

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

FDA

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I. Discussion Guide

A. Introduction

Sex differences may influence susceptibility to substance use disorders, which could have implications for optimal prevention and treatment. Sex differences exist at all levels of biological organization including brain anatomy, neurochemistry, and function, with relevance for understanding sex-based differences in the development, maintenance of, and treatment of addiction. Gender influences also impact public health by influencing prescription rates, care, and treatment seeking behaviors. To identify and treat women and men most at risk, researchers, educators, and clinicians must be able to recognize and consider sex and gender differences in substance use, misuse and addiction.

Building on the fundamental work presented at the U.S. Department of Health and Human Services (HHS) Office of Women's Health 2016 national meeting on [Opioid Use, Misuse and Overdose in Women](#) [1], the U.S. Food and Drug Administration's Office of Women's Health in collaboration with the Center for Drug Evaluation and Research and the Center for Tobacco Products, presents a 2-day meeting, *Opioid and Nicotine Use, Dependence, and Recovery - Influences of Sex and Gender* to address this important issue. This conference will include presentations by experts in the fields of opioid and tobacco research, professional education, and clinical care on the sex and gender influences on misuse and cessation of opioids and tobacco products. By bringing together basic and clinical researchers with leaders in policy, the goals of this meeting are to:

- increase awareness of the biological and environmental factors that differentially impact the development and maintenance of opioid and nicotine use disorders in women and men;
- discuss the unique needs of women battling addiction to better inform policy; and

- advance gender-appropriate treatment options to address opioid and nicotine use disorders in women and men.

B. Opioid and Nicotine Use Disorders as Public Health Crises

Despite increased public awareness, the opioid overdose epidemic continues to grow. The rate of opioid-related deaths has escalated across sex, racial/ethnic group, and age in most U.S. states [2]. More than half of the 632,331 drug overdose deaths in the United States from 1999-2016 involved opioids (including prescription and illicit opioids, such as heroin and illicitly-manufactured fentanyl), with over 42,000 deaths in the US in 2016 alone - a statistically significant increase from 2015 (data from 26 states; [3]). Alarmingly, at least half of the opioid overdose deaths in 2016 reportedly involved the use of fentanyl [4]. Fentanyl is a synthetic opioid pain reliever that is 50-100 times more potent than other opioids, approved for treating severe pain [5]. Most recent cases of fentanyl-related harm, overdose, and death in the US are linked to illicitly manufactured fentanyl sold through illegal drug markets [6]. It is often mixed with heroin and/or cocaine – with or without the user’s knowledge [7]. Due to this recent rise in opioid-related deaths, the epidemic has received considerable attention from scientists, clinicians, and government agencies aimed at addressing the causes and consequences of rampant opioid use disorders and addiction.

Despite recent progress in reducing smoking rates to a record low, tobacco use remains the number one preventable cause of death in the United States. Cigarette smoking and secondhand smoke exposure lead to over 480,000 deaths in the US each year, and for every tobacco-related death at least 30 people are living with a serious tobacco-related illness [8]. These diseases include cancer, cardiovascular disease, diabetes, lung diseases, rheumatoid arthritis, and many other conditions [8]. In the US, smoking-related illnesses total over \$300 billion a year in medical costs and lost productivity due to sickness [8, 9]. Smoking rates are highest among impoverished, less-educated individuals and in specific populations such as those with behavioral health conditions, the lesbian, gay, bisexual, transgender (LGBT) community, and in certain marginalized groups, including certain ethnic/racial minorities (e.g., Native Americans/Alaska Natives) [10-12].

Patients struggling with addiction often have mental health comorbidities and many have experienced adverse childhood experiences (ACEs), such as abuse, neglect, parental discord, criminality and drug use. In fact, each ACE experience increases the likelihood of adolescent initiation of substance use by 2-4-fold [13]. Individuals who experience several ACEs are 7-10 times more likely to report substance use disorders compared to individuals with no adverse childhood experiences [13].

It should be noted that nicotine and opioid addictions are mutually reinforcing, such that individuals with opioid use disorders are more likely to smoke and tobacco use is a strong predictor of prescription opioid misuse [14]. Adolescent exposure to nicotine has been shown to increase susceptibility to opioid addiction in adulthood [15]. In addition, smoking cessation is associated with long-term abstinence following treatment for opioid use disorder [16], suggesting a strong link between the neurobiology of nicotine and opioid addiction.

Understanding the basis of addiction is a critical first step in identification of the biological and sociocultural variables that lead to substance use and use disorders in vulnerable populations. By recognizing distinctions in addiction onset, progression, and recovery in men and women, we can

determine the most effective and accessible prevention and treatment options, which is paramount to quelling this public health crisis.

