The Pennsylvania State University

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ASSOCIATION BETWEEN ORAL CONTRACEPTIVE USE AND CIGARETTE DEPENDENCE IN WOMEN WHO SMOKE CIGARETTES

A Thesis in

Psychology

by

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ABSTRACT

Significance: Recent work indicates that ovarian hormones influence smoking behavior. While more work is needed to better understand the role of hormonal functioning in this context, advancements in neuroendocrinological addiction science may help clinicians create person-specific interventions for smokers, including women who take oral contraceptives (OCs). Prior work suggests the use of OCs significantly increases the rate of nicotine metabolism in women, which is associated with higher rates of cigarette dependence; however, whether OC use is implicated in cigarette dependence remains unclear. The present study investigated whether cigarette dependence differed among females who reported current use of OCs vs. females who did not. **Methods:** Participants answered questions about demographics, reproductive health (including items assessing use of oral contraceptives), and cigarette use via an online survey. Two subgroups were established: female smokers who reported current OC use ($N = 27$; M age = 26.9) and female smokers who did not report OC use ($N = 60$; M age = 29.0). Nicotine dependence was assessed via the Fagerström Test for Cigarette Dependence and compared between subgroups. **Results:** Nicotine dependence scores were lower among OC users compared to non-users ($F(1, 84) = 4.00$, $p < 0.05$). This association became marginally significant when controlling for age and smoking rate ($F(1, 81) = 3.50$, $p = .07$). **Conclusions:** Use of OCs was associated with lower rates of nicotine dependence. With additional validation, these data could inform tobacco cessation strategies considerate of hormonal dynamics specific to women who smoke cigarettes.

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Chapter 1: Introduction

Tobacco use remains the leading cause of preventable death in the United States and worldwide (World Health Organization, 2008). While smoking rates have historically been higher among men than women, data across the past several decades indicate that this gap has narrowed, as current smoking rates are only slightly higher for men (15.3%) than women (12.7%; Cornelius et al, 2020). Furthermore, there is evidence that women face a greater risk for experiencing tobacco-related health problems compared to men, (i.e., lung cancer; Pauk et al, 2005), and that women have poorer cessation outcomes than men following nicotine replacement therapy (Perkins & Scott, 2008).

Sex Differences in Drug Use

Sex differences in drug use have several potential mechanisms. For example, peripheral non-neurological factors, such as percent body fat and metabolic rate, have direct influence on bodily responses to drugs (Soldin & Mattison, 2009). Secondly, possible structural and functional differences in organization of the brain (e.g., reward neurocircuitry) may exist separate from reproductive function (DeCasien et al, 2022). Thirdly, and most central to this investigation are mechanisms stemming from sex-specific hormonal dynamics that may raise or lower risk of experiencing drug-related problems, including tobacco dependence (Wetherill et al, 2016). Specifically, estradiol—the predominant form of estrogen during reproductive years—and progesterone are primarily involved in processes related to sexual maturation and reproductive functioning, and are implicated in several addiction-related processes (Jackson et al, 2006). Because estradiol and progesterone have a greater functional role in females than males and are linked to neurocircuitry implicated in tobacco dependence, as well as the inconsistent data on the male-dominant hormone testosterone (Caine et al, 2004), studying the neural processes that

involve these hormones may shed light on differences observed between the experiences of men and women who smoke.

Ovarian Hormones and Drug Use

Basic science indicates that estradiol modulates the mesolimbic reward system such that greater concentrations of this hormone lead to higher activity within this circuit, which is associated with higher drug reactivity (e.g., greater sensations of "liking" a drug) and increased drug-seeking behavior (Gardner, 2011). Progesterone and its metabolite allopregnanalone counteract the effects of estradiol to reduce drug-related behavior via modulation of Gamma-Aminobutyric Acid $(GABA)_A$ receptors, the Hypothalamic-Pituitary-Adrenal (HPA) axis and several other systems that extend past the scope of this manuscript (Becker & Hu, 2008; Evans & Foltin, 2010) Preclinical studies have utilized drug self-administration models to explore some of the effects of estrogen and progesterone on drug-use behavior. Drug self-administration within this paradigm has not been studied by comparing hormone cycle phase because the time it takes for animals to acquire drug-self administration behaviors exceeds that of menstrual cycle phases (Carroll & Anker, 2010). Instead, animal models that examine hormonal influences on drug-taking behaviors typically involve removal of a female animal's ovaries (OVX) and the introduction of exogenous forms of estrogen (OVX + E) or progesterone (OVX + P). Control groups for these models involve a sham-operation group – which involves performing a surgery while leaving the ovaries in-tact (SH)— and a vehicle-treated group – where an ovariectomized animal would receive direct administration of a drug (SH + V). Drug-taking behavior acquisition studies using these strategies have indicated that (OVX + E) and (SH + V) rats acquired cocaine and heroin self-administration more readily than OVX + V rats (e.g., Hu et al, 2004; Roth et al, 2002). Interestingly, the trend of the seemingly counteractive effect of progesterone on estrogen

