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

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Introduction

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 (10), the U.S. Food and Drug Administration's Office of Women's Health (OWH) in collaboration with the Center for Drug Evaluation and Research (CDER) and the Center for Tobacco Products (CTP), presented this 2-day meeting, *Opioid and Nicotine Use, Dependence, and Recovery - Influences of Sex and Gender* at FDA's White Oak Campus in Silver Spring, MD. The conference included 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. The meeting was attended by individuals from federal and local government agencies, local and national academic institutions, non-profit organizations, industry, as well as members of the public. Attendance reached roughly 1500 combined online viewers and in-person attendees, highlighting the widespread interest in understanding how sex and gender influence opioid and nicotine addiction and recovery.

By bringing together basic and clinical researchers with leaders in policy, the goals of this meeting were 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.

Over the course of this two-day meeting 42 speakers from federal and academic institutions shared their expertise in topics ranging from the cellular and molecular underpinnings of addiction, to epidemiology of opioid and nicotine use, to treatment efficacy and utilization, to innovative approaches in health care and communications, among other topics. Included among these presentations were keynote addresses by FDA's Commissioner of Food and Drugs, Dr. Scott Gottlieb and the Deputy Surgeon General of the United States, RADM Sylvia Trent-Adams. Dr. Gottlieb began his Day 1 keynote address by stating that understanding the basis of addiction is a critical first step in our identification of biological and sociocultural variables that create vulnerability to substance use and substance use disorders (SUDs). By recognizing distinctions in addiction onset, progression, and recovery between men and women, we can determine the most effective prevention and treatment options. This is paramount to properly address this public health crisis. This statement was echoed by many other speakers throughout the conference. Indeed, illuminating the unique needs of men and women, and how biology and sociocultural expectations shape SUDs and treatment outcomes, was a recurring theme of the meeting.

Research on sex and gender differences yields crucial data on sex-specific factors for vulnerability to addiction and a gender-specific context for interpreting epidemiological trends. For the past 25 years, as we have acquired essential knowledge regarding sex and gender differences in addiction and SUDs, FDA and NIH have provided guidance, mandates, and updates regarding women and minorities in clinical trials. Ultimately, science-based public policy necessitates attention to sex and gender to promote public health by preventing initiation of substance use, halting growing SUD epidemics, assisting individuals with SUDs in accessing treatment to improve physical and mental health outcomes, and reducing criminal justice involvement. Throughout this two-day meeting, experts delved into the biological and social influences of sex and gender differences on SUDs, with a focus on the etiology, patient experience, and treatment outcomes of opioid and nicotine addiction in women and men.

Discussing sex as a biological variable: terminology and policy

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*? In the first session of the meeting, Dr. Janine Clayton, Director of the NIH Office of Research on Women's Health (ORWH), and Dr. Marjorie Jenkins, Director of Medical Initiatives and Scientific Engagement at FDA OWH, discussed the importance of including sex as a biological variable (SABV) in clinical and preclinical studies and provided background on biological sex differences and the roles of NIH and FDA in creating and implementing SABV policies for intramural and extramural researchers.

Dr. Clayton began her talk by summarizing the important role of ORWH in enhancing women's health research across NIH's 27 institutes and centers, monitoring the inclusion of women and diverse groups in NIH-supported clinical research, and promoting career advancement for women in STEM fields. Next, she defined the terms *sex* and *gender*. *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. *Gender* is a complex social construct including gender identity, gender norms, and gender dynamics. The concept of gender is highly influenced by our experiences, environment, culture, and societal views of ourselves and others, as well as socially-defined gender roles. Influences of both sex and gender are important for understanding differences in the etiology and treatment of SUDs in men and women.

Dr. Clayton next discussed the basis for NIH's SABV policy, stating that NIH sought to build a knowledge base that better informed the design of clinical research in humans. NIH wants to better deliver personalized care to everyone and include studies of both sexes in basic science research that could inform clinical studies. In addition, NIH aims to maximize their return on investment by considering sex as a biological variable in the research they support. Dr. Clayton described how the SABV policy's necessity stemmed from an overreliance on male cells and animals in preclinical research and a lack of transparency in reporting female inclusion and analysis of sex effects. Because of these prevailing circumstances, there is an incomplete knowledge base. Less is known about female biology than male biology and there is risk of drawing wrong conclusions based on incomplete data. There are also issues with lack of reproducibility of scientific studies, and what Dr. Clayton referred to as "toxicity surprises", where later down the road it is discovered that a pharmacologic treatment is less safe or effective in one sex versus the other. She went on to provide more detail about the SABV policy, which went into effect in January 2016, emphasizing that researchers need to consider sex when formulating research questions, provide justification for performing studies in a single sex, and complete appropriate analyses to interpret potential sex effects. These sex effects must also be communicated clearly in publications and presentations. Finally, she highlighted some of ORWH's programs and ORWH-supported research on addiction, such as work by Dr. Kathleen Brady on how gender mediates the association between distress tolerance and alcohol use among individuals with opioid use disorders (OUDs).

Next in the session, Dr. Marjorie Jenkins discussed how SABV was adopted by FDA, and the ways in which the policy applies in FDA's regulatory environment. Dr. Jenkins defined regulatory science, a term that originated at FDA, as the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products. FDA is the largest public health agency in the world, regulating food, drugs, vaccines and biologics, medical devices, cosmetics, and veterinary products. FDA is interested in patient

and population characteristics that impact the safety and efficacy of a product, such as sex, age, race/ethnicity, disease stage, comorbid conditions, and disability status. Dr. Jenkins described how FDA looks for sex differences in preclinical studies, in data on safety and effectiveness, post-marketing monitoring and safety alerts, and sex analysis in clinical trials. Next, she discussed the history of including women in clinical trials at FDA. In 1977, an FDA guidance stated that women of childbearing age should not participate in early-phase clinical trials. Unfortunately, this led to the product pipeline being populated with data based solely on males for decades, resulting in knowledge on the safety and efficacy of many drugs and products used by both sexes, but without evidence for women. Ten years later, a 1987 guidance recommended that non-clinical pharmacology and toxicology should be performed in animals of both sexes, which laid the foundation for a leap forward in our collective knowledge based on the biology of males and females. In 1993, the 1977 guidance was rolled back within a new guidance, stating that women are expected to be included in clinical trials and the need for data to be reported by gender, age, and race. In 1998, FDA released the Demographic Rule, which mandated that all new drug applications (NDAs) and studies on investigational new drugs report analysis by gender, age, and race/ethnicity. Guidance on sex-specific evaluation of data on medical devices was issued in 2014. These policies and guidance documents clearly impacted inclusion and data analysis approaches as evidenced in the 2013 Food and Drug Administration Safety and Innovation Act (FDASIA) Section 907 Report, which revealed that 100% of clinical pharmacology analyses, 97% of efficacy analyses, and 90% of safety analyses for FDA drugs and biologics included analyses by gender. Similarly, 88% of FDA medical device approvals had included gender analyses.

Finally, Dr. Jenkins provided a brief overview of OWH's role at FDA. OWH was established in 1994 by congressional mandate and is guided by the foundational scientific principles of considering sex as a biological variable. The office performs educational programs with external partners, internal training for FDA reviewers, educational trainings (e.g., CE modules) with NIH ORWH, and funds FDA intramural research related to women's health and sex differences. OWH maintains a dialogue with a broad stakeholder network, communicating health campaigns and safety alerts and hearing stakeholders' concerns.

Part I: Biological and environmental mediators of addiction

Hormonal influences on sex differences in addiction

We know that biological differences in men and women are important for influencing many aspects of addiction, but how do sex differences develop? Dr. Jill Becker from the University of Michigan described the process of sexual differentiation of the brain. Most healthy individuals are born with either two X chromosomes or one X and one Y chromosome making them either female or male, respectively. The *sry* gene on the Y chromosome codes for the protein, testes determining factor. The testes determining factor enables the development of the male reproductive tract and testes (11). In the absence of a Y chromosome, the bipotential gonads develop into ovaries. During their development, the testes secrete high levels of testosterone into the blood. This testosterone reaches the brain resulting in permanent brain masculinization (12). In rodents, testosterone is aromatized to estradiol which mediates most of the masculinizing effects on the developing brain (13).

There is a critical period for sexual differentiation of the brain, meaning that the brain can be masculinized by hormone exposure only during a brief temporal window of development, but not before or after (14). In rodents this critical period for sexual differentiation of the brain occurs around birth, but in humans it likely happens during

the second trimester. After puberty, ovarian hormones in females begin to be secreted in a pulsatile manner that creates the menstrual or estrous cycle. Males produce testosterone continuously. Secondary sex characteristics in males are largely the result of 5-alpha-reductase converting testosterone into dihydrotestosterone, which is necessary prior to puberty to enable gonadal development in boys. Adult gonadal hormones activate the masculinized or feminized neural circuits established during development (15), contributing to sex differences in addiction processes (16). Thus, there are developmental sex difference which are permanent, and sex differences caused by differing profiles of gonadal hormones in males and females (17, 18).

Gonadal hormones are all derived from cholesterol (19). Cholesterol is the precursor for progesterone, which is the precursor for testosterone, which in turn is the precursor for estradiol. Dr. Becker explained that key differences between male and female biology stem from where the enzymes that produce hormones are located. Both males and females have progesterone, testosterone and estradiol, but they are predominantly produced in the ovary in females and in the testes and in the brain or periphery in males (20).

Receptors for estradiol are present in the dorsal striatum, nucleus accumbens and ventral tegmental area among many other important brain regions for reward and drug-seeking behavior. Hormones have both long-term and rapid effects on the brain and behavior. One important example of a rapid action of hormones is seen in the dorsal stratum and nucleus accumbens where estradiol and progesterone rapidly enhance dopamine release and modulate dopamine receptor binding (21). As dopamine signaling plays a major role in reward and motivation, these rapid effects of hormones on the dopamine system in the reward circuits of the brain are hypothesized to contribute to sex differences in addiction, such that women predisposed to substance use escalate from casual to pathological use more rapidly than men (21). Dr. Becker explains that all drugs of abuse increase dopamine in the nucleus accumbens and in the dorsal striatum, which is important for their rewarding and addictive effects.

Dr. Becker studies the effects of gonadal hormones on dopamine release using cocaine. She has shown that estradiol enhances dopamine release induced by cocaine in the dorsal striatum in female, but not male, rats (22). Estradiol treatment in females also enhances learning of self-administration behavior for low doses of cocaine compared to control females (ovariectomized rats that did not receive estradiol injections), intact males, and castrated males (23). At higher doses of cocaine, all females regardless of hormonal status self-administer cocaine at higher rates than males, indicating that this sex difference is independent of gonadal hormones and likely programmed during developmental sexual differentiation of the brain (23). In addition, females have higher motivation to self-administer cocaine compared to males (24). Further, administering estradiol to male rats does not increase their cocaine self-administration, suggesting that organizational (developmental) masculinization precludes estradiol-mediated potentiation of cocaine-associated reward (25). Estradiol also enhances relapse-related behaviors in females after they have extinguished their self-administration behavior (26, 27). If progesterone and estradiol are administered simultaneously, the effects of estradiol are attenuated (25). These studies provide solid evidence that biological sex differences in gonadal hormone status contribute to drug seeking behaviors, reward, and relapse.

Adverse childhood experiences and addiction comorbidities

Childhood trauma is the most significant preventable risk factor for substance abuse, according to Dr. Martin Teicher of Harvard Medical School and McLean Hospital, as evidenced by the Adverse Childhood Experiences Study, other epidemiological studies and meta-analyses. The Adverse Childhood Experience (ACE) Study is an epidemiological survey of the medical, psychiatric, and developmental histories of 17,337 individuals enrolled in

the Kaiser-Permanente Health plan in California (28). In this study, individuals self-reported exposure to ten forms of maltreatment or household dysfunction, including: emotional abuse, physical abuse, sexual abuse, living with a substance abuser, living with a mentally ill family member, witnessing violence against their mother, incarceration of a household member, parental separation or divorce, emotional neglect, and physical neglect. The number of these adverse experiences is tallied to derive an ACE score, ranging from 0 to 10. High ACE scores (generally defined as experiencing >5 of the defined adverse experiences) greatly increase the likelihood of substance use later in life (29). Physical and sexual abuse are two of the most potent ACEs leading to later drug use (30, 31). For instance, one epidemiological study in women reported that non-genital childhood sexual abuse was associated with a 2.93-fold increase in risk for drug dependence while abuse involving intercourse was associated with a 5.7-fold increase in risk (32). This increased risk is partially mediated by post-traumatic stress disorder (PTSD), as there is a high incidence of PTSD in maltreated individuals with SUDs (33). Importantly, there is often a silent period between exposure to trauma and later life outcomes such as substance use as evidenced by cross-sectional and longitudinal data (34).

Dr. Teicher argued that it's not necessarily the accumulation or number of ACEs experienced that leads to vulnerability to substance use later in life, but the type and timing of maltreatment. However, being exposed to numerous types of maltreatment increases the odds that an individual experienced a critical type of maltreatment at a critical age. Based on this theory, he introduced the Maltreatment and Abuse Chronology Exposure (MACE) scale, to supplement ACE and enable analysis of ten forms of adversity and the rate of exposure to each type of maltreatment across development. The scale is retrospective, consisting of 52 items selected using item response theory, which assesses the degree and timing of 10 forms of maltreatment: sexual abuse, parental physical abuse, parental emotional abuse, parental non-verbal emotional abuse, witnessing interparental violence, witnessing violence to siblings, peer emotional abuse, peer physical abuse, emotional neglect, and physical neglect. Typically each of these forms of adversity occurs at specific ages, for instance, parental physical maltreatment peaks around age 6 whereas peer emotional abuse peaks at age 13 (35). There are also gender differences in the prevalence of these adverse events. For example, peer physical abuse is more common in boys than girls (35). According to Dr. Teicher, everyone has their own unique time course of exposure. One can use the MACE scale to determine which types of maltreatments are the most important predictors of later outcomes such as substance use. His research group utilized artificial intelligence and machine learning models using a large number of predictive variables that have strong correlations between severity of exposure to specific types of maltreatment at various ages. Their computational approach enabled determination of the most "important" variables (i.e., type of trauma) for later outcomes. Using this approach, they found that substance use in males is strongly linked to adverse events occurring around the ages of 15 or 16, like peer bullying. In females, the most important risk factor is sexual abuse at age 15. 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.

One of the most consistent observations in maltreated individuals is a hyperactive amygdala response to threat (36). The amygdala is a collection of brain nuclei involved in emotion, fear, learning and neuroendocrine signaling (37). Dr. Teicher stated that the more exposure one has to childhood adversity, the greater the amygdala response is to threatening stimuli. He suggested that amygdala responsiveness is largely shaped by peer emotional abuse at age 15 and by early exposure to physical maltreatment by parents and peers (36).

For highly prevalent mental health disorders like depression, anxiety, and PTSD as well as SUDs, there is a large subset of individuals who have experienced maltreatment and early life adverse events and another subset who have not. Dr. Teicher's research group hypothesized that these subsets are clinically, neurobiologically, and genetically distinct even if diagnosed with the same mental health disorder (30). In fact, individuals who have

experienced maltreatment have earlier disease onset, more comorbidities, greater symptom severity, and are less responsive to treatments than those who have not experienced traumatic early life events (30). Individuals with SUDs and a history of trauma are much more likely to relapse and show abnormalities in brain regions like the hippocampus and cerebellum compared to those without a traumatic childhood (38). These findings are critical for understanding the etiology of substance use and mental health disorders in certain populations and provide insight into how outcomes from early life trauma may be sex-specific.

Part II: Nicotine

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 U.S. each year, and for every tobacco-related death at least 30 people are living with a serious tobacco-related illness (39). These diseases include cancer, cardiovascular disease, diabetes, lung diseases, rheumatoid arthritis, and many other conditions (39). In the U.S., smoking-related illnesses total over $300 billion a year in medical costs and lost productivity due to sickness (39, 40).

