Women, Opioid Use and Addiction

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Nonstandard Abbreviations

(CDC) Centers for Disease Control and Prevention

(CNS) central nervous system

(FDA) Food and Drug Administration

(IOM) Institute of Medicine

(NSDUH) National Survey on Drug Use and Health

(NAS) neonatal abstinence syndrome

(OUD) Opioid Use Disorder

(PAG) periaqueductal gray

Abstract

In the midst of the current coronavirus pandemic, the United States continues to struggle with an ongoing opioid epidemic, initially fueled by widespread prescribing of opioid medications during the 1990s. The primary reason for prescribing opioids is to treat pain. Women have more acute and chronic pain and have been prescribed these drugs in significantly greater numbers than men. Comparison of women and men with chronic pain also shows that women receive the majority of prescription opioids, and the use of these prescribed medications became the major pathway to misuse and addiction for women. Yet, recognition of the extent of women's exposure to opioids and the attendant consequences has been limited. Attempts to stem the overall tide of the epidemic focused on reducing the availability of prescription opioids. However, as these medications became more difficult to obtain and treatment opportunities were limited, many turned to other synthetic opioids, such as heroin and fentanyl. Thus, the public health crisis of opioid addiction has endured. This paper highlights the importance of understanding differences among women and men in opioid use and its biological and psychosocial effects to advance gender-based treatment approaches and effective public health policy.

Keywords: Opioid-Related Disorders, Sex Characteristics, Addiction Medicine

The United States continues to confront an ongoing and devastating epidemic of opioid use and addiction. Fear of COVID-19 and the personal stress related to reduced access to care, physical distancing, self-isolation, and diminished economic resources incur increased misuse and addiction risk for those who struggle with substance use and those experiencing pain.[1,2] Key national agencies, such as the National Academy of Medicine, have formulated plans for directing resources to address this added risk, highlighted the vulnerability these individuals face and emphasized the importance of understanding opioid addiction.[3,4] However, until relatively recently in this epidemic, neither the route to opioid use and misuse for women nor its implications have been widely studied.[5] The purpose of this paper, made even more relevant by the COVID-19 pandemic, is

to focus on opioid use in women as well as the sex and gender differences that can more fully inform our treatment and prevention response for all persons struggling with opioid use and addiction.

The Evolution and Impact of Synthetic Opioids

Narcotics, originally derived from the opium poppy, have long been used to treat a variety of conditions, particularly pain. The potential for addiction with these agents, although not always immediately recognized, rapidly became well-known with their use.[6] From the mid-nineteenth through the early twentieth century in the U.S., women were widely prescribed these opiates and other addictive drugs largely for reproductive ailments, pain, and neurasthenia.[7] This last condition, neurasthenia, was more commonly diagnosed in women and included a wide range of physical disorders that were ascribed to nervousness or anxiety. Epidemiological data from this period indicated that women became the majority of opiate users as a consequence.[7,8] Ultimately, national recognition of the harm induced by such drug use began with acknowledgement by physicians of the dangers posed by opium-derived substances and the establishment of laws to control the flow of addictive drugs. It was at this time that social stigma began to be assigned to women who used opiates and addictive drugs.[7]

Synthetic opioids were introduced in the early twentieth century and as they were widely dispensed, crises arose with the legal and illegal use of these substances.[9] Recognition of the lethality associated with these drugs, particularly heroin, led to federal legislation attempting to limit their use and ultimately making them illegal by the 1920s.[6] Nonetheless, synthetic opioids were employed for war-time use, and legal and illegal synthetic opioids continued to be accessible subsequent to the Second World War.[6,9] However, the 1990s marked a shift in the U.S. to the unbridled promotion and availability of prescription synthetic opioids for the treatment of pain and, by the early 2000s, addiction to these drugs became an epidemic.[10]

The seeds of the current opioid epidemic were sown on the "demand side," in that both acute and chronic pain are very common and result in debilitating symptoms. Multi-modal therapies for pain management, using combinations of behavioral strategies, rehabilitation, complementary medicine and pharmacologic interventions are often limited by availability and cost.[11] But, the real spark that ignited the firestorm of increased opioid use came from the "supply side" when pharmaceutical companies responded to the demand by using misinformation on the addictive properties of opioids to recruit increased prescribing.[12]