has persisted across drugs and studies (for a review of sex differences and ovarian hormones in animal models of drug dependence, see Carroll & Anker, 2010). Because the mechanisms driving the onset and the maintenance of the use of several highly addictive substances seem to overlap, preclinical research into nicotine use has been informed by studies like the ones outlined above, and show similar patterns of female-specific drug-use behavior. For example, meta-analytic data demonstrate female rats self-administer nicotine at a greater rate than male rats, and others have revealed (OVX) rats display a reduction in nicotine self-administration, suggesting that ovarian functionality may be implicated in mechanisms underlying sex-differences in nicotine use (Flores et al, 2016; 2019). These data have revealed possible targets for tailored cigarette cessation research aimed at integrating neuroendocrinological data into clinical interventions.

Methodological Challenges to Naturalistic Ovarian Hormone Research

While preclinical research indicates that progesterone and estradiol are important factors in sex-specific smoking-related behaviors, efforts to translate these findings into clinical populations have yielded inconsistent findings. These inconsistencies are due in large part to tensions between the need to establish feasible clinical paradigms while prioritizing good reliability and ecological validity. For example, significant variability between and within individuals with menstrual cycles exist regarding the temporal dynamics of hormone concentrations (Allen et al, 2016). Additionally, there is a lack of standardized methods across studies for determining menstrual cycle phase. Furthermore, the assumption often underlying menstrual cycle phase-based research that the follicular phase is associated with an increase in estradiol (and therefore, an increase in drug-abuse liability) and that the luteal phase is associated with an increase in progesterone (and therefore, a decrease in abuse liability) lacks the nuance

necessary to capture the complex temporal and concentration dynamics of these hormones. For example, estradiol, in addition to progesterone, also increases during the luteal phase; when comparing the two though, higher concentrations of progesterone tend to characterize this phase, and thus assumptions about the biological implications of this phase are often mistaken. Another often-unaddressed methodological challenge to menstrual phase research is the lack of consideration for a wide range of other factors that influence hormones such as sleep, stress, and caregiver activities. Lastly, hormones are never static, and reliance on self-report measures of cycle phase restricts investigators' ability to capture moment to moment changes (Allen et al, 2015; Weinberger et al, 2015; Wetherill et al, 2016).

Because of the methodological issues described above, studies that examine smoking related outcomes by phase cycle have yielded mixed findings. Allen et al. (2009) found that females who smoke reported greater levels of craving and were more likely to relapse following acute nicotine withdrawal during the follicular (vs. luteal) phase of the menstrual cycle, when estradiol levels are greater than progesterone levels. In contrast, Perkins and colleagues (2000) examined differences in withdrawal symptoms between females who quit smoking during the follicular phase vs. those who quit during the luteal phase and found that those in the luteal phase quit-group reported significantly greater increases in withdrawal symptoms and worse depressive symptoms than those in the follicular phase group. Other studies indicate no association between menstrual phase and tobacco use among women (Marks et al, 1999). While the above studies illustrate the somewhat inconsistent nature of data on estrogen/progesterone and tobacco use, literature reviews of studies examining tobacco use in the context of natural ovarian hormone fluctuations tend to report that higher levels of progesterone are negatively associated with tobacco use vulnerability, whereas estradiol appears to be positively associated (Wetherill et al,

2016). Indeed, tobacco use behavior when the concentration of estradiol is greater than the concentration of progesterone seems to be associated with greater health risks (Weinberger et al, 2015). And conversely, when the concentration of progesterone is greater than the concentration of estradiol, an individual's tobacco use behavior appears to pose less of a risk to their overall health (Schiller et al, 2012).

