Issue 9 | January 2017

SCIENCE FACT OR SCIENCE FICTION: DO SEX AND GENDER INFLUENCE SMOKING CESSATION?

Smoking behaviours, including cessation, are different for men and women. Women tend to have a harder time quitting cigarettes,[1-8] and research demonstrates that popular treatments like nicotine replacement patches are much more effective for men.[9,10] In addition to having greater difficulty quitting, women also experience a heavier health burden from smoking. Understanding how sex and gender interact with genetics to influence smoking behaviours and cessation may help determine why quitting is more difficult for women. Could integrating sex and gender into pharmacogenomics research on smoking be the key to helping women kick the habit?

Women are more susceptible to smoking-related diseases such as lung cancer and heart disease, as well as sex-specific health consequences of smoking such as infertility and cervical cancer.[11-13]

STRESS, GENDER AND SMOKING

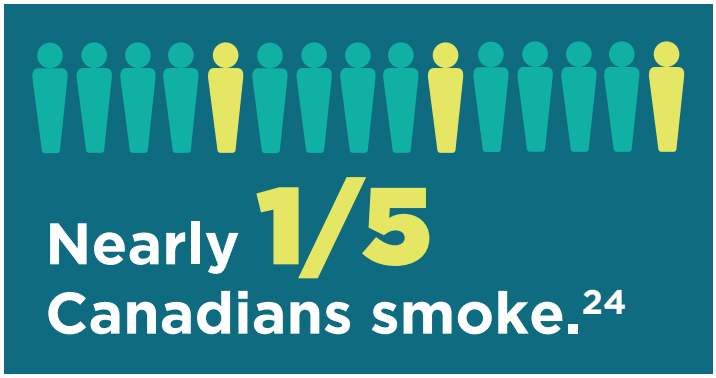
Gender (socially-constructed roles, norms, and behaviours) has a significant influence on why people smoke, how they smoke and how well they respond to smoking cessation treatment.[14] Gender-related factors such as increased stress and pressure to lose weight often drive women's smoking behaviours.[15-17] Research has shown that women are more likely to turn to smoking to reduce stress and report a greater intensity of anxiety when trying to quit.[15] While gender-related factors are an important piece of the puzzle, sex-related factors like genetics also play a substantial role.[18-20]

WHERE THERE'S SMOKE THERE'S SEX DIFFERENCE

Genetics affect how nicotine and smoking-related carcinogens interact with the body, influencing levels of dependence, response to cessation treatment, and even risk for smoking-related cancers.

Two types of genes are primarily responsible for variation in how nicotine acts in the body.[21,22] The first, which codes for the metabolic function of the CYP2A6 enzyme, influences how quickly nicotine is metabolized, affecting how soon a person might crave their next cigarette. The second type, which includes the protein-coding genes CHRNA5 and CHRNA3, plays a role in the downstream release of serotonin and dopamine—two chemicals that influence the reward response to smoking. Variation in the expression of these genes affects how people metabolize and respond to nicotine, which influences how they become addicted to cigarettes and their ability to quit.

Dr. Rachel Tyndale, Senior Scientist and Head of the Pharmacogenetics Lab at the Centre for Addiction and Mental Health, and Professor in the Departments of Pharmacology and Toxicology and Psychiatry at the University of Toronto, says that "while we have substantial data to support a role for nicotine metabolism in optimizing smoking cessation treatments, less work has been done examining the effects of sex hormones." The sex hormone estrogen, which is more prevalent in females, increases the amount of nicotine-metabolizing enzymes. Therefore, we know that women often metabolize nicotine more quickly than men, which means they may require different cessation therapies. In general, smokers with genetically slow nicotine metabolism find it easier to quit than those who metabolize nicotine more quickly. In addition, nicotine replacement therapies, like the nicotine patch, are better at helping slow metabolizers quit than



fast metabolizers.[22,23] Women, who are faster metabolizers, have more success with medications that reduce cravings and withdrawal symptoms, like varenicline.[9,10]

Tyndale suggests that the next step is to pool the clinical data from multiple studies together to look at differences between men and women: "Combining our clinical trial data will enhance our ability to examine interactions between sex and genetics, which will provide a better understanding of whether sex should be included in treatment decisions."

THE DUAL INFLUENCE OF GENDER AND GENOTYPE

We know that women tend to be faster metabolizers of nicotine than men. We also know that gender influences a person's smoking behaviours and the likelihood of quitting success. What will enhance our understanding even further is a sex- and gender-oriented approach that thoroughly accounts for how both of these factors might interact with a person's genes to influence their smoking behaviour and their success in quitting.

In addition to more research on sex and genetic influences on smoking, therapies should aim to account for the unique gendered experiences of individuals. Gender-specific therapeutic approaches could offer support for stress management and weight loss,[15-17] as well as strength-based interventions through online networks.[25] These approaches could lead to more success for men, women and people of all genders who are trying to kick the habit.

CONCLUSION

As we continue to develop approaches for smoking cessation that tailor treatments to genetic variation and environmental influences,[21,22] assessing how to account for sex will be key to ensuring these therapies benefit women as much as men. Bringing together the distinct but interlocking puzzle pieces of sex, gender and genetics offers a path towards improving smoking cessation treatments that accounts for the uniqueness of each person. In our increasingly personalized medical environment, this promising direction for future research and treatment optimization could help more people of all genders quit smoking and have better health outcomes for life.

ABOUT THE RESEARCH

Dr. Rachel Tyndale is a CIHR-funded researcher and the Canada Research Chair in Pharmacogenomics. She studies variation in drug response in the field of addictions and mental health at the University of Toronto and Centre for Addiction and Mental Health. Her focus is on how genetic variation in drug metabolism alters both the risk for addiction and the response to drug treatments.

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