C. Defining Sex and Gender

Central to any discussion of differences between men and women is the issue of semantics; how are sex and gender defined and when do we refer to a *sex difference* versus a *gender difference*? ‘Sex’ refers to an individual’s biological characteristics, stemming from chromosome complement, in which females are defined as XX and males as XY. Genes on sex chromosomes are responsible for sex determination, sexual differentiation, and the orchestration of developmental programs that produce male and female anatomy and physiology. Biological sex differences, such as male/female differences in metabolism, gonadal hormone production, neurotransmitter systems and neurocircuitry are the substrates on which drugs of abuse exert their disparate physiological effects. Alternatively, ‘gender’ refers to the social construct by which we define ourselves as male, female, or other. Our understanding of one’s gender is highly influenced by our experiences, environment, and societal views of ourselves and others, as well as our socially-defined gender “roles”. Influences of both sex and gender are important for understanding male and female differences in the etiology of substance use disorders (see Appendix A), however we will focus much of our discussion on biological sex differences and a basis for variation in opioid and nicotine use, misuse, and addiction.

D. Evidence for a Biological Basis of Sex Differences in Addiction

While epidemiological evidence shows that men have higher reported substance use and disorder rates than women across all drugs of abuse [17], women experience the three stages of addiction progression differently [18, 19]. These stages include binge/intoxication, withdrawal/negative affect, preoccupation/anticipation; although the pattern for nicotine addiction features a negligible binge/intoxication stage relative to other drugs of abuse [20, 21]. Animal models of drug-seeking behaviors enable researchers to remove social facets inherent to human studies to facilitate a mechanistic understanding of the biological factors related to sex differences in addiction.

Studies in rats show that female animals display a greater motivation than males to self-administer opioids and nicotine [22-27], highlighting an underlying sex difference in brain reward circuits. By ovariectomizing rats and providing estradiol replacement, experiments have demonstrated the importance of gonadal hormones in acquisition of opiate self-administration behaviors in females [23, 24, 28]. These sex differences in the onset of the binge/intoxication phase of addiction identified in rodents might translate to the human phenomenon known as “telescoping”, in which women become dependent on substances more rapidly than men [29, 30]. Indeed, clinical studies show that women become dependent on some addictive substances, like opioids and alcohol, more quickly than men [31, 32], which is thought to be due to sex differences in metabolism, absorption and elimination as well as smaller body mass, higher fat-to-water ratios, and sex differences in brain reward circuits [1, 33-35].

Several reports suggest that women also experience the second stage of addiction, withdrawal/negative affect, more intensely than men, which may hinder their successful recovery. Studies in both humans and

rodents show that females exhibit greater stress hormone (cortisol and corticosterone, respectively) responses during nicotine withdrawal than males [36-38]. High cortisol levels have been implicated in the negative-affect associated motivational aspects of drug withdrawal [39], which may explain why women experience the symptoms of withdrawal more severely than men. Sex differences in Hypothalamic Pituitary Adrenal (HPA) stress axis function, which controls cortisol production, are programmed during early brain development and modulated in adulthood by gonadal steroid hormones such as estradiol and progesterone [40].

Social factors often impact substance use, relapse, and treatment-seeking in women more than men. For instance, substance use in women is more often influenced by relationships with family, friends and peers [1, 33]. Roughly 66% of caregivers are women, making them less likely to seek and complete appropriate substance use disorder treatment due to the constraints related to caring for children and loved ones [1, 33].

Clinical studies report that women are more likely than men to experience addiction relapse, with shorter periods of abstinence between relapse events compared to men [41]. This disparity in relapse behavior might be due to enhanced drug cravings reported in women [42, 43], stress associated with withdrawal responses [38, 42, 44], and/or enhanced salience of drug-associated cues in the environment [41]. Preclinical, animal models of relapse mirror clinical findings, suggesting that female rodents are more likely than males to display reinstatement of drug-seeking behavior in response to drug-associated cues and psychological stressors [41, 45]. In addition to worsening withdrawal, sex differences in cortisol production, which enable females to mount a greater physiological response to stressors, likely underlie higher stress-induced relapse rates in women [46].

Of note, there is conflicting data on sex differences in opioid withdrawal, wherein males appear to experience more severe relapse symptoms than females, suggesting a need for additional research [47]. In addition, there is currently a paucity of clinical data on sex differences in relapse behavior from opioids. Identifying research gaps, areas where sex has not been considered, is key to gaining a comprehensive understanding of these issues to ultimately advance treatment strategies towards sex and gender-specific approaches.

