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SEX AND GENDER ISSUES IN BEHAVIORAL HEALTH (CN EPPERSON AND L HANTSOO, SECTION EDITORS)

Challenges for Women Entering Treatment for Opioid Use Disorder

Andrew S. Huhn[1] · Kelly E. Dunn[1]

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Abstract

Purpose of Review Women with opioid use disorder (OUD) face unique challenges the moment they enter treatment. This narrative review focused on recent literature regarding sex- and gender-based issues that could affect treatment outcomes in women with OUD.

Recent Findings Women respond differently to opioids based on hormonal factors, are more likely to present to treatment with mental health conditions, especially depression, and are more likely to have experienced trauma via intimate partner violence compared with men. Women also face stigma when entering OUD treatment, particularly if they have children.

Summary Future research to improve OUD treatment outcomes in women should account for sex as a biological variable and gender as a social construct. Women have a fundamentally different experience than men during the course of OUD and upon treatment entry. Programs that address childcare/family support, mental health, and trauma are warranted for women with OUD.

Keywords Opioid use disorder · Women · Sex differences · Gender differences · Mental health · Trauma

Introduction

The opioid crisis has devastated individuals and families across the USA. Women are directly impacted by the opioid crisis at all levels, including prescription opioid exposure where women have a higher incidence of chronic pain and may be more likely to develop physical dependence to opioid analgesics [1, 2], in treatment for opioid use disorder (OUD) where women may be at increased risk of negative outcomes relative to men [3••, 4], in the family unit where women may face the brunt of childcare responsibilities and/or interpersonal partner violence (IPV) [5, 6, 7•], and in the overdose epidemic where rates of fatal overdoses have increased among women in recent years [8–10]. Historically, OUD treatment studies have recruited predominately male samples and thus have not equally represented women in study findings, which often precludes sex/gender-based and sex/gender-specific research [4]. As such, strategies to improve OUD treatment may be tailored towards men, which might have a detrimental impact on the quality of care for women seeking OUD treatment.

Sex, as a biological variable, and gender, as a social construct, are important factors in the human experience of OUD. However, it is extremely rare that both sex and gender are reported in clinical trials [11], and given the lack of consistency in whether trials ask participants to self-report their sex or their gender, and the likelihood that wording of this question could produce different responses and exclude persons who do not identify as gender binary [12], there are inherent challenges in disentangling the roles of sex and gender in OUD research. Still, research on sex and gender has real-world implications regarding the quality of care for women with OUD, and in light of the deadly and protracted opioid crisis, there is an urgent need to improve OUD treatment for women [13–16].

Women have unique challenges the moment they initiate OUD treatment. Some of these challenges may fit cleanly into sex-based issues, relating to hormonal factors and/or response to opioids [17]; gender-based issues, relating to social constructs and/or societal expectations placed on women [3••];

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✉ Andrew S. Huhn
ahuhn1@jhu.edu

[1] Behavioral Pharmacology Research Unit, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224, USA

and other issues that represent an overlap between sex and gender, including mental health conditions and/or symptoms that have both biological and social underpinnings [4]. As such, the field of OUD treatment would benefit from the guidance of recently published literature that describes and quantifies biological, psychological, and social challenges in women who present to OUD treatment. The goal of this narrative review is to summarize and synergize the most recent literature describing the unique challenges faced by women with OUD, and to identify actionable areas of needed change to improve treatment outcomes. Topics that have been recently reviewed (e.g., pregnancy [18]; neonatal abstinence syndrome [19]) are not reviewed here.