In the past decade we have entered a new phase of this epidemic. After peaking in 2010, prescriptions for opioid analgesics leveled off through 2012 and, from 2012 to 2015, prescriptions declined 18%.[13] Nonetheless, despite this decrease, opioid prescriptions in 2015 were three times higher than in 1999.[13] In addition, national opioid overdoses were markedly increased in 2014 due to greater use of heroin and use of the highly potent synthetic opioid fentanyl, which can be used alone, or can be circulating within the heroin

supply.[14-16] This uptick in opioid use is a downstream effect of the period of widespread prescribing of opioids because many individuals addicted to prescription opioids progress to using an available opioid, such as heroin, when they lose access to the prescribed substance.[17]

Since the middle of the twentieth century, both legal and illegal addictive substances have generally been used more by men than women and have resulted in a higher prevalence of substance use disorders in men. Such substances range from cigarettes[18] and alcohol[19] to cocaine and heroin.[20] Yet, when use of addictive substances is compared for women and men adjusted for exposure to such agents, women are also found to be highly vulnerable to addiction.[21] Moreover, after exposure to addictive substances, women more rapidly become addicted[22] and, for substances such as tobacco, women are more likely to relapse after a quit attempt.[23] Because the primary means of exposure to opioid use for women has been through medical treatment, the widespread escalation of prescribing synthetic opioids dramatically affected women in terms of morbidity and mortality, including women of reproductive age.[24]

Research on the ongoing opioid crisis has largely reported its impact on either the White or the total U.S. population and has not focused on trends by race or ethnicity.[25] Harrison et al[26] suggest this is partially due to the increased likelihood of non-Hispanic White persons receiving opioid prescriptions for pain management, which precipitated the current epidemic. As opioid use, misuse, addiction, and attendant mortality rates greatly increased among the White population from the mid-1990s to its peak in 2010, overdose mortality rates remained stable for the Black population.[25] However, subsequent data from the 2015 National Survey on Drug Use and Health (NSDUH) suggest that Black respondents overall attained a similar prevalence of prescription opioid misuse as White respondents by approximately 2010.[27] This was followed by a rapid acceleration of opioid overdose mortality for Black Americans between 2010 and 2015, during which time mortality increased due to heroin and other synthetic opioid use in both Black and White populations.[25]

Stratification of the NSDUH data by gender showed greater reported misuse for Black men than Black women as well as for White men compared with White women.[28] No significant differences of prescription opioid misuse were shown between Black and White women or between Black or White men, respectively. Yet, other factors intersect with both gender and race. For example, among Black women, reduced socioeconomic status increased the probability of misuse,[28] while access to buprenorphine treatment for opioid addiction has been found to be greater for White persons, those with non-governmental insurance or the capacity to pay out-of-pocket.[29] Data on the current opioid epidemic regarding Black communities are limited, and data on Latinx, Asian American and indigenous communities are severely lacking. Data on the relationship among race, gender and the risk for addiction and/or overdose deaths will be presented when available. However, the relationships among reported race, ethnicity, gender, opioid use, misuse and addiction have not been a target of investigation and, consequently, research studies and national surveys largely report on the White or the total population.

Women, Pain and Opioids

Women have more acute and chronic pain than men.[30,31] Nationally representative survey data reveal that of men and women reporting chronic pain, women are more frequently prescribed opioids in U.S. outpatient care, and the percent of women being prescribed opioids increases with age ≥ 61 (80%).[32] Women also often receive opioids to treat conditions for which there are no data to support efficacy, such as headache. Moreover, women have been more likely to be prescribed opioids in combination with other medications, such as benzodiazepines, thus increasing overdose risk.[33,34]

Overdose deaths from prescription opioids and subsequent use of illicitly manufactured fentanyl have increased steadily increased since 1999 and doubled from 2010 to 2018.[35] Men are more likely to die from opioid overdoses,[35] however the Centers for Disease Control and Prevention (CDC) has reported that the increase in the rate of change in overdoses from 1999 to 2016 was 404% for men and 583% for women.[5] A cross-sectional study of national and state-based samples totaling over 400,00 drug suicide attempts resulting in 21,594 deaths indicate that 54% of opioid-related lethal suicidal drug overdoses occur in women.[36] National survey data from the 2014 NSDUH of past-year frequency of prescription opioid misuse show a positive association with past-year suicidal ideation, planning and attempts, with the strength of these relationships significantly stronger for women compared to men.[37] Importantly, after controlling for mental and general health and demographic characteristics, the same data did not reveal gender differences in these relationships suggesting the importance of these factors in assessing suicidality in women.