E. Sex Differences in Opioid Use Disorders

While men are more likely to die of an opioid-related overdose, the mortality gap is steadily closing (see Appendix B for federal guidance on opioid use and use disorder) [48, 49]. Between 2005-2015, there was a 75% increase in opioid-related hospitalizations among women, whereas hospitalizations of men increased by 55% (2005: 145.6 men vs. 127.8 women per 100,000; 2014: 225 men vs. 224.1 women per 100,000) [50], with the largest increase in hospitalization rate occurring in non-Hispanic whites [51]. Identifying which groups are most at risk for developing opioid dependence, and the different avenues by which women and men are impacted by opioid use disorder, is key to prevention. Women, especially those over the age of 40, are more likely than men to have conditions that cause chronic pain, leading to a higher rate of prescription pain reliever use, at higher doses and for longer treatment durations than men [52-54]. Further, white women are more likely to be treated for chronic pain compared to minority women [52]. A noted behavioral difference between men and women is in “doctor shopping” behavior [55], in which women more frequently seek care from multiple physicians simultaneously and/or pursue

treatment from medical professionals known to be liberal with prescriptions for certain medication types such as opioid pain relievers.

As prescription opioids are primarily prescribed for moderate to severe pain, understanding the intersection between biological sex differences, pain, and addiction is key to addressing opioid use in women and men. As noted above, epidemiological studies report a higher prevalence of chronic pain diagnoses in women vs. men [56]. Laboratory experiments demonstrate that pain tolerance is lower and pain sensitivity is higher in females compared to males [57]. Many biological mechanisms mediating sex differences in pain have been proposed, highlighting the complexity of this field. Recently, sex differences in the immune system have received attention as potentially key mediators of the higher rate of pain diagnoses in women compared to men. Gonadal hormones such as estrogens, progesterone and testosterone have all been shown to have pro- and anti-inflammatory effects on immune cell function, potentially underlying female susceptibility to chronic pain resulting from nerve damage and chronic inflammation [58, 59].

1. Treating opioid use disorder

Medication-assisted treatments (MATs), such as the opioid agonists methadone and buprenorphine, are the most effective pharmacological interventions for opioid use disorders [60], although there are significant disparities on the state and national level between the need for MATs for treating opioid use disorders and their availability [61]. Barriers to accessing methadone include limited treatment sites, long waitlists for federally-regulated opioid treatment programs (OTP), and issues related to prescription access and insurance coverage [62-65]. Access to buprenorphine also requires a prescription, thus insurance coverage, cost, and availability of prescribers are roadblocks to accessing this life-saving treatment option [66-68]. Both methadone and buprenorphine can be used during detoxification and maintenance stages of addiction treatment. A third drug, naltrexone works as an opioid antagonist, blocking the actions of opioids to prevent their effects. Naltrexone is specifically used as a maintenance therapy to prevent relapse, since taking naltrexone before detoxification will result in immediate withdrawal [69]. Women seeking treatment for opioid use disorders often face special challenges. As caregivers, fear of prosecution for illegal opioid use, and the associated fear of child custody loss, may lead fewer women to seek treatment and can result in women neglecting to seek prenatal care if pregnant [70].

Psychosocial treatments should accompany use of pharmacological interventions to treat opioid use disorders. Counseling interventions combined with MATs increase the likelihood of successful addiction recovery [71]. These treatments can vary in modality and format, from group and individual counseling sessions, 12-step programs, social skills training, cognitive behavioral therapy, contingency management, among others [72]. The goal of these treatments is to provide support to patients during recovery, to encourage their abstinence, address concurrent mental health issues, and to help patients cope with issues surrounding their addiction. There are significant data gaps related to the efficacy of specific psychosocial treatments combined with particular MATs [71]. These knowledge gaps must be filled to help determine which pharmacological/psychosocial treatment combinations are most effective for specific populations

2. Medication-assisted treatments and pregnancy

MATs are recommended to pregnant women as they improve adherence to prenatal care programs and reduce pregnancy complications compared to untreated opioid use (see Appendix D for resources related to MATs and pregnancy) [73, 74]. In addition, MAT use during breastfeeding decreases symptomology of neonatal abstinence syndrome (NAS)[75]. NAS is a syndrome associated with drug withdrawal present in 30-80% of newborns exposed to MATs *in utero* [76, 77]. MAT-associated NAS is expected and treatable. Symptoms, including irritability, sleep disturbances and trouble feeding, typically resolve within days to weeks of birth [73, 78]. Severity of NAS symptoms is correlated with MAT dosing and poly-substance use during gestation [79]. Studies show that infants born with methadone- and buprenorphine associated NAS show no significant impairments in growth, cognitive function, language capabilities, and temperament in childhood compared to healthy controls [80, 81]. In 2017 the American College of Obstetricians and Gynecologists advised that medically-supervised withdrawal could be considered if the patient refuses MATs [82], however withdrawal poses significant risks to the pregnancy such as preterm delivery and fetal death [83, 84] in addition to a high rates of addiction relapse postpartum [85, 86].

