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Use of hormonal contraceptives and smoking cessation: A preliminary report

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HIGHLIGHTS

- Endogenous sex hormones influence smoking cessation outcomes.
- We explored the role of hormonal contraceptives (HCs) in smoking cessation.
- Women on HCs had more adverse levels of withdrawal, craving and negative affect.
- Compared to men, women on HCs had higher odds of abstinence (OR = 3.73).
- Fully-powered, prospective studies on the role of HCs in cessation are warranted.

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ABSTRACT

Although endogenous sex hormones influence smoking-related outcomes, little is known about the effect of exogenous sex hormones. Therefore, the goal of this preliminary study was to examine differences in withdrawal symptoms and cessation between women using hormonal contraceptives (HC), women not using hormonal contraceptives (no-HC) and men.

Utilizing data from two recently completed smoking cessation randomized clinical trials, we selected participants who were between the ages of 18–35 years old. Participants were classified based on use of hormonal contraceptives and gender, then matched based on pharmacotherapy randomization assignment and baseline cigarettes per day. Participants provided self-reported assessments on withdrawal, craving and negative affect, and smoking status was assessed for 52 weeks after quit date.

Participants (N = 130) were 28.7 ± 0.4 years old and smoked 16.8 ± 0.6 cigarettes/day. Compared to both no-HC and men, the HC group had significantly greater withdrawal one week prior to the quit date, on the quit date and one week after the quit date. During the first week of attempted abstinence, craving declined in HC and in men, but increased in no-HC. At end of treatment, the HC group was at 3.73 times higher odds of being abstinent compared to men (95% confidence interval: 1.12–12.40). There were no group differences in abstinence rates at Week 26 or 52.

These data suggest that HC users may experience more adverse levels of withdrawal, though may be more likely to achieve short-term abstinence. Future research is needed to replicate our observations and explore mechanisms of action.

1. Introduction

Research continues to accumulate indicating that endogenous sex hormones (e.g., progesterone and estradiol) influence cessation-related outcomes in premenopausal women. Weinberger, Smith, Allen, et al. (2015) recently conducted a meta-analysis of 36 research studies and found that withdrawal and, perhaps, craving was significantly higher in the luteal phase (e.g., high progesterone, low estradiol) compared to the follicular phase (e.g., low progesterone, low estradiol). The literature on the effect of endogenous sex hormones and/or menstrual phase on smoking cessation outcomes is mixed but suggestive of a differential effect based on the presence or absence of nicotine replacement therapy (NRT). Specifically, two studies that did not use NRT for cessation observed improved outcomes in the luteal phase (Allen, Bade, Center,

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Finstad, & Hatsukami, 2008; Mazure, Toll, McKee, Wu, & O'Malley, 2011). Conversely, two studies that used NRT for cessation observed improved outcomes in the follicular phase (Carpenter, Saladin, Leinbach, Larowe, & Upadhyaya, 2008; Franklin, Ehrman, Lynch, et al., 2008). A fifth study examined the direct effect of endogenous sex hormones on cessation and observed increasing progesterone was predictive of smoking abstinence when NRT was used but not when varenicline, a non-nicotine pharmacotherapy, was used (Saladin, Gray, Carpenter, Baker, & McClure, 2014). Together, these data suggest that sex hormones may interact with nicotine and influence cessation-related outcomes in women who have regular, natural menstrual cycles, although the direction of the effects is not clear.

An estimated 27% of premenopausal smokers use oral contraceptives, with even more using other forms of hormonal contraceptives (McClave, Hogue, Brunner, & Ehrlich, 2010). Despite the popularity of hormonal contraceptives, only a few published studies have explored their effect on cessation-related outcomes. Two studies, one conducted in adults and one in adolescents, observed that women on oral contraceptives have faster nicotine metabolism (Benowitz, Lessov-Schlaggar, Swan, & Jacob, 2006; Berlin, Gasior, & Moolchan, 2007). The estrogen in oral contraceptives is thought to be linked to an increased activity of CYP 2A6, the primary enzyme responsible for the metabolism of nicotine (Benowitz, 2004; Sinues, Fanlo, Mayayo, et al., 2008). Faster nicotine metabolism has been linked to smoking more, greater withdrawal during cessation attempts, reduced effectiveness of nicotine-based pharmacotherapies, and poorer cessation outcomes(Chen, Bloom, Baker, et al., 2013; Lerman, Jepson, Wileyto, et al., 2010; Schnoll et al., 2009; Sofuoglu, Herman, Nadim, & Jatlow, 2012; Strasser et al., 2011; Swan & Lessov-Schlaggar, 2009). A third study observed that adult women on oral contraceptives had greater physical symptoms (e.g., heart rate, blood pressure) both during an acute state of abstinence, as well as after smoking a cigarette (Masson & Gilbert, 1999).

