White Paper: Opioid Use, Misuse, and Overdose in Women

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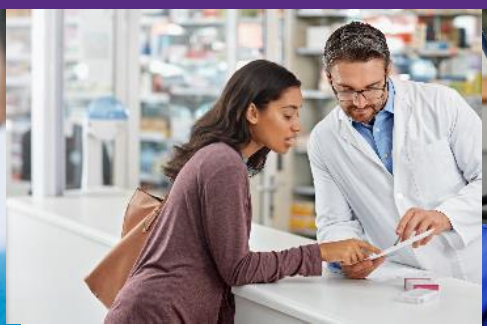

OFFICE ON WOMEN'S HEALTH

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Executive Summary

This report was developed as part of an initiative supported by the U.S. Department of Health and Human Services (HHS) Office on Women's Health (OWH) to examine the prevention, treatment, and recovery issues for women who misuse, have use disorders, and/or overdose on opioids. The White Paper was developed with the goal of ensuring that all stakeholders attending a September 2016 HHS OWH national meeting started from a shared level of understanding of how the unique aspects of the opioid epidemic impact women across age, race, geography, and income levels. To develop this report, we conducted a review of the literature focused on topics around opioid use disorders and women, as well as consulted with subject matter experts within and outside HHS.

Opioid use disorder is increasing at alarming rates for both men and women in the United States. While the epidemic is being addressed at many different levels, much still needs to be done. The prevalence of prescription opioid and heroin use among women is substantial. Between 1999 and 2010, overdose deaths from prescription pain killers increased more than 400% among women, compared to an increase of 237% among men; between 2002 and 2013, heroin use among women increased 100% compared to an increase of 50% among men. [1, 2] At the same time, the differences in how it impacts women and men are often not very well understood. This paper explores what is currently known about the opioid epidemic and describes promising practices for addressing opioid use disorder prevention and treatment for women, as well as identifies areas that are less well understood and may warrant further study. There is emerging knowledge about the many factors that affect a woman's path to opioid misuse and opioid use disorder, including biological and social influences, past experiences, geography, and demographic characteristics, but more needs to be learned about each aspect of this path. As we move forward to address the opioid epidemic generally and its impact on women specifically, we must evaluate the impact of multiple interventions considering the unique aspects of women across age, race, and socioeconomic spectrums.

Introduction

This White Paper was developed to serve as a starting point for a September 2016 national meeting hosted by the U.S. Department of Health and Human Services (HHS) Office on Women's Health (OWH) to examine prevention, treatment, and recovery issues for women who misuse, have use disorders, and/or overdose on opioids. This effort builds on the HHS Opioid Initiative aimed at reducing prescription opioid and heroin related overdose, death, and dependence.[3]

Opioids are a class of drugs used to reduce pain. They are often prescribed to treat moderate to severe pain, despite their potential for serious risks and side effects. Common opioids include oxycodone (OxyContin), hydrocodone (Vicodin), morphine, and methadone. Fentanyl is a synthetic opioid pain reliever that is typically prescribed for severe pain, such as advanced cancer; however, the availability and use of illegally made and distributed fentanyl is on the rise. Heroin is an illegal opioid, use of which has increased across the U.S. among both men and women, most age groups, and all income levels. Opioid use has been deemed an "epidemic" in the U.S., as deaths from drug overdose have never been higher and the majority of drug-related deaths involve opioids (more than six out of ten in 2014)[4]. This White Paper was originally developed with the goal of ensuring that all meeting stakeholders started from a shared level of understanding of how the unique aspects of this epidemic impact women across age, race, geography, and income. Through that meeting and other activities, OWH is exploring the opioid epidemic through the lens of the specific needs of women with the overall mission to:

- Foster a national conversation on best practices to prevent, diagnose and treat opioid-related hazards and death among women in the U.S.;
- Bridge gaps between researchers and public health practitioners by creating platforms to share best practices, promising approaches, and priority questions;
- Consolidate what is already known about opioid use and hazards of opioid-related harms specific to women or that are more pronounced among women, as well as the research on prevention, diagnosis and treatment of opioid use disorder (OUD) among women; and,
- Explore options for federal, state, and local governments, health insurers, law enforcement, and clinicians to address this epidemic of death, disability, and dependence among women.

To develop this report, we conducted a review of the literature focused on topics around OUDs and women, as well as consulted with subject matter experts within and outside HHS. This report begins by providing an overview of the opioid epidemic and what it means for women, followed by a description of the Secretary's Initiative and how it specifically relates to women. Issues of prevention and treatment are then explored, all with the lens of the unique or pronounced needs of women. We conclude with a resource section with links to key information.

What Does the Opioid Epidemic Mean for Women?

There is growing recognition that the United States is facing an epidemic due to an increase in opioid misuse, use disorders, and overdose, and that disparities exist between men and women with regard to both prescription opioid and heroin use. Although between 1999 and 2014 men were more likely than women to die of opioid overdoses, the gap in mortality has been closing.[5] Between 1999 and 2010, overdose deaths from prescription pain killers increased more than 400% among women, compared to an increase of 237% among men.[6] Although nonmedical use of prescription opioids among women has generally been decreasing since then,[7] heroin use among women has been increasing, and increasing faster among women than among men.[8, 9] For example, between 2002 and 2013, heroin use among women increased 100% compared to an increase of 50% among men.[10]

The picture of substance use is different for women compared to men. According to the Centers for Disease Control and Prevention (CDC), women are more likely to experience chronic pain and use prescription opioid pain medications for longer periods and in higher doses than men.[11] Women tend to use substances differently than men, sometimes using a smaller amount of drugs for a shorter amount of time before they become dependent.[12] For example, a national multisite effectiveness trial suggests that women who use opioids not only progress to dependence more quickly than men, but also experience more cravings than men.[13] Psychological and emotional distress have also been identified as risk factors for hazardous prescription opioid use among women, but not among men.[14] Many people with a substance use disorder may transition to injection drug use; thereby putting themselves at risk for viral hepatitis and HIV. Notably, new cases of hepatitis C among women increased more than 260% from 2010 to 2014,[15] likely increasing the risk of perinatal hepatitis C transmission to their infants.[16] Finally, women who are caregivers may face additional barriers to treatment for substance use disorders (SUDs), such as lack of childcare.[17]

Why Was it Critical That This Group Convene?

The HHS OWH convened experts and stakeholders to examine issues associated with the opioid epidemic through the lens of women's health. The September 2016 national meeting benefited from recent work by federal agencies and other organizations. The meeting provided an opportunity to foster a national conversation about best practices in OUD prevention and treatment for women, and supported a vigorous collaboration among researchers, public health practitioners, clinicians, policy makers, women with lived experience, and others to bring this epidemic to an end. This White Paper summarizes what is already known about opioid use and its hazards for women and briefly reviews the evidence base for prevention, diagnosis and treatment among women.

What Does the HHS Opioid Initiative Mean for Women?

On March 26, 2015, HHS Secretary Sylvia M. Burwell announced a department-wide initiative focused on combatting the opioid epidemic.[18] The HHS Opioid Initiative focuses on three priority areas:

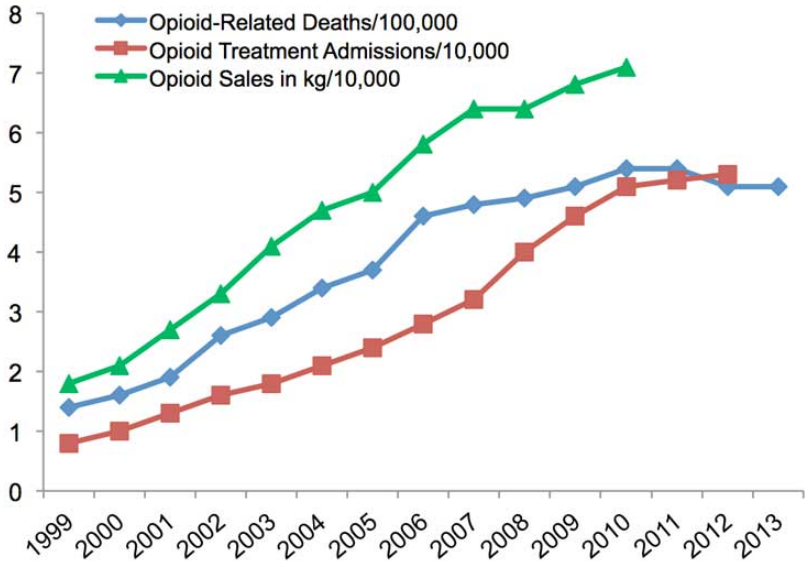
- "Opioid prescribing practices to reduce opioid use disorders and overdose,
- The expanded use of naloxone, used to treat opioid overdoses,
- Expanded use of Medication-assisted Treatment (MAT) to reduce opioid use disorders and overdose."[19]

In this section, we explore each of the priority areas of the HHS Opioid Initiative from the perspective of women and women's health.

