week for both the ad libitum smoking and the acute abstinence conditions. During the exogenous progesterone week, during ad libitum smoking, women had, on average, 0.25 point higher scores for smoking satisfaction on the mCEQ (95% CI: 0.003-0.50 points higher; uncorrected $p=0.047$) compared to the placebo week. This association was not statistically significant after correction for multiple testing ($p=0.66$). None of the other associations during ad libitum smoking or acute abstinence were statistically significant ($p>0.05$).

3.5. Association between SRS and serum hormone levels in ad libitum smoking

In Figure 2, we summarize the adjusted associations between SRS measures and the serum hormone levels during ad libitum smoking. A doubling of the P/E_2 ratio was associated with 0.08 points lower total smoking urges (95% CI: 0.02-0.14 points lower; uncorrected $p=0.014$), 0.09 points lower anticipated relief from negative affect (95% CI: 0.03-0.15 points lower; uncorrected $p=0.008$), and 0.11 points lower psychological reward (95% CI: 0.03-0.18 points lower; uncorrected $p=0.006$). After correction for multiple testing, these associations were not statistically significant: total smoking urges ($p=0.17$), anticipated relief from negative affect ($p=0.10$), and psychological reward ($p=0.09$).

3.6. Association between SRS and hormone levels in acute abstinence

In Figure 3, we summarize the adjusted associations between SRS measures and the sex hormone levels during the acute abstinence period. There were no statistically significant associations between sex hormone levels and SRS measures.

4. Discussion

This counterbalanced, double-blind, placebo-controlled, crossover study assessed change in SRS during two conditions (ad libitum smoking and following acute overnight abstinence) in women using a standardized monophasic combination oral contraceptives during active exogenous progesterone (200 mg twice daily) administration and placebo. Contrary to our hypotheses, administration of exogenous progesterone, as compared to placebo, had no significant effect on any SRS measure during either condition. We observed an inverse relationship between the endogenous P/E_2 ratio and three SRS levels. Specifically during ad libitum smoking only, a

higher P/E_2 ratio was associated with lower total smoking urges, lower anticipated relief from negative affect, and lower psychological reward. However, while the direction of these associations fitwith our hypotheses, these associations were not statistically significant after correction for multiple testing and the effect sizes were small with questionable clinical meaningfulness. Further, there were no associations observed between endogenous progesterone, estradiol, or the P/E_2 ratio and SRS in our sample following acute overnight abstinence. Overall, we identified few associations with small effect sizes. This is in contrast to preclinical studies (Lynch and Sofuoglu 2010; Lynch et al., 2002; Carroll et al., 2004) and clinical neurobiological evidence (Tanner et al., 2015; Cosgrove et al., 2012; Kudo et al., 2002; Takashima et al., 2002) that suggests that progesterone blunts SRS and related behaviors.

The progesterone levels we observed during the exogenous administration week (median 6.7 ng/mL) are consistent with what is typically seen in the luteal phase (Strauss and Barbieri, 2014), but we did not observe any effect on withdrawal or craving in contrast to both a recent meta-analyses on menstrual phase effects (Weinberger et al 2015) and studies that examined exogenous progesterone effects (Sofuoglu et al., 2001; Sofuoglu et al., 2009; Sofuoglu et al., 2011; Allen et al., 2018a; Forray et al., 2017). In terms of the conflicting observation with menstrual phase effects, this may be related to differing endogenous versus exogenous progesterone effects. For example, we have previously demonstrated that smoking satisfaction during ad libitum smoking is higher during the follicular phase compared to the luteal phase in naturally cycling women, whereas in participants on a triphasic combination oral contraceptive, smoking satisfaction is higher during the week of high progestin [a synthetic form of progesterone] dose (i.e., ethinyl estradiol 35 mcg and norgestimate 0.25 mcg) versus the week of low progestin dose (i.e., ethinyl estradiol 35 mcg and norgestimate 0.18 mcg) (Hinderaker et al., 2015). This suggests that the effect of progesterone on SRS may differ based on whether progesterone is endogenous (i.e., produced naturally) or exogenous delivery of natural or synthetic progesterone. It is also possible that the type of exogenous progesterone (natural versus synthetic forms) may have differing effects. Thus, one possible explanation for these seemingly discrepant findings may be related to our use of oral contraceptive to standardize the natural variability of the menstrual cycle and sex hormones. Prior work indicates that there may be differences in SRS by hormonal contraceptive use (Allen et al., 2019). For example, in samples of adolescent and adult women in cessation trials, as compared to women who are not using hormonal contraceptives and have regular, natural menstrual cycles, women who are using hormonal contraceptives had higher levels of craving (Dickmann et al., 2009; Allen et al., 2018b). Further, motives for smoking and physiological stress response also varies by hormonal contraceptive use (Allen et al., 2018c). These observations may be related to differences in emotional and/or cognitive processing or structural brain changes, as these appear to differ by oral contraceptive use (Petersen et al., 2014; Lisofsky et al., 2016). Additional research is needed to further investigate and elucidate the effect of progesterone on SRS and whether it differs by type (i.e., natural versus synthetic) and/or delivery (endogenously produced versus exogenously administrated).