Yet, general recognition of increased opioid use in women and its risks has been limited, even leading to findings that women who died from opioid overdoses were three times less likely to receive the "rescue drug" naloxone (Narcan) through emergency medicine services than men.[38] As Sumner et al point out, opioid overdoses have historically been related to heroin used by males under age 50. However, there is an urgent need for improved understanding of the demographics of the current opioid epidemic, as well as for training in clinical decision-making given the societal preconceptions surrounding who may use opioids. Importantly, this lack of recognition extends to government blueprints for how to mitigate this epidemic. For example, the 2017 final report of The President's Commission on Combating Drug Addiction and the Opioid Crisis lacked any mention of treatment services specifically for women other than for pregnant women.[39] Similarly, in 2018, the coordinated federal plan for health science and technology's response to the opioid crisis also overlooked the pre-clinical, clinical and epidemiological data that highlight the specific needs of women, and the plan mentions women only in the context of being mothers or caregivers.[40]

Defining Terms: Sex and Gender

In this paper, working definitions of the terms sex and gender are used as developed by the Institute of Medicine's (IOM) 2001 Committee on Understanding the Biology of Sex and Gender Differences.[41] These definitions were offered at a time when biomedical science was debating whether there was any added value in studying the biology of female vertebrates beyond their reproductive biology.

The IOM committee defined sex as a biological classification, generally as male or female, linked to reproductive organs, chromosomal complement, hormonal milieu, and anatomy. This definition was made for the purpose of differentiating sex as a biological variable from the concept of gender, defined as a self-representation or sociocultural identification influenced by social, cultural and personal experience.

By tradition, our understanding of sex was a "male" and "female" dichotomy, though scientific research on disorders such as androgen insensitivity syndrome, 21-hydroxylase deficiency, and 5 alpha-reductase deficiency have complicated this binary distinction.[42] Gender as an internal sense of identity can be binary "men" and "women," but also non-binary or entail genderqueer identities.[42] Additionally, one's gender can be consistent with the sex assigned at birth (cisgender) or can differ (transgender). Since most biomedical research literature does not use these terms or differentiate between sex and gender, we will utilize the language with which studies described their participants.

The following sections provide data on opioid use in women and sex and gender differences in biological and psychosocial factors that relate to use, addiction and treatment, including considerations of substance misuse in the context of reproductive health. We conclude with the resulting intervention and health policy considerations that can be drawn from such data.

The Prevalence and Biology of Pain

Gender Differences in Pain Prevalence

Pain is a common symptom and can be classified in many ways: chronicity (chronic, acute), site (low back, pelvic), number of sites (regional, widespread), tissue type (musculoskeletal, neuropathic), or etiology (iatrogenic, trauma, insidious).[43] The 2016 National Health Interview Survey of over 27,000 adults estimated that chronic pain alone affects almost a third of the population, and the age-adjusted prevalence of both chronic pain and high-impact chronic pain, defined as frequently limiting life or work activities, were significantly higher among women.[44] Due to its prevalence and associated disability, chronic pain exacts a costly toll both personally as well as economically with an estimated cost of $560 billion each year in direct medical costs, lost productivity, and disability programs.[44]

Women report pain more frequently, show greater sensitivity to experimentally-induced pain, and often report more severe levels of clinical pain than do men.[30,40,45] Women also experience higher rates of regional

pain, widespread pain, musculoskeletal pain, neuropathic pain, osteoarthritis, orofacial pain, abdominal pain, headaches, and postoperative/postprocedural pain.[30]

In terms of racial differences, Black women experiencing pain are reported to suffer greater physical disability than White women.[46] Black adults compared to White adults when not stratified by gender also report greater pain sensitivity,[45] as well as more severe pain, pain-related disability and mood disorder symptoms than White persons. These differences have been shown for both younger[47] and older[48] adults.

