Executive Summary

Opioid and Nicotine Use, Dependence, and Recovery: Influences of Sex and Gender

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HealthyWomen
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University of Colorado
University of Michigan Department of Psychology
University of North Carolina at Chapel Hill
VA Health System
Yale University School of Medicine

EXECUTIVE SUMMARY

Substance use disorders are complex chronic health conditions, often characterized by multifaceted etiologies stemming from biological, psychosocial, and environmental factors. Sex and gender are two such factors influencing substance use and misuse. In September 2018, FDA's Office of Women's Health (OWH), Center for Drug Evaluation and Research (CDER) and Center for Tobacco Products (CTP) brought together thought leaders and researchers from federal and academic institutions to focus on the influences of sex and gender on nicotine and opioid use disorders. *Sex*, a term referring to an individual's biological characteristics, and *gender*, related to personal and societal identity and sociocultural norms, impact our daily lives in sometimes unperceivable ways. Throughout this two-day scientific conference, 42 speakers presented to approximately 1,500 online and in-person attendees about how sex and gender can strongly influence susceptibility for substance use and how these variables impact an individual's trajectory toward addiction and recovery.

Nicotine

Tobacco use is the largest preventable cause of disease and disability in the U.S. and results in roughly 480,000 deaths annually [1, 2]. More men use tobacco products than women [3, 4], but lung and other cancers, chronic obstructive pulmonary disease (COPD) and heart disease impact both sexes. Importantly, smoking during pregnancy increases the risk for long-term adverse health outcomes in both mother and baby [1]. Decades ago smoking rates were significantly higher in men; however, smoking rates in women and men are now more similar than ever before [2]. Although use of traditional tobacco products like combustible cigarettes has been steadily declining, rates of electronic cigarette (e-cigarette) use are increasing in certain vulnerable populations, like children and teens [5-7]. Notably, there is little research on the safety and long-term health impacts of e-cigarettes, despite public perception that e-cigarettes are healthier than traditional cigarettes [8].

Opioids

Rates of opioid overdose deaths are increasing, with about 47,600 deaths reported in the U.S. in 2017; 17,029 of these deaths involved prescription opioids [9]. Prescription opioid analgesics are labeled for conditions that cause moderate to severe pain. As conditions causing chronic pain are more often diagnosed in women than men [10-12], women are more likely to be prescribed opioid pain medications and for longer durations than men [13]. Although the risk of dying from an opioid overdose is higher in men than women, data suggest a sharp increase in opioid overdoses in women compared to men in recent years [14].

Several themes related to substance use and misuse emerged from presentations by national experts and patients in recovery from nicotine and opioid use disorders:

Men and women experience addiction differently. Substance use onset, patterns of use, and recovery are influenced by sex and gender. Stress, pain, relief of negative affect, and social factors are more salient influencers of substance use and misuse in women versus men [10-12, 15-17]. While nicotine addiction is the driving factor of cigarette cravings in men, women are especially sensitive to non-nicotine factors mediating craving, such as seeing, smelling and hearing others talk about smoking [18, 19]. Opioid misuse escalates faster in women compared to men, a phenomenon known as telescoping [20, 21].

Gender plays a critical role in how one's environment shapes substance use patterns. Adverse early life experiences greatly enhance the likelihood of adult substance use and misuse [22], but different types of trauma occurring at different developmental stages impact men and women's propensity for substance use differently [23]. In females, the number of types of maltreatment and the severity of maltreatment are also very important predictors of later substance use; however, this is not true for males [23]. Relationships influence nicotine and opioid addiction in women more so than men, such that women are more likely to use substances if their partner does [24].

Addiction neurobiology is complex, involving multiple neurotransmitter systems, cell types and brain regions, which often display sex differences. The sexually dimorphic brain circuits regulating addiction are intertwined with systems regulating pain, stress responsivity, addiction and recovery [17, 25-35], which may contribute to differences between men and women in initiation of substance use as well as in recovery and relapse. Hormonal differences in men and women and changes in hormones across the menstrual cycle contribute to drug cravings and might make quitting smoking more difficult in women compared to men [36-38].

Patients suffering from both nicotine and opioid use disorders often have co-occurring substance use and psychiatric disorders, particularly stress-sensitive disorders which are female-biased. Cigarette smoking is reported in 39% of adults with co-morbid psychiatric disorders, versus 15.5% of adults without psychiatric co-morbidities [39]. Depression is strongly linked with smoking, and this association is greater for women than men [39]. Individuals who smoke are more likely to self-report opioid use disorders compared to non-smokers [40]. Men who smoke report higher daily opioid doses compared to non-smoking men [40]. Opioid use disorders commonly co-occur with mood and anxiety disorders and post-traumatic stress disorder (PTSD), particularly in women [41, 42].

Access to and implementation of evidence-based, integrated treatment poses significant challenges for battling nicotine and opioid addiction. A meta-analysis of nicotine replacement therapies (NRT) and FDA approved pharmacotherapies for smoking cessation suggests that most approved therapies may be less effective in women than men due to sex and gender differences influencing cigarette craving [43]. This is a very important women's health topic given that quitting or reducing smoking early in pregnancy can significantly improve health outcomes for infants [44]. The likelihood of successful long-term smoking cessation is enhanced by social support. Medication-assisted treatments (MAT), combining behavioral interventions with pharmacotherapies, are highly effective, evidence-based integrative programs for treating opioid use disorder [45, 46], including in pregnant women [47-50]. Nevertheless, MAT is highly underutilized and there are often gender-related barriers to treatment [51], such as caregiving-related concerns among women [52]. Importantly, federal and academic researchers alike stressed the need for research and development of less addictive, non-opioid pain treatments.

Finally, and perhaps most importantly, data gaps still exist in our knowledge of the impact of sex and gender on substance use and misuse. There is a dearth of information on the basic neurobiology of the impact of sex differences in animal models of opioid and nicotine use. Although there is a wealth of research on nicotine and opioid use and recovery in humans, there is inconsistent reporting and analysis by gender. We do not know if sex and gender differences exist in many areas of research simply because many researchers may not be aware of the ubiquitous influences of sex and gender and have not performed the relevant statistical analyses to detect those differences. This was seen by all as an opportunity to revisit and mine potentially rich sources of data on sex and gender differences in all aspects of substance use, misuse, addiction, and recovery. Understanding sex and gender differences in addiction and disseminating this knowledge to health care providers and the public will enable better identification of substance use disorders in men and women and aid in more effective prevention and treatment.

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