Commentary

Innovations in Translational Sex and Gender-Sensitive Tobacco Research

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Tobacco use is a global epidemic with more than 5 million people dying every year from smoking-related causes.¹ In the United States, tobacco use leads to 440,000 deaths per year² and an annual economic burden of \$96 billion in medical expenses and \$97 billion in lost productivity.³ Smoking causes extensive medical consequences and many of these risks are greater for women compared to men, even after equating for tobacco exposure. Female smokers appear to be at a greater risk of developing lung cancer^{4,5} and are more susceptible to tobacco carcinogens⁵ than male smokers. Smoking is associated with an earlier age of breast cancer,⁶ and female smokers experience greater risks of oral cancer than male smokers.⁵ Even cancers that have historically been more prevalent in men (e.g., bladder cancer) are now demonstrating similar prevalence as rates continue to increase among female smokers.⁷ The risk of coronary heart disease is greater for female smokers than for male smokers.^{8–11} A meta-analysis examining the impact of smoking on coronary heart disease by gender in 76 cohorts from 1966–2010 (2.4 million participants) showed that, after controlling for other cardiovascular risk factors, female smokers demonstrated a 25% greater risk of coronary heart disease than male smokers.¹²

In addition to experiencing greater relative risks than men for common and serious smoking-related diseases, women face sex-specific health consequences from smoking. Smoking in women is associated with dysmenorrhea and menstrual irregularity,¹³ and altered ovarian cycle and hormone levels during menstrual cycle phases.^{14,15} Pregnancy- and perinatal-related consequences of smoking include conception delays and infertility, ectopic pregnancy, spontaneous abortion, preterm delivery, preeclampsia, and perinatal mortality.¹³ Compared to female nonsmokers, female smokers have a shorter reproductive lifespan,^{13,16,17} lower ovarian reserve,¹⁸ and quicker entry into all stages of the menopausal transition.¹⁹ Thus, women experience significant health-related disparities regarding tobacco use, underscoring the need to conduct gender-focused research that can help reduce the deadly effects of smoking for both female and male smokers.

Successfully stopping smoking can prevent and/or reduce many of the harmful effects of smoking for male and female smokers with

even greater benefits related to cardiovascular²⁰ and respiratory²¹ health for women compared to men. Unfortunately, there are no currently available treatments which promote high rates of long-term abstinence from tobacco for either gender. With the most effective treatments, tested under optimal conditions, 70% or more of smokers still relapse to smoking within 12 months.^{22,23} Further, despite being more likely to report a quit attempt than men,²⁴ women have greater difficulty achieving smoking cessation. This disparity in quitting has been found in numerous clinical trial investigations^{25,26} and population-based investigations. Women identified as “former smokers” in the first wave of the National Epidemiologic Survey on Alcohol and Related Conditions had 44% greater odds of having relapsed to cigarette smoking over the next 3 years than men.²⁷ It is important to note that not all studies have found this gender difference in likelihood of successful quitting smoking, particularly when accounting for other forms of tobacco use.^{28,29} However, studies that isolated single quit attempts have nearly unequivocally found women have more difficulty sustaining abstinence, even when accounting for other forms of tobacco use.³⁰

In addition to gender differences in overall cessation, some smoking cessation medications have also demonstrated differential efficacy across gender. Studies have demonstrated that women may be less responsive to nicotine replacement therapy as a cessation aid,^{31–33} and findings for gender differences in bupropion efficacy have been mixed.^{34–37} Smith et al.³⁰ examined sex differences in smoking cessation medication effectiveness that used population-based data from smokers attempting to quit in real-world contexts. Results demonstrated that the use of any medication appeared to attenuate the sex difference in likelihood of successfully quitting smoking, supporting the promotion of smoking cessation medication use among women.