Sex Differences in the Biology of Pain

The response to pain is initiated at the spinal cord and transmitted via ascending pathways to the brain. The transition from acute to chronic pain is thought to involve neurons as well as microglia, brain-based immune cells, at the level of the spinal cord and the periaqueductal gray (PAG).[49,50] The microglia perform two functions when activated by injury or infection. They release inflammatory chemicals normally important for the immune response, and some transform into macrophages which are important for destruction of damaged cells.[49]

When pain is perceived, a neural circuit that modulates pain is initiated to release endogenous endorphins, the brain's own opioids,[51] and the descending central nervous system (CNS) circuit to the PAG, ventromedial medulla and dorsal horn of the spinal cord produces pain reduction.[50] It has been demonstrated in animal models that opioids injected into the PAG are sufficient to alleviate chronic pain, and there are sex differences at the level of the PAG that produce this response.[52] As reviewed by Averitt et al,[50] sex differences are found in: 1) the descending circuit from the PAG to the spinal cord, 2) activation of the PAG by inflammatory pain, 3) the PAG microglia and neuroimmune signaling, and 4) the influences of gonadal hormones on opioid receptor expression, opioid metabolism, and the PAG responses to pain mediated by microglia and the immune system.

As noted previously, preclinical and clinical studies find that males exhibit a greater opioid analgesic response to pain than females.[50,53] This greater analgesic response is thought to be due to an attenuated microglia inflammatory response in the PAG in males compared with females.[50] Sex differences in microglia in the dorsal horn are also associated with differential expression of pain in males and females.[54] Yet, the macrophage responses in the dorsal root ganglia, which are reactions to tissue damage or pathogens, are not related to sex differences in neuropathic pain.[55] Thus, sex differences are found at the level of the PAG, as well as at dorsal horn of the spinal cord and the dorsal root ganglia where the response to nerve injury results in pain and to the transition to chronic pain occurs.

The descending input from the CNS to the PAG that mediates the analgesic response also receives input from the cortex, hypothalamus and amygdala to integrate the central response to pain. This integrated response

can be sex-specific and preferentially trigger a stress response that is different for males vs. females and this can differentially impact the response to pain in males or females and impact the response to pain.[53] For example, male odors trigger a stress response in male animals, presumably due to a perceived threat.[56] Studies with rats and mice have shown that whether an experimenter is male or female, or a female is wearing a T-shirt with male odors, influences the analgesic response of male animals, but not females.[56] Thus, pain inhibition can be affected by central stress responses in a sex-specific way, in addition to the sex differences in the descending circuit from the PAG and sex differences at the level of the spinal cord.

The Prevalence and Neurobiology of Opioid Addiction

Gender Differences in the Prevalence of Opioid Use and Misuse

According to a 2020 report from the National Center of Health and Statistics, 5.7% of U.S. adults used one or more prescription opioids in the 30 days prior to sampling between 2015 and 2018.[57] This prescription opioid use was significantly higher among women than men (women: 6.4% vs. men: 4.9%), and overall use increased with age (20-39 years: 2.8%; 40-59 years: 6.6%; 60+ years: 8.2%). Available data on race by gender for all pain prescriptions (opioid and nonopioid) indicated that use was higher among women than men for non-Hispanic White (13.7% vs 9.4%), non-Hispanic Black (12.2% vs 7.4%), and Hispanic (10.2% vs 6.8%) adults.

Earlier available analyses of opioid prescribing between 2006 through 2010 also showed variation by medical specialty (with the highest rates prescribed by pain medicine, surgery, and physical medicine/rehabilitation)[58] and widely different rates depending on location (with greater rates in U.S. counties with a larger non-Hispanic White population, smaller cities, and higher rates of unemployment and Medicaid enrollment).[13]

CDC data show that opioid prescribing rates declined between 2012 and 2017, indicating that prescribers became more conservative in their practices. This was likely guided at least in part by the CDC's 2016 Guidelines for Prescribing Opioids for Chronic Pain[13] and influenced by the Food and Drug Administration (FDA)'s 2011 Risk Evaluation and Mitigation Strategy (REMS) program mandating prescriber and patient education, appropriate patient screening and monitoring as well as post-marketing studies for potentially dangerous medications, including opioids.[59] Data on dispensing of opioid prescriptions from a nationwide U.S. database for the period 2008-2018 show a 31% national decline in opioid prescription fill rates for all ages over this period. However, opioid prescriptions remained disproportionately higher in women compared to men for all ages, and this gender difference was greatest among adults aged 65 or older, whose rates were highest and declined the least.[60]