An estimated 13.5% of U.S. women smoke cigarettes compared to 17.5% of men (41, 42). 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%) (41). In addition, comorbidities such as mental health disorders and SUDs, are common in smokers (43, 44). Cigarette smoking is reported in 39% of adults with co-morbid psychiatric disorders, versus 15.5% of adults without psychiatric co-morbidities (45). In particular, depression is strongly associated with smoking, and this association is greater for women than men (45). Individuals who smoke are more likely to self-report OUDs compared to non-smokers (46). In addition, men who smoke report higher daily opioid doses compared to non-smoking men (46).

Lung cancer is a leading cause of death in both men and women in the US (47). 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 (48, 49). 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 (39, 47). As discussed in detail below, 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, all conditions that can cause long-term impacts on infant and maternal health (39).

Nicotine products manufactured and sold by tobacco companies have been manipulated and designed to deliver nicotine in a highly effective manner. The tobacco industry has acknowledged that persistent use of tobacco is primarily related to psychological and social drivers and reinforced by the pharmacological action of nicotine (50). Nicotine dependence, attitudes toward smoking, and perceived harm have been characterized by several different scales and approaches, such as the Fagerstrom Test for Nicotine Dependence, Modified Fagerstrom Tolerance Questionnaire, and Classifying a Smoker Scale (51-53). Some are further divided into different sub-scales to further assess nicotine dependence. The majority of literature on nicotine dependence comes from studies of cigarette and combustible tobacco product use, which presents a significant challenge because of the diversity of tobacco products currently available. It is challenging to understand the mechanism of nicotine-driven use in non-combustible nicotine delivery systems, such as electronic cigarettes (e-cigarettes). Basic science and animal

studies can help to fill in gaps, but it is important to acknowledge that not all nicotine products are created equal. As expressed by Dr. Maciej Goniewicz of the Roswell Park Comprehensive Cancer Center, ultimately the most popular and most commonly used product that delivers nicotine is the most harmful (54).

Insights from a former smoker

During the *Conversations with Patients* panel, Lisa, a former smoker and current employee at FDA's Center for Tobacco Products, described her personal experiences and struggles with nicotine addiction. She started smoking cigarettes at age 17 around 1983 and became a regular smoker in college. Her first quit attempt was in 1994 after learning she was pregnant. Knowing it was bad for the health her baby, she tried to cut back on the amount she smoked. Nevertheless, her daughter was born ten weeks before her due date, at 2 pounds, 12 ounces. Lisa knew in the back of her mind that smoking was the likely cause of her premature delivery, and she felt the weight of guilt. She continued to smoke for another decade, interrupted by quit attempts using nicotine gum, inhalers, patches, and bupropion, but she was unsuccessful each time. In 2004, she became pregnant with her second child and once again smoked throughout her pregnancy. Her second daughter was born 3 weeks early and weighed just over 5 pounds. That spring, her mother was diagnosed with lung cancer and soon passed away at age 62. Smoking became extremely stressful for Lisa. She dealt with intense worry, shame and became a "closet smoker"; her family and coworkers knew that she was still smoking, but she continued to try to hide it. The biggest factor that drove Lisa to quit was watching her mother suffer.

She tried varenicline for ten weeks, which masked her withdrawal symptoms. She had the support of her family and friends. Through her attempts to quit, she was afraid of quitting. What would she do without her "go-to girl"? What if she failed to quit again and had to admit that failure to her family? Smoking was also a means to not gain weight, and Lisa feared that weight gain could accompany quitting. Throughout this quit attempt, she still had cravings. She struggled with overcoming triggers for smoking and being around other smokers. She felt excluded from friends who smoked and her "best friend" (cigarettes) of 23 years. She was lost and lonely. She also had to cope with the weight gain of 30 pounds.

Lisa smoked her last cigarette on January 28, 2008, and each year she celebrates this date as her "re-birthday." She is ten years smoke free and has maintained that without a doubt, quitting smoking was the hardest thing she has ever done in her life. Her biggest regret was not quitting sooner and not helping her mother to quit. Her biggest fear is that her daughters will start smoking or be pressured into to trying e-cigarettes. She also fears the temptation of using e-cigarettes herself. She reminds herself of a phrase that got her through quitting: NOPE- Not One Puff Ever, because she knows if she starts smoking again, she doesn't think she could quit again.

Epidemiology of nicotine use

Dr. Brenna VanFrank from the Centers for Disease Control and Prevention (CDC) began her talk by reaffirming that tobacco use remains a significant global public health concern. As the leading preventable cause of disability, disease and death in the United States, tobacco use impacts nearly every organ system in the body (39, 41). Currently, about 34 million adults utilize tobacco products in the U.S. (39, 41). Great strides have been made in public health science to capture and record demographic groups and statistics of smoking in the U.S. and smoking has decreased in youth and adults; however, 13.9% of U.S. citizens still smoke (55). As mentioned above, there are disparities in smoking within racial/ethnic groups, socioeconomic status, behavioral health conditions, and

sexual orientation (41). About a quarter of the U.S. population are living with behavioral health conditions, yet this population accounts for 40% of the cigarettes smoked (56). There are disparities as well between men and women with serious psychological distress (57).

The Population Assessment of Tobacco and Health (PATH) Study is a national, longitudinal cohort study of over 46,000 individuals in the United States, aged 12 and over. This prospective study looks at initiation, cessation, relapse, and transition between different tobacco products. Dr. Goniewicz gave a succinct overview of the study and highlighted a unique opportunity to collect biospecimens from a subset of the study participants to examine biological outcomes, such as biomarkers of toxicant exposure (58, 59). Thus far, findings of the PATH Study show that cigarettes are the most "sticky" tobacco product, meaning that most smokers of combustible cigarettes continue to smoke and very few smokers switch to alternative products. Within this study, dependence is quantified separately by tobacco product. Users seem more dependent on cigarettes and smokeless products rather than hookah or electronic cigarettes (60, 61).

As previously mentioned, smoking affects both sexes, but there are more male deaths compared to female deaths (41). This disparity is likely driven by differences in biology, patterns of use, and gender differences in product choice. Lung cancer, for example, is the number one cause of cancer death, and lung cancer risk doubled in male smokers and increased tenfold in female smokers between 1959 and 2010 (39). Based on these and other data, researchers have concluded that women have started smoking more like men; at younger ages, and more often. The differences between race/ethnicity by sex show a similar trend, where differences between non-Hispanic white and non-Hispanic black men and women have narrowed over time (62).

In his talk, Dr. Brian King from the CDC stated that combustible tobacco products are responsible for the overwhelming burden of death and disease from tobacco use and are a key target for prevention and cessation efforts. Another variable that is important to be taken into account is occupation (63). There is variation in smoking prevalence and adverse health outcomes among adult men and women in different occupations (64). Tobacco product use among young people is also critical to consider because 9 out of 10 adult smokers begin use before age 18, and 99 percent start before young adulthood (64).

The use of e-cigarettes in the general population has increased among U.S. adults and youth since entering the market in 2007 (65-67). 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 (68). In 2012, only 11.5% of surveyed adults believed that e-cigarettes were equally harmful as traditional cigarettes, but by 2015 this figure grew to 35.7% (69). 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 (70). Much less is known about the effects of e-cigarettes on human health than other tobacco products. While there do appear to be gender differences in patterns and reasons for use, more research is needed (54).

As of 2018, more than 3 million middle school and high school students reported using e-cigarettes, making these products the most commonly used tobacco products among teens (71). Studies have shown that youth who use e-cigarettes are more likely than non-users to initiate smoking traditional cigarettes (72, 73). 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 (70).

Challenge Question: How does smoking influence the use of other substances such as opioids?

Dr. VanFrank stated data suggest that nicotine and opioid addictions are mutually reinforcing and that smoking cessation has the potential to improve recovery from SUDs and increase long-term abstinence from other substances, including opioids.

Modeling biological sex differences in nicotine addiction and craving

Dr. Marilyn Carroll of the University of Minnesota introduced the topic of sex differences in animal models of drug self-administration to study craving and relapse. Lu and colleagues show that incubation of craving lasts for up to 60 days in rats; other researchers have seen this period extend for a year (74, 75). According to Dr. Carroll, long-term craving after discontinuation and withdrawal of a substance could be a reason why relapse is a common problem for smokers. To investigate this, she and her colleagues developed an animal model of incubation of craving using cocaine (76). Female rats acquire cocaine self-administration behaviors more readily than males (77). Rats show drug-taking escalation if they have access to cocaine for two or more hours over a period of ten days to 3 weeks. In Dr. Carroll's model, after escalation occurs, her group removed access to cocaine and recorded a burst of responding followed shortly by a decrease in responding that then remains at a low level. She found that females are more reluctant to give up a drug even if they cannot access it, and they continue to respond. Her group tests for relapse and incubation of craving by giving rats one of the following priming conditions: injection of the drug, stress, drug cues, or a combination of stimuli. If the rats receive a priming condition, or a glimpse of the drug in a drug environment, they will start responding right away. Over time craving continues to develop, according to Dr. Carroll, a phenomenon referred to as incubation of craving.

Dr. Carroll stated that incubation of craving can last for weeks to months, though traditional addiction treatment programs only last for weeks at the most. She referenced the findings of Dr. Yavin Shaham (a researcher in the intramural program at the National Institute on Drug Abuse), who demonstrated that social interaction was effective at stopping incubation of craving after a month in rat models (78), and she explained how exercise may also quell cravings. In her model, after self-administration and extinction of self-administration behaviors, rats were moved to a different environment for a short (3-7 days) or long (30 days) incubation period with access to either a locked or unlocked running wheel. Her lab examined incubation of craving by returning rats to the original drug self-administration chamber to test for what she called *context-induced reinstatement,* wherein responses on the previous drug-associated response lever are counted as relapse attempts or evidence of drug craving. Wheel running was shown to reduce incubation of craving in both females and males (76). Males showed elevated cocaine seeking after 3 days of cocaine withdrawal and incubation of craving after 30 days (79). Dr. Carroll is currently replicating this study using nicotine and has found that wheel running reduced incubation of craving in males. Her group also conducted multi-triggered relapse (MTR) studies in which they recorded responses of rats presented with several priming conditions and combinations (saline, nicotine, caffeine, yohimbine) (80). Wheel-running and progesterone reduced MTR relapse of nicotine craving in female and male rats (unpublished data). She also referenced a study published in 2015, which found that lower frequency methamphetamine users (less than 18 times a month) were able to significantly reduce their craving scores with aerobic exercise compared to those who use methamphetamine more than 18 times a month (81). She concluded her talk by stating that treatment interventions should consider that incubation of craving occurs long after drug use ends and that self-

motivated exercise reduces incubation of craving. Sex differences were found on the effects of wheel running on incubation of craving (males=females for cocaine; males > females for nicotine).

Appreciating sex and gender in treatment approaches to nicotine addiction

Data from the 2015 National Health Interview Survey (NHIS) and the NHIS Cancer Control Supplement show that adult female smokers do not differ significantly from adult male smokers in prevalence of interest in quitting, making a past-year quit attempt, recent successful smoking cessation, receiving a health professional's advice to quit, and use of evidence-based cessation treatments (i.e., counseling and medication) (82). 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.

Seventy percent of U.S. adult smokers are interested in quitting, but few are successful (82-85). A key take-away from Dr. VanFrank' s talk was that it is known what works to treat nicotine addiction. There are data that evidence-based treatments help people quit smoking, and group or individual counseling combined with FDA-approved cessation medications can increase cessation success (85). In fact, combining counseling and medication can double quit success rates (82). Building upon this foundational knowledge with additional research and increasing barrier-free access to evidence-based therapies is an important step to take. NHIS data show that two thirds of adults who have attempted to quit smoking did not use evidence-based therapy and less than 5% used both counseling and medication (82).

Dr. Sherry McKee from Yale University kicked off the panel, *Sex and Gender Influences within Integrative Approaches to Treatment of Addiction*, with the sobering statement that women smokers face critical health disparities. Women are more susceptible to tobacco-related carcinogens, more likely to develop certain cancers, more likely to develop coronary heart disease and COPD, and women have a number of sex-specific health risks primarily related to their reproductive health (39). Her research group reviewed every study available that had segregated data by gender and identified 190 studies evaluating the impacts medication, behavioral treatment, and unassisted quit attempt. Looking across the various methodologies, the data showed that women have a more difficult time quitting smoking regardless of the method used (84). Dr. McKee stated that many factors have been identified as to why women have poorer outcomes; she focused her talk on medication response.

There are 3 classes of FDA-approved smoking cessation aids and all demonstrate sex differences in efficacy. The three classes are: nicotine replacement therapy (NRT; over-the-counter), bupropion, and varenicline (both by prescription). NRT includes nicotine gums, patches, lozenges, nasal spray, and inhalers, which 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. NRT is not as effective for women as it is for men, and a study by Dr. Ken Perkins of the University of Pittsburgh showed nicotine replacement is 40% more effective for men versus women at 6 months post quit attempt, foundational research that holds true today (86, 87). Women have increased rates of nicotine metabolism, which is associated with reduced ability to quit using NRT (88). 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 (89). 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 (89).

Bupropion was originally developed as an anti-depressant and has dopaminergic and adrenergic agonist and noncompetitive nicotinic receptor antagonist activity (90, 91). In addition to its efficacy for tobacco cessation, bupropion may aid withdrawal-associated depressive symptoms and weight gain associated with smoking cessation (92, 93). 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 (94). Varenicline is a partial nicotinic agonist, with high affinity for α4β2 receptor, which mediates nicotine-related positive reinforcement (95). A meta-analysis of varenicline clinical trials conducted by Dr. McKee and her colleagues 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) (96).

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 (97). Because there was no mention of sex in the report, Dr. McKee's group analyzed these data by sex. In total, Dr. McKee's group pooled a sample of 14,000 smokers. For men, there are no differences among the three medications; all are equally effective (98). For women, a distinct pattern emerged. Varenicline was more effective than the nicotine patch, and there were no differences found between bupropion and the nicotine patch (98). These data suggest that the advantage of varenicline over bupropion and transdermal nicotine is greater for women than men (98).

Currently, Dr. McKee's research is focused on identifying alternative treatments to nicotine addiction. Her research group has looked at noradrenergic targets and are beginning to investigate glucocorticoids. In a proof of concept randomized controlled trial, guanfacine, a presynaptic noradrenergic agonist, was shown to double the quit rate over placebo. When the results were analyzed by gender, guanfacine was shown as effective in both genders, but the beneficial effects are larger for women compared to men. Looking into the underlying mechanisms of why there is a greater efficacy in women, Dr. McKee's group found that guanfacine increases the ability to resist smoking following stress in women only, and it reduces smoking-related positive reinforcement in men (99). These data suggest that guanfacine may target sexually differentiated systems in the brain to promote cessation via different modes of action in men versus women. She referenced an article by conference speakers, Drs. Jill Becker and George Koob, that classified different ways to identify sex differences in addiction models, including "mechanistic interaction" (100), which is a concept that highlights that men and women can arrive at the same behavioral outcome, for example smoking cessation, through different mechanisms, in our example, via reduced stress reactivity in women and positive reinforcement in men. Delving into integration approaches, Dr. McKee cited a Cochrane Review article that looked at integration of medication with behavioral treatment for smoking cessation. The Review found that a combination of treatment approaches is more effective than either behavioral therapy or NRT alone, but there was no sex analysis performed (101). Using the PATH dataset, Dr. McKee asked whether e-cigarettes are useful cessation aids and found that women were 24% less likely to quit than men, and e-cigarettes had no impact on either rate of quitting in women or rate of relapse among former smokers (in press). For men, e-cigarettes increase rates of quitting for tobacco smoking but increased rates of relapse among former smokers (in press).

Of note, 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 (102). 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 (103). Other studies have shown that most e-cigarette users do not completely discontinue use of traditional cigarettes, resulting in no improvement in health outcomes (104, 105).

Challenge Question: Are sex and gender differences in nicotine addiction and treatment outcomes sufficiently robust to warrant sex-specific cessation approaches?

Current clinical care guidelines for smoking cessation have not been updated since 2008. Dr. McKee posed a question regarding whether sex/gender should be a considered in selecting medications for treating specific populations. From the information provided in her talk, Dr. McKee called for updates in clinical care guidelines to reflect the state of knowledge regarding sex differences in medication response, as well as targeting factors that differentially maintain smoking in women and men. She also called for researchers to be held accountable for analysis and reporting by sex. Based on current evidence, she concludes that varenicline should be recommended as a first-choice option for women (6).