Oral Contraceptive and Cigarette Use

An alternative approach to examining the role of ovarian hormones on smoking in clinical populations that bypasses some of the methodological issues convoluting cycle phase research involves administering exogenous forms of ovarian hormones to women who smoke. One convenient and clinically-relevant way to conduct smoking research in line with this approach involves examining women who take oral contraceptives (OCs). An estimated 35-45% of all women between 2008 and 2014 used hormone-containing contraceptives of some kind, and nearly 30% of premenopausal women who smoke use some form of OC (Allen et al, 2018; Kavanaugh & Jerman, 2018). Although there are over 90 types of OCs on the market, physicians will typically prescribe one of two types of OCs: a progestin-only pill, which contains a synthetic form of progesterone, or a combination pill, which contains both estrogen and progesterone (Hall & Trussell, 2012). While some variability in endogenous hormone levels is observed, generally, progesterone and estrogen levels tend to be lower and more stable over time with use. Theories underlying research into OC use and smoking suggest differences between OC users and non-users who smoke may be due in part to the manipulation of naturally cycling ovarian hormone concentrations (Allen et al, 2020; Montoya & Bos 2017).

There has been some work on associations of OC use and tobacco abstinence-related behaviors. One study reported higher odds of reported current smoking in an OC-using group vs.

non-users (2.42, 95% CI: 1.8 – 3.14; Lee et al, 2013). In a study of females who smoke during a brief abstinence period, OC users reported greater physiological withdrawal symptoms (i.e., rapid heartbeat, $p < .05$) than non-users, but there was no difference between the two in overall withdrawal symptoms (Masson & Gilbert 1999). Interestingly, in a study tracking withdrawal symptoms in adolescents who smoke following a quit-attempt, girls not taking OCs reported significantly higher levels of craving than both girls who were taking OCs and boys (Dickmann et al, 2009), representing a departure from the trend that OC use heightens risk for tobacco-related problems. Other research has examined associations between OC use and pharmacokinetic properties of nicotine (i.e., nicotine metabolism). In a study of 120 daily smoking adolescents (ages 13-17 years; OC users: $n = 30$; nonusers: $n = 54$; boys: $n = 36$), the concentration of the nicotine metabolite, 3HC-continine, was significantly higher in OC users (i.e., nicotine metabolism was faster) than non-users and boys ($p < .001$; Berlin et al, 2007). Similar results were obtained by a study that compared rates of nicotine metabolism among male and female smokers (Benowitz et al, 2006), which found that nicotine metabolism was faster in females than males and fastest for women who reported current use of OCs ($ps < .05$). Women who reported OC use in this study reported lower rates of nicotine dependence than women who did not use OCs and all men. Furthermore, Chenoweth et al (2014) reported faster nicotine metabolism in women taking estrogen-containing OCs vs. nonusers, although the difference did not reach significance ($p < .09$). Taken together, data from these studies suggest that oral contraceptive use (with potentially heightened risk associated with OCs containing estrogen) increases nicotine metabolism, which is typically considered a risk factor for greater dependence, as faster nicotine metabolism would require more frequent smoking in order to maintain

homeostatic levels of blood nicotine concentration. However, exactly why OC use appeared to buffer against nicotine dependence in the case of Benowitz et al (2006) remains unclear.

The Present Study

The primary aim of the present study was to assess patterns of cigarette dependence among women of reproductive age who smoke based on whether they used OCs using cross-sectional data from an internet survey in which individuals who smoke answered questions about cigarette use, OC use, and nicotine dependence severity. Though prior work has indicated OC use is associated with lower rates of dependence, the data backing this hypothesis (Benowitz et al, 2006) are presented in the context of a targeted investigation of nicotine metabolism. As was discussed above, Benowitz et al, (2006) observed that oral contraceptive use was associated with faster nicotine metabolism. Because faster (vs. slower) nicotine metabolism is known to drive higher rates of tobacco dependence (Kubota et al, 2006), it was hypothesized that this same mechanism would be at play in the current study, and thus, would lead to higher rates of dependence in women who take OCs vs. those who do not, and that these associations would remain significant after controlling for age and smoking rate.

Chapter 2: Method

Participants

Individuals who smoke cigarettes were invited to complete an online survey on reproductive health factors and smoking (N = 275). For the current analysis, we selected the subset of survey completers meeting the following inclusion criteria: (1) Self-reported female gender identity; (2) 18 – 49 years old; (3) self-reported current smoking; (4) smoking at least 10 cigarettes per day; (5) smoked at least 100 cigarettes during lifetime; and for the subset of OC users, (6) use of OCs.