One outcome of this waxing and waning of widespread opioid prescribing was the transition of many individuals addicted to prescribed opioids to illicit opioids, such as heroin, when they lose access to the prescribed substance. As shown in data from the national Survey of Key Informants' Patients Program, 75% of those using heroin were introduced to opioids through prescription drugs, and these more recent heroin users tended to be white, middle-class, and suburban.[61] Furthermore, the percent of heroin users who identified as women surpassed that of men, from a 1960s baseline male predominance of 4:1 to essentially 1:1 in the 2010s.[61] Data from the National Survey on Drug Use and Health also show that use of heroin in the U.S. increased as prescription opioid use decreased.[20] This study compared gender differences in heroin and nonmedical prescription opioid use in the U.S. between 2007 and 2014 and found that women's misuse of prescription opioids was decreasing at a slower rate while heroin use was increasing at a faster rate relative to men.

Another opioid linked to illicit use is fentanyl, a highly potent synthetic opioid approved for the management of severe pain. Limited research is available on the sex and gender differences in illicitly used fentanyl and related morbidity and mortality. However, 2013-2015 selected state data from the CDC showed that fentanyl deaths in some states increased faster in men compared to women,[62] while other regional data reported deaths due to fentanyl-contaminated heroin were more likely to occur in women.[63]

Sex Differences in the Neurobiology of Opioid Addiction

The endogenous opioids act at four classes of opioid receptors: mu, delta, kappa and nociception receptors. There are sex differences in mu- and kappa- opioid receptor neuroanatomical organization as well as regulation of receptor expression by gonadal hormones.[64] Synthetic opioids, including morphine, heroin, oxycodone and fentanyl act primarily at the mu receptor to alleviate pain. However, the effects of these drugs on the CNS that result in addiction are thought to include the downstream effects on the kappa receptors.[64]

Studies of addiction tend to focus on the action of these drugs in the forebrain and other areas of the CNS, [64,65] while studies of opioid modulation of pain tend to focus on the descending pain circuit.[50] Findings from these different neural circuits have yet to be integrated, so we do not have a comprehensive understanding of how sex differences in opioid analgesia are related to sex differences in addiction. Moreover, addiction can present in different ways for women and men.[66] For example, there are sex differences in the rate of escalation of drug taking behavior, with women showing more rapid escalation than men for all classes of drugs of abuse.[65,67]

In basic animal research, female rats are found to acquire heroin self-administration more rapidly than males,[68,69] and estradiol, the primary hormone produced by the ovary, enhances acquisition of heroin self-administration.[70] In a recent study using behavioral economics to assess fentanyl intake in male and female rats, females self-administered more fentanyl and worked harder for the drug than did males.[71] However, under

conditions of fentanyl vs food, sex differences were only present at select doses when males chose fentanyl over food and females did not.[71] Thus, the doses and conditions under which animals self-administer opioid drugs affect whether sex differences are found as well as the direction of the sex difference. This illustrates that even in our animal models, sex differences in opioid-taking behaviors are influenced by the context of the choices being made.

Research on the neural mechanisms of heroin self-administration indicates the core of the nucleus accumbens is necessary for acquisition of this behavior in male rats.[72] Females have not been investigated to date in this regard, though there are demonstrated sex differences in and hormonal influences on the nucleus accumbens[73,74] and the neural mechanisms of opioid addiction.[64] Next steps need to identify how and where sex differences in the neural systems for reward and pain interact to affect sex differences, such as enhanced susceptibility to addiction in some women.