Although this study was strengthened by the, counterbalanced, double-blind, placebo-controlled crossover design with biochemical confirmation of smoking status and direct

measurement of serum hormone levels, there are limitations worth noting. First, while we collected repeated measures of SRS during ad libitum smoking via EMA, we collected SRS following acute abstinence only once in the lab. It is possible that SRS varies by environment and/or measurement method. This may limit the comparison of our ad libitum versus abstinence results. Second, it may be that the SRS data collected during ad libitum smoking varied in a way we did not anticipate. Next, we had a large proportion of possible participants that were either not eligible or did not complete the protocol. Thus, selection bias is likely present. Last, participants in this study did not want to quit smoking permanently. Thus, it is unknown how these observations may apply to the general population of women who are attempting to quit smoking permanently.

5. Conclusions

Our findings do not support a strong relationship between exogenous progesterone administration and SRS within oral contraceptive users. Additional research is needed to identify the causal mechanisms responsible for the menstrual phase differences in SRS, as well as to replicate the findings here.

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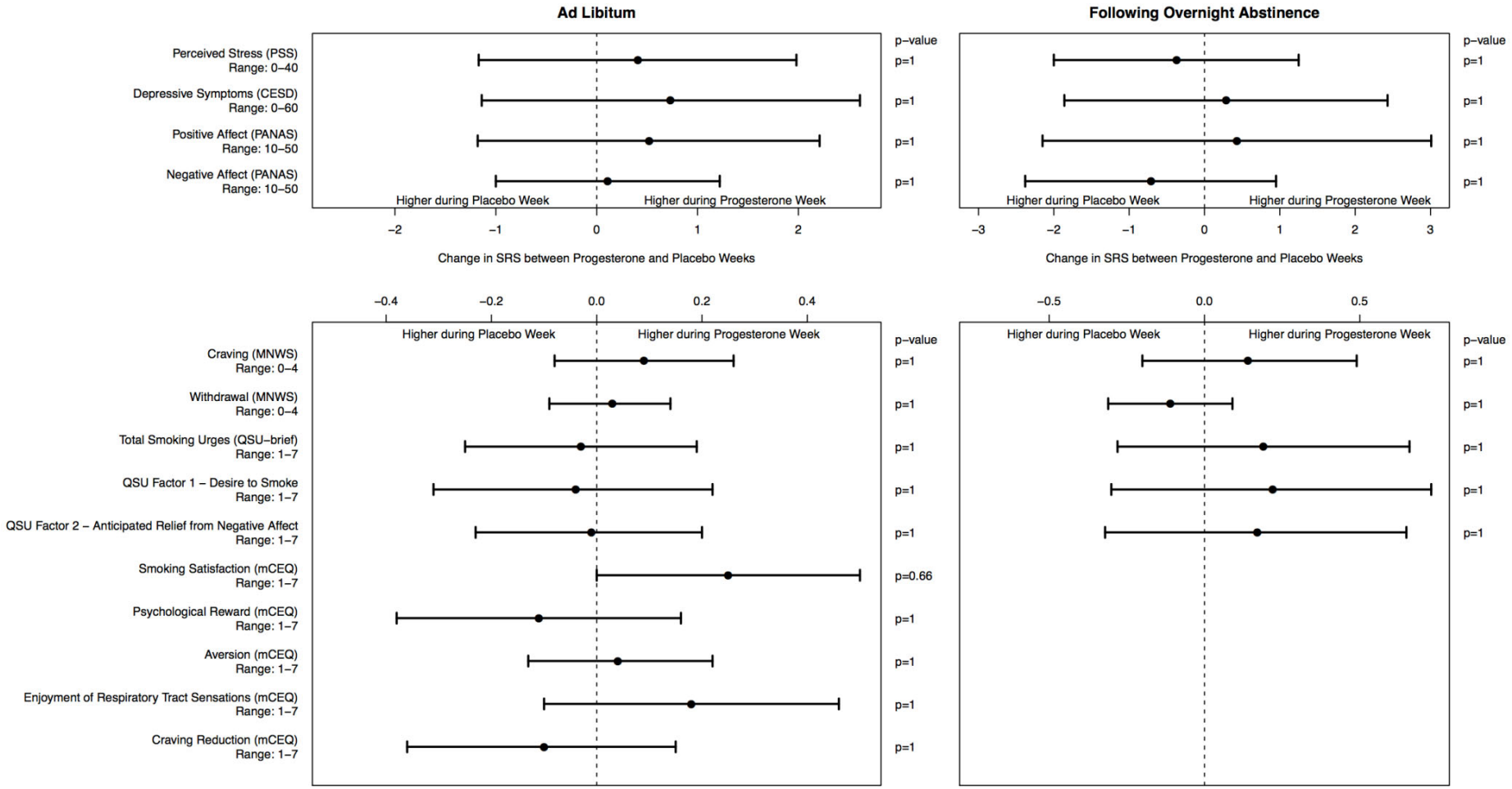
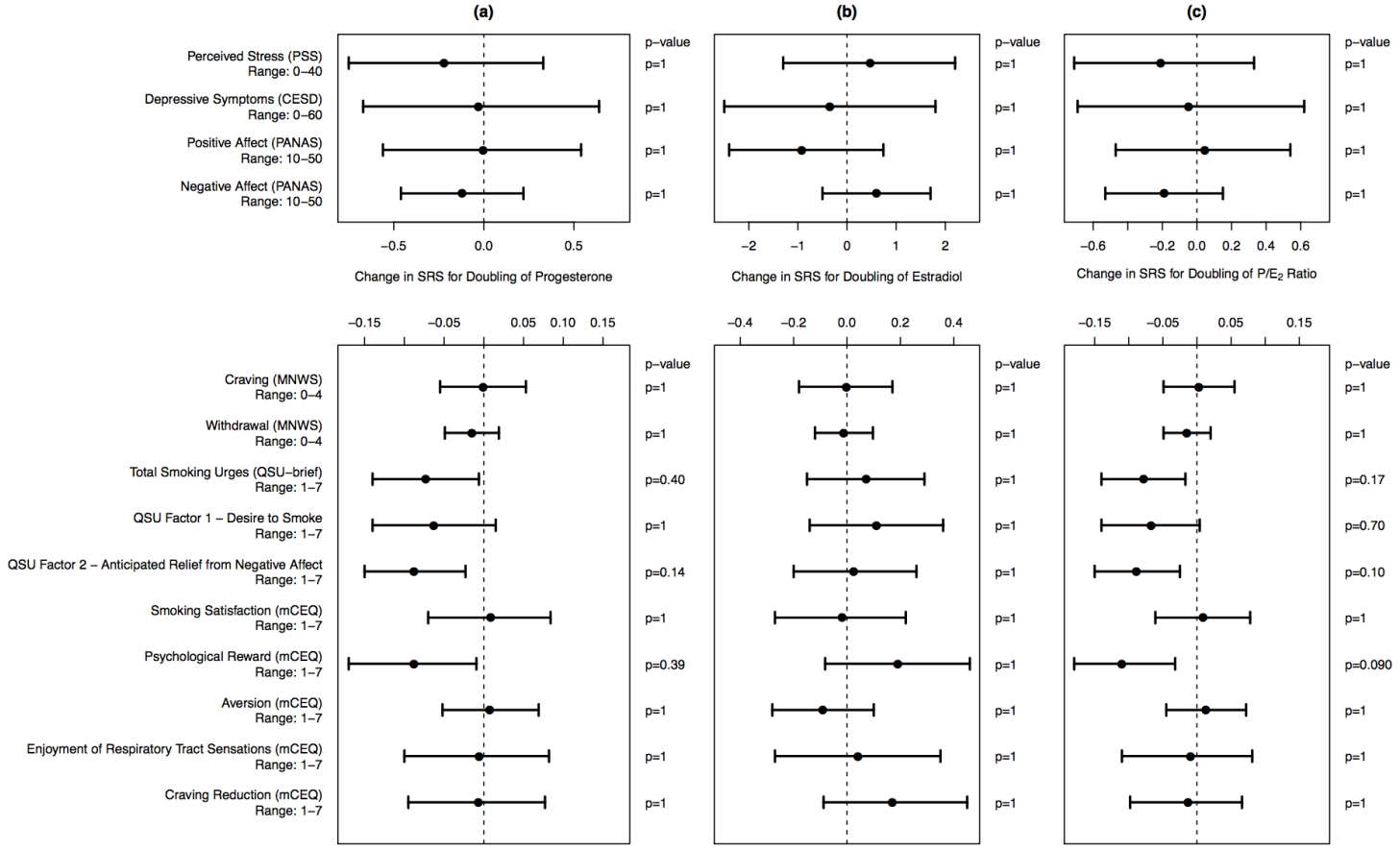
Figure 1. Within-individual differences in smoking-related symptomatology (SRS) between the exogenous progesterone and placebo administration. The bands indicate 95% confidence intervals. P-values were corrected for multiple testing using the Holm method (Aickin and Gensler, 1996).