Improving Opioid Prescribing Practices for Women

Over the last fifteen years, prescription opioids have been increasingly prescribed to treat acute and chronic pain; they have also been increasingly misused and implicated in drug overdose deaths. After a sharp increase in the number of opioid prescription filled in the U.S. during the first decade of the twenty-first century, opioid prescribing and deaths began to level out around 2012, though each remain high (see Exhibit 1).[20, 21, 22, 23, 24] In fact, at least half of all U.S. opioid overdose deaths involve a prescription opioid.[25]

Exhibit 1: Opioid Sales, Admissions for Opioid Treatment, and Deaths Due to Opioid Overdose in the U.S, 1999–2013



The prevalence of prescription opioid use among women is substantial, and the hazards of opioid use are similarly great. A 2015 CDC Morbidity and Mortality Weekly Report (MMWR) article found that between 2008 and 2012, more than one quarter of privately insured women ages 18-44 and more than one third of women of the same ages enrolled in Medicaid filled a prescription for an opioid medication.[26] The Substance Abuse and Mental Health Services Administration's (SAMHSA) 2015 National Survey on Drug Use and Health reported that 4% of females ages 12 and older misused prescription pain relievers in the last year.[27] A 2013 Vital Signs report from CDC indicated that "every 3 minutes, a woman goes to the emergency room for prescription painkiller misuse." Although more men die from drug overdoses than women, the percentage increase in deaths seen between 1999 and 2010 was greater among women: deaths from opioid pain relievers increased five-fold during that time for women versus 3.6 times for men.[28]

The March 2016 CDC Guideline for Prescribing Opioids for Chronic Pain summarizes the research literature about the benefits and risks associated with prescription opioids, and provides an evidence-based guide for clinicians and patients in shared decision-making about the use of these medications (see Exhibit 2) for chronic pain management.[29] The CDC prescribing guideline states: "long-term opioid use has uncertain [pain management] benefits but known, serious risks."[30]

The Guideline acknowledges that prevention, assessment, and treatment of chronic pain are challenges for health care providers. The Guideline also reports that patients within certain groups, including women, can be at risk for inadequate pain treatment and that patients can experience persistent pain that is not well controlled. There are clinical, psychological, and social consequences associated with chronic pain – including limitations in complex activities, lost work productivity, reduced quality of life, and stigma – that emphasize the importance of appropriate and compassionate patient care. The CDC Guideline recommends patients receive appropriate pain treatment based on a careful consideration of the benefits and risks of treatment options.[31]

Ultimately, although the CDC Guideline focuses specifically on opioids and chronic pain, acute and postoperative pain are also important to consider. In fact, Recommendation 6 of the CDC Guideline notes that long-term opioid use often begins with treatment of acute pain, stating specifically "When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed."[32] Some states, including Ohio and Arizona, have developed state specific opioid prescribing guidelines for acute pain.[33, 34, 35] The Arizona prescribing guidelines include an appendix that specifically focuses on considerations of opioid use during pregnancy and among women of childbearing age.[36]

Exhibit 2: CDC recommendations for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care

Determining When to Initiate or Continue Opioids for Chronic Pain

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

Assessing Risk and Addressing Harms of Opioid Use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

* All recommendations are category A (apply to all patients outside of active cancer treatment, palliative care, and end-of-life care) except recommendation 10 (designated category B, with individual decision making required); see full guideline for evidence ratings.

In February 2016, the American Pain Society released a clinical practice guideline similar to the CDC Guideline, but focused on post-surgical pain management.[37, 38] The American Pain Society's post-surgical guideline includes recommendations to limit use of opioids to manage post-operative pain. The guideline also discusses the need for education aimed at correcting misperceptions including "that opioids are always required for postoperative pain, or that opioid use inevitably leads to addiction."[39] Although the recommendations do not focus specifically on women, they do include guidance around opioid use following cesarean sections, as well as a discussion of the need to educate parents and caregivers about issues around post-operative pain management for children, such as assessing pain and concern about OUD.

The Surgeon General also recently launched a national campaign called "Turn the Tide Rx" which encourages improved prescribing practices and acknowledges the role of clinicians in addressing the opioid epidemic. The campaign seeks to "educate and mobilize prescribers to take immediate action to stem the opioid epidemic, provide patients with information to protect themselves and their families from opioid misuse and overdose, learn from communities around the country that are finding creative ways to tackle the epidemic, and change the cultural perceptions about addiction so that it is not seen as a moral failing but a chronic illness."[40] The website, TurnTheTideRx.org, informs providers about different treatment options, including a pain treatment toolbox, as well as an educational section for patients that discusses different types of opioids and risks associated with their use. The Turn the Tide Rx campaign has the potential to improve opioid prescribing practices in general, including for women.

Prescription Drug Monitoring Programs (PDMPs) are also showing promise as a strategy to improve prescribing practices. PDMPs, which are statewide electronic databases that track the dispensing of certain controlled substances including prescription opioids to patients, can help prescribers and pharmacists identify patients who are at risk for substance use disorders. Evidence suggests that PDMPs are also effective as clinical support tools and aid in public health surveillance. PDMPs appear to be effective in changing prescriber behavior and reducing the number of patients who visit multiple providers seeking the same or similar drugs.[41,42,43] Although 49 states currently have established PDMPs, not all are mandatory, and uptake is much lower in states where use is voluntary.[44] In July 2016, the Indian Health Service (IHS) issued a new PDMP policy for all providers who prescribe opioids and who work in IHS federally operated facilities. The policy requires providers to check state PDMPs "prior to prescribing and dispensing opioids for pain treatment longer than seven days and periodically throughout chronic pain treatment."[45] In October 2016, the Department of Veterans Affairs established a new policy requiring Veterans Health Administration providers "to query State Prescription Drug Monitoring Programs (PDMPs) to support safe and effective prescribing of controlled substances."[46] A number of states have similar policies requiring providers to check PDMPs prior to prescribing certain medications.[47]

Increasing Use of Naloxone for Women

Naloxone is a medication called an "opioid antagonist" used to reverse the physical effects of opioid overdose. Specifically, naloxone is administered during an opioid overdose to reverse life-threatening depression of the central nervous system and respiratory system, restoring normal breathing for the person experiencing the overdose. Naloxone is a prescription medication with no potential for either physical or psychological dependence. Although traditionally administered by emergency response or hospital personnel, naloxone can be administered by Good Samaritans or minimally trained bystanders, such as family and peer networks, which makes it a valuable resource in reversing the epidemic of opioid overdose deaths. Good Samaritan and Naloxone Access laws, including laws allowing standing orders for naloxone in community pharmacies in many states and tribes, and strong support by HHS for its use, are making naloxone more available.[48] However, women may not be benefiting as much as they could from the expanding availability of naloxone. A 2016 study found that men were nearly three times more likely than women to receive naloxone in Emergency Medical Services (EMS) opioid overdose resuscitation efforts.[49] Reasons for this lower use among women are not well understood. In 2014 and late 2015, the Food and Drug Administration (FDA) approved an auto-injector version and a nasal spray version of naloxone, respectively. Prior to that, naloxone had previously only been available in less consumer-friendly formats, such as with an atomizer device that could spray injectable naloxone into the nose. With multiple formulations now available, increased availability and usage will hopefully follow for both men and women. Given the trends in increased heroin use among women, increased availability and usage of naloxone may soon be that much more critical to prevent death from overdose among women.

Expanding Use of Medication-Assisted Treatment for Women

Medication-assisted treatment (MAT) is "the use of medications with counseling and behavioral therapies to treat substance use disorders and prevent opioid overdose."[50] There are currently three FDA-approved drugs used for medication-assisted treatment of OUDs (methadone, buprenorphine, and naltrexone), each with different advantages and disadvantages, as well as different uses and effects.

Each medication also has different requirements around how they can be prescribed; not all of these medications are indicated for use by pregnant women. Methadone can only be provided by an opioid treatment program (OTP). OTPs are closely regulated, certified, and accredited through SAMHSA.[51, 52] Naltrexone, which can be delivered as a daily oral dose or as a long-acting injection, can be provided by any physician or other health care provider operating within their scope of practice. Buprenorphine and the combination medication buprenorphine and naloxone can be provided by an OTP, but can also be provided by physicians who have received a minimum of eight hours of training on the medication in addition to having received a waiver from the Drug Enforcement Administration. In their first year, certified providers may only treat 30 patients at a time with buprenorphine, followed by up to 100 patients in subsequent years after submitting an additional notification. A final rule published in July 2016 increased the patient limits to 275 patients at a given time for certain qualified physicians.