Gender-specific Treatment Considerations

Barriers to Treatment

Population and treatment-seeking data indicate fewer women than men with substance use disorders enter treatment.[75] Taking the step of entering substance use treatment can be difficult and even more challenging for women than men, resulting in a significant gendered treatment gap.[76] Three major reasons are largely responsible for this disparity. First, women report more intense social stigma associated with their addiction than do men, thus making it more difficult to admit to and seek help for use and misuse of substances.[7,22] This stems from societal perceptions of women who are addicted that run dramatically counter to expectations assigned to women, and thus engender a greater sense of shame and/or embarrassment, and/or a fear of discrimination that raises the bar for entry.[77]

Second, treatment programs have typically been utilized by and designed for the health needs of men, consequently, women tend to report that the environment does not seem welcoming and the services often do not target their needs.[22] For example, national data on those seeking treatment for opioid addiction indicate that men require specific additional services relative to alcohol use at much greater rates than women,[78] while women have higher rates of co-occurring mood and anxiety disorders and current medical conditions than do men.[79] As lethal opioid-related drug overdoses are associated with these mental and general health conditions, enhanced screening of women for suicide ideation and planning, as well as past history of suicide attempts, becomes particularly important for women seeking care and throughout treatment.[36] Data from a large multi-site clinical trial also indicate that women with Opioid Use Disorder (OUD) are more likely than men to report using substances in response to both negative emotional states as well as pain.[80] Other reviews and meta-

analyses indicate that men in opioid treatment programs are more likely to have been involved in the criminal justice system than women in these programs.[78,79] Yet, women vs men with OUD report greater impairment in functioning, thus reducing capacity to obtain and maintain employment and housing, and to develop and ensure supportive relationships and personal care.[79] Women with OUD frequently report intimate partner violence and using substances to cope with physical and emotional abuse, and the co-occurrence of domestic abuse and OUD increases risk of relapse and reduces treatment engagement.[81] These differences between women and men suggest both the need for gender-specific approaches to treatment services as well as consideration of different pathways to addiction that necessitate gender-based prevention and early intervention approaches.

Third, women who are pregnant or parenting have serious concerns that they will be prosecuted and/or lose custody of their children if they present for treatment.[82] It is recognized, even by women seeking treatment, that circumstances sometimes require periods during which alternatives to parental care must be provided for children, such as those obtained through Child Protective Services.[82] However, the potential for women, in particular, to be the focus of blanket discrimination is significant. As highlighted by Meyer and colleagues,[83] twenty-five states and the District of Columbia consider substance use during pregnancy to be a child abuse offence and can be reported. Further, some states have civil child-welfare requirements, which stipulate prenatal substance use as grounds for ending parental rights on the basis of child abuse or neglect.[84]

Treatment for Opioid Use and Reproductive Health

Gender-centered Treatment

In attempting to both reduce barriers to treatment entry and meet the gender-specific needs with which women present, the 1980s and 1990s saw the inception of women-only programs, followed by women-centered programs. Women-only programs compared to mixed-gender alternatives showed greater success in treatment outcomes even in the face of more severe substance use and psychiatric morbidity.[85] Such success served to make clear the importance of programming directed toward the specific needs of women, such as treatment for commonly co-occurring depression and anxiety as well as experiences of trauma, accommodation for child care, individual and family therapy and other family services. As reviewed in detail by McHugh et al,[86] women reported greater comfort, safety and outcomes in gender-specific treatment and had better adherence in continuing care. Further, randomized controlled trials also support gender-specific approaches across sub-groups of women with children, co-occurring psychiatric disorders, and for those women in the criminal justice system.

Medication for Opioid Use Disorder

The three medications approved by the FDA for treatment of OUD are methadone, buprenorphine, and extended-release naltrexone. Each has a different mechanism of action, but all reduce opioid cravings by

targeting the mu-opioid receptor within the endogenous opioid system.[87] Although some studies have found sex differences in treatment outcomes with these medications, most research either has not examined differences between women and men or has had insufficient enrollment of women to conduct sex-specific analyses. For example, a recent review of randomized trials of buprenorphine found that only half of twenty-five studies provided data related to sex differences, and sample sizes for women participants were small.[88]

Methadone is a long-lasting opioid agonist that "replaces" the action of opioids on the mu-opioid receptor. Consequently, it must be carefully monitored as cessation can result in withdrawal symptoms, and it can only be dispensed in government-approved clinics. Buprenorphine is a high-affinity partial opioid agonist that reduces withdrawal as well as the rewarding effects of any concurrent opioid use. Both methadone and buprenorphine treatment are associated with reduced mortality during the first critical month of treatment.[89] In combination with Cognitive Behavioral Therapy, buprenorphine has shown promising results especially for the treatment of prescription opioid use dependence,[90] and buprenorphine can be used in office practice thus providing greater access for women who are more likely to seek office-based care.[91] Buprenorphine is also used in combination with naloxone, an opioid antagonist, for continuation therapy to reverse the effects of opioids should they be taken.