Presentation to Treatment

Physiological Factors that Affect Women With OUD

Women may face unique physiological challenges upon OUD treatment entry relative to men. These include increased prevalence of chronic pain and greater pain severity [20], as well as greater physical dependence to opioids compared with men. Gonadal hormones in women and men play a role in both pain response and response to opioid analgesics [17, 20], and in women there is an inverse relationship between plasma testosterone and musculoskeletal pain [21]. Relatedly, women versus men with cooccurring OUD and chronic pain may experience greater opioid withdrawal [22]. There is also evidence from clinical trials of medications to treat opioid withdrawal that women experience a more severe withdrawal syndrome than men [23•]. These findings may be due, in part, to the relationship between sex hormones and opioid neurotransmitter systems [24]. Variability in estrogen levels during the menstrual cycle is associated with opioid receptor availability [21], and women are more likely to present to treatment with greater physical opioid dependence than men [25, 26]. Likewise, there is a correlation between higher estradiol levels and higher methadone dose needs in women in OUD treatment [26]. There is also some evidence of "telescoping" effects in women with OUD; i.e., women may progress though the stages of OUD and/or become physically dependent at a faster rate than men. While some treatment studies have observed telescoping among women [27, 28], another study that focused on persons with active heroin use did not observe sex-based evidence of telescoping [29]. In summary, there is significant evidence from human studies of OUD that women have a fundamentally different response to opioids than men, and physiological conditions including chronic pain might contribute to acquisition of OUD and act as a barrier to OUD treatment.

Differences in Substance Use and Mental Health Profiles

Women may have a different profile of substance use than men, specifically a higher rate of nonmedical prescription opioid and polysubstance use. For example, a cross-sectional study (n = 328) found that women were more likely than men to initiate opioid use with nonmedical prescription opioids [30]. Studies using the National Survey on Drug Use and Health (NSDUH) (n = 160,371) also found that 23.6% of women who were using opioids reported co-use of other substances, most often alcohol, cannabis, and tobacco [31], and that 87% of parenting women who reported recent prescription opioid misuse were engaging in polysubstance use [32]. A study using the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III) database (n = 330) found the presence of major psychiatric comorbidities (e.g., schizotypal personality disorder, depressive disorder) to be associated with a higher likelihood of sedative co-use in women but not men [33•]. An analysis within the Pennsylvania Behavioral Risk Factor Surveillance System found that the majority (95%) of parenting women who were receiving OUD treatment (n = 152) reported an adverse childhood experience and 65% had experienced four or more adverse childhood experiences [34]. Altogether, these outcomes suggest that women are at elevated risk of prescription opioid misuse, which is especially problematic in light of evidence from pharmacy prescription fill rates that women are more likely than men to be prescribed opioid medications [35] and to be co-prescribed sedatives and opioids (which is a major risk factor for opioid overdose) [36, 37]. This may be further exacerbated by the fact that 54–80% of women fill opioid prescriptions after giving birth [38], which is a highly stressful period that could promote opioid misuse.

Differences in substance use profiles may also extend to differences in overdose risk profiles. Though overdose rates among men still outpace those of women [39], the CDC has reported that drug-related overdose among women increased by 260% between 1999 and 2017 and that, in contrast to trends observed in men, this change was largely driven by deaths related to prescription opioids rather than heroin and synthetic opioids (e.g., fentanyl) [9]. A study of more than 29,000 persons in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) trial also found a greater risk of death among women who were prescribed opioids relative to men [40] and a population-based cohort study in California (n = 602,185) suggested that drugs (3.68 per 100,000 person-years) were second only to obstetric-related (6.52 per 100,000 person-years) causes of death for new mothers [37]. Studies suggest that victimization among women may also contribute to increased overdose risk. For instance, 47.1% of women who had OUD in one study (n = 218) reported polyvictimization, which refers to having experienced multiple instances of verbal/physical abuse and/or

domestic violence, and researchers found that every one unit increase in polyvictomization scores was associated with a 4% increase in odds of overdose [41••]. Another study that interviewed women who experienced a "near-miss" overdose ($n = 60$) or family members of women who had experienced a fatal overdose ($n = 39$) found that victims had substantial histories of abuse and loss, including stress due to limited social support, interpersonal conflict, and untreated mental health disorders [42]. Further complicating this issue are potential disparities in adequate overdose prevention. For instance, an evaluation of medical examiner files from 2012 to 2014 ($n = 124$) found that women were three times less likely than men to be prescribed naloxone (Narcan) following suspected overdose [43]. Moreover, women are less likely than men to get direct referral to treatment or follow-up with treatment following an ED visit [16].