Limitations on the number of patients a provider can treat at one time are designed to ensure that each patient receives high-quality care, appropriate behavioral health services, care coordination, care continuity during emergencies, and that risk of diversion is minimized.[53] Additionally, the Comprehensive Addiction and Recovery Act of 2016 includes a provision that, for the first time, allows physician assistants and nurse practitioners to prescribe buprenorphine.[54]

The evidence of the effectiveness of MAT is overwhelmingly positive.[55, 56, 57] However, despite a 2015 Practice Guideline from the American Society of Addiction Medicine that focuses on the use of medications in the treatment of substance use disorder involving opioid use (ASAM National Practice Guideline), and a recommendation within the CDC prescribing Guideline that clinicians offer or facilitate MAT for patients with OUD[58], MAT remains underutilized. Only 20% of adults with an OUD get the treatment they need each year, with cost and access reported as a primary barrier.[59] Many substance use treatment programs are reluctant to offer opioid dependent patients MAT. Stigma and negative attitudes towards MAT (based on the misconception that buprenorphine or methadone "substitute a new dependence for an old one")[60] persist among clinic staff and administrators. This leads to insufficient dosing or limitations on the duration of use of these medications (when they are used at all), which often results in treatment failure and the perception that the drugs are ineffective, further reinforcing the negative attitudes toward their use.[61]

Another barrier to care is insurance coverage. Private insurance policies are inconsistent in their coverage of MAT, the duration of treatment they will cover, number of episodes of treatment, or requirements that patients "fail" (meaning relapse) first before MAT is approved.[62] The Mental Health Parity and Addiction Equity Act (MHPAEA) does require that those insurance plans that cover SUD offer coverage for services that are no more restrictive than the coverage for medical and surgical conditions. However, MHPAEA does not require insurance plans to offer coverage for SUD in general, nor does it require coverage for specific treatments or services for SUDs.[63] In addition, according to a 2013 report, only 28 states currently cover all three FDA-approved medications under Medicaid, and requirements to obtain these medications vary from state to state.[64] Medicaid state pharmacy programs must cover buprenorphine, buprenorphine naloxone combination products, and naltrexone products; however, state Medicaid programs may require prior authorization, step therapy, or fail preferred medication first policies.

The comprehensive nature of MAT, when implemented as recommended, lends itself well to addressing the many physiological, psychological, and psychosocial factors facing women with OUD. For example, individual, group, and family therapy may help address psychosocial complications associated with family dynamics or guilt over the adverse effects of OUD on the family.[65] To increase the use of MAT for women services need to be both comprehensive and woman-focused, and barriers, such as concerns about what will happen to a woman's children if she seeks treatment, need to be addressed. SAMHSA

has issued guidance about the types of services that should be included in comprehensive MAT for women, such as:

- "Special groups to address problems of pregnant women who are opioid addicted
- Available treatments for women addicted to opioids, including pharmacotherapies
- Education and discussion groups on parenting and childcare
- Special groups and services for children and other family members
- Couples counseling
- Case management and assistance in locating safe, affordable housing."[66]

In future sections, we explore these and other elements of the opioid epidemic and their specific effect on women.

Exploring Issues in Prevention: Research and Promising Practices

Many factors may affect a woman's diagnosis of OUD, including biological and social influences, past experiences, geography, and demographic characteristics. In this section, we explore some of these issues as they relate to the prevention of opioid misuse and use disorder in women.

Biological Pathways to Substance Use Disorder

Women's path to substance use is complicated, and relatively little empirical information is available regarding biological pathways in women. The biological differences between men and women in substance use are better understood with regard to nicotine and alcohol than for opioids. For instance, women metabolize nicotine faster than men, which may be related to why women generally do not respond as well as men to nicotine replacement therapies. With alcohol, evidence shows that women often become intoxicated after fewer drinks and in a shorter amount of time than men. Higher blood alcohol concentrations, smaller amounts of water in the body due to proportion of body fat, and differing levels of sex hormones may all play a role in how women metabolize alcohol and other substances.[67, 68] In addition, evidence shows that women develop heart and nerve damage and cirrhosis after fewer years of heavy drinking than men, as well as experience more lung damage than male smokers.[69, 70] These physiological sex differences may also put women at a higher risk for medical problems associated with substance use disorders.[71]

Women may also become physically dependent on opioid pain medication more quickly than men, a phenomenon known as "telescoping." Telescoping refers to the progression of time from first use of an addictive substance to physical dependence on that substance.[72] Women tend to use substances differently than men, sometimes using a smaller amount of drugs for a shorter amount of time before

they become dependent.[73] These differences in use and basic physiological differences (e.g., body fat percentages, metabolic rate, and hormonal fluctuations)between the sexes are what likely leads to telescoping.[74] The telescoping phenomenon supports the need for both screening and early intervention among women in order to impede the progression of opioid use to the realization of opioid-related harms.

In addition to dependence, some research has shown that women also may be more sensitive to cravings. For example, one study demonstrated that women are more sensitive to cue-induced cravings for cocaine.[75, 76] Another study examining cigarette smoking found women's smoking was more intensely influenced by craving than by mood, with the converse being true for men.[77] A study specifically examining opioids found cravings were significantly higher among women than among men.[78]

Social Pathways to Substance Use Disorder — Adverse Childhood and Adult Experiences

Relationships and family history can also play a critical role in women's introduction to substance use. Women are more likely to initiate hazardous drug use in the context of some type of intimate partner relationship, particularly after introduction of the substance by a boyfriend or spouse.[79] While women are likely to be introduced to substances by an intimate partner, men are more likely to be introduced to substances by a peer.[80]

Additionally, psychological and emotional distress have been identified as risk factors for prescription opioid nonmedical use among women, but not in men.[81] For example, victims of violence and/or sexual abuse are at an increased risk for adverse outcomes from substance use.[82] Research indicates that opioid use disorders are associated with intimate partner violence victimization, particularly among women, and that women may also be particularly susceptible to such violence when under the influence of opioids.[83]

A history of traumatic childhood events, such as physical or sexual abuse and domestic violence, has also been associated with the initiation of substance use among women.[84] Research has shown that physical and sexual trauma followed by post-traumatic stress disorder (PTSD) is more common in drug-misusing women than in men seeking treatment.[85]

Studies have repeatedly found that rates of both childhood and adult sexual abuse are higher among women than among men[86] and that this abuse is correlated with substance use disorders. A research review by Najavits et al. found that a lifetime history of trauma was found in 55% to 99% of women who misused substances, compared with rates of 36% to 51% in the general population.[87] Compared to men, a higher proportion of women with substance use disorders have histories of trauma, including sexual and/or physical abuse. Often this abuse was perpetrated by people the women knew and trusted.[88]

Adverse childhood experiences are limited not only to physical and sexual abuse, but may also include other forms of trauma including emotional abuse, neglect, substance use disorders among family members, mental illness in the home, separation/divorce of parents, an incarcerated household member, or having a mother who was treated violently.[89] The CDC's Adverse Childhood Experiences Study has demonstrated a strong relationship between adverse childhood experiences and a variety of negative health outcomes including smoking, alcohol use, and harmful drug use.[90]

Women are also more likely than men to have co-occurring mental and substance use disorders. For women, anxiety disorders and major depression have been associated with substance use disorders and are typically the most common co-occurring diagnoses. In addition to depression and anxiety, studies have identified common comorbidities to also include PTSD, eating disorders, and agoraphobia with or without panic attacks.[91, 92]

Women typically report they use substances more often to cope with negative emotions.[93] Research has demonstrated that trauma followed by PTSD tends to be more commonly seen in drug-misusing women than men who are seeking treatment.[94] Therefore, health care and other service providers should be aware of and understand trauma theory, and how to provide or refer to trauma-informed services for their clients.[95] In addition, prevention strategies to eliminate exposure to trauma in childhood and adulthood should be considered an important part of a comprehensive approach to substance use disorders.

Social Determinants and Demographics

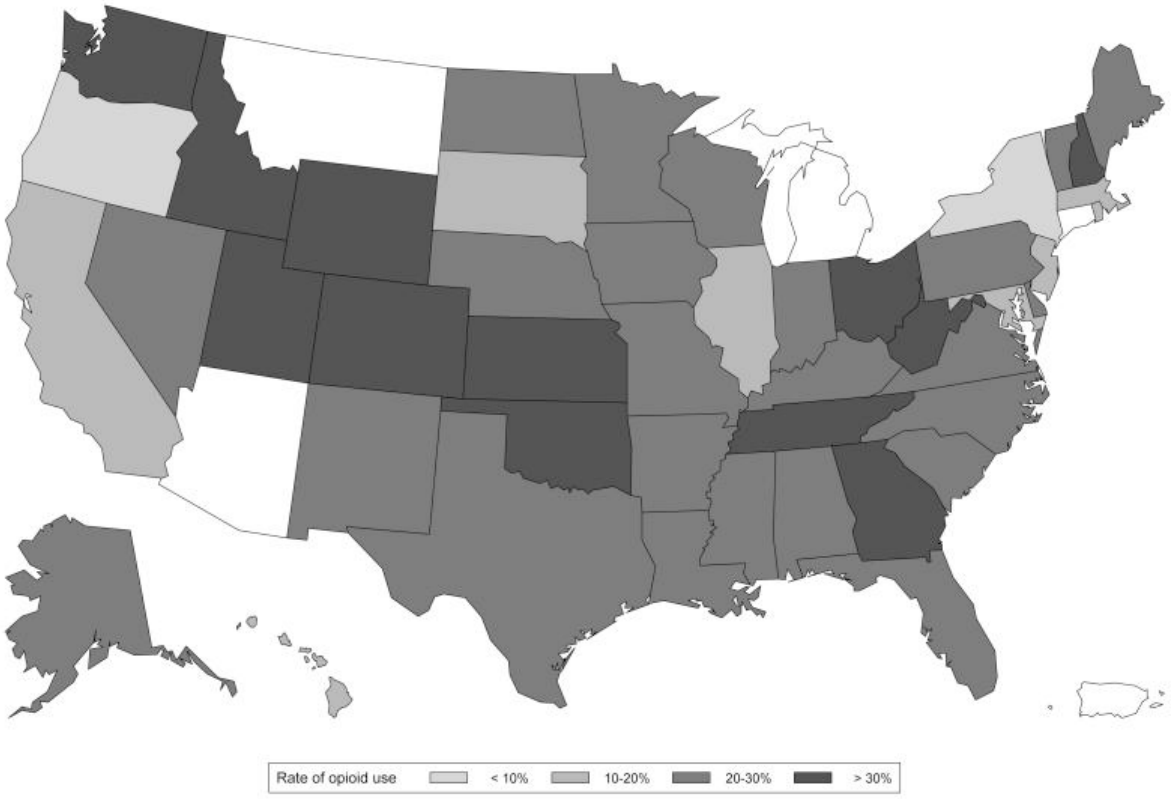
Factors such as geography, race/ethnicity and socioeconomic status are also determinants for rates of opioid use and misuse in U.S. women. Although these factors are often generally correlated with rates of opioid use and misuse, some differences appear to exist between genders. Understanding trends can help target prevention programming, treatment efforts and monitoring efforts.