To summarize, tobacco use is the leading cause of preventable morbidity and mortality among women in the United States and women have poorer rates of smoking cessation and greater exacerbated health risks compared to men. In order to effectively treat women smokers, intervention strategies need to target factors that serve to maintain smoking behavior in women and underlie poor treatment response. This issue of *Nicotine & Tobacco Research*, “Innovations

in Translational Sex and Gender-Sensitive Tobacco Research,” brings together leading tobacco use researchers to report innovative findings on gender/sex differences in factors maintaining tobacco use and how these findings are being translated to treatments. The articles in this issue span preclinical, clinical, laboratory, and epidemiologic methods to advance our knowledge related to gender and tobacco in three important areas of research: (a) the influence of ovarian hormones and menstrual cycle on smoking behavior; (b) stress, negative affect, and withdrawal; and (c) smoking cessation treatments.

Ovarian hormones, such as estrogen and progesterone, which fluctuate across the monthly menstrual cycle, may be a critical factor impacting smoking outcomes for women. Preclinical research suggests that these hormones play a role in the rewarding effects of nicotine.^{38,39} Previous human subject studies of ovarian hormones, often measured through the proxy variable of menstrual cycle phase, have suggested differences in withdrawal, cravings, and quit outcomes at different points in the menstrual cycle (e.g., Carpenter et al.,⁴⁰ Franklin et al.,⁴¹ Allen et al.⁴²). Articles in this issue present novel data on the impact of ovarian hormones on smoking behavior including stress effects, neuroimaging of cue reactivity, interactions with pharmacotherapy, and meta-analytic findings.

Stress, negative affect, and withdrawal symptoms also play critical roles in the smoking maintenance and relapse to smoking after quit attempts^{43–45} with evidence supporting stronger relationships for women. Women are more likely to smoke to reduce negative affect^{46,47} and depression is more strongly associated with smoking behavior and smoking relapse for women than men.^{48–50} Female smokers are more reactive to stress than men,^{51,52} with stress having a greater impact on relapse in women.⁵³ Finally, women, compared to men, experience both greater withdrawal symptoms and also more variable withdrawal symptoms during smoking abstinence.^{54–56} Together, the research suggests that stress, negative affect, and withdrawal may be especially important targets for female smokers. Articles in this issue advance our knowledge of gender differences in aspects of smoking related to stress, negative affect, and withdrawal covering topics that include preclinical stress system effects in withdrawal, mood and withdrawal by nicotine content (i.e., nicotine vs. denicotinized cigarettes), and cue-reactivity in the daily environment.

As discussed above, women have more difficulty quitting and remaining abstinent from smoking and some smoking cessation medications demonstrate reduced efficacy for women. Improving rates of quitting in women will require that we develop treatments which translate our knowledge about gender-sensitive factors that maintain smoking and/or hinder attempts to quit. Studies of smoking cessation treatments in this issue include those that evaluate sex differences in existing treatments and those that provide data for the development of novel treatments for women smokers including contingency management in pregnant and newly postpartum women, pharmacological and subjective reactivity to e-cigarettes, treating smoking in adolescents and young adults with mental health concerns, the efficacy of smoking cessation medications using epidemiological data, and considering the noradrenergic system as a gender-sensitive treatment target.

Spearheaded by the National Institutes of Health's Office of Women's Health Research (NIH-ORWH) and the Federal Drug Administration's (FDA) Office of Women's Health, there has been numerous recent changes advancing the consideration of sex and gender differences in biomedical research. These include NIH's commitment to consider sex in animal research,⁵⁷ the development of publication standards by leading journals which include the reporting of the sex composition of samples in preclinical research,^{58,59} and the Food and Drug Administration Safety and Innovation Act (FDASIA) Section 907 to improve the completeness and quality of demographic subgroup data including sex

and gender for drugs and devices.⁶⁰ Importantly, these efforts serve strengthen biomedical science by supporting researchers to incorporate sex and gender in the design, analysis, and reporting of their results.⁵⁷ The continued advancement of gender-specific and gender-sensitive research in the tobacco field, as highlighted in this issue, will serve to improve treatment for both women and men.

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Declaration of Interests

None declared.

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