In addition to differences in substance use profiles, several studies have reported that women are more likely than men to report psychiatric comorbidities, especially major depressive disorder or depressive symptoms. For example, a large survey study ($n = 36{,}309$) reported that women with OUD were more likely to report psychiatric comorbidities including major depressive disorder [44], and a large observational study of women in methadone treatment ($n = 10{,}454$) reported that women were more likely than men to report depression, self-injury, and suicide attempts [45]. Likewise, women in a large comparative effectiveness trial of buprenorphine versus extended-release naltrexone ($n = 570$) were more likely to report psychiatric comorbidities including major depressive disorder, anxiety/panic disorders, bipolar disorder, and history of suicidal behaviors compared with men [46]. Aging may also exacerbate mental health issues in women, as women > 25 compared with ≤ 25 may present to treatment with more mental health comorbidities [47]. Finally, although attention deficit hyperactivity disorder (ADHD) is more prevalent in men than women, a large survey study in Italy found that women versus men in opioid maintenance therapy (OMT) were more likely to have ADHD, and that women with ADHD were more likely to misuse benzodiazepines [48]. In light of the consistent evidence that women are more likely than men to evidence mental health issues upon presentation to OUD treatment, targeted efforts to improve mental health outcomes among women might also improve OUD treatment response.

Intimate Partner Violence

Extensive historical research has suggested that women who are receiving treatment for OUD experience a greater frequency of intimate partner violence (IPV) and sexual assault/coercion relative to the general population and that IPV rates remain relatively stable over time [49, 50, 51•, 52]. Survey studies have revealed that almost half of the men who are receiving treatment for OUD admit perpetrating IPV against their female partners or mothers of their biological children [7•, 53, 54]. IPV in these cases included physical, sexual, and/or injurious events, with approximately 1 in 5 considered to be severe [53, 54]. Interviews with women receiving OUD treatment ($n = 416$) revealed that low levels of non-partner support were associated with a higher rate of IPV [55], and one-third of women in another study ($n = 203$) experienced disability, chronic pain, and/or depression as a result of these acts [56, 57]. Another qualitative interview study with women who were receiving OUD treatment ($n = 40$) reported that 100% of them had experienced IPV and many believed it was preventing them from fully engaging in recovery, gaining independence from their partner, and remaining abstinent from substances [58]. Finally, two cross-sectional studies ($n = 235$ and $n = 230$) reported similar results that being female and experiencing IPV and/or adverse childhood experiences increased the likelihood of opioid misuse [6, 59].

Additional evidence that women who have OUD may live in dangerous environments is evident from studies of their children. One examination of opioid-exposed infants ($n = 3842$) found that they are more likely to later be admitted to hospitals for treatment of infections, substantial injury (e.g., burns, poisonings), assaults, malnutrition, and treatment for behavioral or mental health disorders, and that readmissions occurred at a significantly higher rate than controls through adolescence [60]. The majority (80%) of young adults ($n = 30$) who were receiving treatment for OUD in another study also reported experiencing significant childhood trauma [61].