Sex and gender matter when considering non-nicotine aspects of tobacco addiction

Dr. McKee stressed that to improve smoking cessation rates, medication development strategies need to target factors that maintain smoking in men and women. Her working hypothesis is that women are more likely to smoke to alleviate stress and negative affect, and men are likely to smoke for nicotine-based positive reinforcement. Indeed, 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 (106).

This concept is largely based on seminal research by Dr. Kenneth Perkins from the University of Pittsburgh on sex differences in nicotine vs. non-nicotine influences on smoking reward and reinforcement. According to Dr. Perkins, relative to men, women's acute smoking reward and reinforcement are driven less by nicotine intake and more by non-nicotine stimuli. He explained that non-nicotine stimuli include the sensory and behavioral effects focused during the act of smoking, such as seeing and smelling smoke. By manipulating nicotine dosing while controlling non-nicotine stimuli *or* manipulating non-nicotine stimuli while controlling nicotine dosing, his studies isolate the impact of each factor to assess sex differences. Prior to these studies, it was believed than women were more sensitive to nicotine than men, since they chose "light" cigarettes more often than men. However, according to Dr. Perkins, women's preference for light cigarette brands was likely due to marketing by tobacco companies. His early studies using nicotine nasal sprays showed that men are more responsive to nicotine replacement, such that nicotine nasal spray (versus placebo) reduced the number of cigarettes they smoked and the number of puffs taken (107, 108). The finding of greater relative reinforcing effects of nicotine in men vs. women was corroborated by studies using cigarettes containing low and moderate doses of nicotine (109), as well as intravenous nicotine administration (110). In addition, Dr. Perkins and others showed that men are more sensitive to the subjective reward properties ("liking", etc.) of nicotine dose in cigarettes and dose-dependent withdrawal relief (111, 112). Taken together, these studies provide strong evidence for sex differences in nicotine sensitivity. A meta-analysis revealed that men have better quit outcomes than women using nicotine vs. placebo patch, perhaps because NRT delivers nicotine but no non-nicotine, sensory stimuli (113).

To isolate the non-nicotine influences on smoking reward and reinforcement, Dr. Perkins designed experiments manipulating the ability of men and women to see, smell, and taste cigarettes and asked participants to rate their smoking satisfaction. Blocking perception did not significantly decrease smoking satisfaction ratings in men, but

blocking smell and taste in women produced marked decreases in their liking and satisfaction ratings of smoking and the number of puffs taken (114). Based on these findings, Dr. Perkins suggests that perhaps tailoring cessation strategies based on sex might be beneficial. Indeed, one study showed that women had better success with cessation when using very low nicotine cigarettes, whereas men were more successful with NRT (115).

Neuroendocrine influences on nicotine addiction: opportunities for innovative therapies

As discussed in detail above, the two major motivators for smoking relapse are 1) pharmacologic withdrawal from nicotine, and 2) exposure to smoking reminders. Both of these motivators lead to craving and relapse. Pharmacologic withdrawal from nicotine is characterized by a constellation of symptoms including insomnia, irritability, fatigue, anxiety, and withdrawal-induced craving and relapse. The cycle lasts approximately 30 days, and the first three days are the most intense. Exposure to smoking reminders include the smell of a cigarette, alcohol, matches, and lighters and even include mood states such as stress, low and high mood. Exposure to smoking cues leads to cue-induced craving which in turn lasts for weeks, months, or even years.

Dr. Teresa Franklin of the University of Pennsylvania focuses on the lasting impact of cue-induced craving utilizing functional magnetic resonance imaging (fMRI). As mentioned previously by Dr. Perkins, there is evidence of sex differences in the factors that drive craving and withdrawal. In men, smoking behavior may be influenced more by pharmacological withdrawal; the actual absence of nicotine in the brain. Dr. Franklin's work has shown that in women, exposure to smoking reminders more readily influences smoking behavior, such as sensory aspects of smoking (e.g., flicking ash). fMRI can be a useful tool in examining smoking cue reactivity because it provides a sensitive and direct neurobiological approach that allows the researcher to use smaller sample sizes to demonstrate effects and tease out mechanism (116).

Perfusion fMRI measures blood flow related to neural activity (117). Dr. Franklin uses a smoking cue paradigm that includes a pre-session cigarette to minimize withdrawal effects and standardize the time since each participant last smoked. After acquiring baseline scans, acquiring images of the brain while 'at rest', additional scans are collected during the smoking cue task. This task consists of an audio/visual non-smoking clip and an audio/visual highly appetitive smoking clip. Pre and post smoking cue exposure craving scores are acquired to generate a smoking cue-induced craving score. Using these images, her hypothesis was that women would show greater responses than men to smoking cues in brain regions previously associated with smoking cue-reactivity. The hypothesis was based on previous work demonstrating activation of reward-related brain circuitry during smoking cue exposure (118) and it has been supported by over forty years of preclinical research, though most of this research was conducted only in males.

Dr. Franklin described two circuits involved in addiction as the *go* circuit and the *stop* circuit. The neural response was stronger in *go* regions in men, but both men and women reported that smoking cues induced craving. This raised the question, could heterogeneity in hormonal status be masking our ability to see a stronger effect in women? The sample of women participating in the study varied significantly in their hormonal status as it included post-menopausal, premenopausal women on birth control, and premenopausal women cycling naturally.

Her lab then hypothesized that during the follicular phase when estradiol is high, women would show greater responses to smoking cues in *go* regions compared to during the luteal phase when progesterone dominates the hormonal milieu (119). Thus, in further study, they examined naturally cycling women grouped by menstrual cycle

phase (follicular vs. luteal). Follicular phase women had higher smoking cue reactivity in *go* regions, reported smoking cue-induced craving, and showed brain/behavior correlates in relevant regions, including the anterior ventral insula, a region strongly implicated in drug craving (119). Luteal phase women had no response to smoking cues, no smoking cue-induced craving and no brain/behavior correlations (119).

To learn more about how the brains of follicular and luteal females differ, Franklin and colleagues examined the brain at rest in follicular and luteal women. Resting State Functional connectivity is a method to examine the functional interactions between a relevant region of the brain and the rest of the brain in the absence of a task. Dr. Franklin and colleagues hypothesized that follicular women would show less functional connectivity between *stop* and *go* regions, providing less cognitive control over the *go*. Resting state functional connectivity was compared between follicular phase and luteal phase women using the dorsal anterior cingulate cortex as the region of interest because this region is involved in cognitive control, craving reappraisal, and modulation of cue reactivity. Less functional connectivity was observed between the anterior cingulate and *go* regions (the medial orbitofrontal cortex/ventral striatum) in follicular phase women (120). In sum, follicular phase women showed heightened vulnerabilities to appetitive smoking cues and reduced resting state functional connectivity between *stop* and *go* regions. Franklin and her group postulate that women are at greater risk for relapse during the follicular phase of the menstrual cycle, when reward is high and suggest that these preliminary findings could explain inconsistencies in the literature. Franklin acknowledges limitations to the studies including retrospective analyses and combining early (low estradiol and progesterone) and late follicular (high estradiol/low progesterone) phase women together. Ongoing studies are examining premenopausal women prospectively and biochemically confirming hormonal status to confirm the influence of hormones on smoking cue responses. Importantly, these studies provide preliminary evidence that timing quit attempts with menstrual cycle phase may help quit success.

Dr. Mehmet Sofuoglu of Yale University continued the conversation by introducing progesterone as a possible treatment for tobacco and cocaine addiction. His lab researches the impacts of sex and menstrual cycle phase on response to drugs of abuse. Their foundational work led to the hypothesis that progesterone can treat SUDs. They performed two clinical trials using progesterone focusing on the early postpartum period. In an intravenous self-administration study, male and female smokers were presented with 6 choices of drug A or drug B (nicotine or saline). The dose of nicotine increased from 0.1 to 0.4 mg (2 puffs of a cigarette to smoking half a cigarette). Nicotine was administered intravenously to enable researchers to observe the rewarding effects of nicotine alone, without the influences of other chemicals or non-nicotine cues. Male smokers tended to titrate their nicotine intake; when presented with a lower amounts of nicotine, they opted for more puffs than when they were presented with higher nicotine doses (110). Female smokers did not display the same trend; they took the same number of puffs, no matter the nicotine dose (110). These findings imply that males and females smoke for different reasons and demonstrate sex differences in nicotine reinforcement (110).

Dr. Sofuoglu addressed the impact of menstrual cycle and sex differences on addiction using the same intravenous delivery paradigm described above. He found that women in the follicular phase of the menstrual cycle have similar response to nicotine as men; nicotine is rewarding to both men and follicular phase women (121). Luteal phase women exhibit a diminished response to nicotine (121). These findings are not new; they are representative of the findings produced twenty years ago when research was conducted with cocaine (122). Further studies confirmed that the hormonal effects on drug self-administration are clinically significant (123).

Next Dr. Sofuoglu's lab investigated why women in the luteal phase demonstrated diminished drug response. One large difference between the follicular and luteal phases of the menstrual cycle is the increased progesterone during the luteal phase, thus the use of exogenous progesterone could be beneficial in cessation techniques. Pregnant women typically reduce cocaine use during pregnancy, but after childbirth relapse rapidly (unpublished data). During pregnancy the amount of progesterone rises almost 100-fold and then drastically diminishes in the postpartum period, coinciding with high rates of relapse (122). Women who used cocaine before pregnancy and abstained during pregnancy were administered 100 mg of progesterone twice daily combined with cognitive behavioral therapy to prevent relapse during the first three months after childbirth (124). Dr. Sofuoglu and colleagues found that progesterone significantly reduced relapse rates, though the study was a short-term, 12-week study (124). Their next study used 200 mg of progesterone twice daily in women who smoke before pregnancy (125). Women given placebo relapsed to smoking in about four weeks, whereas relapse in women treated with progesterone was delayed significantly to ten weeks (125).

Challenge Question: How have study population demographics changed over the course of your research?

Dr. Sofuoglu found a striking difference in the presence of comorbidities with other addictions in his study populations over the past 15 years. Dr. Franklin pointed out that while the gender gap in smoking is closing, smoking in both men and women is decreasing. In addition, the number of cigarettes smoked per day is decreasing as well as nicotine dependence. Studies are showing that men have greater cue reactivity, which was previously theorized to play a larger role in nicotine dependence in women.

Challenge Question: What are some of the major challenges involved in clinical studies on hormones and drug-seeking behaviors?

Dr. Sofuoglu said that there are several challenges associated with studies manipulating hormones. First, hormone treatments can impact the menstrual cycle. Hormones can also interact with other drugs taken by trial participants, including nicotine in women who smoke, which can result in substantial health risks. In addition, Dr. Sofuoglu said there is little interest in using hormones as therapeutics from pharmaceutical companies. In postpartum women, administering progesterone is not possible as it inhibits lactation. Dr. Franklin monitors endogenous hormones in her studies, which is challenging because estradiol peaks for only a few days per month, and in young women menstrual cycles can be highly variable.

Tobacco use and cessation during pregnancy

About 7% of women smoke during pregnancy; 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 underestimate this statistic (126, 127). Currently, surveys used to determine the effects of smoking on pregnancy need to be updated to include smokeless tobacco products. Most of the data on tobacco exposure during pregnancy is based on cigarette smoking, but the landscape is changing with increased use of e-cigarettes and hookah smoking, which contain different chemicals.

Between 2000-2010, 1 in 5 pregnant or postpartum women reported smoking before pregnancy (128). Fifty percent of women who smoke reported quitting by late pregnancy, though many relapse (128). Smoking during

pregnancy is associated with an increased risk of miscarriage (129, 130), preterm and still birth (129, 131), low birth weight (132), neurodevelopmental dysfunction (133), and alterations in placenta function (134). This can lead to long-term health complications in children exposed to cigarette smoke *in utero*, such as poor respiratory (135) and ophthalmological function (136).

Dr. Cheryl Oncken of the University of Connecticut School of Medicine began her talk with an overview of the composition of cigarette smoke. It contains over 4,000 ingredients including carbon monoxide, which can limit fetal growth and neurodevelopment, and nicotine, a known teratogen that can result in neurodevelopmental deficits (137). One of the most well-known risks of *in utero* nicotine exposure is the increased risk of low birthweight. Low-birthweight infants have increased morbidity and mortality compared to infants of normal birthweight. Cigarette smoking triples the risk of sudden infant death syndrome, which has been linked to nicotine (137). Current data show that nicotine exposure during pregnancy does not cause decreased birthweight or stillbirths (138-140).

According to Dr. Oncken, data suggest that treating nicotine addiction during pregnancy can be beneficial for infant birthweight outcomes. When women quit early in pregnancy, birthweight improves (141). There are promising data indicating that even when women quit late in pregnancy, birthweight improves. Cutting down the number of cigarettes smoked also improves outcomes (142-145). Psychosocial interventions are the most effective types of therapies in pregnant populations (146-149). Counseling has been shown to increase quit rates by a third, and financial incentives such as gift vouchers have been shown to nearly double quit rates during pregnancy (149). Studies on NRT show little to no benefit in pregnant women, which may partly be due to increased nicotine metabolism during pregnancy (150, 151). A study of bupropion use during pregnancy for depression showed that the medication decreases craving for tobacco in pregnancy and markedly increased quit rates (152). 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 (153). Randomized controlled trials report mixed results for NRT efficacy during pregnancy (154), and NRTs appear to have similar effects as smoking on maternal blood pressure and maternal and fetal heart rate (155). Large rigorous randomized controlled trials for the safety and efficacy of bupropion and varenicline have not been completed in pregnant women and lactating women; therefore, current data, according to Dr. Oncken, is insufficient to weigh the benefits and risks of cessation pharmacotherapy for pregnant women (156, 157).

Dr. Christine Nguyen from FDA CDER told the audience that FDA-approved products for smoking cessation in adults are also approved for the same use in pregnant women and lactating women. The available safety data in pregnancy and lactation, however, are lacking or limited. Furthermore, the new labeling rules under the Pregnancy and Lactation Labeling Rule (PLLR) require the inclusion of available safety data about the use of medications in pregnancy and lactation in narratives in lieu of the pregnancy letter category of risks (A, B, C, D, X). For nicotine nasal sprays, the known harmful effects on maternal and fetal health are from data on cigarette smoking. However, nicotine nasal spray has not been studied in pregnant women, and its specific effects on fetal development are unknown. Thus, the label notes that nicotine nasal sprays should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of using it in the pregnant patient, who might continue to smoke. Similarly, labeling indicates that the safety of nicotine nasal spray therapy has not been examined during lactation in nursing infants, but nicotine is known to pass into breast milk. Nicotine concentrations in milk are expected to be lower with nasal spray compared to cigarette smoking based on plasma nicotine concentrations with nicotine replacement. Knowledge gaps in smoking cessation treatment safety in pregnant and lactating populations include concerns related to dosing, limitations to the quality and quantity of

safety data, sparse clinical trial data, and no information on the long-term outcomes of fetuses exposed to drug treatments *in utero*.

Challenge Question: What can we improve to reach more pregnant women struggling with nicotine addiction?

Dr. Oncken argues that improving point of care treatment (3) and translating this into prenatal care is important. Increased training for obstetricians and other healthcare providers can improve care. Baby and Me Tobacco Free program incentivizes women by giving them free diapers, which may enhance quit rates. Further research is needed on the efficacy and safety of pharmacotherapies such as bupropion and varenicline, as well as the effectiveness of combined pharmacological and psychosocial treatments in pregnant women.

Federal policies and research initiatives related to tobacco products

This panel included representatives from FDA, NIDA, and CDC, federal agencies with distinct roles that often work together to obtain data on tobacco products and to disseminate information regarding tobacco dangers, prevention, and quitting.