Geography

Opioid prescribing rates vary widely across the U.S. When controlling for gender, rates are generally highest in Appalachia, along with counties in Southern and Western states.[96] CDC analysis of geographic region data from private insurance claims illustrated similar trends for women, finding opioid prescription rates were highest among 15-44 year old women in the South and were lowest in the Northeast. Death rates from drug overdose for women are more pronounced in rural areas in the South and Midwest. Geographic differences are also apparent for prescription opioid dispensing during pregnancy as illustrated in Exhibit 3.[97] Rates of opioid use during pregnancy are highest in the Rocky

Mountains. Similar to the trends for death rates from drug overdose for women, dispensing to pregnant women is also high (20-30%) in the Midwest, South, and northern New England. Discussed later in the "Women as Family Caregivers and Parents" section, opioid use during pregnancy is particularly risky as it potentially affects not only the woman, but also her child. Access to prescription opioids, overdose deaths, and other factors may also indicate that a community or state is at risk for infectious disease outbreaks. For example, CDC identified 220 vulnerable counties in the U.S. at risk for outbreaks of HIV and hepatitis C among people who inject drugs.[98]

Exhibit 3. Regional variation in the rates of prescription opioid dispensing during pregnancy, Medicaid 2000-2007



*Note: States in white were excluded from the study due to incomplete data.

Source: Desai et al. "Increase in Prescription Opioid Use During Pregnancy Among Medicaid-Enrolled Women." Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4020039/

Reasons for geographic differences cannot be explained by differences in health of the population as there is no significant evidence to show that women in specific regions have more pain-related issues than others. Instead the differences may be accounted for by a lack of consensus of when it is appropriate to prescribe opioid pain relievers. As CDC Director, Dr. Tom Frieden, stated in 2014, "We're

not seeing consistent, effective, appropriate prescribing of opioid pain medication across the Nation, and this is a problem because of the deaths that result."[99] Inconsistent and inappropriate prescribing is resulting in higher prescription rates and overdoses in some regions compared to others. Therefore, all states, especially those with high prescription rates, need to reexamine the way opioids are prescribed.

In an effort to improve appropriate prescribing of opioid pain medication, some states are seeing success in instituting PDMPs to track a patient's prescriptions and identify potential prescription problems, such as multiple doctors prescribing opioid pain medications to the same patient.[100] Many states throughout the South now have PDMPs, which may help to address the high rates of opioid prescriptions and death from overdose among women in that region. North Carolina's PDMP, for example, mandates monitoring patients' prescription history at OTP intake and at least every six months. Any discovered undisclosed prescriptions will result in patients having to sign a release of information (ROI) form allowing their treatment status to be communicated to their prescribers in order to coordinate care. The ROI is a requirement to remain in treatment.[101] Because patients are aware their prescription data will be checked, they may be more likely to disclose, but the evidence of the impact of this model is not yet determined.

Race, Ethnicity, and Socioeconomic Status

Racial and ethnic background can also be determinants in substance use disorder development. Though Americans in general are living longer, death rates are increasing for white, non-Hispanic women. Death rates for white, non-Hispanic women age 15 to 54 between 2005 and 2013 for accidental poisoning, a category that includes drug overdoses (largely comprised of prescription drugs), increased 121% compared to 80% for men.[102, 103] Though men are more likely to die from a drug overdose, the rate at which women, especially white women, are closing that gap is alarming. The increase in death rates for white American women has coincided with a shift towards prescribing opioids for more types of chronic pain rather than purely acute pain and cancer treatments, as was the case in the late 1980s to mid-1990's. There is little epidemiological evidence as to why death rates among white women have increased while other racial groups have decreased. Further, white women, specifically the middle class, are more likely to be treated for chronic pain compared to minority women, including increasing prescription of opioids.[104]Research has shown that prescriber bias may contribute to the disparity in prescribing rates, with minorities being less likely to be prescribed opioids.[105] For Medicaid beneficiaries, CDC researchers found opioid prescriptions were nearly one and a half times higher among white, non-Hispanic women age 15-44 as compared to non-Hispanic black or Hispanic women.[106]

As noted previously, the increased risk of adverse childhood experiences and violence into adulthood may contribute to increased substance misuse and the need for drug prevention and treatment programs that address the unique needs of these populations. American Indian/Alaska Native and black, non-Hispanic women are more likely than women of other racial and ethnic groups to be victims of rape,

physical violence, and stalking by an intimate partner during their lifetime[107] and American Indian or Alaska Native women have the highest risk of dying from a prescription painkiller overdose.[108]

In addition, women with substance use disorders are more likely to have lower incomes, be unemployed, and have less education compared to women without substance use disorders.[109] Generally, socioeconomically disadvantaged minority drug users experience a disproportionate number of overall health consequences from harmful drug use.[110] One reason for such trends can be traced to differences in treatment and access to care for minorities. Opioid treatment among women is generally low. One study found that although there was not a significant difference between males and females in rates of seeking treatment for OUD, treatment-seeking rates are low when compared to mental health disorders and other substance use disorders.[111] However, one study did show that treatment was even more unlikely for those of lower socioeconomic status and for those women who were recently incarcerated. The National Academy of Medicine also noted health care, legal and regulatory systems vary across socioeconomic status providing disparities that may account for the racial-ethnic disparities for substance use treatment in the U.S.[112]

Chronic Pain and Pain Management

The 2012 National Health Interview Survey (NHIS) reported that approximately 25 million adults in the United States have daily pain and that adults who reported having severe pain also had worse health, used more health care, and reported more disability than those reporting less severe pain. When pain is chronic and continuous, people can experience emotional responses including anxiety and depression which can lead to more pain.[113] Of adults who report daily pain, the NHIS found an association between pain severity and gender, as women are more likely than men to report any pain.[114] Epidemiologic and clinical findings support these findings and also demonstrate women are at increased risk for chronic pain and some evidence suggests that women may experience more severe clinical pain.[115] While the sex/gender differences in chronic pain are not clearly understood, possible explanations include biological and psychosocial mechanisms. Some studies have shown a link between sex hormones and pain sensitivity, including changes in pain perception across the menstrual cycle.[116, 117]

In addition to being at increased risk for chronic pain, women are also more likely to be prescribed prescription opioids, be given higher doses of opioid pain medication, and use them for a longer duration of time than men.[118] Research suggests women may also be more likely to use prescription opioids to self-medicate for other problems including anxiety or stress.[119] Childhood abuse has also been linked to chronic pain later in life; individuals who have reported a history of abuse early on in life also are more likely to experience chronic pain.[120]

In 2010, the National Institutes of Health (NIH) contracted with the Institute of Medicine (IOM) to undertake a study and make recommendations “to increase the recognition of pain as a significant public health problem in the United States”. The report called for a cultural transformation in pain

prevention, care, education, and research. In response to the report, the HHS Assistant Secretary for Health directed the Interagency Pain Research Coordinating Committee to oversee creation of a National Pain Strategy (NPS). The objectives of the NPS are to decrease the prevalence of pain across its continuum from acute to high-impact chronic pain and its associated morbidity and disability across the lifespan. The NPS addresses the public health significance of opioid use and misuse, and notes that public health concerns related to the misuse or diversion of prescription opioid pain medications and risk for dependence and overdose with long-term opioid prescribing need to be considered during the development of policies and programs related to pain management. The NPS further notes that programs to curb inappropriate prescribing practices and prescription opioid abuse should be balanced with the use of and access to these drugs for appropriate and quality pain management.[121]

Alternative Approaches to Opioid Pain Management

The first recommendation in the CDC Guideline discusses how nonpharmacological therapies, including physical therapy and exercise therapy, are preferred for chronic pain.[122] The Guideline notes evidence that both physical and exercise therapy can reduce chronic pain, noting high-quality evidence of exercise therapy for knee,[123] hip,[124] and low back pain.[125] The Guideline also discusses psychological therapies combined with exercise as a strategy that can reduce long-term pain.