F. Nicotine Use and Addiction

An estimated 13.5% of US women smoke cigarettes compared to 17.5% of men [10, 87] (see Appendix C for federal resources on tobacco and nicotine use and smoking cessation). Notably, smoking rates are highest in adults who are American Indian/Alaska Native (31.8), living in poverty (25.3%), have 0-12 years of education (24.1%) or a GED (40.6%) [10]. In addition, comorbidities such as mental health disorders and substance use disorders, are common in smokers [11, 12]. Cigarette smoking was reported in 39% of adults with co-morbid psychiatric disorders, versus 15.5% of adults without psychiatric co-morbidities [88]. In particular, depression is strongly associated with smoking, and this association is greater for women than men [88]. As mentioned above, individuals who smoke are more likely to self-report opioid use disorders compared to non-smokers [89]. In addition, men who smoke report higher daily opioid doses compared to non-smoking men [89].

Lung cancer is a leading cause of death in both men and women in the US [90]. Some studies suggest a possible increased risk for lung cancer among women who smoke compared to men who smoke, though the evidence is still unclear [91, 92]. Compared to women who do not smoke, women who smoke are more likely to have chronic obstructive pulmonary disease (COPD) including emphysema and chronic bronchitis, heart disease, premature aging, and cancers of the mouth, throat, pancreas, kidney, bladder, and cervix [8, 90]. Women who smoke also experience significant dangers related to pregnancy outcomes including an increased risk for ectopic pregnancy, premature birth, low birth weight and placenta previa, conditions that can cause long-term impacts on offspring and maternal health [8].

1. Treating nicotine addiction in women and men

There are three FDA-approved medications for smoking cessation which include various forms of nicotine replacement (gums, patches, lozenges, nasal spray, and inhalers), bupropion, and varenicline. All medications have demonstrated sex-differences in their efficacy for smoking cessation. Nicotine replacement therapies (NRT) are designed to deliver controlled amounts of nicotine to the user to minimize withdrawal symptoms associated with smoking cessation while eliminating harmful constituents of cigarettes. Studies suggest poorer cessation outcomes in women compared to men, even when assisted by NRT [93-96], but more research is needed in this area. In a meta-analysis, transdermal nicotine was

40% more efficacious for men compared to women at 6-months post quit attempt [97]. Women have increased rates of nicotine metabolism, which is associated with reduced ability to quit with nicotine replacement [98]. Further, higher levels of estrogens have been shown to increase the rate of nicotine metabolism in women, which might be one biological mechanism leading to blunted responses to NRT in women versus men [35]. Nicotine metabolism is highest in women taking oral contraceptives and lowest in menopausal and postmenopausal women, who show similar levels of nicotine metabolism to men [35].

Bupropion was originally developed as an anti-depressant, and has dopaminergic and adrenergic agonist and noncompetitive nicotine receptor antagonist activity [99, 100]. In addition to its efficacy for tobacco cessation, bupropion may aid withdrawal-associated depressive symptoms and weight gain associated with smoking cessation [101, 102]. In a meta-analysis of bupropion efficacy, there was no difference in the efficacy by sex at end of treatment, although rates of quitting were lower overall among women [103]. Varenicline is a partial nicotinic agonist, with high affinity for $\alpha 4\beta 2$ receptor, which mediates nicotine-related positive reinforcement [104]. A meta-analysis of varenicline clinical trials, found greater efficacy for women compared to men at the end of treatment and at 6-months (46% more efficacious at end of treatment; 34% more efficacious at 6-months) [105].

The Cochrane Tobacco Addiction Group conducted a head-to-head comparison of NRT, bupropion, and varenicline and found that varenicline was more efficacious than NRT and bupropion, with no difference in efficacy between NRT and bupropion [106]. When this same analysis was conducted by sex, varenicline was more efficacious than transdermal nicotine and bupropion in women. For men, outcomes were similar across the three medications. These data suggest that the advantage of varenicline over bupropion and transdermal nicotine is greater for women than men [107].

While nicotine addiction is a significant driver of smoking behavior, smoking is also reinforced by non-nicotine factors like smoking cues, verbal information related to cigarettes, and other social and environmental factors. While addressing these psychosocial factors is important for both men and women who smoke, these factors may be more reinforcing for women and are important to consider when treating women for tobacco dependence [108]. Of note, in 2015, based on data from the National Health Interview Survey (NHIS) and the NHIS Cancer Control Supplement, adult female smokers did not differ significantly from adult male smokers in the prevalence of interest in quitting, making a past-year quit attempt, recent successful smoking cessation, receiving a health professional's advice to quit, use of cessation counseling, use of cessation medication, and use of cessation counseling and/or medication [109]. Therefore, an argument could be made that the greatest barrier to smoking cessation in women is not the inadequacy of current cessation counseling and medication approaches, but that use of these treatments is low among women, as it is among men.