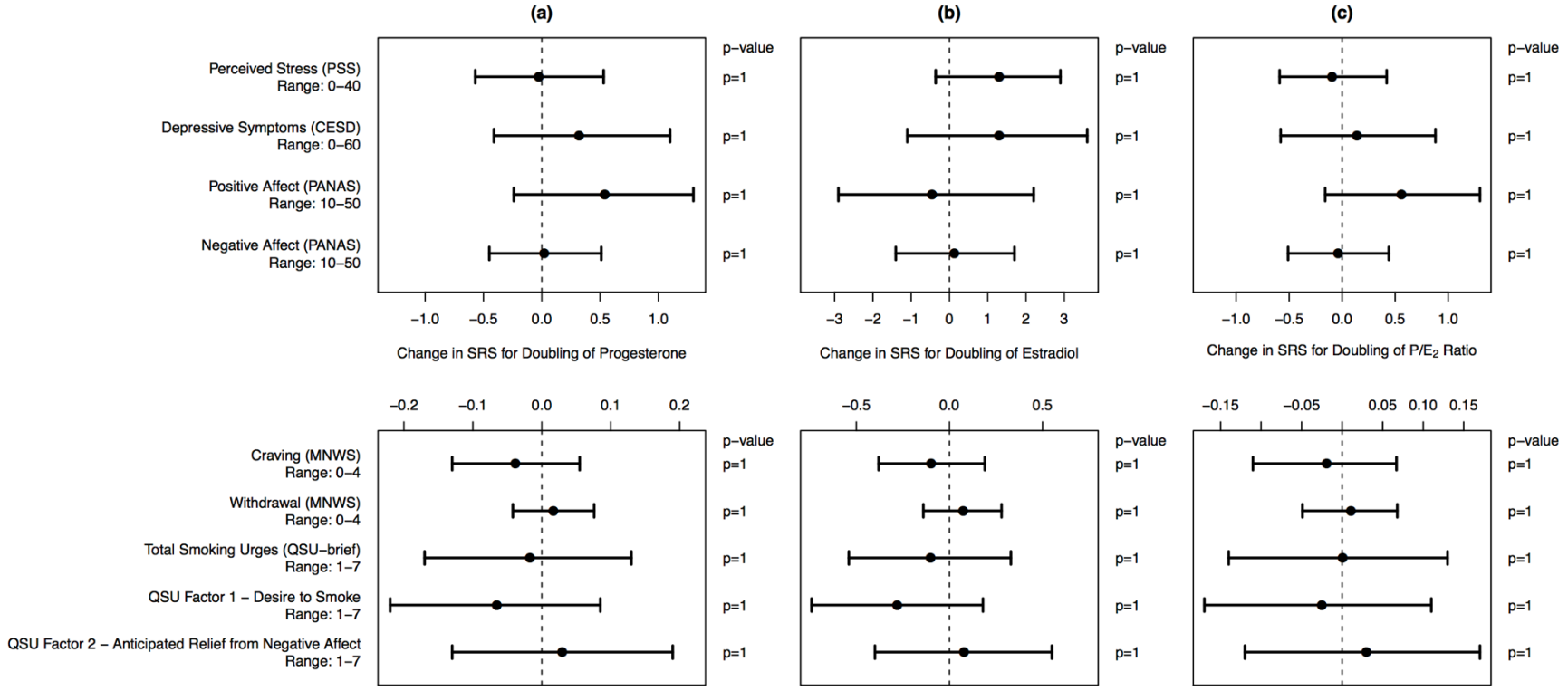
The surveys used were: Perceived Stress Scale (PSS) (Cohen et al., 1983); Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes and Hatsukami, 1998; Hughes and Hatsukami, 1986); Brief Questionnaire of Smoking Urges (QSU-brief) (Tiffany and Drobes, 1991); the Center for Epidemiologic Studies Depression Scale (CESD) (Radloff, 1977); Positive and Negative Affect Scale (PANAS) (Watson et al., 1988); and Modified Cigarette Evaluation Questionnaire (mCEQ) (Cappelleri et al., 2007). The mCEQ was not administered following overnight abstinence, as it is designed to be used while ad libitum smoking.