SAMHSA's "Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders" also discusses nonpharmacological therapies for managing chronic pain, including: therapeutic exercise, physical therapy, cognitive-behavioral therapy, and complementary and alternative medicine. There is some evidence that exercise can help manage various types of pain as well as reduce anxiety and depression, which as previously noted, women cite as reasons for using opioids.[126] Some studies have shown that cognitive-behavioral therapy can help patients manage and reduce pain, often while addressing the depression and anxiety that often accompany chronic pain.[127, 128, 129] Alternative and complementary strategies for pain management are also discussed throughout a number of the objectives of the National Pain Strategy, particularly as an element of comprehensive and patient-centered pain management.[130]

Women as Family Caregivers and Parents

According to the Family Caregiver Alliance's National Center on Caregiving, approximately 66% of caregivers are women.[131] Increased levels of stress and depression can be common among women who are in caregiving roles, whether they are caring for children, parents, family members, friends, or other loved ones. The role women often play in society as caregivers means they tend to define themselves based on the relationships in their lives. Therefore, women are more likely to seek out and stay in treatment longer if they are able to maintain their caregiving role while in treatment, and either stay within the same treatment services or retain relationships with treatment providers throughout the provision of services.[132]

Becoming pregnant can also have an effect on women's substance-misusing behaviors. Oftentimes, women will stop using harmful substances during pregnancy, only to begin hazardous substance use shortly after birth.[133] SAMHSA's "Substance Abuse Treatment: Addressing the Specific Needs of Women" refers to this as the "double edged sword" in treatment planning.[134] Pregnancy can serve as a key moment to address harmful substance use in a woman's life; however any progress made toward recovery may not have lasting effects if pregnancy is the only reason for abstaining.

SAMHSA's "Advancing the Care of Pregnant and Parenting Women with Opioid Use Disorder and Their Infants: A Foundation for Clinical Guidance" reports that from 2000 to 2009, prenatal maternal opioid use increased from 1.19 to 5.63 per 1,000 hospital births per year.[135] Opioid misuse during pregnancy is especially risky as it not only impacts the health of the woman but also can impact that of her unborn child.[136] For example, studies have found that use of codeine in the first-trimester of pregnancy is correlated with congenital heart defects.[137, 138, 139, 140, 141] Prenatal exposure to oxycodone, propoxyphene or meperidine have also been shown to increase the risk of birth defects.[142, 143] Chronic untreated heroin use is associated with an increased risk of fetal growth restriction, placental abruption, fetal death, preterm labor, and intrapartum passage of meconium.[144] Further, pregnant women with opioid use disorders often seek prenatal care late in their pregnancy and their infants experience poor weight gain and poor birth outcomes.[145]

Opioid use puts the neonate at risk of neonatal abstinence syndrome (NAS) – hyperactivity of the central and autonomic nervous system. SAMHSA's "Advancing the Care of Pregnant and Parenting Women with Opioid Use Disorder and Their Infants: A Foundation for Clinical Guidance" reports a nearly twofold increase in the incidence of NAS from 2009 to 2012. Further, a 2015 study found the rate of neonatal intensive care unit admissions with NAS from 2004 through 2013, increased from 7 cases per 1000 admissions to 27 cases per 1000 admissions.[146] Infants with NAS may have uncoordinated sucking reflexes that can lead to poor feeding, irritability, and high-pitched cries. Infants born to mothers who misused opioids during pregnancy must be monitored and treated accordingly. The recommended treatment for pregnant women with an OUD is methadone or buprenorphine assisted therapy to prevent complications with withdrawal. These treatments improve pregnancy outcomes and can potentially reduce the risky behavior in the mother, and while they still confer some risk of NAS, the risk is less severe than it would be in the absence of treatment.[147, 148] Infants exposed to methadone can experience withdrawal as early as 72 hours from birth. Those exposed to buprenorphine can experience NAS within 12-48 hours of birth. Additionally, injection drug use is a risk factor for viral hepatitis and HIV. These infectious diseases can be passed from a mother to her baby. Notably, an increasing proportion of people who inject drugs and become infected with hepatitis C are young women of reproductive age. CDC recommends all pregnant women get screened for hepatitis B and HIV.[149, 150] Pregnant women with risk factors for hepatitis C – such as current injection drug use or having a history of injection drug use – should also be screened.[151] Women with risk factors for hepatitis B should be vaccinated.

Adolescents

In 2015, 3.9% (n=969,000) of adolescents age 12 to 17 misused pain relievers in the last year. More than half of those adolescents who misused pain relievers in the last year are female (n=518,000). Further, 122,000 of adolescents age 12 to 17 had a prescription pain reliever substance use disorder in the last year.[152] The rates for prescribing opioids to adolescents age 15 to 19 nearly doubled from 6.4% to 11.2% between 1994 and 2007.[153] Though doctors typically have the ability to prescribe medication as they see fit, the FDA's approval in 2015 of OxyContin for adolescents ages 11 through 16 years with "pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate" has offered guidance to help pediatricians to prescribe opioid pain medications safely.[154] However, most adolescents who misuse prescription pain relievers get them from a friend or relative (54.2% for free and 16.6% taken/bought). Only a small percentage of those who use these pain relievers obtain a prescription from a medical professional (18.1%).[155, 156] Teens may misuse opioids to experience the euphoria and high; lessen the feelings of anxiety, stress and physical pain; and/or use them in response to peer pressure.[157] The primary reasons teens listed for using opioids rather than other drugs are that they are easy to get from their parents' medicine cabinets, are easily available, are not illegal drugs, and/or can be claimed as their own prescription if caught.[158] Because adolescents' brains are not fully developed, exposure to opioids puts them at risk for misuse; there is evidence that the use of these drugs in adolescence can evolve into OUD in adulthood. A University of Michigan study found people who have taken prescription opioids for legitimate medical purposes during high school have a greater risk of opioid misuse by the age of 23.[159] Youth who misuse prescription medications are also more likely to report other drug use.[160]

Looking at adolescent use by gender, girls age 12-17 years are more likely than boys in that age group to use all psychotherapeutics including pain relievers for nonmedical reasons. Moreover, of the nonmedical users of prescription drugs, girls in this age range are more likely to become dependent. This gender difference is not the same for all age groups, however. For individuals age 18 years and older, as previously stated, males are more likely than females to misuse prescription drugs.[161] Little research has been done to account for why girls age 12-17 years display such a unique trend towards nonmedical use compared to their male counterparts and compared to other age groups. However, as noted previously, women are more likely than men to have co-occurring disorders. Data show, for example, that girls in this age group are more likely to experience other disorders such as eating disorders (over half of teenage girls use unhealthy weight control behaviors and those who diet are 12 times more likely to binge).[162] The rate of such co-occurring disorders may account for the increased rate of nonmedical use.

Older Adults

Some 40-50% of adults age 65 and older report the presence of a chronic pain disorder.[163] Approximately one-third of all prescription drugs in the U.S. are used by individuals in this age range. Women age 65 years and older have a higher percentage of long-term use of prescription drugs than women below 65 years and of men in all age groups 18 years and older.[164] Specifically, among patients

65 and older, 19% of men and 23% of women take at least five prescription drugs.[165] In addition, the use of opioids may be associated with a range of side effects including constipation, nausea, and dizziness. The use of opioids is also known to increase the risk of falls in this population.[166] Health professionals may treat patients for falls, however, rather than exploring the underlying cause of the falls such as OUD. Health professionals need to explore the possibility of opioid use as they assess the reasons for an older adult's fall. In general, OUD often goes unrecognized and untreated in this age group and research on treatment of substance use disorders for this population is limited.[167]

Recently Incarcerated Women

In 2014, 1,508,600 individuals were sentenced to more than one year in state and federal facilities. Of those, 109,200 were women.[168] According to data from the U.S. Department of Justice, approximately half of state and federal prisoners meet the DSM-IV criteria for substance use disorders.[169] Though the need for safe and effective detoxification or continuing medication-assisted treatment for opioid use disorders is appropriate for these individuals, studies have found that these types of services are infrequently available. The majority of jails report that they do not provide medications for opioid detoxification and those that do often do not use evidence-based practices.[170] Failure to provide safe and effective detoxification, treatment and counseling for incarcerated individual's dependence on heroin also puts them at high risk for HIV and viral hepatitis transmission through unsafe injection in prisons and possible loss of tolerance after detoxification that could result in fatal overdoses, and recidivism upon release.[171]

Incarcerated women have additional risk when entering jails and prisons with substance use disorders. At any given time, approximately 6% to 10% of incarcerated women are pregnant; many of these women first learn they are pregnant when they enter into a correctional facility.[172] For these women, as discussed previously, it is especially important that they receive medication-assisted treatment and counseling.[173]