Mr. Mitch Zeller, Director of the Center for Tobacco Products (CTP) summarized the history of FDA's efforts to regulate tobacco products. FDA asserted regulatory jurisdiction over cigarettes and smokeless tobacco products in the 1990s under FDA Commissioner David Kessler. After 4 years, the Supreme Court shut down this initiative by ruling that only Congress has the power to determine whether FDA should be regulating tobacco products. Nine years later, in 2009, Congress passed the Family Smoking Prevention and Tobacco Control Act, allowing FDA regulatory control of tobacco products (158). This law was passed with overwhelming bipartisan support in both chambers putting FDA in control of regulating every aspect of the manufacture, sale, and distribution of tobacco products. The goal of the Act is to reduce harm at a population level by lowering the number of people who start using tobacco, encouraging more users to quit, and using the tools of product regulation to reduce adverse health outcomes for people who continue to use tobacco products. FDA has unique regulatory powers, using tools and resources given by Congress to review products on a premarket basis, claims to reduce exposure or risks before being marketed, the power to restrict marketing and distribution, and the power to decrease the harms associated with the use of tobacco products. Congress wrote mandatory considerations into law to define public health standards, which reflect impacts on users and non-users, impacts on initiation, cessation and former users. FDA is tasked with using the science that all FDA partners are generating to assess net population-level impacts.

Upon Dr. Scott Gottlieb's arrival as FDA Commissioner in 2017, he asked CTP Director Mitch Zeller how FDA could make the greatest impact on public health using the various tools, resources and authorities at their disposal. Zeller stated that every death from tobacco use is avoidable and preventable. Despite the reduction of consumption and prevalence of tobacco products over the past 50 years, there is actually a higher annual death toll because there is now a longer list of tobacco-associated diseases. He called for striking a balance between smart regulation and innovation, guided by science. FDA issued three Advanced Notices of Proposed Rule-Making (ANPRM) in March 2018 on nicotine reduction, flavors and cigars. The nicotine ANPRM included questions on the amount that would render nicotine minimally or non-addictive in cigarettes, how to measure it, what the ultimate scope of the regulation should be, and unintended consequences.

Regulation of these products is not enough. Mr. Zeller also called for a sustained national dialogue with the general public on nicotine to address issues including dispelling misperceptions of nicotine safety, explaining where the continuum of risk is relevant, helping addicted adults transition to potentially less harmful products, and use in youth and vulnerable populations. Public education has been focused on youth prevention campaigns, as well as initiating young adult and adult programs. The primary youth campaign, "The Real Cost," launched in February 2014. A recent measure, "The Real Cost" e-cigarette preventions campaign launched in September 2018 and is the first large-scale effort of its kind. "Every Try Counts" is public education campaign to encourage cessation attempts that focuses on smokers between ages 25 and 54 who made an unsuccessful quit attempt in the past year. The idea is to promote positive messages at the point of sale. In 2017, Commissioner Gottlieb established the Nicotine Steering Committee which meets monthly to examine the expanding role of medicinal nicotine products to help more smokers quit. There is a huge knowledge gap when it comes to sex and gender in tobacco and nicotine research. Who makes up the smoking population today? What are the implications of disparities across socioeconomic statuses and smoking? Why is there a prevalence difference between education levels? Looking at today's smoking population, it is important to address disparities across different dimensions, such as race, ethnicity, sex and gender to reduce the leading cause of disease and death in this country.

Dr. Wilson Compton from NIDA said that NIDA and NCI have complementary research portfolios and fund approximately equal shares of the tobacco research supported by NIH. NIDA emphasizes, among other topics, basic neuroscience research which has established that nicotine is a reinforcing drug like other substances. Current genetics research has identified specific genetic diatheses toward the onset of nicotine dependence and inform a clinically meaningful treatment response. Further aims in this space are to consider if there are sex and gender differences or similarities.

Currently funded studies, such as one conducted by the Centers of Regulatory Science, look at what would happen if nicotine were reduced in tobacco products. These findings could have large regulatory impacts. A major epidemiology survey funded by NIDA, "Monitoring the Future," was the first study to show that e-cigarettes had skyrocketed in popularity among teens, documenting in 2014 that e-cigarettes were more popular than combustible cigarettes. Current research includes how to balance the potential value of e-cigarettes used to quit smoking versus risks for adolescents who use as a new pathway into tobacco dependence and addiction. The NIDA-led longitudinal "Adolescent Brain Cognitive Development" (ABCD) study will be looking at repeated MRI scans of nine- and ten-year old subjects and follow them for about a decade to study brain development in response to exposure to tobaccos products, alcohol, marijuana, and other substances. This large-scale population study will address large gaps in the literature in this space and will analyze results by sex and gender. NIH NIDA has also spear-headed the development of research around e-cigarettes. A key goal of this project is to develop a research product to be used in both clinical neuroscience and studies to evaluate the impact of e-cigarettes on health and outcomes.

Dr. Brian King represented the CDC's Office on Smoking and Health (OSH), which is the lead federal agency for comprehensive tobacco efforts, working at the federal level, as well as with states and communities to address tobacco prevention and control. He identified the following four key areas of focus for CDC OSH: 1) youth prevention, 2) promotion of youth and adult cessation, 3) eliminating exposure to secondhand smoke, and 4) identifying and eliminating tobacco-related disparities. Dr. King noted that 80% of CDC OSH's funding dollars go to state and local initiatives. CDC collaborates with multiple federal agencies, including NIH and FDA, on tobacco related initiatives. For CDC's part, its focus is on funding state efforts, as well as providing technical assistance and supporting quit lines across the country. CDC also houses a world-class tobacco laboratory that studies tobacco product constituents and biomarkers of exposure. Also, CDC launched a campaign in 2012, "Tips for Former

Smokers," which has helped about half a million adult smokers quit since its inception. This campaign is ongoing and continues to help adult smokers access quit line resources.

CDC also focuses on surveillance of data to inform public health policy planning and practice. It implements several surveys, most notably the National Youth Tobacco Survey, which has run since 1999 and collects data on youth utilization of a variety of tobacco products. Since 2011, CDC has collaborated with FDA on this effort to ensure that it functions as an annual national survey to assess tobacco product use among both middle and high school students. This is an important joint-agency collaboration because of the rapidly changing and emerging trends of e-cigarette use among youth. CDC also partners with FDA on the PATH Study by assisting with the analysis of biomarker data collected through the study.

As discussed throughout the meeting, there are sex differences in all aspects of tobacco product use. Disparities are also present in public policy, with variations in coverage of proven tobacco control interventions such as smoke-free policies. Therefore, it is not only important to ensure demographic risk factors are recognized and analyzed, but also equity in policy coverage and accessing cessation resources to help mitigate risks. Dr. King stated the critical need to continue assessing sex differences across the diversity of tobacco products being used in the United States. Finally, he concluded with a call to action from the federal level. It is a trifecta of efforts across the CDC, FDA, and NIH, he says, that will truly make a difference through the complementary yet distinct roles of each agency.

Digital tools to aid smoking cessation

Dr. Yvonne Prutzman from the National Cancer Institute (NCI) shared real-world examples of how sex and gender are considered in building and designing national mHealth smoking cessation resources. Smokefree.gov is an evidence-based, digital federal smoking cessation program supported by NCI. Their resources are available online or via mobile apps and are intended for general audiences, with efforts to reach and engage different subsets of the population. Their multiplatform network of websites, text-based programs, apps, and social media platforms have reached 3-6 million users per year, providing behavioral smoking cessation support to people who are trying to quit smoking. Smokefree.gov's goal is to make smoking cessation resources accessible to everyone and to ensure that the information is consistent with clinical practice guidelines.

Digital interventions aim to do three things. First, they aim to reach people who need assistance in quitting smoking. This can include raising awareness of resources and helping people form intentions to quit. After reaching their audience, they aim to engage users with resources to help promote and support quit attempts. Finally, they pay close attention to retaining people in their networks, as dropout and relapse is a major problem, particularly early on in treatment. If patients do relapse, the program tries to reengage them quickly to reduce the time between quit attempts.

NCI uses its knowledge of sex and gender differences in smoking behavior to design and tailor their resources towards specific populations. As men are more likely to smoke than women, they are a particularly important audience for Smokefree.gov. However, men are more difficult to engage in cessation treatment and health services in general and a difficult target for digital interventions. To increase male engagement, Smokefree.gov used a paid media campaign in 2016 to target men. They developed content that spoke to the male experience in smoking cessation. The campaign ran for eight months and increased the number of men visiting their site by roughly 500,000 users.

Women tend to smoke fewer cigarettes per day, be less nicotine-dependent than men, and are more likely to be triggered by non-nicotine cues; therefore, content on pages focused on reaching women contains messaging sensitive to these gender-specific needs. Usage data from Smokefree.gov shows that women are much more likely than men to engage in digital resources. Dr. Prutzman mentioned that the flagship website receives roughly 300,000 visits per month, and 61% of those visitors are women. The webpages are designed to help women navigate to gender-specific resources, such as content related to pregnancy, weight concerns, body image, negative affect, and mood. Dr. Prutzman noted that pregnancy-related resources receive the highest traffic of all content on the Smokefree Women webpages. Content also addresses evidence-based concerns related to women's use of tobacco products such as use to reinforce relationships. As mentioned by Lisa in the *Conversations with Patients* panel, women often smoke with friends and partners and when they quit they often feel disconnected from their peer groups, thus the website provides tips to deal with these challenges and advice on how to receive support.

Dr. Prutzman presented the challenges faced by mHealth cessation interventions. Getting people to use these resources is the most important factor. mHealth focuses much attention on making their content appealing, they refresh content often, and use a mix of videos, images, and user-centered designs, including clickable links that easily deliver the resources people are looking for. Content needs to be relevant to an individual's motives for quitting and the issues they struggle with during the quitting process.

Part III: Opioids

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 (159). 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 U.S. in 2016 alone - a statistically significant increase from 2015 (data from 26 states; (160)).

This is not the first opioid crisis that the U.S. has endured. Dr. Hendrée Jones of the University of North Carolina at Chapel Hill recounted the history of opioid use and misuse in the US. The first opioid crisis in our country occurred in the 1800s, during which 66-75% of opioid users were women. Well-meaning prescribers often treated women with opioids for menstrual symptoms, pregnancy, and psychiatric issues (161, 162). In the late 1960s and 1970s opioid use was common in Vietnam veterans. The current opioid addiction and overdose epidemic began in the mid-1990s, likely in part resulting from over-prescription of opioids for pain conditions.

Dr. Tamra Meyer, a Lead Epidemiologist from CDER's Office of Surveillance and Epidemiology, defined key terms associated with opioid use and addiction as follows. *Misuse* is the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse (163). *Abuse* is the intentional, non-therapeutic use of a drug, product, or substance, even once, to achieve a desirable psychological or physiological effect (163). *Opioid use disorder (OUD)* is defined as a problematic pattern of opioid use ranging from mild to severe and characterized by impaired control of use, impaired social functioning, risky use, tolerance, and withdrawal (164). *Opioid addiction* is a chronic disease of brain reward, motivation, memory and related circuitry (165), which generally corresponds to moderate to severe OUD. Finally, *overdose* is an injury to the body (e.g., poisoning) that happens when a drug is taken in excessive amounts. An overdose can be fatal or nonfatal (166).

Accounts of opioid addiction and recovery

FDA's Chief Scientist, RADM Denise Hinton noted that SUDs are neither personal weaknesses nor character flaws, but serious diseases with biological roots and deep consequences for public health. SUDs are chronic illnesses that affect everyone. Both opioid and nicotine misuse have resulted in personal hardships and suffering for many people and their loved ones, in addition to creating massive economic burdens for individuals and society. We heard several stories illustrating the pain and hardship caused by substance use on Day 1 of the meeting. The *Conversations with Patients* panel helped to focus attention on the reasons why this scientific meeting was convened: to advance research and policy to help those suffering from a SUD. Individuals in recovery from opioid use shared their stories of how they initiated use and eventually decided to enter recovery, illustrating how anyone can be vulnerable to developing an opioid addiction.

Daniel, a businessman from Brooklyn, NY, began his talk by sharing his rock bottom moment of waking up in a jail cell, without knowledge of his whereabouts or ability to recognize his girlfriend and being $1 million in debt. Shortly thereafter he learned that his mother had to sell the house he grew up in and declare bankruptcy to settle his debt, illustrating that addiction can pose extreme hardships for entire families. His drug use started when he was 18 years old when he received a prescription for hydrocodone following a surgery and escalated from that point. Following his rock bottom moment, he was faced with a choice: get clean or go to prison. He entered a pretrial intervention program which required him to get sober and maintain employment. He elected to receive buprenorphine/naloxone treatment, a pharmacotherapy that curbs withdrawal, which he believes is the motivating cause for the opioid crisis. In his opinion, addicts will do anything to prevent experiencing withdrawal. He expressed gratitude for the family that hired him while he was in recovery, saying that the job saved his life by creating a sense of community, love, support, and most importantly, purpose. He concluded by stressing the importance of finding a purpose to motivate the journey of recovery and sobriety.

Amanda, a Peer Recovery Support Specialist for the Baltimore County Health Department, described her experiences with opioid use and recovery. Her first exposure to opioids was at age 16 following removal of her wisdom teeth. Her misuse of opioids started about a year later, as she had very easy access to opioid pain medications in addition to benzodiazepines. When controlled-release oxycodone was reformulated, and she could no longer crush or melt pills, she very quickly turned from being a purely pharmaceutical drug user to an intravenous drug user. After witnessing a traumatic event while purchasing heroin, Amanda decided it was time to get clean. She was admitted to a mental health treatment facility and went into medically-induced detox. When she was released, she entered an intensive outpatient program, received counseling, and connected with a social group called Self-Management and Recovery Training (SMART) (167), which helped her manage the thoughts, feelings, and emotions contributing to her substance use. Amanda told the audience that she has an Adverse Childhood Experience (ACE) score of 8 and had experienced high levels of abuse and violence in childhood and adolescence. As mentioned throughout the meeting, experiencing trauma is a potent risk factor for later substance misuse (28). She said, "I've heard a lot of talk about how, you know, there is some overlap with mental health and substance use. It's all overlap. I have yet to meet a person in active addiction that is happy. I have yet to meet one that isn't experiencing some form of trauma currently in their use or have experienced it in their past." She also stressed how lucky she was to have good health insurance, a support network, and a safe place to live, which she emphasized is extremely rare for people in recovery.

Epidemiology of opioid use disorders: sex and gender matter

Dr. Tamra Meyer presented data used by FDA to evaluate opioid use, misuse, and related outcomes. Her talk included several messages. First, prescription opioid use, misuse and related outcomes occur among patients for whom medical professionals prescribe opioid analgesics for moderate to severe pain, as well as other, unintended users whom receive diverted medications. Second, it is important to consider if data sources capture opioid use, misuse, and related outcomes in people with and without a legitimate prescription. Health care utilization data, surveys and death records are the main sources of information about opioid use, misuse and related outcomes. No single data source gives us the full picture. Dr. Meyer stated that a mosaic approach must be used to gauge trends. To do this, multiple data sources can be used to capture smaller pieces of the overall picture. Third, recording and analysis of sex and gender differences varies across data sources. Sometimes it is unclear whether data sources include self-reported gender or are based on information on an individual's insurance card, what a patient tells a pharmacist, or even a person's appearance. Carefully considering the sources of data on a patient's sex or gender is important to fully understand the trends being analyzed.

More opioid analgesic prescriptions are dispensed to women compared to men, but men are more likely to misuse opioids, have OUDs, and overdose. About 60% of patients receiving prescriptions for opioid analgesics between 2006-2017 were women (168). Although statistics generally show higher rates of misuse and overdose in men versus women, the magnitude of gender differences varies across opioids, such that 69% of calls to poison control centers for heroin were for men, whereas 30.4% were for women. In contrast, the number of calls to poison control centers related to intentional misuse and abuse of drugs such, as codeine (51.7% men, 47.9% women), tramadol (49.8% men, 50% women) and morphine (55.5% men, 44.2% women), have narrower gender differences (169). Interestingly, more men visit emergency departments for nonmedical use of oxycodone-containing products compared to women, however, more women visit for morphine-containing products (170). Whether these differences are due to prescribing practices or biological sex differences is unknown.

Dr. Wilson Compton, Deputy Director of NIDA, presented nationwide trends in opioid-related deaths in 2009 versus 2016, illustrating that overdose deaths rates have markedly increased throughout the country; however, rates vary by geographical region. Overdose distribution maps such as these provide evidence that necessary services and outreach may need to be implemented differently based on region.