2. *Smoking cessation during pregnancy*

About 7% of pregnant women smoke during gestation; rates are highest among young, high school-educated women with lower socioeconomic status, although social pressures to deny tobacco use at the time of delivery might impact this statistic [110, 111]. Smoking during pregnancy is associated with an increased risk of miscarriage [112, 113], preterm and still birth [112, 114], low birth weight [115], neurodevelopmental dysfunction [116], and alterations in placenta function [117]. This can lead to long-term health complications in children exposed to cigarette smoke *in utero*, such as poor respiratory [118] and ophthalmological function [119]. Only about 1 in 5 pregnant smokers quit by the third trimester [110],

and most women who successfully quit do so in their first trimester [120]. Pharmacological treatments alone are less effective in pregnant women compared to behavioral therapies [121, 122] perhaps because of increased nicotine metabolism during pregnancy [123]. Incentive (contingency management) programs combined with counseling are a promising treatment route for pregnant women [124].

Nicotine is a known teratogen and *in utero* exposure can result in neurodevelopmental deficits [125, 126]. Additional clinical studies on cessation pharmacotherapy in pregnant women and lactating women are needed to determine the risks and benefits associated with NRTs for both the mother and fetus [127]. Randomized controlled trials report mixed results for NRT efficacy during pregnancy [128] and NRTs appear to have similar effects as smoking on maternal blood pressure and maternal and fetal heart rate [129]. Rigorous randomized controlled trials for the safety and efficacy of bupropion and varenicline have not been completed in pregnant women and lactating women [130, 131]. In summary, current data is insufficient to weigh the benefits and risks of cessation pharmacotherapy for pregnant women [132, 133].

3. Use of electronic cigarettes

The use of electronic cigarettes (e-cigarettes) in the general population has increased among US adults and youth since entering the market in 2007 [134-136]. E-cigarettes are handheld devices that produce an aerosol, typically containing nicotine, flavorings and other chemicals. Most adult e-cigarette users are current or former cigarette smokers, however 11.4% of e-cigarette users have never smoked traditional cigarettes [137]. As of 2016, more than 2 million middle school and high school students reported using e-cigarettes, making these products the most commonly used tobacco products among teens [138]. Studies have shown that youth who use e-cigarettes are more likely than non-users to initiate smoking traditional cigarettes [139, 140]. As nicotine exposure alters brain development, which continues until one's mid-twenties, addressing e-cigarette and other tobacco product use in teens and young adults should be a priority [141].

The use of products containing nicotine also poses significant risks for pregnant women and fetuses [141]. One study found that many pregnant women believe e-cigarette use during pregnancy is less harmful than traditional cigarettes and safe to use for smoking cessation during pregnancy [142]. This finding points to the necessity to inform women of childbearing age that nicotine alone has harmful effects on fetal growth and development.

In 2012, 11.5% of surveyed adults believed that e-cigarettes were equally harmful as traditional cigarettes, but by 2015 this figure grew to 35.7% [143]. In addition to the harmful effects of nicotine, e-cigarette aerosol can contain other carcinogens and harmful substances such as heavy metals and volatile organic compounds [141].

FDA has not approved e-cigarettes as a smoking cessation aid. The efficacy of e-cigarettes for long-term abstinence from conventional cigarettes is uncertain [144]. A review of randomized controlled trials found that e-cigarette use may help some smokers quit long-term compared to placebo, however the data are mixed and it is still unknown whether e-cigarette use reduces health risks or if they are more efficacious than NRT or nicotine cessation medications [145]. Other studies have shown that most e-cigarette users do not completely discontinue use of traditional cigarettes, resulting in no improvement in health outcomes [146, 147].

II. Symposium Objectives and Questions for Discussion

In relation to the sex and gender differences associated with opioid and nicotine use, dependence, and recovery, meeting participants will:

- appreciate sex and gender interactions in outcomes across the lifespan;
- understand the unique role of HHS and other federal stakeholders;
- recognize research gaps and emerging therapeutic areas for drugs, devices and behavioral approaches; and
- recognize the necessity of a comprehensive, integrative approach to the treatment of addiction.

III. Scientific Presentations and Panel Discussions

Presentation: Discussing Sex as a Biological Variable: Terminology and Policy

Objective: To discuss the importance of including sex as a biological variable (SABV) in clinical and preclinical studies. Review important terminology, i.e. sex vs. gender and provide a basic background on biological sex differences. Introduce opioid and nicotine addiction and its growing influence on women's health.

Panel Discussion: Resources and Opportunities to Explore Sex and Gender: Epidemiology of Opioid and Tobacco Use Disorders

Objective: This panel will discuss the data and databases available to inform the epidemiology of opioid and nicotine use, dependence and recovery highlighting opportunities to determine sex differences and gender influences in this space and across demographic groups.