Additional work has examined the association of oral contraceptive use with withdrawal symptoms. In contrast to the previously described research, a study conducted with adolescent smokers observed that girls who were using oral contraceptives had lower cigarette craving during cessation compared to girls not using oral contraceptives (Dickmann, Mooney, Allen, Hanson, & Hatsukami, 2009). Finally, we conducted a laboratory study in adult women that compared naturally cycling women to women on a standard, study-supplied tri-phasic oral contraceptives (Hinderaker et al., 2015). Compared to naturally cycling women, oral contraceptive pill users reported lower levels smoking satisfaction during ad libitum smoking, as well as lower positive affect and greater negative affect during smoking abstinence. Further, a trend on the third day of smoking abstinence suggested that the oral contraceptive pill users may have had lower craving for cigarettes than naturally cycling women (Hinderaker et al., 2015). In sum, with the exception of the data regarding craving which suggests that oral contraceptive pill users have lower craving during smoking abstinence, these data indicate that the women who are using oral contraceptives may experience more adverse withdrawal symptoms and may be at higher risk for smoking relapse.

To date no published studies have explored the association between the use of hormonal contraceptives and smoking cessation in adult women. Therefore, this exploratory study examined differences in withdrawal symptoms (including total withdrawal, craving, and negative affect) and abstinence rates among women using cyclical hormonal contraceptives (HC) versus women who were not using any form of hormonal contraceptives (no-HC) and men. Our first hypothesis was that more adverse withdrawal symptoms would occur in the HC group compared to the no-HC group and men. Similarly, our second hypothesis was that the HC group would be less likely to be abstinent compared to the no-HC group and men.

2. Methods

2.1. Study sample

This research is a secondary-data analysis that pooled data from two recently completed clinical trials. The first trial was a double-blind placebo-controlled randomized clinical trial that enrolled 1504 smokers to compare the efficacy of five smoking cessation pharmacotherapies (Piper, Smith, Schlam, et al., 2009). The second trial was an unblinded randomized clinical trial that enrolled 566 smokers to compare the efficacy of three smoking cessation pharmacotherapies (Baker, Piper, Stein, et al., 2016). Participants in these trials had to be motivated to quit smoking, not have any psychotic disorders, and not be using any smoking cessation medications. Additional details on eligibility can be found in the respective publications.

To be eligible for the present analyses participants had to: (1) be between the ages of 18 and 35 years at trial's baseline; given clinical recommendations that female smokers over the age of 35 should not use estrogen-based hormonal contraceptives (Frieden, Harold Jaffe, James Stephens, et al., 2013), and (2) be randomly assigned to receive either transdermal nicotine patch alone or in combination with the nicotine lozenge. We excluded those who were randomly assigned to a non-NRT treatment (e.g., varenicline) given that sex hormones are thought to have a differential effect on cessation outcomes when non-NRT treatments are used as compared to when NRT treatments are used (Franklin & Allen, 2009; Weinberger et al., 2015). After these initial inclusion criteria were applied, we classified participants into one of three groups based on data collected at baseline on use of concomitant medications: women on hormonal contraceptives (HC), women not on hormonal contraceptives (no-HC), and men. Among those in the HC group, we further excluded participants who were using long-acting hormonal contraceptives (e.g., the hormonal injection - Depo Provera ®, hormonal intrauterine device); thus, the HC group consisted of only those who were on cyclical hormonal contraceptives (e.g., oral contraceptives, Nuva Ring ®). We did this for two reasons. First, longer-acting hormonal contraceptive does not contain estrogen. This is an important distinction because estrogen is thought to have an effect on nicotine metabolism (Benowitz, 2004) and faster nicotine metabolism influences our study outcomes of cessation-related symptomatology (Rubinstein, Benowtiz, Auerback, & Moscicki, 2008) and cessation (Lerman, Tyndale, Patterson, et al., 2006; Schnoll et al., 2009). Therefore, it is plausible that the effect of long-acting hormonal contraceptives may differ from the effect of cyclical hormonal contraceptives that do contain estrogen. Second, the number of female participants who met eligibility for inclusion in this project and were on a long-acting hormonal contraceptive was relatively few (n = 5). Women who were using non-hormonal forms of contraceptive (e.g., tubal ligation, barrier methods) were eligible for inclusion in the no-HC group. The HC participants were then matched with no-HC participants and men based on treatment assignment (transdermal nicotine patch alone or in combination with the nicotine lozenge) and within five cigarettes per day (except one HC participant who was matched within 15 cigarettes per day) using a ratio of 1:2:2. Matching was completed using a SAS macro developed by the University of Minnesota, Division of Biostatistics (Grandits, 2010).

2.2. Clinical trial procedures

Trial participants were screened for eligibility via a telephone interview followed by an in-person clinic visit. Eligible participants completed informed consent and baseline assessments, and were then randomized to a treatment condition. Length of medication treatment varied by trial with one trial providing eight weeks of treatment (Piper et al., 2009) and the other providing 12 weeks of treatment (Baker et al., 2016). Treatment with patch consisted of a 21 mg patch (four or eight weeks) that was down titrated to 14 mg (two weeks) and 7 mg