Naltrexone is an antagonist of the mu-opioid receptor and blocks the experience of opioid "highs" as well as analgesic effects. It causes immediate withdrawal symptoms in anyone with active physical dependence on opioids, and typically requires opioid withdrawal under medical supervision prior to starting it. During the early initiation of treatment, it also has been shown to cause greater adverse effects in women than men.[92] As a consequence, it is more difficult for patients to comply with naltrexone treatment and may be especially difficult for women to tolerate.

Pregnancy and Opioid Use Disorder

Pregnancy poses additional challenges for those currently addicted to opioids or in recovery. Considerations include pain management during delivery, as well as neonatal outcomes including risk of neonatal abstinence syndrome (NAS) — a constellation of symptoms in the offspring secondary to opioid withdrawal. The most recent national U.S. data tracking the percent of pregnant women hospitalized specifically for treatment of prescription opioid abuse showed a dramatic increase from 2% to 28% between 1992 to 2012.[93] The most recent CDC data from 2016 indicates that seven of every 1,000 hospitalized newborns, or nearly 80 newborns per day, were diagnosed with NAS.[94]

Two evidence-based medications that are used for treating OUD during pregnancy are methadone and buprenorphine, and reports suggest that each can be prescribed without apparent significant adverse outcomes for patients or neonates.[95-97] Neither methadone nor buprenorphine has been shown to be excreted in breastmilk, suggesting safety of these therapies during lactation. *In utero* exposure to either drug has not yet been

demonstrated to have deleterious effects on infant development.[98] Pregnant patients with OUD who received buprenorphine compared to those receiving methadone used significantly less morphine at delivery and had shorter hospital stays, and the average duration of NAS in their offspring was less than half as long.[99-101] Considering scheduling of therapy, ongoing methadone maintenance programs have been shown to be more efficacious during pregnancy than methadone-assisted withdrawal treatment.[102]

Additional studies point to the importance of treating coexisting conditions in pregnant patients with OUD to optimize outcomes. For example, neonates born to pregnant women treated with methadone who also smoked 20 or more cigarettes per day were significantly more likely to exhibit signs of NAS than babies born to light smokers (10 or fewer cigarettes per day).[103] Further, pregnant women with co-occurring diagnoses of OUD and mood disorder are more likely to test positive for illicit opioids and/or cocaine while in substance use treatment compared to both those with a co-occurring anxiety disorder and those without co-occurring psychiatric disorders.[104] Those with co-occurring mood or anxiety disorders also had more psychosocial impairment and a higher incidence of suicidal ideation compared to pregnant women without co-occurring psychiatric disorders.[104]

Further Considerations

Sexual Minority Individuals

As sex and gender are increasingly recognized as not binaries but spectra, populations other than cisgender women should be considered when assessing opioid use and adapting treatment modalities to serve transgender, non-binary, and gender non-conforming (TNG) communities. No national survey data on opioid use in TNG populations have been published to date, but TNG individuals have disproportionately high rates relative to cisgender individuals of other substance use problems, including tobacco,[105] cannabis,[106,107] and alcohol.[106,107] Stress experienced by marginalized groups as a result of societal prejudice, discrimination, and internalized stigma is widely used as an explanatory model for transgender health disparities,[108] including increased substance use.[109] The importance of such stress as well as other psychosocial and biological contributions require further examination.[106]

Lesbian, gay, and bisexual people

The 2015 and 2016 National Survey on Drug Use and Health Data found increased prevalence of prescription drug misuse among lesbian, gay, and bisexual young adults compared to heterosexual peers,[110] replicating previous studies demonstrating increased misuse of prescription[111-113] and illicit opioids. [112,113] In addition, earlier age of first prescribed opioid was the most significant factor associated with increased likelihood of future misuse of both opioids and other categories of prescription drugs.[111]

Women and Opioids: Important yet Challenging Opportunities

In reflecting on what is now known about the current opioid epidemic, there appear three broad opportunities that can advance the nation's efforts to address this continuing health crisis and its sequelae.