Procedure

The survey included questions about demographics, cigarette use, OC use, and a measure of cigarette dependence severity. Online advertisements informed participants that they would be entered into a raffle with a chance to win a gift card as an incentive for their participation. The survey was administered and data were stored via REDCap, which is a secure, web-based application designed to support data capture for research studies. All procedures were reviewed and approved by The Pennsylvania State University Institutional Review Board.

Measures

Cigarette Dependence

The Fagerström Test of Cigarette Dependence (FTCD; formerly known as the Fagerström Test of Nicotine Dependence) is a widely used six-item self-report measure of cigarette dependence (Fagerström, 2011). In response to the increase in nicotine product diversity across the past two decades, this measure was renamed to specify its utility in capturing dependence on cigarettes versus other forms of tobacco. Scores range from 1-10 with higher

scores indicating greater cigarette dependence. This measure has been shown to reliably measure cigarette dependence in women who smoke (Sharma et al, 2021).

Oral Contraceptive Use

Whether participants were currently taking OCs was measured via a single author-constructed item: *"Are you currently taking birth control pills? Please answer 'yes' if you are currently taking birth control pills for any reason (that is, even if you are taking them for a reason other than to help prevent pregnancy.)"* For individuals who answered 'yes' to this question, a follow-up question was administered in order to gain additional information about the type of pill they use: *"Are you taking a progestin-only pill, also known as the "mini-pill" or POPs (ex. Norethindrone, Norgestrel, Aygestin, Camila, Errin, Heather, Jolivette, Nora-BE, Nor-QD, Micronor, Ortho Micronor, Ovrette)?"*

Personal characteristics

To collect sample characteristics and identify potential covariates, participants filled out an investigator-constructed demographics questionnaire that collected information such as gender, age, education, employment/marital status, race and ethnicity. Additionally, participants were administered smoking history questionnaires that asked about the onset and current status of participants' smoking behavior (e.g., age of first cigarette, cigarettes smoked per day)

Analytical Approach

Two subgroups were established: females who reported current use of OCs (OC users), and those who reported no current use of OCs (non-OC users). Linear regression models, in which OC use status (yes/no) served as the predictor and FTCD total scores (1-10) served as the outcome, were used to assess the association between OC use and cigarette dependence. In order

to control for potential confounding variables, age and cigarettes smoked per day were included in a separate adjusted model.

Chapter 3: Results

Sample Characteristics

Among OC users (N = 27), the mean age was 26.9 years (SD = 8.30); 75.0% identified themselves as Caucasian / White, 14.3% American Indian or Alaska Native, 3.6% Black / African American, 7.1% provided no response, while zero respondents identified as Asian and zero as multi-race. Among non-OC users (N = 60), the mean age was 29.0 (SD = 8.30); 81.8% identified as Caucasian / White, 1.5% American Indian or Alaska Native, 6.1% Black or African American, 4.5% Asian, and 6.1% multi-race. The OC users reported fewer cigarettes per day than the non-OC users, at 10.9 (SD = 9.5) and 11.9 (SD = 8.7), respectively. Sample characteristics are summarized in Table 1.

Cigarette Dependence

FTCD scores were lower among OC users compared to non-OC users, $F(1, 84) = 4.00$, $p < .05$. This effect became marginally significant when adjusted for age and smoking rate, $F(1, 82) = 3.5$, $p = .07$ (see Figure 1). Though the authors intended to examine whether the type of oral contraceptive (e.g., progestin-only pill vs. combination pill) predicted significantly different rates of dependence, power limitations due to small sample sizes restricted our ability to do so.