Exploring Issues in Treatment: Research and Promising Practices

Unique Needs to Women in Treatment

In general, there tends to be a lack of substance use disorder treatment to meet overall demand, particularly in rural areas, and this is particularly true for opioid use disorders.[174, 175, 176, 177] Looking at treatment for both men and women, approximately 96% of states, including the District of Columbia, have opioid use or dependent rates higher than their treatment capacity rates.[178] Many states are also already operating at significant capacity; 38 states (77.6%) have at least 75% of their OTPs operating at 80% capacity.[179] According to SAMHSA's 2014 National Survey of Substance Abuse Treatment Services

(N-SSATS), 44% of treatment programs provided special programs or groups for adult women and only 20% offered programs or groups for pregnant or postpartum women.[180] Analysis of data from over 50,000 participants in the National Survey on Drug Use and Health found that among prescription opioid users, men reported significantly higher rates of treatment utilization (11% lifetime, 5% past year) as compared to women (6% lifetime, 3% past year).[181] The reasons are not well understood, although the N-SSATS research suggests a lack of services for women may play a role. When women do enter treatment for substance use disorder, they typically present with medical, behavioral, psychological, and social problems that are generally more severe than for men, suggesting a need for gender-specific treatment approaches.[182]

Women as Caregivers and the Impact on Treatment

Many women who are in caregiving roles often will not seek treatment or do not complete treatment because they are unable to manage their caregiving responsibilities and participate in treatment programs at the same time. Women with children may also fear that their children will be removed from their custody. In addition, the responsibilities of caregiving in addition to undergoing treatment can become overwhelming for some women. Successful treatment programs may need to consider providing increased supports to address this barrier.[183]

Treatment options and levels of care are not sex or gender specific and both men and women require a variety of treatment services along the continuum of care. However, women who are in caregiving roles require additional consideration as to what types of services best fit their needs. When caring for children, women who are allowed to stay with their children in treatment, such as programs that include residential care, are more inclined not only to enter into treatment, but to participate and stay in the program, and even to maintain abstinence.[184]

Women, Treatment, and the Justice System

In many states, pregnant women or women with children can be reported to child protective services for using illicit drugs, leading to loss of child custody. Involvement with the child welfare system plays a critical role in a woman's decision to seek care, because admitting to a substance use disorder may lead to involvement with the criminal justice system and potential loss of custody. The 2011 National Drug Control Strategy has acknowledged the importance of women not having to choose between seeking treatment and caring for their children.[185]

The Office of National Drug Control Policy has encouraged sentencing alternatives to incarceration, expanding family-based treatment programs, and treatment interventions that are trauma-informed.[186] Drug courts are one sentencing alternative that has shown strong evidence in reducing drug-related recidivism.[187] Drug courts provide offenders with substance use disorders an alternative to jail by providing intense supervision, drug testing and treatment. These new approaches may be helpful in addressing women's needs.

Child-Friendly and Family-Friendly Treatment Options

Many of the existing, traditional residential drug treatment programs do not allow children to be present. As a result, parenting women may feel torn between seeking the needed treatment and caring for children.

Approximately 70% of women entering substance use treatment services have children.[188] Children of one or more parent or caregiver with substance use disorder are at increased risk of developmental, behavioral, and emotional difficulties. Therefore, early intervention is important for women seeking treatment and, as appropriate, for their children and family members. The SHIELDS for Families programs based in Los Angeles, CA have successfully incorporated children into treatment, incorporating youth programs and child development centers into many of their programs. For example, their Exodus program is the only family-centered treatment program in the country that allows entire families to live in individual apartments within the treatment environment. The SHIELDS' Exodus program consistently reports program completion rates of 80% and family reunification rates of over 90%.[189]

A family-centered treatment model looks at the role of the family in the treatment of women with substance use disorders. In addition to clinical treatment, this model includes a continuum of family-based clinical and community support services that address many factors for women and their families such as: substance misuse, mental health; physical health; developmental health; and social, economic, and environmental needs. Because women place high values on their relationships and families, treatment should focus on promoting and supporting healthy attachment and relationships between parents and children and on women's relationships with others. Family-centered treatment helps not only the woman dealing with adverse outcomes of drug use, but with her family and their needs.

Health Insurance Coverage Issues for Women in Treatment

As noted above, public and private coverage for treatment may serve as barriers to access. In an effort to encourage state adoption of appropriate treatment options, in July 2014, the Director of the Center for Medicaid and CHIP Services within CMS issued a joint Informational Bulletin with the Director of CDC and the Administrator of SAMHSA as well as the directors of the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism[190] to highlight the use of MAT. CMS also issued a brief in January 2015[191] to emphasize that states have the flexibility to tailor programs—within defined requirements and subject to federal approval—to meet the needs of their beneficiaries and local providers. More recently, in a January 2016 guidance on "Best Practices for Addressing Prescription Opioid Overdoses, Misuse and Addiction," CMS encouraged states to "assess their Medicaid benefits coverage, delivery systems, payment mechanisms and provider networks for substance use disorder services to ensure that effective treatments are available to beneficiaries when medically appropriate." CMS also supports the Medicaid Innovation Accelerator Program (IAP), which provides states with expert resources, coaching opportunities, and program support to accelerate policy, program, and

payment reforms appropriate for a robust SUD system. The goal of the IAP initiative is to help participating states to better identify individuals with SUD, enhance provider capacity to effectively treat individuals with SUD, and expand coverage for promising and evidence-based SUD services, such as MAT.[192]

Although Medicaid is encouraging state efforts to prevent and treat opioid use disorders, limitations and requirements for Medicaid reimbursement may serve as real or perceived barriers to treatment. One example of such a barrier is the lifetime limitation for buprenorphine-naloxone required by some states. This limitation offers a challenge for payers because OUD is chronic and therefore, places individuals at risk for relapse when their Medicaid-covered treatment limit is up.[193] A number of states also require evidence that patients are receiving behavioral therapy with their medications; however, care needs to be taken that documentation does not become burdensome and turn into a barrier to accessing medications.[194] Similarly, only 28 states cover all three FDA-approved substance use disorder treatment medications under Medicaid. Many private health plans also exclude coverage of methadone maintenance treatment altogether, even though it is demonstrated to be the most effective treatment option for many people with an OUD.[195]

Insurance coverage can be challenging with respect to non-pharmaceutical pain management, as well. Because there is limited evidence of effectiveness of some alternative treatments such as yoga, chiropractic and osteopathic manipulation, meditation, or massage therapy, Medicaid and private insurance plans may not cover such treatments making these methods expensive for individuals choosing to use them. Some states and private insurers, however, are moving towards coverage of alternative treatments. In July 2016, Oregon's Medicaid program, for example, began covering acupuncture, chiropractic and osteopathic manipulation, and cognitive behavioral therapy for patients with chronic back pain if these treatments are appropriate upon initial evaluation.[196]

Training

HHS is actively working to stem the overprescribing of opioids through providing prescribers with access to the tools and education they need to make informed decisions. In particular, HHS has developed a number of activities that support opioid prescriber education.[197] The Surgeon General's Turn the Tide Rx campaign includes a pain treatment toolbox for prescribers, as well as other educational resources for prescribers.[198] SAMHSA funding has also been used to create continuing medical education courses on prescribing opioids for chronic pain developed by local and state health organizations across the country. These courses offer training on practice management, legal and regulatory issues, opioid pharmacology, and strategies for managing challenging patient situations.[199] With respect to training around acute pain prescribing, some states have developed provider training to correspond with their acute pain prescribing guidelines. In June 2016, for instance, prescribers in Ohio were asked to complete an online training program around their new acute pain opioid prescribing guidelines.[200] Beginning in fall 2016, over 60 medical schools started requiring students to take some type of prescriber education

based on the CDC Guideline.[201] Similarly, almost 200 nursing schools and more than 50 pharmacy schools have committed to requiring prescriber training in their educational programs. Beginning in fall 2016, participating schools of nursing will require advanced practice registered nursing students to take some form of prescriber education in line with the CDC guideline by the time they graduate. Colleges and schools of pharmacy will also provide education in their curricula on overdose interventions and how to counsel patients on appropriate use of naloxone.[202]

In addition, CDC is offering a suite of tools and resources to ensure distillation of the information within the CDC Guideline into practical and implementable tools to assist providers. For example, CDC has developed a clinical decision making checklist as well as a webinar series to provide a training opportunity for clinicians to learn about the recommendations within the Guideline and how they can be implemented within practice.

Opportunities for Research and Evaluation

While this paper explores what is known about the opioid epidemic and describes promising practices towards addressing opioid prevention and treatment among women, it also identifies numerous areas that are less well understood and can serve as a platform for further research and evaluation. There is emerging knowledge about the many factors that affect a woman's diagnosis of OUD, including biological and social influences, past experiences, geography, and demographic characteristics, but more needs to be learned about each aspect of this path. As more is learned about the factors of opioid misuse that are specific to women, evidence-based successful strategies aimed towards prevention and treatment for women can be evaluated and shared across the numerous stakeholders who have an opportunity to prevent and treat this deadly epidemic. As noted in the introduction, this paper and the September 2016 HHS OWH meeting provide an opportunity to bridge knowledge and gaps among researchers, public health practitioners, and other stakeholders by creating opportunities to share best practices and promising approaches and identify areas for further research and evaluation.
Potential key areas for further exploration include:

- Assessing the biological and environmental differences related to physical dependence and risk of death from prescription opioids among women.
- Supporting health services research and evaluation to further explore differences in motivations for treatment utilization and barriers to seeking treatment for substance use disorders.
- Supporting health services research and evaluation on access and health insurance coverage for pharmacologic treatment of opioid use among women.
- Conducting health services research and evaluation on how external factors and social determinants may serve as barriers to implementation of treatment programs, and to women's access to such programs.