Questions to address:

- What are the resources needed to analyse nicotine and opioid data by sex/gender?
- Are there opportunities to amend data systems to evaluate unanalysed data?
- What directions could we go to investigate sex/gender with current opioid data sources?
- Are there understudied populations in the tobacco and opioid space? What are some measures we can take to better study these populations?

Panel Discussion: Landscape of Federal Research Policy and Regulation of Opioids and Nicotine

Objective: In this panel, federal representatives will present a regulatory review of NRTs, MAT and nicotine cessation drug indications and approval processes and will discuss the policies and processes in place to evaluate and consider population data in relation to opioids and nicotine use and treatment. The panel's aim is to provide a better understanding of what each federal entity does in the space of opioids and nicotine as it relates to sex and gender, including challenges and opportunities for moving forward.

Questions to address:

- What is your agency's role in addressing opioid or nicotine addiction and recovery?

- Are there opportunities to consider sex and gender in research and policy from your agency's perspective?
- How is your agency working with other federal agencies to address addiction?

Presentation: Pain, Sex, and Death

Objective: To highlight nervous system mechanisms mediating the perception and inhibition of pain. Address sex differences in pain research, implications for treatment, and the link between addiction and the lack of treatment for pain.

Panel Discussion: Sex and Gender Influences within Integrative Approaches to Treatment of Addiction

Objective: This panel will discuss the current research landscape related to sex and gender differences associated with NRTs, MAT and nicotine cessation drug use and effectiveness.

Questions to address:

- Are we successfully applying/implementing the knowledge we already have in regards to nicotine and opioid addiction treatment? What needs to be done differently to make an impact in underserved areas/populations?
- Do men and women respond differently to treatments and what is the current understanding of the bases for these differences?
- In your professional opinion, how can we better institute gender-focused addiction treatment programs?
- As caregivers, what additional challenges do women face for completion of treatment programs? Are there treatments that work better than others for underserved populations? If so, which treatments?

Presentation: Innovative Program and Research Initiatives: Thinking Outside the Box

Objective: Speakers will discuss groundbreaking research and its potential impacts on policy for battling addiction epidemics.

Panel Discussion: Conversations with Patients Overcoming Opioid and Nicotine Dependency

Objective: To hear patient perspectives highlighting the experiences, challenges associated with substance initiation and dependence and the victories accompanying recovery.

Presentation: Adverse Childhood Events and Trauma Across the Lifespan: Sex and Gender Contributions to Development of Substance Use Disorders

Objective: To understand the link between early life physical, sexual, and emotional maltreatment and bullying, and adult depression, anxiety, post-traumatic stress, and substance use disorders.

Panel Discussion: SABV: Brain, Pain, and Addiction

Objective: In this panel, speakers will share foundational scientific research on the brain, pain, and addiction. Discussion will focus on sex differences in the addicted brain, the opioid system and pain mechanisms, and the development of behavioral and pharmacological methods of reducing and preventing substance use disorders.

Questions to address:

- Are biological sex differences in the brain sufficiently robust to warrant development of sex-specific therapies for opioid and nicotine addiction?
- What is the biological basis for efficacy of stress-reduction therapies in addiction prevention and treatment?
- Are current addiction therapies and treatments adequately addressing our knowledge of the basic biological mechanisms underlying sex differences in substance abuse, withdrawal and relapse?
- What are the relationships between pain and addiction that aren't being addressed with current research?
- What are the knowledge gaps (relevant to the biology of addiction) between studies performed in animal models and human studies/epidemiological evidence? In your professional opinion, how can we fill these gaps?

Panel Discussion: Hormones: From Basic Research to Addiction Medication

Objective: Panelists will address the role of gonadal steroid hormones in addiction, behavioral and brain outcomes in substance use disorders, and studies of progesterone as a potential treatment for nicotine addiction.

Questions to address:

- What are the organizational (developmentally programmed) contributions to sex differences in reward circuitry and what aspects are influenced by adult gonadal hormones? (i.e. self-administration in gonadectomized animals)
- How has studying sex as a biological variable (and including female animals in basic research) advanced our understanding of the mechanisms whereby hormones modulate reward circuitry?
- Where are the data gaps in our understanding of hormonal mediation of addiction in men and women?
- How have study population demographics changed over the course of your research?
- How can we use our knowledge of sex differences and hormone cyclicity to develop more effective treatments?
- What are some of the major challenges involved in clinical studies on hormones and drug seeking behaviors?

Panel Discussion: Opioid and Nicotine Use, Dependence, and Recovery: Challenges of Pregnancy and the Postpartum Period

Objective: Panelists will address current guidances recommending how and when to include pregnant women in clinical trials, prenatal exposure to nicotine and opioids, and addiction treatments specific to pregnant and postpartum women.