Next, Dr. Compton described how most opioid overdoses from 1999-2016 involved prescription opioids (171), likely the result of overprescribing practices. As the population of those misusing prescription opioids reached high rates in the early 2010s, use shifted to heroin and illicit opioids. Finally, in recent years synthetic opioids (generally fentanyl-related) overdose rates have skyrocketed. Fentanyl is an extremely potent synthetic opioid that can be illicitly-manufactured, making it a less expensive and stronger drug than heroin. Later in the conference, Dr. Nora Volkow, Director of NIDA, added that these shifts in usage patterns show us how rapidly the epidemic is changing such that the solutions that may have applied 10 years ago to contain the crisis must be revisited and modified or updated as needed.

How does this switch from prescription to illicit and synthetic opioid-related overdoses differ by sex? Dr. Volkow, referenced new data showing that males still overdose more than females in absolute terms (172, 173). More males are dying from heroin overdoses, however, in the past few years the data show an increase in heroin-related

overdoses in women (172, 173). For prescription opioids, some age groups of women are dying at similar rates as men (172, 173).

Challenge Question: What are the challenges of interpreting patterns of opioid use, misuse, and related outcomes by sex and gender using existing data sources?

Incorporating sex and gender analyses into the misuse and abuse patterns for specific opioid medications is both a challenge and opportunity to learn more about the current epidemic. Researchers are often focused on overall use patterns or patterns related to specific medications and sometimes fail to think about how sex and gender might influence some of the overall patterns or how considering sex and gender could improve addressing these patterns. Further, many data sources are not stratified by key variables that we know differ by gender and sex. Designing studies with sex and gender in mind would allow us to include certain populations that are more immediately generalizable with better external validity.

Importantly, there is a need for longer-term prospective studies to incorporate endpoints that are clinically significant, such as retention in treatment and functional status, which are often not included. In addition, critical characteristics vary by sex and gender and inclusion criteria for studies are often narrow. This hinders the generalizability to populations that need treatment who are often underrepresented in studies.

As mentioned above, women are more likely to be prescribed opioid pain relievers and are more likely to use them for longer treatment durations (174). Dr. Shelly Greenfield of Harvard Medical School emphasized that while the overall prevalence of SUDs is greater in men than women, this gender gap is closing, or has already closed for some substances especially in cohorts of younger women. She notes that in the current opioid use epidemic, women are dying at unprecedented rates, and high rates of OUD in pregnancy and neonatal opioid withdrawal syndrome are occurring (discussed in detail below). Over the past 4 decades, heroin use has increased among women, such that women are now using heroin at similar rates as men (175). Since 1990, the risk of women dying from an opioid overdose has increased by 471%, compared with a 218% increase in men (176). Data from 2014 reveal that in adolescents aged 12-17, there is no sex difference in SUDs, as 5.3% of males and 5.2% of females in this age group have SUDs (177). Dr. Greenfield summarized that there is convergence of evidence that demonstrates that women now initiate substance use at an earlier age than in previous generations and at approximately the same age as their male counterparts.

The overall prevalence of alcohol and drug use has increased in women in the past 2-3 decades with lower levels of abstinence and higher levels of dependence (178, 179). In addition, Dr. Greenfield stated that there is evidence for the *telescoping,* or accelerated course of substance use disorders in women, such that women advance more rapidly than men from initial substance use to their first episode requiring treatment (180, 181). Women enter treatment sooner, with fewer years of use and often have more medical, psychiatric, and adverse social consequences upon entering treatment compared to men (180, 182). Women and men have unique risk factors for OUDs. Women over 54 years of age are more at risk for OUDs, whereas OUD risk is highest in men younger than age 34. Women with a history of drug overdose, alcoholism and inhalant use are at high risks for OUDs, whereas for men, recent depression and living with children are factors that increase the odds for OUDs (183-185).

Similar to women with other SUDs, women with OUD have higher rates of co-occurring psychiatric disorders, especially depression, anxiety, and PTSD. They may face other barriers to entering treatment, including trauma

history, financial vulnerability, partners using substances, lack of social support, challenges associated with pregnancy and parenting, and higher levels of stigma/discrimination. Dr. Volkow presented data indicating that more than half of opioid prescriptions in the US are written for people with anxiety, depression and other mood disorders. In fact, 19% of the 38.6 million Americans with mood disorders are prescribed opioids, compared to 5% of the general population (186). Further, women are more likely than men to have a mental health disorder and more likely to use opioid prescriptions with or without mental health disorders (186). Opioid-dependent women have a greater risk of mortality compared to the general population, however, women have a lower instantaneous hazard (i.e., the hazard function at a given point in time) of all-cause mortality compared to men (187). Concurrent opioid and methamphetamine/cocaine use increases mortality risk among women but decreases risk in men (187). Among men, mortality risk is decreased by maintaining full-time employment and increased by periodic heroin use and medical issues (187).

Challenge Question: What are the biggest challenges to using healthcare utilization data to understand opioid misuse and related outcomes?

Health care utilization data includes mostly coded encounters, such as instances when a patient visits an emergency department, calls poison control, is hospitalized, or fills a prescription at a pharmacy. There are several potential issues with these data sources. Pharmacy dispensing records provide documentation of the prescriptions a patient receives, but do not necessarily translate into accurate information regarding how much of this medication the patient actually took and how much of the medication may have been taken by others. Health care utilization data generally provides poor detail on adverse events, intent, and overdose death. Surveys can help to capture use of prescription and illicit opioids and may capture intent, but typically provide limited information about which specific drugs or products were used, are unlikely to capture overdose deaths, and may be biased due to their self-report nature.

Sex differences in pain

Three hundred million opioid prescriptions are written each year, and half of the U.S. opioid market goes toward treating chronic, non-cancer pain. In her talk, Dr. Kelly Barth from the Medical University of South Carolina described chronic pain as complex and poorly understood and defined it as pain that lasts longer than 6 months. About 126 million patients in the U.S. reported experiencing pain in the last three months, with 25 million cases of chronic pain and 23 million reports of severe pain. Individuals with severe pain have worse health status and utilize more heath care services than the general population. Pain conditions cost around $635 billion/year in medical expenses and lost productivity. Chronic pain conditions have serious negative impacts on quality of life, are associated with anxiety and depression, impact interpersonal relationships, daily activities, sleep quality, work productivity, and increase the risk of suicide. Women are disproportionately affected by chronic pain conditions, making up 80% of the chronic pain treatment population (188-190). Chronic pain conditions like fibromyalgia and irritable bowel syndrome (IBS) occur more often in women than men (189, 191), and women have increased sensitivity to laboratory pain and rate pain higher in intensity and unpleasantness (189, 192, 193). These factors likely contribute to why opioid and other pain-reducing medications are more often recommended for women than men (189, 194, 195). Further, Dr. Barth described the complicated nature of treating chronic pain, stating that pain cannot be treated in isolation. She said that we know pain is associated with trauma, depression, and

anxiety, both before and after pain develops. It is also associated with opioid use, poor sleep – all factors that interact to impact quality of life.

Dr. Jeffrey Mogil of McGill University is an expert in pain neurobiology and spoke about several biological mechanisms mediating pain. He began his presentation by reminding the audience that there are currently two crises occurring simultaneously. One is the opioid crisis, which is quickly accelerating. The second is a chronic pain crisis that has been moving in slow motion, escalating over time such that it hasn't been as readily noticed by the public. The chronic pain crisis initially gave rise to the opioid crisis and continues to drive it. He noted that the only long-term solution to the opioid crisis is the development of better, non-opioid, non-addictive analgesics. Research and development of these opioid alternatives has been slow, with poor outcomes. Dr. Mogil believes that one reason why successful development of alternative analgesics has been lacking is due to sex and gender differences in pain.

As noted above, it has been long known that chronic pain-related disorders occur at a higher prevalence in women compared to men (196). Is this because women are more sensitive to pain than men, or could there be other explanations? Perhaps women are more likely to go to the doctor and report pain conditions than men. The only way to truly know the answer to this question according to Dr. Mogil, is to study pain in men and women in the laboratory. He analyzed hundreds of laboratory studies on different aspects of pain, using metrics like threshold, tolerance, intensity and unpleasantness for different types of pain including electrical, ischemic, cold, heat, pressure and muscle pain in men and women and has shown that women are unequivocally more sensitive to every measure and type of pain (191). He stated that the existence of sex differences in pain is as close to a proven fact in biology as anything he has ever seen, and that we need to start to ask why this is true.

Dr. Mogil pointed out that a large problem in the field of pain research is that animal models of pain do not accurately represent the human population experiencing chronic pain disorders. He asserted that the problem is not that we are using rats and mice to model a middle-aged woman with a headache, but that we are using young male rats of a single strain. In fact, in 2005, Dr. Mogil reviewed 10 years of publications in the scientific journal *Pain* and found that 79% of the studies using rodents were performed in males only (197). By 2015, the percentage of studies using only males in animal models of pain was still 79% (198), although the 2016 NIH SABV policy will hopefully lead to better inclusion of female animals in these studies.

One of the most important advances in the field of pain research in the past 20 years has been the recognition that glia, astrocytes and microglia, play very important roles in modulating pain signals. In fact, according to Dr. Mogil, it is now believed that microglia signaling in the spinal cord mediating pain is an entirely male-specific mechanism. T-cell signaling in females appears to perform the same functions as microglia in males to regulate pain responsivity. If female animals had not been used in these studies, we simply would not know that there are sex differences in this critical mechanism underlying pain. Dr. Mogil noted that his lab has been performing studies in T-cell deficient mice and have noticed that mice lacking T-cells are deficient in morphine analgesia (199). Transferring CD4+ T-cells from wildtype mice to T-cell deficient animals restores the analgesic properties of morphine in these animals, suggesting the importance of the immune system in regulating pain responsivity.

Next, Dr. Mogil discussed the role of telomeres in chronic pain development. Telomeres are repeat sequences of DNA at the distal ends of chromosomes that lose copies as cells divide. Telomere length has been associated with cellular and actual mortality. Individuals with shorter telomere length, due to genetics or environmental influences, are known to have shorter relative lifespans compared to people with longer telomeres (200). Dr. Mogil's lab recently found that telomere length is associated with pain threshold in male mice only and that

chronic pain shortens the lifespan of male, but not female, mice with short telomeres (Muralidhara et al., unpublished). More research is needed to fully understand the mechanistic basis of this sex difference.

Pain memory is currently one of the biggest topics in pain research. This is the concept that chronic pain can be thought of as a phenomenon related to the memory of an adverse, painful experience. Conditioned pain hypersensitivity models are used in rodents to study this phenomenon by subjecting animals to a painful stimulus, such as a heat beam on the paw, and coupling this experience with nausea induced by acetic acid. Placing the animal back into the same laboratory context the following day increases the animal's sensitivity to the same heat stimulus, whereas animals placed in a different context, in which they were not administered acetic acid, do not have greater sensitivity. This is presumably because they do not have a negative association with the novel context of the second heat beam exposure. Importantly, conditioned pain sensitivity in mice is a male-specific phenomenon. A similar experiment can be performed in humans, wherein subjects are tested for thermal sensitivity and simultaneously administered a painful submaximal tourniquet test in which a blood pressure cuff is tightly wrapped around the subject's arm and they are asked to exercise their arm for 20 minutes. The following day the subjects are asked to return to the lab, wherein they presume they will be subject to both the thermal sensitivity and submaximal tourniquet test. However, on day 2 subjects only receive the thermal sensitivity test and return to either the same testing room with the same experimenter as day 1, or they go to a new building with a new experimenter. Men, but not women, who return to the same context as day 1, wherein the thermal sensitivity test was paired with the painful submaximal tourniquet test, were hypersensitive to the thermal sensitivity test, similar to what is seen in male mice. Further inspection of the data reveals that the sex and context-specific differences seen in this experiment are due to higher reported stress levels in men returning to the same context on day 2 expecting to experience the painful tourniquet test (201). This study illustrates the potential links between pain and stress and how these associations may be sex specific.

Challenge Question: What can we do to better prevent OUD in chronic pain patients?

Dr. Mogil's appeal to develop less addictive, non-opioid treatments for pain was echoed throughout the meeting by many other experts. In addition, many speakers expressed concern related to the lack of training and education that clinicians receive for prescribing potentially dangerous opioid pain medications. Training clinicians would enable better appreciation for what presentation of OUDs look like in men versus women and could lead to earlier interventions.

Neurobiology of opioid addiction: intersections with pain and stress

In her Capstone lecture, Dr. Nora Volkow, Director of the NIDA, explained that the molecular target of all opioid pain medications, heroin, and methadone, is the mu opioid receptor. She noted that some of these drugs may interact with other receptors, but it is the mu opioid receptor that is mainly responsible for the analgesia and rewarding effects that can lead to addiction in vulnerable individuals. There are three different forms of receptors for endogenous opioids: 1) the delta opioid receptor, which according to Dr. Volkow has a predominant role in the regulation of mood (decreasing anxiety and depression), generating a sense of happiness, and a complex but poorly understood role in analgesia (202); 2) the kappa opioid receptor which generates dysphoria, anxiety, and distress when activated; and 3) the mu opioid receptor, which as mentioned above, regulates reward and produces analgesia (58). Dr. Volkow explained that when you take a medication for pain, it not only inhibits pain

signaling, but also activates the sensation of reward. These two phenomena happen simultaneously and thereupon, according to Dr. Volkow, lies the big challenge of using these medications and why under certain conditions they can result in addiction even when properly prescribed.

Mu opioid receptors are located in multiple areas of the brain, but they are particularly concentrated in areas that are part of a circuit including the periaqueductal gray (PAG; an important area for pain circuitry), the thalamus (which filters and relays relevant signals to higher-order brain regions), the nucleus accumbens (the main reward center of the brain), and the cortex (which allows awareness of sensation). Dr. Anne Murphy, Professor at Georgia State University, notes that the mu opioid receptor is highly promiscuous. It is found in the brain, spinal cord, periphery, and GI system, which is why there are negative side effects associated with opioid consumption – because these drugs are working in so many diverse areas.

Young women have higher expression of mu opioid receptors in several regions of the brain compared to men, including the prefrontal cortex, anterior cingulate cortex, temporal cortex, parietal cortex, caudate, cerebellum, and amygdala (203). Mu opioid receptor expression declines to male-like levels in menopausal women (203), potentially suggesting hormonal mediation of mu opioid receptor expression in the brain. A study presented by Dr. Volkow demonstrated that estradiol increases mu opioid receptor activation in the thalamus, nucleus accumbens, amygdala, and hypothalamus in response to pain, suggesting that fluctuations in hormones due to menopause might lead to enhanced pain sensitivity in older women (204). Conversely, studies have shown that women have lower kappa opioid receptor availability for the endogenous opioid dynorphin than males, which could mediate increased anxiety and distress associated with pain in women and perhaps contribute to gender differences in pain catastrophizing (205). Given the moderating effect of pain catastrophizing and its possible predictive value for opioid prescription, it has been suggested that treatments for pain catastrophizing may hold specific therapeutic value for females at levels considered clinically subthreshold for outpatients with chronic pain (206). Dr. Volkow suggests that this sex difference in kappa opioid receptor availability might explain why women are more vulnerable to comorbid mood disorders and chronic pain.

Given that women are far more likely than men to experience chronic pain and that opioid-based analgesics are the most common treatment to alleviate persistent pain, Dr. Anne Murphy posed the question, “does morphine produce the same level of pain relief in males and females?” She began answering this question by noting that most animal models and experimental assays assess *acute* pain, which are poor models for determining sex differences in opioid responsiveness, as opioids are prescribed for moderate to severe, *chronic* pain conditions. She argued that pain researchers need to focus on more clinically relevant models. Studies quantifying opioid consumption following surgery found that males typically consume more morphine than females for post-surgical pain modification (207, 208), which has been interpreted by some as evidence that females experience less pain. However, females experience more negative side effects following opioid consumption (209), which dampens their drive to self-administer morphine for post-surgery pain. Dr. Murphy’s lab models chronic pain to assess whether there are differences in morphine analgesia in male and female rats and their data have consistently shown that morphine produces greater analgesia or pain modulation in males compared to females (210-212). These sex differences in response to morphine are not due to sex differences in baseline pain sensitivity or estrus cyclicity. Dr. Murphy said that her data suggest that there is something inherently different about males and females in terms of how their central nervous systems respond to morphine.