- Studying approaches to best train providers to help prevent and treat OUD, and assess for related health outcomes such as HIV, viral hepatitis, and overdose risk.

Approaches and Opportunities for Moving Forward

Hazardous and deadly opioid misuse, including prescription opioids and heroin, is increasing at alarming rates for both men and women in the United States. While the epidemic is being addressed at many different levels, much still needs to be done, including special efforts designed to address the unique needs of women. As discussed above, the prevalence of prescription opioid use among women is substantial, and the hazards of opioid use are similarly great. Even in areas where differences are apparent between sexes, such as women progressing more quickly to use disorders than men, very little is understood about *why* those differences occur. As we collectively move forward to address the opioid epidemic generally and its impact on women specifically, it will be very important to systematically evaluate the impact of each intervention while considering the unique aspects of women across age, race, and socioeconomic spectrums.

As we have discussed, there are many more questions than answers when it comes to understanding the unique aspects of women and hazardous opioid use. Ultimately, the opioid epidemic will not be addressed through a one-size fits all approach and we must consider how the epidemic is impacting women differentially.

Appendix: HHS Work in Support of the Secretary's Initiative

Many HHS agencies have taken multiple concrete steps this year to support the Secretary's targeted initiative aimed at reducing prescription opioid and heroin related overdose, death and dependence. Examples include:

Centers for Medicare & Medicaid Services (CMS)

Medicare[203, 204]

In July 2016, CMS issued a proposal to remove the Pain Management dimension of the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey for purposes of the Hospital Value Based Purchasing Program. The proposed rule, which was finalized in November 2016, removes HCAHPS survey pain management questions from hospital payment scoring calculations. These changes were implemented in response to clinicians who reported feeling pressure to overprescribe opioids because scores on the HCAHPS survey pain management questions are tied to Medicare payments to hospitals. Under the CMS final rule, hospitals will continue to use the questions in patient surveys, but the responses will not affect the level of payment hospitals receive.

Medicaid[205]

In January 2016, the Center for Medicaid and CHIP Services issued an Informational Bulletin on "Best Practices for Addressing Prescription Opioid Overdoses, Misuse and Addiction" to highlight emerging Medicaid strategies for preventing opioid-related harms. Medicaid programs can encourage the use of safer, effective alternatives to opioid pain medications—in particular, alternatives to methadone prescribed for pain relief—by working collaboratively with other state agencies to educate Medicaid providers about opioid prescribing and dispensing practices. Medicaid programs can consider pharmacy benefit management strategies such as reassessing preferred drug list placement, introducing clinical criteria, prior authorization, step therapy, quantity limits, and implementing drug utilization review processes.

Centers for Disease Control and Prevention (CDC)[206]

In March 2016, CDC issued new provider recommendations for prescribing opioid medications for chronic pain, excluding cancer, palliative, and end-of-life care. CDC also released materials to assist physicians with implementing the recommendations including a fact sheet, checklist, and posters, and online trainings for which continuing education credits are available.[207]

The *CDC Guideline for Prescribing Opioids for Chronic Pain, United States, 2016* are is designed to help primary care providers improve patient care for chronic pain. The principles recommend:

- Non-opioid therapy is preferred for chronic pain outside of active cancer, palliative care and end-of-life care.
- Clinicians should establish treatment goals with patients, and include a plan for discontinuation of opioid therapy if risks outweigh benefits.
- Clinicians should discuss the risks and benefits of opioid therapy with patients prior to treatment, and revisit possible harms and benefits not less than every three months.
- When starting opioid therapy, clinicians should prescribe immediate-release opioids instead of extended-release (or long acting) opioids.
- When opioids are used, the lowest possible effective dosage should be prescribed to reduce risks of OUD and overdose.
- Clinicians should review patients' history of controlled substance use and consult PDMPs to determine risk for overdose.
- Clinicians should use drug testing to identify other prescribed medications as well as illicit or undisclosed drugs.
- Clinicians should avoid prescribing opioid pain medications and benzodiazepines at the same time when possible.
- Clinicians should offer or make arrangements for evidence-based treatment with medication-assisted treatment for patients with OUD.

Food and Drug Administration (FDA)[208]

In February 2016, FDA announced the agency will:

- Re-examine the risk-benefit paradigm for opioids and ensure the agency considers their wider public health effects
- Convene an expert advisory committee before approving any new drug application for an opioid that does not have abuse-deterrent properties;
- Assemble and consult with the Pediatric Advisory Committee regarding a framework for pediatric opioid labeling before any new labeling is approved;
- Develop changes to immediate-release opioid labeling, including additional warnings and safety information that incorporate elements similar to the extended-release/long-acting (ER/LA) opioid analgesics labeling that is currently required;
- Update Risk Evaluation and Mitigation Strategy requirements for opioids after considering advisory committee recommendations and review of existing requirements;
- Expand access to, and encourage the development of, abuse-deterrent formulations of opioid products;
- Improve access to naloxone and medication-assisted treatment options for patients with opioid use disorders; and
- Support better pain management options, including alternative treatments.

- Seek guidance from outside experts in the fields of pain management and drug abuse including the National Academies of Sciences, Engineering, and Medicine, which has been asked to help develop a framework for opioid review, approval and monitoring that balances individual need for pain control with considerations of the broader public health consequences of opioid misuse and abuse.
- Convene independent advisory committees composed of physicians and other experts when considering any new opioid drugs for approval that do not contain abuse-deterrent properties.
- Convene a meeting of the Pediatric Advisory Committee to make recommendations regarding a framework for pediatric opioid labeling and use of opioid pain medications in the pediatric population.
- Strengthening the requirements for drug companies to generate post market data on the long-term impact of using extended release/long acting opioids to create comprehensive data in the field of pain medicine and treatments for OUD. The data will further the understanding of the known serious risks of opioid misuse, overdose and death.

Health Resources and Services Administration (HRSA)

HRSA/Bureau of Primary Health Care[209]

In March 2016, HRSA awarded $94 million to 271 health centers in 45 states, the District of Columbia, and Puerto Rico to improve and expand the delivery of substance abuse services in health centers, with a specific focus on treatment of opioid use disorders in underserved populations. These awards will increase the number of patients screened for substance use disorders and connected to treatment, increase the number of patients with access to MAT for opioid use and other substance use disorder treatment, and provide training and educational resources to help health professionals make informed prescribing decisions. This investment is expected to help awardees hire approximately 800 providers to treat nearly 124,000 new patients.

HRSA//Federal Office of Rural Health Policy[210]

In September 2015, HRSA announced the award of $1.8 million to support rural communities in reducing morbidity and mortality related to opioid overdoses. The Rural Opioid Overdose Reversal Grant Program supported the purchase and placement of naloxone and training for its use by licensed healthcare professionals and emergency responders in rural areas. The pilot program supported local partnerships to coordinate care including local emergency responders, health facilities, academic organizations, fire departments, law enforcement, and other non-profit or for-profit entities involved in the prevention and treatment of opioid overdoses. The partnerships collaborated to increase the availability and use of naloxone in rural communities with emphasis on the importance of referring those with an opioid use disorder to an appropriate substance use disorder treatment center. Each of the 18 recipients, representing 13 states, were awarded $100,000.

HRSA/Bureau of Health Workforce

HRSA awards grants to academic institutions to increase the number of behavioral health providers in medically underserved areas, which will increase access to substance use treatment. For example, as part of the President's *Now Is The Time* initiative, HRSA is partnering with SAMHSA to expand the behavioral health workforce by supporting clinical training for behavioral health professionals. This activity, the Behavioral Health Workforce Education and Training Program, awarded $44.5 million in 2016. Additionally, the Graduate Psychology Education (GPE) Program supports academic programs to prepare psychologists to provide behavioral health care, including substance abuse prevention and treatment services to underserved and/or rural populations. For 2016, GPE distributed $7.9 million in awards.

National Institutes of Health (NIH)

NIH supports a robust portfolio of research and other programs that align with the three priority areas of the Secretary's Opioid Initiative as described below.

Improved Opioid Prescribing Practices to Reduce Opioid Use Disorders and Overdose:

Improved Pain Treatment

- The NIH Pain Consortium was established to enhance pain research and promote collaboration among researchers across the many NIH Institutes and Centers that have programs and activities addressing pain. The Consortium, along with its federal partners on the Interagency Pain Research Coordinating Committee, developed the National Pain Strategy, which was released on March 18, 2016 and outlines actions for improving pain care in America.
- NIH is funding the development of the first open-access, no-cost, clinically based, retrospective and prospective chronic pain data registry. The registry will identify pain-management interventions that are most effective for specific patient types with chronic pain.
- NIH funds a broad range of research grants in this area, including grants to support the basic science of pain, as well as development of analgesics with non-opioid mechanisms and reduced misuse potential, development non-pharmacological pain treatments (including nerve stimulation, surgical interventions, behavioral and psychosocial interventions), and novel technologies and pain treatment delivery devices.