Questions to address:

- What is the current landscape of treatment received by pregnant/postpartum women?
- What care is needed to treat substance use disorders in pregnancy? Where are the gaps in this care?
- What data have we collected on the long-term impacts of prenatal opioid and nicotine exposure? Where are the gaps in the data? Are we missing opportunities to improve data collection or analysis?
- From a regulatory perspective, what efforts have been made to address nicotine and opioid use in pregnant/postpartum women?
- What do we know about the safety and efficacy of NRTs and MAT drugs in pregnant women?
- What can we do improve our knowledge of the impact of these drugs on women and the potential long-term effects on offspring?

Presentation: Sex and Gender Contributions in the Trajectory of Opioid and Nicotine Use and Addiction

Objective: To tell the behavioral and biological story of addiction, from initiation to addiction and the development of addiction treatments. Speakers will discuss factors that differentially affect initiation of opioid and nicotine use in men and women, and the differential effectiveness of addiction treatments.

Presentation: Recognizing the Benefits of Health Communications Research in Substance Abuse

Objective: Speakers will discuss gendered communications and health communications outcomes, social media mining research and other outreach initiatives associated with tobacco and opioid communication and cessation resources.

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Appendixes

Appendix A. Information on Sex Differences and Substance Use in Women

- a. [Understanding Sex Differences at FDA](#). Includes links to key reports, actions, and FDA policies on sex and gender considerations.
- b. [DrugFacts: Substance Use in Women](#). Describes sex and gender differences in substance use
- c. [Substance Use in Women Research Report](#). Includes information on sex and gender differences in substance use, substance use while pregnant and breastfeeding, sex and gender differences in substance use disorder treatment (highlighting smoking cessation), and other important information related to women's health and addiction.

Appendix B. Federal Guidance on Opioids and Opioid Use Disorder Treatments

1. FDA CDER guidelines for prescription opioids and addiction treatments

- a. [FDA Information on Opioid Medications](#). Lists key points for each of FDA's 4 priorities: 1) decreasing exposure and preventing new addiction, 2) supporting treatment of those with opioid use disorder, 3) foster development of novel pain therapies, 4) improve enforcement and assess benefit/ risk.
- b. [FDA Opioid Action Plan](#). Comprehensive plan to take steps to reduce the impact of opioid misuse in the U.S.
- c. [Safe Use Initiative](#). Current projects involving pain management medications.
- d. [Risk Evaluation and Mitigation Strategy \(REMS\)](#). for opioid analgesics (OA). The OA REMS has a broad scope of topics and target audiences (not just prescribers, but also pharmacists and nurses). The REMS obligates sponsor companies to provide free or low cost CME. Those programs for the extended release and long acting (ER/LA) REMS can be found [here](#). The programs for the OA REMS are currently being written and should be available September, 2018 or shortly thereafter.
- e. [Abuse-deterrent opioids](#). Evaluation and labeling guidance for industry, describing seven categories of abuse-deterrent technologies.
- f. [Evaluating Abuse Deterrence of Generic Solid Oral Opioid Drug Products](#). Guidance for industry describing the principles for developing and evaluating abuse deterrence of oral opioids.
- g. [Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment](#). Draft guidance on MAT drugs that discusses what endpoints might be used to measure clinical outcomes.
- h. [Opioid Dependence: Developing Depot Buprenorphine Products for Treatment](#). Draft guidance on depot buprenorphine products (i.e., modified-release products for injection or implantation).

2. FDA opioid and MAT medication guides (for additional guides click [here](#))

- a. [Abstral](#) (fentanyl) [2016 version]

- b. [Buprenorphine and Naloxone, Sublingual Film](#) [6/2018 version]
- c. [Dolophine](#) (methadone hydrochloride) [2/2018 version]
- d. [MS Contin](#) (morphine sulfate) [2014 version]
- e. [Percodan](#) (asprin; oxycodone hydrochloride; oxycodone terephthalate) [2016 version]
- f. [Probuphine](#) (Buprenorphine implant) [5/2016 version]
- g. [Roxybond](#) (oxycodone hydrochloride) [4/2017 version]
- h. [Suboxone](#) (buprenorphine and naloxone) [2/2018 version]
- i. [Subsys](#) (fentanyl) [2016 version]
- j. [Subutex](#) (buprenorphine) [2/2018 version]
- k. [Xtampza ER](#) (oxycodone) [2016 version]