The periaqueductal gray (PAG) is a midbrain structure that is the primary control center for pain responses. It has an extremely high density of mu opioid receptors. Dr. Murphy’s research group has shown that there are large sex differences in mu opioid receptor expression in this region, with males expressing higher densities of this

important pain-modulating receptor (211). This is likely one of the primary factors explaining why females exhibit less analgesia than males in response to morphine and other opioid pain relievers.

Another mechanism mediating sex differences in morphine responsiveness involves microglia, the brain's resident immune cells. When microglia become activated they release pro-inflammatory cytokines and chemokines to combat pathogens. In addition to binding to the mu opioid receptors on neurons in the PAG, morphine also binds to a receptor located on microglia called the toll-like receptor 4 (TLR4) (213). When opioids bind to TLR4 receptors on microglia, it causes these cells to release a variety of cytokines, including tumor necrosis factor (TNF). TNF binds to the TNF receptor on PAG neurons, resulting in a change in neurotransmitter signaling causing decreased inhibitory and increased excitatory signaling in the PAG (213). Dr. Murphy explained that typically morphine works through creating hyperpolarization (inhibition) of neurons, which is needed to block pain. However, in the presence of neuroexcitability induced by TLR4 activation on microglia, morphine does not produce strong inhibition, but rather, a much weaker hyperpolarization. This weak hyperpolarization of PAG neurons is the mechanism whereby activation of microglia directly opposes the analgesic effects of morphine (210). Her lab showed that there is a greater percentage of activated microglia in the PAG of females compared to males, making morphine less effective at blocking pain in females. Blocking microglia in the PAG increases morphine's analgesic effects in females (210, 214).

The neurobiological systems regulating stress and pain intersect, which is relevant to sex differences in opioid use and misuse, as women are more likely than men to use opioids to cope with stress or pain. Dr. Rita Valentino, Director of the Division of Neuroscience and Behavior at NIDA, explained that the endogenous opioid system in the brain has opposing interactions with brain stress systems. The increased sensitivity of females to stress impacts their vulnerability to opioid use. Women are more likely than men to experience mental health disorders precipitated by stress and characterized by features of hyperarousal such as anxiety and panic disorders, PTSD, and depression (215). The stress response is orchestrated by corticotropin-releasing factor (CRF), which is released to the pituitary as well as into discrete circuits in the brain where it initiates behavioral, autonomic, immunologic, and cognitive aspects of the stress response. One key area where CRF is released in response to stress is the locus coeruleus (LC), which is the major norepinephrine-containing nucleus of the brain that sends projections to brain regions involved in mood, executive function, decision making and memory, forming the arousal system of the brain. When animals are stressed, when LC cells are exposed to CRF, or during opioid withdrawal, cells in the LC fire at a much faster rate, which results in hyperarousal in the animal. This is an adaptive state which allows animals to be hypervigilant in their environment to escape danger, however when cells are in this mode long-term, and there is no imminent life-threatening challenge, this hyperactivity of the LC can be maladaptive and resemble symptoms of stress-related psychiatric disorders. The endogenous opioid enkephalin dampens excitability caused by CRF in the LC by inhibiting neuronal activity (216).

There are several biological mechanisms that lead females to be more vulnerable to stress. First, LC neurons in females are more sensitive to CRF compared to males due to sex differences in CRF receptor signaling (217, 218). Second, neurons in the female LC do not adapt to high levels of CRF in the same way that male cells do. When CRF receptors are activated, they are internalized into the neuron's cytoplasm to reduce activity of the CRF system. This happens more efficiently in male LC neurons compared to female (217, 219). Dr. Valentino explained that there is an increased sensitivity of female LC cells to CRF and a decreased ability to adapt to excess CRF, which is seen in conditions of depression and PTSD. Another reason why females are more vulnerable to stress is because, just as in the PAG, there are fewer mu opioid receptors on neurons in the LC in females compared to males (220). This means that the endogenous opioid system of the brain can shut down excitability in the LC more efficiently in males vs. females. Exposing LC neurons to enkephalin also produces different cognitive responses in males and

females, with males exhibiting impulsive behaviors whereas females make perseveration errors (220), which might translate to impulsive drug seeking behavior in men and perseverative behavior seen in women. Dr. Valentino's work showing the imbalance of excitability in the LC may provide a biological mechanism whereby females take opioids to cope with stress to "tone down" the system and compensate for less efficient endogenous opioid signaling in stress-related brain regions.

Challenge Question: What is the biological basis for the efficacy of stress-reduction therapies in addiction prevention and treatment?

According to Dr. Rita Valentino, a function of the endogenous opioid system is to attenuate the stress response. If this system is not functioning optimally, individuals will look for other means to tone down stress. Stress reduction therapies such as exercise, yoga, and mindfulness may substitute for pharmacological use of opioids. Additionally, some of these therapies may tap into or boost endogenous opioid systems.

Dr. Kathleen Brady from the Medical University of South Carolina and her research group have shown greater hypothalamus-pituitary-adrenal (HPA) stress axis dysregulation and greater noradrenergic sensitivity in females compared to males (221-224). This may be mechanistically connected to high PTSD and affective disorder comorbidities in women. Adrenergic agents as pharmacotherapeutic interventions might be more efficacious in women compared to men. These agents include clonidine, guanfacine, and lofexidine, which are used in detox. Recent evidence suggests they might be helpful in stress-related relapses and cravings, particularly in women (223, 225).

Dr. Brady argued that psychiatric comorbidities, in particular stress-sensitive disorders which are female-biased, are a major contributing factor to sex differences in OUDs. Having an OUD is a risk factor for co-occurring mood and anxiety disorders and PTSD, particularly in women (226, 227). As mentioned above, adverse childhood events are risk factors for both SUDs and psychiatric comorbidities. Dr. Brady suggested that epigenetic mechanisms might be responsible for programmatic changes in the brain following early life trauma. A study in mice showed that exposure to subchronic variable stress caused long-term alterations in gene expression patterns related to stress regulation (228). Female mice displayed changes in DNA methylation, an epigenetic modification that represses gene expression, in the nucleus accumbens, which was associated with more depressive-like behaviors (228). Genetic manipulation of DNA-methylating enzymes enhanced female resilience to early life stress, suggesting that DNA methylation patterns are a mechanism whereby early life stress imparts long-term, sex-specific changes to the brain, altering stress and addiction circuitry (228).

Dr. George Koob, Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), began his talk by highlighting the recent increased mortality rates due to poisonings, suicides, and chronic liver disease in the US (229), which he referred to "deaths of despair." He argues that "the dark side of addiction," the negative emotional state that emerges when access to a drug or stimulus is discontinued (e.g., dysphoria, anxiety, irritability), is a neglected area that needs focused attention in addiction research. Conceptually, addiction can be divided into three stages: binge/intoxication, preoccupation/anticipation, and negative affect/withdrawal. This final stage of addiction is largely controlled by the extended amygdala, which regulates negative emotional state during stimulus withdrawal. Dr. Koob suggested that negative reinforcement is an enormous component of addiction wherein there is an increased probability to take a drug not to feel good, but to avoid feeling bad. In other words, removal of an aversive stimulus (i.e., withdrawal), increases the probability of a response (i.e., drug seeking). The

powerful incentive to avoid withdrawal was also noted by Daniel during the *Conversations with Patients* panel as a key driver of continued opioid use. Dr. Koob coined a term to discuss withdrawal called hyperkatifeia. Hyperkatifeia is defined as the increased intensity of negative emotional/motivational symptoms and signs observed during withdrawal from abused drugs (230). The term refers to the increases in emotional distress and pain experienced by addicts during abstinence (230). It represents elements such as dysphoria, irritability, alexithymia, or symptoms often described as feeling ill at ease, uncomfortable within one's own skin, or simply not hedonically normal, with symptoms historically difficult to define (230).

The extended amygdala is a network of brain regions including the central amygdala and its connections to the bed nucleus of the stria terminalis (BNST) and nucleus accumbens, which projects back to the LC and PAG. The neurochemical substrates in the extended amygdala mediate aspects of hyperkatifeia. For instance, CRF-producing cells project to the amygdala, enhancing feelings related to negative reinforcement. CRF antagonist treatment blocks many symptoms of withdrawal in animal models (231, 232). Another major player mediating negative symptoms during withdrawal is the endogenous opioid dynorphin, which is heavily expressed in both the amygdala and nucleus accumbens and binds to kappa opioid receptors (231, 233, 234). As mentioned above, kappa opioid receptor activation is aversive in both animals and humans. In addition to CRF and dynorphin, there are several other neurotransmitters that converge on the extended amygdala that lead to negative affect during withdrawal, such as norepinephrine, vasopressin, orexin, substance P, glucocorticoids and neuroimmune factors (231, 235). However, there are also substances in this region that buffer the system and act as anti-stress neurotransmitters, such as neuropeptide Y, nociceptin, endocannabinoids, and oxytocin (231, 235). Although few studies have explored sex effects during the three stages of addiction, Dr. Koob explained that the negative affect component of addiction seems to be larger in females than males in both humans and rodents (100).

Dr. Koob also discussed opioid withdrawal-induced hyperalgesia in heroin-dependent individuals, showing data that patients undergoing withdrawal are significantly more sensitive to pain sensations than non-users (236). Importantly, this withdrawal-associated hypersensitivity to pain persists for up to 12-18 months after the individual experiences withdrawal (236).

Challenge Question: What gaps need to be addressed between basic neurobiology research and clinical data?

Dr. Murphy explained that using only male animals in basic and preclinical research has limited our understanding of how drugs affect the larger population. Male animals are a poor model for studying pain and opioid addiction, since the majority of opioid-prescribed pain patients are female. Drs. Valentino and Koob think we need to focus more on systems regulating negative affect to better understand addiction and to develop interventions that combat withdrawal. Dr. Koob urged animal researchers to base animal models of addiction on clinical laboratory studies.

Treating opioid use disorders

Medication-assisted treatment (MAT), which combines behavioral interventions with pharmacotherapy, is the most effective therapy for OUDs (237), although there are significant disparities on the state and national level between the need for MAT and its availability (238). 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 and can be dangerous (239). 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 (240-243). Access to buprenorphine and naltrexone also requires a prescription, thus insurance coverage, cost, and availability of prescribers are roadblocks to accessing these life-saving treatment option (244-246). Women seeking treatment for OUDs 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 they become pregnant (247).

Psychosocial treatments should accompany use of pharmacological interventions to treat OUDs. Counseling interventions combined with MAT increase the likelihood of successful addiction recovery (248). 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 (249). The goal of these treatments is to provide support to patients during recovery, to encourage 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 pharmacological interventions (248). These knowledge gaps must be filled to help determine which pharmacological/psychosocial treatment combinations are most effective for specific populations.

Dr. Hendrée Jones of UNC Chapel Hill presented data on buprenorphine and methadone maintenance efficacy. When randomly assigned to receive buprenorphine (4 or 12 mg) or methadone (20 or 65 mg), women had higher rates of abstinence from illicit opioids, better retention, and fewer opioid-positive urine samples compared to men (250). When randomly assigned to buprenorphine, levomethadyl (LAAM), or methadone, women receiving buprenorphine had less objective drug use than those receiving methadone (251). Within-subjects analysis revealed that all three medications benefit both sexes (251). Sex differences in side effects of opioid agonist medications like methadone and buprenorphine have also been reported with greater body mass index (BMI) increases and constipation scores in women compared to men (252, 253) and larger declines in bone density occurring in men vs. women (254).

One study found that women report more adverse side effects than men when taking naltrexone (255), a medication designed to keep individuals in treatment drug free by blocking the effects of opioids. Together these findings indicate that pharmacological interventions to treat OUD and maintain opioid abstinence may be more efficacious in women than men and side effects may differ by sex. A study of the long-term outcomes of methadone treatment on opioid abstinence revealed that 25 years after being treated with methadone for heroin dependence, none of the surviving female study participants were using heroin vs. 31.1% of the surviving males (256). However, it should be noted that men accounted for 76.2% of the study population, there was high mortality in the group, and 39.6% of the surviving study population were still enrolled in methadone treatment programs (256). In a 7 year follow up of patients prescribed buprenorphine, 64% of participants were retained in the program, employed and abstinent from drugs (257). In this study, women were more likely than men to have stopped heroin use and had a higher rate of continuous absence and employment retention (257). Further, all women in the study had regained custody of their children and there were fewer women imprisoned and in non-institutional care compared to men over the course of the 7-year study (257).

Data from the National Drug Abuse Treatment Clinical Trials Network comparing 7 vs. 28-day buprenorphine and methadone tapering strategies found that women typically do not respond as well as men to tapering and are more likely to use opioids during the course of tapering (258). In addition, this study found that medical issues were more likely to predict opioid use during treatment for women but not for men (258). Relationship power

dynamics are an important influence on treatment adherence in women, as individuals with greater household decision making power have more days abstinent than those with less household power (259).

Women and men typically enter treatment at different stages of their addiction according to data presented by Dr. Jones. By the time women present to treatment they have a wider array of more severe problems including financial, family, medical, and psychiatric issues (260, 261). Men typically present to treatment with more legal and conduct issues. Upon treatment entry, women are typically younger than men, are more likely to identify as bisexual, live with a sexual partner, and have had a shorter duration of use compared to men with a similar age of onset of use (260, 261). Dr. Jones also addressed gender-related disparities in preventing overdose deaths. Women are less likely than men to received naloxone overdose reversal (262), although women are more likely to accept and receive naloxone kits than men (263).

Challenge Question: Do men and women respond differently to treatments and what is the current understanding of the basis for these differences?

Dr. Greenfield stated that in most instances, treatment for opioid use disorders are generally effective in both men and women, although outcomes can vary by type of treatment. She noted that predictors of treatment outcome vary by gender. These predictive factors include trauma, co-occurring psychiatric disorders, employment, education and social support. Dr. Greenfield also briefly discussed the Prescription Opioid Addiction Treatment Study (POATS), the largest study of prescription opioid addiction treatment. This study, conducted by NIDA's Clinical Trial Network, showed no gender differences in opioid dependence severity or treatment outcome; however, it revealed that women had greater functional impairments, severity of psychiatric disorders, and were more likely to use prescription opioids to cope with negative affect and pain, whereas men had more opioid cravings and alcohol misuse compared to women (4, 5). These differences may lead to clinically significant differences in long-term treatment retention and outcomes.

Dr. Barth focused her talk on the challenges associated with treating OUD in chronic pain patients. She pointed out that women are more likely to start opioid use in medical settings but are less likely to enter traditional substance use treatment programs. As previously mentioned, opioid misuse can escalate very quickly into use disorder in women, making it difficult to tell whether a patient has poor functioning because of chronic pain or because of OUD. This makes it very difficult to diagnose OUDs in patients seeking treatment for chronic pain. Further, there is currently no "exit plan" for the estimated 7 million patients who are poorly functioning with chronic pain on opioids and do not clearly meet the criteria for OUD. Even following non-fatal opioid overdoses, chronic pain patients are often put back on the same opioid pain medications because there is no good alternative plan for pain treatment. Evidence-based treatments for chronic pain, including psychotherapy, exercise therapy and comprehensive pain rehabilitation, are highly effective long-term treatments for chronic pain conditions; however, these programs can be prohibitively expensive and require time away from work and other responsibilities, making access very difficult. Dr. Barth noted that in the present clinical culture it is easier for both the patient and the provider if providers prescribe medications instead of attempting to access alternative treatment options.

Acceptance and commitment therapy is a proven form of cognitive behavioral therapy that focuses on mindfulness (264). It focuses on accepting unpleasant experiences while increasing engagement in value-oriented life activities. The formula used in this type of therapy is *pain* x *resistance* = *suffering*. Pain might not be controllable, but mental resistance and acceptance can be used to decrease suffering. Interestingly, data suggest that the efficacy of this form of therapy is high in women, but low in men (265). Exercise therapy improves both

pain and function but may work differently based on the individual's gender. A study looking at pain tolerance after engaging in a competitive sport (exercise/physical activity) or videogame (sedentary activity) revealed that women experience less pain after physical activity, whereas pain seems to be reduced in males by competition (266).