Prescriber Education

- As of October 2015 a total of 113,631 clinicians were certified in the accredited CME/CE courses *Managing Pain Patients Who Abuse Prescription Drugs* and *Safe Prescribing for Pain*. (Accreditation has now expired.) Developed by the National Institute on Drug Abuse (NIDA), this NIDAMED initiative is currently working to develop a CME/CE course on Adolescent Substance Use for general healthcare providers that will include modules on prescription opioid misuse.
- On September 18, 2015, the NIH Pain Consortium established a new Physician Centers of Excellence in Pain Education (CoEPEs). The initiative selected 11 CoEPEs to develop and disseminate pain curricula and improve medical education on the treatment and management

of pain while minimizing the abuse of opioid medications, an area that current medical training under-emphasizes.

Expanded Use of Naloxone to Treat Opioid Overdose:

- In 2013 NIDA partnered with Adapt Pharma/Lightlake Therapeutics, Inc (a partner of Adapt Pharma Limited) to develop an intranasal formulation of the drug naloxone to reverse opioid overdose. This user-friendly formulation, NARCAN® Nasal Spray, achieves therapeutic blood levels of naloxone via a quick spray into the nasal passages, and can be used by first-responders, family, friends and bystanders to save lives. Approved by the FDA on November 18, 2015, it became commercially available on February 25, 2016.
- NIDA-funded research suggests primary healthcare providers have limited knowledge about naloxone and misplaced concerns about its misuse and safety which are barriers to its adoption and distribution.
- NIDA supported research is evaluating naloxone distribution across a range of health care settings and populations.

Expanded Use of MAT to Reduce Opioid Use Disorders and Overdose:

- NIDA supported the development of Probuphine through its partnership with Titan/Braeburn Pharmaceuticals. This implantable formulation of buprenorphine provides six months of continuous medication for patients stabilized on buprenorphine, eliminating the need for daily dosing. Probuphine was approved by the FDA on May 26, 2016.
- NIDA supports a broad portfolio of research on the basic science of OUDs, and on novel treatments ranging from brain stimulation to heroin vaccines.
- NIDA's Clinical Trials Network (CTN) is developing evidence-based clinical decision support for the management of OUDs in general healthcare settings, as well as supporting research on MAT.

NIH is also supporting research and collaboration relevant to the effects of the opioid epidemic on special populations. NIH convened a scientific workshop in April 2016 focused on "Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes", and is partnering with the Appalachian Regional Commission to provide one-year planning research grants to address increased opioid injection drug use in Appalachia.

Substance Abuse and Mental Health Services Administration (SAMHSA)[211]

In May 2016, SAMHSA accepted applications for Targeted Capacity Expansion: Medication Assisted Treatment-Prescription Drug Opioid Addiction grants totaling up to $33 million over three years. This program is designed to provide funding to 27 states identified as having an increase of 25% or more in admissions for OUDs in recent years (2007-2012). The purpose of the grants are to enhance/expand their treatment service systems to increase capacity and provide accessible, effective, comprehensive,

coordinated care, and evidence-based medication assisted treatment (MAT) and recovery support services to individuals with OUDs seeking or receiving MAT. The goal of the funding is to:

- increase the number of individuals receiving MAT services with pharmacotherapies approved by the FDA for the treatment of OUDs;
- increase the number of individuals receiving integrated care;
- decrease illicit opioid drug use at six-month follow-up; and
- decrease the use of prescription opioids in a non-prescribed manner at six-month follow-up.

SAMHSA expects up to $11 million will be available each year to provide up to 11 grants of up to $1 million each for states using a certified Electronic Health Record (EHR) system or planning to certify their currently non-certified EHR system. States not using a certified EHR system or not planning to certify their EHR system can receive up to $950,000 a year.

In July 2016, SAMHSA also finalized a rule to increase access to buprenorphine to allow a greater number of individuals to be treated for OUD.[212] Under the new rules, practitioners with an active waiver can treat up to 100 patients for 1 year; that can be increased to 275 patients with additional credentialing.

Resources

HHS Resources

AHRQ Resources

- The Effectiveness and Risks of Long Term Opioid Treatment of Chronic Pain
- An HCUP Statistical Brief on Hospital Inpatient Utilization Related to Opioid Overuse Among Adults, 1993-2012
- Infographic: Opioid Overuse on the Rise; More Widespread Across U.S.
- Medication-Assisted Treatment Models of Care for Opioid Use Disorder in Primary Care Settings
- Supporting HHS's Opioid Initiative

ASPE Resources

- ASPE Issue Brief: Opioid Abuse in the U.S. and HHS Actions to Address Opioid-Drug Related Overdoses and Deaths

CDC Resources

- Common Elements in Guidelines for Prescribing Opioids for Chronic Pain
- CDC Guideline for Prescribing Opioids for Chronic Pain
- July 2013 Vital Signs: Prescription Painkiller Overdoses
- Fact Sheet: Hepatitis C and Injection Drug Use
- Hepatitis Risk Assessment
- Viral Hepatitis and Young Persons Who Inject Prescription Opioids and Heroin
- HIV and Injection Drug Use in the United States

FDA Resources

- Opioid Medications
- General Principles for Evaluating the Abuse Deterrence of Generic Solid Opioid Drug Products. (Draft Guidance).
- Fact Sheet – FDA Opioids Action Plan
- A Proactive Response to Prescription Opioid Abuse

NIH Resources

- Prescription Drug Abuse: Opioids
- Drugs of Abuse: Opioids
- NIDAMED: Medical & Health Professionals
- Substance Use in Women

- Review Article Outlines Strategies To Reduce Opioid Abuse Risk
- Drug Facts: Substance Use in Women
- Probuphine: A Game-Changer in Fighting Opioid Dependence
- NIH Pain Consortium
- NIH Centers of Excellence in Pain Education (CoEPEs)
- National Pain Strategy

ODPHP Resources

- National Action Plan for Adverse Drug Event Prevention

OHAIDP Resources

- AIDS.gov: Substance Abuse Issues
- Viral Hepatitis
- Technical Consultation: Hepatitis C Virus in Young Persons Who Inject Drugs

SAMHSA Resources

- Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs: A Treatment Improvement Protocol. (TIP 43)
- Quick Guide for Clinicians Based on TIP 43: Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs.
- Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction: A Treatment Improvement Protocol. (TIP 40)
- Quick Guide for Clinicians Based on TIP 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction.
- Clinical Use of Extended-Release Injectable Naltrexone in the Treatment of Opioid Use Disorder: A Brief Guide.
- Substance Abuse Treatment: Addressing the Specific Needs of Women: A Treatment Improvement Protocol (TIP 51).
- A Treatment Improvement Protocol: Managing Chronic Pain in Adults with or in Recovery from Substance Use Disorders (TIP 54).
- Medication-Assisted Treatment for Opioid Addiction. Fast Facts for Families and Friends.
- Methadone Treatment for Pregnant Women
- Alcohol, Tobacco, and Other Drugs: Opioids
- A Collaborative Approach to the Treatment of Pregnant Women with Opioid Use Disorders: Practice and Policy Considerations for Child Welfare, Collaborating Medical, and Service Providers
- Buprenorphine Training for Physicians
- Women, Children & Families: Training and Technical Assistance

Other HHS Resources

- Fact Sheet: Medication Treatment for Opioid Use Disorders: Increasing the Buprenorphine Patient Limit
- Medication Assisted Treatment for Opioid Use Disorders
- Opioids: The Prescription Drug & Heroin Overdose Epidemic
- The Surgeon General's Call to End the Opioids Crisis: Treatment Options for Physicians and Patients
- U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS, November 2016

Other Federal Resources

DOJ Resources

- 2015 National Drug Threat Assessment Summary

ONDCP/White House Resources

- 2014 National Drug Control Strategy
- Women, Girls, Families, and Substance Abuse
- Substance Abuse and Maternal and Child Health
- Women and Treatment
- Women Research and Resources
- Office of the National Drug Control Policy at the White House

Other Resources

- NASHP Site Highlighting State Laws to Combat Opioid Crisis
- UN Women Policy Brief: A Gender Perspective on the Impact of Drug Use, the Drug Trade, and Drug Control Regimes
- National Commission on Correctional Health Care: Women's Health Care in Correctional Settings
- Providers' Clinical Support System for Medication Assisted Treatment (PCSS-MAT) Educational Training
- ASTHO Prescription Drug Misuse and Abuse: Neonatal Abstinence Syndrome
- ASTHO State Action to Prevent and Treat Prescription Drug Abuse
- National Center on Substance Abuse and Child Welfare
- ASAM Opioid Addiction 2016 Facts & Figures
- ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use

- ASAM Committee Opinion: Opioid Abuse, Dependence, and Addiction in Pregnancy

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