3. NIDA resources for opioid addiction and treatment

- a. [DrugFacts: Prescription Opioids](#). Information on common prescription opioids and misuse.
- b. [DrugFacts: Heroin](#). Information specific to heroin, heroin use, effects, and overdose.
- c. [DrugFacts: Fentanyl](#). Information on the dangers of the synthetic opioid fentanyl.
- d. [Prescription Opioids and Heroin Research Report](#). Describes risk factors for prescription opioid misuse and heroin use
- e. [Medications to Treat Opioid Use Disorder Research Report](#). An informative report on how MATs work, MAT efficacy, misconceptions about opioid use disorder treatments, impact of MATs on HIV/HCV outcomes, information about how opioid use disorder is treated in the criminal justice system, and more.
- f. [Misuse of Prescription Drugs Research Report](#). Describes the scope of prescription drug misuse, health consequences, drug interactions, prescription drug use during pregnancy, and prescription drug addiction.
- g. [Opioid Summaries by State](#). 2015 and 2016 opioid-related overdose deaths by state.
- h. [Improving Opioid Prescribing Policy Brief](#). Information on how opioid prescribers can help to stop the opioid overdose epidemic.
- i. [Naloxone for Opioid Overdose - Life Saving Science Policy Brief](#). Information on naloxone use, Good Samaritan laws, and how naloxone can be used by bystanders to save lives.
- j. [Opioid Facts for Teens](#). Resources for teens regarding opioid use and misuse.
- k. [NIDA's Role in the NIH HEAL Initiative](#). In June 2018, the NIH launched the Helping to End Addiction Long-term (HEAL) Initiative. This new initiative is funded by Congress and provides scientific solutions to the national opioid overdose crisis. NIDA is coordinating four overarching research projects around the country:
 - i. Focused opioid use disorder medications development research project
 - ii. HEALing Communities Study
 - iii. The Clinical Trials Network opioid use disorder research enhancement project
 - iv. The Justice Community Opioid Innovation Network

Appendix C. Federal Guidance on Nicotine Use and Cessation

1. FDA Center for Tobacco Products (CTP) guidelines for tobacco products

- a. [CTP Website](#). General Information on tobacco products
- b. [Rules and Regulations](#). CTP's regulatory documents for specific tobacco products.
- c. [Guidance](#). Documents to help industry understand and comply with regulations.
- d. [Other Tobacco Products](#). Information on e-cigarettes and other tobacco products.

- e. [Family Smoking Prevention and Tobacco Control Act](#). Law giving FDA the broad authority to regulate the manufacturing, distribution, and marketing of tobacco product.
- f. [Women’s Health and Smoking](#). Information for women about the impacts of smoking and links to resources to quit.
- g. [Men’s Health and Smoking](#). Information for men about the impacts of smoking and links to resources to quit.

2. FDA CDER Medication guides for nicotine addiction

- a. [Chantix](#) (varenicline tartrate) [2016 version]
- b. [Zyban](#) (bupropion hydrochloride) [5/2017 version]

3. NIDA resources on tobacco products

- a. [DrugFacts: Cigarettes and other tobacco products](#). Information on the use of tobacco products, health effects, options to quit smoking.
- b. [DrugFacts: Electronic Cigarettes](#). Information on e-cigarettes and safety.
- c. [Tobacco, Nicotine, and E-Cigarettes Research Report](#). A more in-depth guide to tobacco products, the effects of smoking, gender differences, and treatments.

4. Other federal resources related to tobacco and nicotine use

- a. [Smokefree.gov](#). Resources and tools to aid smoking cessation
- b. [Surgeon General’s Reports on Smoking and Tobacco Use](#). Including links to 2016 report on E-Cigarette Use Among Youth and Young Adults and 2014 report on The Health Consequences of Smoking: 50 Years of Progress.
- c. [Tips from former smokers](#). CDC’s campaign profiling real people living with the life-long health effects from smoking.

Appendix D. Federal Guidance and Information for Prescription and Illicit Drug Use During Pregnancy

- a. [FDA Draft Guidance](#) Describes revised labelling and recommendations for prescription drug use during pregnancy, lactation and exposure in females and males of reproductive potential.
- b. [FDA statement about MAT and pregnancy](#). Safety labeling changes required for MAT products. The intent is to “appropriately inform prescribers about the risks of NOWS without inadvertently discouraging treatment for pregnant women with opioid addiction” (NOWS = Neonatal Opioid Withdrawal Syndrome).
- c. [NIDA Treating Opioid Use Disorder During Pregnancy Policy Brief](#). Describes the risk of opioid misuse during pregnancy including information on NAS.
- d. [NIDA Institute Director, Dr. Nora Volkow’s blog](#): Could Naltrexone Be Used to Treat Pregnant Women with Opioid Addiction?
- e. NIDA Science Highlights.
 - I. [Study](#) suggests that marijuana and cigarette smoking leads to higher likelihood of decreased birth weight, maternal stress and aggression

- II. [Study](#) finds that pregnant women in Appalachia face barriers to opioid use disorder treatment