Figure 2. Adjusted associations between smoking-related symptomatology (SRS) and (a) progesterone levels, (b) estradiol levels, and (c) P/E_2 ratios during ad libitum smoking. The bands indicate 95% confidence intervals. P-values were corrected for multiple testing using the Holm method (Aickin and Gensler, 1996).



Adjustment was made for reported cigarettes per day at the screening visit and log baseline hormone level. The surveys used were: Perceived Stress Scale (PSS) (Cohen et al., 1983); Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes and Hatsukami, 1998; Hughes and Hatsukami, 1986); Brief Questionnaire of Smoking Urges (QSU-brief) (Tiffany and Drobes, 1991); the Center for Epidemiologic Studies Depression Scale (CESD) (Radloff, 1977); Positive and Negative Affect Scale (PANAS) (Watson et al., 1988); and Modified Cigarette Evaluation Questionnaire (mCEQ) (Cappelleri et al., 2007).

Figure 3. Adjusted associations between smoking-related symptomatology (SRS) and (a) progesterone levels, (b) estradiol levels, and (c) P/E_2 ratios after overnight abstinence. The bands indicate 95% confidence intervals. P-values were corrected for multiple testing using the Holm method (Aickin and Gensler, 1996).



Adjustment was made for reported cigarettes per day at the screening visit and log baseline hormone level. The surveys used were: Perceived Stress Scale (PSS) (Cohen et al., 1983); Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes and Hatsukami, 1998; Hughes and Hatsukami, 1986); Brief Questionnaire of Smoking Urges (QSU-brief) (Tiffany and Drobes, 1991); the Center for Epidemiologic Studies Depression Scale (CESD) (Radloff, 1977); Positive and Negative Affect Scale (PANAS) (Watson et al., 1988); and Modified Cigarette Evaluation Questionnaire (mCEQ) (Cappelleri et al., 2007).