Comprehensive pain rehabilitation programs incorporate recommended evidence-based pain management, including physical, occupational, and psychotherapy and bundle co-pays. These programs have been shown to restore function and improve long-term quality of life, including improved pain and function, lower health care utilization, significant decreases in medical costs, and opioid discontinuation (267). According to Dr. Barth, by relieving pain effectively while avoiding prescription opioids, these programs are needed to address the opioid crisis, particularly in women who are more likely to experience chronic pain and less likely to enter traditional treatment programs.

Integrated, multidisciplinary treatment approaches to chronic pain can prevent initiation of opioid use, prevent unnecessary and expensive surgeries, and provide a civilized way to discontinue opioids while addressing pain. Dr. Barth recommended changing the culture of chronic pain treatment, especially for women, by improving access and availability to evidence-based pain care, by improving insurance coverage for non-pharmacologic interventions and integrating evidence-based pain treatment into addiction treatment centers.

Challenge Question: In your professional opinion, how can we better reach underserved populations and institute gender-focused addiction treatment programs?

According to Dr. Jones, we already know that comprehensive care works, but efforts need to be more focused on addressing the needs of the individual by taking into account sex, gender, and gender identity in OUD treatment approaches. To do this, there needs to be structural changes at the federal, state, and county levels, such that availability and financing for substance use treatment and recovery programs, particularly medications for OUD, are accessible to those in need. Dr. Jones asserted that we need to do a better job of assessing our policies not only through a sex and gender lens, but also through a gender identity lens, as gender identity minorities are at a higher risk for substance use. We need to continue to collect and disaggregate data by sex and gender, train healthcare workers to recognize SUDs as serious illnesses, provide a living wage to all types of behavioral and physical health providers, including adequate reimbursement for all substance use disorder treatment, recovery and prevention services. Finally, Dr. Jones suggested that we need more integrated funding streams that can better ensure compressive prevention and care and evidence-based insurance coverage policies to sustain treatment and recovery.

Opioid use and treatment during pregnancy and the postpartum period

The National Survey of Drug Use and Health found that 2.3% of reproductive aged women and 0.8% of pregnant women reported non-medical opioid use in the past 30 days (268). Pregnant women use fewer substances than non-pregnant women and use decreases by trimester with the largest decrease happening prior to pregnancy through the first trimester, although these patterns differ by substance. Dr. Anthony Campbell from the Center for Substance Abuse Treatment at the Substance Abuse Mental Health Services Administration (SAMHSA) said that pregnancy presents a unique window of time to reach women with SUDs. The earlier in pregnancy a woman stops or reduces substance use, the more likely there is to be a positive outcome, not only for her but also for her child. He encouraged researchers, health care advocates, and providers to read SAMHSA's new treatment

guidance issued for pregnant and parenting mothers with OUD (269). Opioid use during pregnancy poses a risk for neonatal abstinence syndrome (NAS). NAS is a group of physiological and neurobehavioral symptoms of withdrawal that can occur in newborns exposed *in utero* to psychotropic substances, such as opioids. In 2000, neonatal opioid withdrawal impacted 1 out of every 1,000 births but by 2015 this number grew to 5-6 of every 1,000 births (270, 271). Some states including West Virginia and Maine had greater than 30 cases of NAS per 1000 births in 2012-2013 (271).

Dr. Mishka Terplan of Virginia Commonwealth University began his presentation by posing the question, "what happens when women who use drugs get pregnant?" Dr. Terplan noted that women cut back on alcohol the most, cigarettes the least, and opioids and other illicit drugs somewhere in between. He said the data suggest that all pregnant women are motivated to maximize their health and that of their baby-to-be. All engage in behavioral change. Some women can stop using and others can't; those who can't likely have a use disorder. He said that pregnancy can be thought of as a natural experiment which differentiates use from use disorder.

How is substance use identified in pregnant women? Assessments should be universally performed across all domains of healthcare including but not limited to prenatal care and should not be based on selective screening, which can perpetuate discrimination. Dr. Terplan stressed the importance of asking permission prior to screening to build a therapeutic alliance upon which healthcare for addiction treatment can thrive. There are multiple validated screening tools available including questionnaires like the T-ACE (272), TWEAK (273), DAST and MAST (274), 4P's Plus (275), and CRAFFT for pregnant adolescents (276). Urine tests are an essential part of treatment, but not a screening test for addiction, as urine does not give information about behaviors related to addiction. There are also several limitations to urine tests, including their binary results, substance-dependent detection window, and potential for false positives and negatives. Dr. Terplan asserted that urine is not a test of parenting fitness, although it is often used as such.

Challenge Question: What care is needed to treat substance use disorders in pregnancy?

Care should be evidence-based and person-centered. This essentially means that pregnant women with SUDs should receive integrated pharmacotherapy and prenatal care through the postpartum period.

Dr. Jones stressed the importance of training the next generation of healthcare providers to recognize and identify SUDs, to understand that these disorders are brain illnesses, to know which treatments work, and who in their community can provide MAT. She says, "… what I often hear is, *I don't want to screen. I don't want to know the answer because if I get a yes, what do I do?"* Giving the next generation of providers the tools to know what to do is a means to address care access in the future.

Integrated treatment for pregnant women with SUDs consists of medication plus behavioral counseling in the context of prenatal care. This system of integration has been the gold standard of care since the 1970s, and studies have shown that maternal outcomes are identical between women treated for addiction versus those without addiction (277-280). Dr. Hendrée Jones explained that use of methadone, buprenorphine, and naltrexone is considered in-label for use during pregnancy, contrary to what many people believe. She continued by reiterating that we already know what's needed to treat addiction in pregnancy and have effective principles of addiction treatment, one of which is that effective treatment attends to multiple needs of the individual not just his or her use disorder. The problem, she noted, is that women are scared to go into treatment. They are scared that Child Protective Services is going to take their child or that they will end up in jail or in an incarcerated setting. In addition

to fears related to opioid use and parental fitness, access to treatment, as noted above, can be challenging and these difficulties are often exacerbated by the familial responsibilities assumed by women.

As previously discussed, current medication options include methadone, buprenorphine alone, buprenorphine plus naloxone, and naltrexone. Dr. Nora Volkow highlighted an important study by Dr. Jones and colleagues showing that infants of mothers that received buprenorphine during pregnancy had shorter hospital stays (10 vs. 17.5 days), shorter durations of NAS (4.1 vs. 9.9 days), and required less morphine to treat NAS than infants of mothers that received methadone (281). During her presentation, Dr. Jones pointed out that both methadone and buprenorphine are safe and effective for mothers and babies (281). Meta-analyses have reported moderately strong evidence of lower risk of preterm birth, greater birth weight, and larger head circumference with buprenorphine compared to methadone for babies born to mothers with OUD (282, 283). Dr. Jones stated that these findings do not mean we need to switch mothers-to-be from methadone to buprenorphine, but instead we need better patient-treatment matching, which should be an area of research that receives more attention. Studies have shown that there are no apparent benefits to the combination product, buprenorphine plus naloxone, in terms of maternal and NAS outcomes (284), however, there have not been randomized controlled trials with side-by-side comparisons looking at the safety and efficacy of these medications.

Medically-assisted withdrawal or detoxification is commonly thought to increase the risk of early fetal loss, premature delivery and other deleterious outcomes. Dr. Jones reported that the literature does not actually support this, however, detoxification is not recommended because it is associated with an increased risk of maternal relapse and poor treatment engagement and does not improve the health of the baby (285). Treatment of chronic maternal disease, including OUD, should be directed toward optimal long-term outcomes. According to the 2014 World Health Organization Guidelines, “pregnant women dependent on opioids should be encouraged to use opioid maintenance treatment whenever available rather than to attempt opioid detoxification.” (286)

There is much less known about naltrexone use during pregnancy, however, the increased use of long-acting naltrexone formulations will likely increase the chances that women will become pregnant while using naltrexone. Preliminary clinical studies have not associated adverse fetal events with naltrexone use during pregnancy, but preclinical studies report mixed results (287). Dr. Jones acknowledged that questions surrounding naltrexone use still exist, such as the potential for precipitated withdrawal and exacerbation of opioid-related neuroendocrine dysregulation. We still need to know the relative safety and efficacy of naltrexone for the maternal-fetal dyad and potential long-term impacts of naltrexone on children born to mothers using this medication while pregnant.

The Maternal Opioid Treatment: Human Experimental Research (MOTHER) study assessed child outcomes up to 36 months after birth following prenatal exposure to opioids to determine long-term developmental outcomes. The study found no differences in physical or behavioral development supporting medication superiority and no differences in infants treated for NAS versus untreated infants (288). The findings suggest that children born exposed to opioids follow a path of normal development in terms of growth, cognition, and psychological development. However, Dr. Jones mentioned that the environment in which children are raised may explain outcomes better than prenatal exposure to opioids alone, implying the importance of considering research methods when assessing studies on childhood outcomes.

Children growing up around family members with active addiction are at greater risk for SUDs themselves (289, 290). Dr. Jones briefly spoke about how children are now at greater risk for taking opioids. In fact, pediatric poisonings (including opioid overdoses) have doubled from 1997-2012 (291). Although younger adult men and older adult women are the most likely population subsets to misuse opioids, among children and adolescence, 10-18 year-old girls outnumber boys in medication misuse (174, 292).

Challenge Question: What is the current landscape of treatment received by pregnant/postpartum women?

Most women receive no care during pregnancy. For those that do, care is often discontinued postpartum.

Pregnant women are a priority population within federal statutes and regulations (2), which means that they are given priority to treatment at any point during pregnancy. Pregnant women do not need to meet DSM criteria for use disorders to received MAT. However, whereas pregnant women with past month drug use are more likely to meet criteria for a use disorder, they are no more likely to receive treatment than non-pregnant women (7). Dr. Terplan stated that most pregnant women do not receive treatment for OUD because adequate treatment capacity does not exist. He found that women-centered treatment services and services for pregnant and postpartum women in drug treatment facilities declined between 2002-2009 (8). Even if women are in treatment, they may not receive evidence-based standard of care. A recent analysis suggests that only about half of pregnant women in treatment received pharmacotherapy despite the evidence that it improves both maternal and child health outcomes (9).

Importantly, Dr. Terplan argued that the relationship between opioids and maternal mortality has not been adequately studied. Global maternal mortality rates have declined since 1937 (293), but in the United States maternal mortality rates have recently increased between 2000 and 2014 (294). In states that have performed in-depth analysis, data show that at least 20% of all maternal deaths are related to overdose (295).

Dr. Christine Nguyen from FDA CDER provided an overview of the regulatory strategies used to inform safe and effective use of treatments for both opioid and nicotine use disorders in pregnant women and lactating women. As noted above by Dr. Jones, when drugs are approved by FDA for adult use, they are also approved for the same use in women who are pregnant or lactating, unless otherwise contraindicated in these populations. Although pregnant and lactating women are usually not included in clinical trials to assess a product's efficacy, the product's efficacy findings in non-pregnant individuals are extended to those who are pregnant or lactating. Up until recently, drug safety in pregnancy has been summarized in the drug label by the letter category – A, B, C, D, and X. With the 2015 implementation of the new labeling rules under the Pregnancy and Lactation Labeling Rule (PLLR), these letter categories will be removed from all drug labels removed by 2020. In their place will be standard sections that contain narratives on safety information of medications during pregnancy and lactation. These new drug label sections are: 1) Risk Summary, which integrates the assessment of risks to pregnancy or during lactation; 2) Clinical Considerations, which includes dose adjustment information, if available; and 3) Data from clinical and nonclinical sources that support the information provided in the Risk Summary section. Although PLLR requires FDA to include available evidence on drug labels, reliable clinical evidence of safe use in pregnancy and lactation is often lacking.

Dr. Nguyen next discussed selective drug labels for OUD treatments. For methadone, the Risk Summary section includes expected and treatable NAS, but mentioned that there are no adequate, well-controlled trials in pregnant women. Under Clinical Considerations, the label indicates that there is pharmacokinetic clinical evidence that supports dose-adjustments. The Data section describes findings based on multiple studies that FDA has reviewed suggesting no signal teratogenicity or miscarriage, and inconclusive signals of premature delivery, decreased fetal growth, mild persistent deficits in childhood tests, and visual developmental anomalies. Clinical data on methadone use during lactation indicate that low methadone levels can be measured in nursing infants; therefore, infants should be monitored for drowsiness and breathing difficulties. Dr. Nguyen also summarized the limited safety information in pregnancy and lactation in the drug labels for buprenorphine and naloxone. As mentioned

above for smoking cessation treatments, knowledge gaps in opioid agonist treatment safety and efficacy in pregnant and lactating populations are considerable and include specifics of dosing adjustments, limitations to the quality and quantity of safety data, sparse clinical trial data, and a lack of information on the long-term outcomes of fetuses exposed to drug treatments *in utero*. These gaps leave prescribers without evidence-based information to guide clinical decisions. Addressing these gaps is a critical public health need.

Challenge Question: How are we working to improve knowledge of the safety and efficacy of treatments used in pregnancy and during lactation?

The 21st Century Cures Act passed in December 2016 established the Pregnant Women and Lactating Women (PRGLAC) Task Force to identify, address, and provide recommendations to fill knowledge gaps in research regarding the safety and efficacy of therapies in pregnant women and lactating women. This was the first time a federal mandate was issued to address these critical gaps. Fifteen recommendations were put forward by the task force, all centered on changing the culture of integrating pregnant women and lactating women into the research agenda. In April 2018, FDA issued a draft guidance titled, Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials. The guidance contains recommendations on how and when to include pregnant women in drug development, and it discusses the ethical and scientific issues related to including pregnant women in clinical trials. FDA considers it ethically justifiable to enroll pregnant women in research when it is conducted in a pre-approval setting where adequate nonclinical studies have been completed, there is a potential for a direct benefit to the mother and/or the fetus, and treatment is not available outside of research or by any other means. Pregnant women may be considered for enrollment in post-market trials if adequate nonclinical studies have been completed, there is an established safety database in nonpregnancy women or preliminary safety data in pregnancy, and efficacy cannot be extrapolated and/or safety cannot be assessed by other study methods, such as through observational studies.

Federal landscape of research and policy on opioid use and misuse

The U.S. Department of Health and Human Services (HHS) outlined five strategies to address the opioid addiction and overdose epidemic. First, HHS seeks to provide better access to prevention, treatment, and recovery services. Second, HHS wants targeted distribution of overdose-reversing drugs, such as naloxone. Opioid overdoses frequently occur in places where naloxone is not readily available. Research and practice development is needed to ensure that there is larger distribution of naloxone to the community. NIDA and NIH are focused on improving access to naloxone, including prioritizing development of new formulations of the lifesaving drug that can be distributed to the public. This includes new research initiatives to combat the rise of fentanyl-related overdoses via longer-acting and more potent forms of naloxone and research on other potentially lifesaving interventions and devices. Third, HHS's strategy includes collecting more timely and specific public health data on the epidemic. Fourth, HHS calls for better pain management strategies.

Dr. Wilson Compton, Deputy Director of NIDA, postulated that if excess prescribing led to the opioid crisis, then changing the availability of opioids by providing new, less harmful treatments for pain and focusing on diverting unused opioids away from unintended users should improve the current crisis. In addition, more research on addiction and pain is needed to fully address the issue. Dr. Compton stressed the importance of ensuring that our current technologies have widespread implementation and that improvements are executed based on need. He emphasized his excitement regarding the recent HHS funding increase, whereby $500 million was allocated to NIH

to spearhead new research in the areas of pain and addiction. This represents an opportunity for NIH to increase allocation of resources toward research to inform policy and practice related to the opioid crisis.