The first opportunity lies in our support of research to further unmask the complex experience of pain, often cited as one of the oldest persisting human maladies, through an increased focus on sex and gender differences. The empirical exploration of sex differences in pain and analgesia via basic and translational research is a powerful tool for discerning underlying mechanisms that inform the potential for opioid misuse as well as pharmacological and behavioral interventions.[114] For example, given preclinical and clinical studies showing greater opioid analgesic response to pain in males than females,[50,53] future studies could investigate whether sex and gender-specific opioid analgesic responses to pain are associated with either quantity or frequency of opioid use or other proxies of misuse and increased potential for addiction. A concurrent increased emphasis in basic and translational research on sex and gender differences to better understand opioid use and addiction is also warranted, as is a focus in clinical and epidemiological research on improving our prediction of gender-specific risk and protective factors. For example, stress is a known risk factor for both chronic pain and opioid misuse. Exposure to stress, although moderated by levels of distress in response to stressors, is related to worse outcomes for those with OUD[115,116] as well as those with chronic pain.[116] In addition, sex and gender-specific responses to stress are found in relation to OUD, such as women showing a greater increase in opioid craving as a function of stress,[117] yet this complex topic leaves more to uncover as suggested by Roos et al,[118] who report findings that depressive symptoms mediate the indirect effect of perceived stress on opioid use.

Importantly, the recognition that pain, analgesia and opioid use are inextricably linked in human experience indicates that these conditions and their potential physical and psychological mechanisms, such as stress, be scientifically approached as related areas of study. Moreover, the potential for discovery that will reap the greatest practical benefit for all members of the population will be found in studying sex and gender differences at the intersection of opioid use and addiction.

The second opportunity is found in the potential to more fully implement into clinical care what we now know from the empirical literature about sex and gender differences in opioid use, misuse and addiction. For example, we know that buprenorphine in the context of medication assisted treatment (MAT) is effective in reducing morbidity and mortality.[119] In its last review of substance abuse treatment facilities in the U.S., the Substance Abuse and Mental Health Services Administration (SAMHSA) found the percentage of opioid treatment programs offering MAT with buprenorphine had risen from 11 percent in 2003 to 58% in 2015.[120] The increasing growth of MAT opens the door to targeting services more effectively within these programs to better account for the different types of personal experience, co-occurring disorders, and greater functional

impairment of women and men.[81,87] This would allow us to optimize the practical benefit of the services being offered and enhance outcomes across and among women. As has been shown, women-centered services and therapies that address high-valence needs of women, such as child care, depression and anxiety disorders, domestic counseling, intimate partner violence, experiences of trauma, unemployment and housing needs, show better outcomes.

Third, recognizing that OUD is a chronic, relapsing condition, many have called for national and state policies to interrupt the spread of this epidemic[121,122] and address its long-term sequelae.[123] Considerable governmental efforts have been expended outlining and initiating plans to fight this continuing health crisis. However, if women are referenced in these reports, the focus is almost exclusively on management of maternal opioid misuse.[5,40] Maternal health and parenting are, of course, vital areas of concern. However, a focus is missing on addressing punitive and discriminatory policies and laws that must be reversed to ensure appropriate protection for women who fear losing custody of their children if they seek treatment. Moreover, much more is entailed in our response to the challenge of opioid use and addiction in women. Those advising, legislating and enforcing national health care policies and practice guidelines have the opportunity to focus on supporting and implementing initiatives that address the unmet needs of women. One meaningful example would be to ensure insurance coverage for non-opioid pain management and for OUD, another would be to increase the existing workforce of those trained to provide treatment for addiction, and yet another would be to ensure that health care policy recognizes everyone in our population.

We have highlighted the importance of research dedicated to understanding opioid use in all persons and have provided data illustrating the need to recognize sex and gender differences in research, treatment planning and health policy. We need to intentionally consider the health of all women and incorporate the spectrum of sex and gender differences in our population to best serve the public health and derive better health outcomes.

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