Chapter 4: Discussion

Results from this preliminary study suggest that oral contraceptive use is negatively associated with severity of cigarette dependence. In other words, women using OCs reported lower levels of cigarette dependence. While dependence is only one of several ways to measure tobacco-related problems, our findings align with previous data that also indicate an association between OC use and lower FTCD scores. As such, it appears that this area of research holds promise to help with person-specific cessation efforts. However, more work is needed to replicate and extend these findings in order for clinicians to integrate these advancements into their work (e.g., establishing best practices when considering OC prescriptions for women who smoke). If women who smoke cigarettes and take OCs consistently report lower rates of cigarette dependence than those who do not take OCs, perhaps prescribers could prioritize this method of birth control over others in an effort to decrease an individual's severity of cigarette dependence, which could be accompanied by health-promoting behaviors (e.g., smoking fewer cigarettes). Caution when interpreting clinical implications should be exercised though, as these data are scarce, and the mechanisms driving this association are unknown. Additionally, given that the area of smoking research that looks at OC use as a predictor for tobacco outcomes is still developing, there may be risks related to prescribing OCs to a woman who smokes cigarettes (e.g, Kaminski et al, 2013). For example, while OC use seems to be consistently associated with lower rates of cigarette dependence, it may be that faster nicotine metabolism reported by Benowitz et al, (2006) is a more important factor to consider when determining what is best for a woman's overall health, and thus, prescribing OCs in this case may not be in a patient's best interest.

Limitations

The present study has some limitations that should be noted. Although biological mechanisms drive some tobacco-related health disparities, there is evidence that sociocultural factors are also at play. For example, differences observed in externalizing behaviors between men and women appear also to be driven in part by social variables (e.g., perceived gender roles; Huselid et al, 1994) and that women tend to experience greater levels of drug-use related stigma (Meyers et al, 2021). Therefore, future studies with integrative approaches sensitive to both biological and sociocultural factors will be better-suited to advance clinical work with more valid data. Also, the sample of OC users was mixed in that some individuals reported progestin-only pill-use, while others reported combination pill-use. Although assessing FTCD differences between these groups would have provided an opportunity to assess differential risk between types of oral contraceptives, we lacked statistical power to run these analyses. The approach taken in the current study lacks the ability to disentangle the mechanisms driving associations between OC use and smoking outcomes, such as those suggested by the preclinical research described earlier (Hu et al, 2004; Roth et al, 2002; Carroll & Anker, 2010); efforts to develop novel approaches capable of elucidating these mechanisms in humans are encouraged. Lastly, the investigators acknowledge the limitations of conducting online survey-based research. While this surveillance method is advantageous in terms of flexibility and accessibility for individuals with access to the necessary technology (e.g., internet, electronic device), future studies with in-person or phone-based recruitment methods would be able to capture data from individuals with limited technological access.

Future Directions

We suggest that extension studies collect more robust data on OC use and ovarian hormone dynamics (e.g., phase-of-cycle data) in order to increase validity. Additionally, as of the time of this manuscript's emergence, no study has examined cessation outcomes or smoking relapse for women using OCs compared to women not using OCs. Furthermore, examining differences within OC users defined by the type of OC used (e.g., progestin-only vs. combination pill), would help to advance clinical knowledge about refining treatment and prevention best-practices. At the same time, such research would yield information that would potentially be relevant to the growing concern that estrogen-containing OCs are associated with physiological (e.g., cardiovascular) risk (Benowitz et al, 2006; Curtis et al, 2016; Kaminski et al, 2013; Masson & Gilbert, 1999). Given progesterone modulates $GABA_A$ receptors along the HPA axis via its metabolite allopregnanalone, and that the HPA axis is implicated in stress responses, it may be useful to examine whether these factors are modulated when OCs (particularly progestin-only types) are introduced.

Conclusion

Overall, our findings suggest that OC use may buffer risk for cigarette dependence, but more work is needed to further characterize this relationship. Replication and extension studies will help refine our understanding for how OCs and smoking are associated. It is recommended that future researchers into OC use and cigarette dependence integrate biological (e.g., nicotine metabolism speed) and sociocultural (e.g., access to OC prescribers) measures that, taken together with OC use status, account for more of the variance in cigarette dependence than OC use alone, in order to inform cessation efforts for women who smoke and take oral contraceptives.

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Appendix A

Table 1. Client Demographics

	Oral Contraceptive Users (n = 27)	Non-users (n = 60)
Self-reported race/ethnicity (%)		
American Indian or Alaska Native	**14.3**	**1.5**
Asian	**0**	**4.5**
Black or African American	**3.6**	**6.1**
Caucasian / White	**75**	**81.8**
More than one race	**0**	**6.1**
No response	**7.1**	**0**
Age (SD)	**26.9 (8.3)**	**29.0 (8.3)**
Cigarettes/day (SD)	**10.9 (9.5)**	**11.9 (8.7)**

Appendix B

Figure 1. Group Comparison of Cigarette Dependence