HHS agencies work together closely on several levels. Agencies meet regularly to share information and prevent duplication, including meetings of the Drug Safety Board and Interagency Working Groups. FDA works with NIH to identify new endpoints for MAT, and there are many other research initiatives and opportunities between federal agencies and with external partners. Dr. Compton highlighted a collaboration with CDC, SAMHSA, and the Appalachian Regional Commission to fund research around the country on how best to organize and implement prevention and treatment services related to infectious disease transmission via intravenous drug use. Further, he highlighted recent NIH-funded research findings on how relapse rates can be decreased by initiating buprenorphine treatment in emergency departments (296) and prescribing extended release naltrexone in criminal justice settings (297, 298). Dr. Scott Winiecki described FDA's Safe Use Initiative (299), which funds research to reduce preventable harm from drugs by partnering with researchers outside of FDA, in other federal agencies, academia, and healthcare professionals. These studies and initiatives represent examples of how research can influence future public policy.

Challenge Question: What is being done to prevent new opioid addiction?

Dr. Campbell emphasized SAMHSA's focus on the Screening, Brief Intervention, and Referral to Treatment (SBIRT) model and educating current and future providers about how to screen for and recognize potential drug abuse. Dr. Winiecki answered the same question by stating that we should not be exposing patients to opioids who don't truly need them, asserting that in some cases Tylenol and ibuprofen have the same or better pain controlling effects with fewer side effects. Dr. Compton acknowledged a need to address opioid supply and aim educational efforts at middle and high school aged adolescents.

During his Keynote speech, Commissioner of Food and Drugs Dr. Scott Gottlieb remarked that a key element of FDA's effort to address the opioid crisis involves taking steps to reduce the rate of new addiction by decreasing overall exposure to opioids in medical settings and fostering more rational prescribing. He went on to express FDA's mindfulness of patients' legitimate needs for pain-relieving prescriptions and noted that prescribers may not have been sufficiently informed of the intensely addictive nature of opioid medications, leading to practices of overprescribing, and thus fueling the opioid crisis. He urged the audience to be mindful of this history, to learn from it, and to make sure we act aggressively to confront new trends that may continue to fuel the current crisis or lead to new epidemics of addiction. Dr. Gottlieb emphasized the necessity of identifying groups most at risk for developing OUDs and the importance of recognizing that men and women may develop and experience OUD differently.

Dr. Winiecki spoke about FDA's role in addressing the opioid overdose epidemic. FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, for advancing public health by helping to speed innovations, and for helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health (300). One of FDA's highest priorities is advancing efforts to address the crisis of opioid misuse and abuse. To do this, the Agency is working across the full scope of its regulatory authority. FDA's approach to reducing misuse and abuse of opioids is outlined in FDA's 2018 Strategic Policy Roadmap (301). FDA's priorities parallel HHS's priorities mentioned above and include: decreasing exposure and preventing new addiction, supporting the treatment of those with OUDs, fostering the development of novel pain therapies, improving enforcement and assessing benefit-risk. To decrease exposure and prevent new addiction, FDA is working to facilitate appropriate prescribing practices and soliciting

public input from physicians, prescribers, families and patients. In addition, FDA is evaluating indication-specific dosing to help inform prescribers. The goal is for patients to receive a sufficient number of pills to address their need for pain relief while minimizing the number of surplus opioids, which can be diverted towards misuse or abuse. The Agency is also exploring how products are packaged, stored, and discarded to ensure that opioids are dispensed in appropriate amounts and are disposed of safely. FDA is also considering whether mandatory education is appropriate. A new Risk Evaluation and Mitigation Strategy (REMS) program will make voluntary training available at low- or no-cost for physicians and other healthcare professionals such as nurses and pharmacists. This training will address the broader topic of pain management, including pharmacologic and non-pharmacologic treatments. To support the treatment of those with OUD, FDA is exploring ways to expand access to naloxone by facilitating a switch from prescription to over-the-counter naloxone, prioritizing the development of new MAT options, taking steps to promote more widespread use of FDA-approved MAT pharmacotherapies, and joining efforts to break the stigma associated with medications used for treatment of addiction. To foster the development of novel pain treatment therapies, FDA is expanding the use of partnerships with non-profits, utilizing public input and advisory committees, collaborating with agencies across HHS, and supporting the development of innovative abuse deterrent formulations (ADFs). Opioid ADFs are not less addictive than traditional prescription opioids, but they may be more difficult to abuse because they are harder to crush and dissolve. In terms of improving enforcement, FDA is considering how to fully leverage its seizure and import authority in collaboration with U.S. Customs and Border Protection. There is a concerted effort to reduce the quantity of opioids being smuggled into the U.S. at international mail facilities and via illegal online sales.

Dr. Campbell spoke about the importance of considering the intersection of SUDs and mental health conditions. He emphasized that pregnant and postpartum populations are of particular interest to the Administration and mentioned the development of new guidelines for these populations. As described above, though the data are sparse, treating SUDs in pregnant and postpartum women provides measurable benefits to both the mother and infant.

Challenge Question: Are there opportunities to consider sex and gender in research and policy from your agency's perspective?

Dr. Winiecki discussed FDA's Drug Trail Snapshots website (1), which displays demographic information on clinical trial participants for new molecular entities and highlights whether there are any differences in the benefits or side effects of a drug among gender, race, and age groups. Drug Trial Snapshots is part of a widespread effort by FDA to make demographic data more available and transparent, and Snapshots are posted within 30 days of drug approval. As an example, Dr. Winiecki displayed the webpage for lofexidine, a drug used to lessen the symptoms associated with opioid withdrawal following abrupt opioid discontinuation. This is a drug in which women experienced more adverse side effects than men at higher treatment doses in the clinical trials. He noted that these differences wouldn't be noticed in clinical trials if FDA didn't require sponsors to look for them. Understanding how certain drugs affect men and women differently could have clinical significance, such that prescribing and treatment could be tailored by both indication and gender/demographic criteria.

Utilizing social media to gain real-world insight into opioid addiction

Dr. Christine Lee from FDA CDER Professional Affairs and Stakeholder Engagement (PASE) spoke about utilizing social media as a potential real-world data source on drug use and recovery. She began her presentation recounting her own experiences using social media to search for answers to health-related questions for her family. She noted that people often turn to social media in times of despair and when they are in need of answers

or insider information from others with shared experiences that doctors might not be able to provide. Traditional outcomes-focused research utilizes data sources such as focus groups, interviews and surveys to understand patient experiences. Social media offers a unique opportunity to capture unfiltered patient voices to better understand unmet patient needs. FDA recognizes the importance of incorporating patient experiences into regulatory decisions by considering patient input in clinical trial design, trial endpoint development and selection, regulatory reviews, and benefit-risk assessment.

Three patient-centric initiatives stand out for their low cost/high benefit and ease of implementation. These include advocacy group support and involvement, patient advisory panels and focus groups, and social media and online engagement. A recent PASE project had the following two objectives. First, to support CDER and FDA strategic priorities to understand the patient's voice by systematically gathering patient perspectives on their conditions and available treatments. Second, to support CDER and FDA's strategic priorities by understanding the audience and gaps in communication. A major challenge for Dr. Lee and her group was utilization and mining of unstructured, qualitative data. An additional challenge was determining if the data collected through traditional sources and social media were representative of patient populations. Thus, although FDA has access to many sources of unstructured data, such as advisory committee transcripts, docket comments, and social media, the scientific rigor of analyzing unstructured data is a challenge.

Pilot studies conducted by PASE research team members sought to increase scientific rigor of data utilization from structured and unstructured sources. The team developed a code book to translate qualitative data on topics such as stigma, access to care, and barriers into quantitative computational entities to eliminate subjectivity and make the data as objective as possible. Through their work, the team encountered several challenges and considerations for working with data derived from social media, which is clearly not configured for research purposes. For example, formatting the data structure from social media into a data form that can be analyzed by qualitative software was a challenging and time-consuming process. However, the project showed that social media is a promising source of support for regulatory decision making by increasing confidence in data from multiple sources, providing a more comprehensive understanding of conditions and urgent unmet patient needs, and increasing our understanding of the patient journey, individual patient experiences, progression of symptoms, and clinical outcomes.

Innovative research and outreach initiatives for preventing opioid misuse and overdose

During the meeting's *Innovative Program and Research Initiatives* session, speakers from federal agencies shared recent groundbreaking research projects that have the potential to directly impact public policy for battling addiction and overdose. Dr. Mitra Ahadpour, Principal Deputy Director in the Office of Translational Science at FDA, spoke about the Rapid Opioid Alert and Response (ROAR) system, which is a real-time identification tool for opioid overdose spikes that can provide alerts to the community about tainted heroin and other substances. The project competed with 80 other submissions to the HHS Idea Lab in 2016. Using a Bayesian method, the team established the probability distribution of reported opioid overdoses in Baltimore City and Anne Arundel County. When an opioid overdose spike occurred, an email alert was sent to the team and, through geomapping, the team could determine exactly where the overdoses were occurring. This information was then sent via an email alert to the Baltimore Health Department, who in turn sent email alerts to their networks to reach those with SUDs to inform them of potentially dangerous batches of heroin. The Director of the Washington/Baltimore High Intensity Drug Trafficking Area heard about the ROAR system and scaled up the system for their Overdose Detection

Mapping Application Program. When first responders are called to the scene of an overdose, they collect and input data to the system on the patient's suspected substance used, age, gender, if naloxone was administered, and the outcome. The system has now been implemented in 29 states.

Dr. Jack Stein, Director of the Office of Science Policy and Communications at NIDA, explained that we have very effective evidence-based interventions for SUDs, but they have not fully infiltrated communities. Integrated strategies based on needs are essential across multiple settings. He said the challenge is not only identifying individuals who are at risk but engaging them in treatment and continuing them in treatment. As a result, the NIH have taken on a broad-based initiative called Helping to End Addiction Long-term (HEAL), based on three concepts: 1) better management of pain by developing safe, effective treatments; 2) better approaches to opioid addiction treatment by developing new and innovative medications and technologies; 3) rapidly addressing the overdose problem by developing newer approaches to overdose reversal. The HEALing Communities study is an ambitious implementation research study stemming from the HEAL initiative. The goal of this study is to develop an evidence-based strategy that reduces overdose fatalities by 40% in 3 years across communities that are highly affected by the opioid crisis. The goal is to utilize effective strategies based on everything we know to date, such as better prescribing practices for pain, better provider training, better naloxone distribution, screening, access to medications, and retention in treatment. Another goal is to link community systems like the health community and justice systems such that they work together seamlessly to make an impact. Dr. Stein concluded his presentation by directing researchers to the HEAL initiative's website and to NIH's recent Funding Opportunity Announcement (FOA) for this large-scale program (302), which will consist of up to three research centers and one data coordinating center.

Dr. Michelle Tarver, Director of the Patient Science and Engagement Program in the Center for Devices and Radiological Health (CDRH) at FDA, spoke about the FDA Innovation Challenge. The Innovation Challenge is part of FDA's ongoing efforts to combat the opioid crisis and fits within HHS's Strategic Priorities. The challenge supports four key aspects of the Strategic Priorities: 1) decrease exposure to opioids and prevent new addiction, 2) support the treatment of those with OUD, 3) foster the development of novel pain treatment therapies, 4) improve enforcement and benefit-risk assessment. Over the past few years, FDA has cleared, granted, or approved more than 200 devices related to pain management. This includes 10 with new and novel technologies, such as brain and spinal cord stimulators that can be used to relieve pain and reduce the need for opiate drugs. FDA has also recently granted a new indication to an electric stimulation device for use in helping to reduce the symptoms of opioid withdrawal. The goals of the Innovation Challenge are to foster innovative and creative approaches to the use of medical devices in combatting the U.S. opioid crisis, develop non-opioid treatment for acute and chronic pain, and expedite development and review of innovative, safe, and effective medical devices to help prevent and treat OUD. Any medical device that helps prevent or treat OUD at any stage of development is eligible to apply. FDA is especially interested in devices that can help underserved populations such as pediatric populations, women, and pregnant women. The deadline for submission was September 30th 2018 with an intent to announce selected applicants in November 2018.

What can you do?

After surgery 67-92% of patients report having unused opioids. These are typically not stored in secured locations and most of the time are not disposed of properly (303). Unused opioids are often diverted and lead to someone else's OUD or addiction down the road. One way you can help is to properly dispose of opioid medications. FDA

recommends several methods of disposal including: dropping them off at a medicine take-back site or event or mixing them with unpalatable substances such as dirt, cat litter, or used coffee grounds in a sealed container and throwing it in household trash. Certain medicines can be flushed down a toilet, which reduces the risk of exposure to children and animals. For more information, visit https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/ucm186187.htm#Medicines_recommended

RADM Sylvia Trent-Adams, Deputy Surgeon General of the United States, referred the audience to the Surgeon General's Spotlight on Opioids, which provides the latest data on OUD and overdoses, a list of what effective treatment entails, and progress that has occurred to address the opioid epidemic (304). The Spotlight on Opioids calls for a cultural shift in the way Americans talk about the opioid crisis and recommends actions that can prevent and treat opioid misuse and promote recovery (304). To help the public understand the role they can play in preventing opioid misuse, the Office of the Surgeon General released a digital postcard, highlighting five tangible actions that all Americans can take to raise awareness, prevent opioid misuse, and reduce overdose deaths. The Surgeon General is calling on all individuals to: 1) talk about opioid misuse and what we can all do to prevent drug misuse and overdose, 2) be safe, by only taking opioid mediations as prescribed and making sure to store mediations in a secure place and dispose of unused medications properly, 3) understand pain by talking with healthcare providers about the correct treatment plan, including the use of non-opioid pain relievers in managing pain, 4) know that addiction is a chronic disease and with the right treatment and support, people can and do recover, and finally 5) be prepared by obtaining and learning to use naloxone, the opioid overdose-reversing drug.

Opportunities to address substance use disorders in men and women

In her concluding remarks, Dr. Marjorie Jenkins urged the audience not to unsee or unhear the critical information on the impacts and influences of sex and gender on substance use and treatment presented throughout the two-day meeting. Dr. Jenkins highlighted quotes from the meeting including, "I don't think it's been studied", "there are still research gaps", "we need more data", "we need to take a new look at the data", and "let's consider the unintended consequences of not considering sex and gender", stating that these sound like opportunities for future work to examine issues surround sex and gender in opioid and nicotine addiction.

Dr. Jenkins advised the audience to turn these opportunities into realities, to close the loop on what was discussed at the meeting into tangible activities to make an impact. When it comes to efforts to reduce SUDs, we must be willing to take a hard look at our entire approach and recognize that sex and gender matter. The science presented at this two-day meeting can help inform public policy. To this end, we are currently planning follow-up discussions with leaders in these arenas to continue our discussions and to initiate realistic, tangible outcomes.

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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) [9/2018 version]

e. Percodan (asprin; oxycodone hydrochloride; oxycodone terephithalate) [2016 version]
f. Probuphine (Buprenorphine implant) [5/2016 version]
g. Roxybond (oxycodone hydrochloride) [9/2018 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 guides for nicotine addiction

a. Chantix (varenicline tartrate) [2016 version]
b. Zyban (bupropion hydrochloride) [5/2017 version]
c. Habitrol (Film, Extended Release; Transdermal)
d. Nicoderm CQ (Film, Extended Release; Transdermal)
e. Nicorette (Nicotine Polacrilex; Gum, Troche/Lozenge; Oral)
f. Nicotine (Film, Extended Release; Transdermal)
g. Nicotine Polacrilex (Nicotine Polacrilex; Gum, Troche/Lozenge; Oral)
h. Nicotrol (nicotine) (Spray, Metered; Nasal | Film, Extended Release; Transdermal | Inhalant; Oral)
i. Prostep (Film, Extended Release; Transdermal)

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 produces, the effects of smoking, gender differences, and treatments.

4. NCI resources related to tobacco and nicotine use

a. Tobacco Control Monograph Series. These documents provide timely information on emerging public health issues in smoking and tobacco use.
b. Smokefree.gov. Resources and tools to aid smoking cessation
c. SmokefreeWomen
d. SmokefreeVet
e. SmokefreeTeen
f. SmokefreeEspañol
g. Smokefree60+

5. CDC resources and data

a. Tips from former smokers. CDC's campaign profiling real people living with the life-long health effects from smoking.
b. Morbidity and Mortality Weekly Reports (MMWR) on Smoking & Tobacco Use. A series of reports containing public health information and recommendations.

6. Surgeon General's Reports on Smoking and Tobacco Use. Including links to reports on E-Cigarette Use Among Youth and Young Adults and on The Health Consequences of 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