Unique Challenges Related to Motherhood

Access to OUD Treatment

Women are often primary caretakers for children and this role can sometimes act as a barrier to treatment. For instance, women in an interview study ($n = 14$) reported that they had been discharged from treatment for missing appointments related to childcare issues [62]. Another study suggested that having children may motivate treatment entry [63], yet a large-scale evaluation of approximately 2 million persons from the NSDUH found no difference in the likelihood of receiving treatment for OUD among those who did (27.7%) and did not (31.0%) have children in their households. Those who were receiving OUD treatment were also generally engaged in nonmedical treatments such as self-help groups that may not promote sustained abstinence and/or recovery [64•]. Persons who were living with children were more likely than those without children to endorse stigma, treatment access barriers, and not believing treatment was a current priority as reasons for not receiving treatment [64•]. The need to reduce barriers to treatment among these women is vital for both the mother and child, as evidenced

by a study of more than 1 million parent-child dyads who found that infants who were born after parent enrollment into opioid treatment had a reduced risk of mortality relative to those born to parents who were not receiving treatment [65].

Likelihood of Being a Parent

Broadly speaking, it is estimated that between 0.9 and 3.8% of parents meet criteria for OUD and that 2.1 million children (2.9%) under the age of 17 live in a household with one or more parents who have a substance use disorder (SUD) [66, 67]. Data from the NSDUH reveal that parents who have OUD ($n = 623{,}000$) experience significant concurrent life stress relative to parents who do not have OUD, including significantly lower income and ratings of physical health, as well as high rates of suicidal thoughts and behaviors (> 20%) and serious mental illness (> 25%) [67]. Only 28% of these parents had received OUD treatment in the past year [67]. Another retrospective chart review of parents who were receiving OUD treatment ($n = 100$) revealed they had significant psychosocial issues such as low income (75%), unemployment (54%), and food insecurity (51%). Moreover, 74% had a history of depression (31% with current moderate-to-severe symptoms) and 81% had a previous traumatic event (with 52% screening positive for PTSD) [68]. Finally, a birth registry evaluation of more than 1 million parent-child dyads found more than half of the children whose parents had ever received methadone treatment for OUD lived in or close to poverty. Parents in this study were also more likely than persons not receiving treatment to be unemployed and have a comorbid mental health disorder [65]. Sadly, 1.4% of these children died before their sixth birthday, with the largest number of them dying before they turned one [65]. Infant mortality was most closely associated with both parents having OUD, coupled with low (< 2500 g) infant birth weight [65].

Impact of Opioids on Parenting

The addition of a new child may add additional significant life stress for a multitude of reasons. For instance, a qualitative interview study ($n = 14$) reported that women receiving treatment for OUD expressed remorse because they believed their opioid use led to lower quality parenting, an inability to provide adequate emotional support to their children, and persistent financial pressures [62]. Problems with parenting that are reported by persons with OUD may have some biological origins. Parental caregiving practices are heavily influenced by neuroendocrine systems that interact meaningfully with the endogenous opioid system [69], and neuroimaging studies have revealed neural reward deficits among parents who do versus do not have recent opioid exposure [70]. These variations may manifest in clinically meaningful ways, such as increased annoyance to the sound of their infant crying under conditions of stress in parents with opioid exposure relative to controls [70]. One study that used the Nursing Child Assessment Satellite-Training Scale (NCAST-Feeding) to examine mother-infant interactions ($n = 12$) during bottle feeding found that opioid-exposed mothers and infants ($n = 12$) scored significantly lower than normative values, with infants demonstrating poor clarity in their cues for food and responsiveness to their caregivers and mothers demonstrating lower sensitivity to infant cues ($n = 33$) [71].

Difficulties in mother-infant interactions could lead to problems later in childhood, and disorganized attachment styles with children at 12 months have been associated with less adaptive behaviors towards the child (e.g., were more negative and critical of the child), an effect that was partially mediated by maternal depression in mothers with OUD [72]. Data also suggest that children of persons who have OUD may be more likely to display behavioral and learning problems upon entering school [72] and demonstrate poorer performance on cognitive functioning tasks relative to controls [61]. These effects may also translate to greater risk for the child. For instance, a MarketScan medical claims propensity score-matched evaluation of parents (aged 30–50; $n = 121{,}306$) and children (aged 10–19; $n = 332{,}537$) found that parents who filled more opioid prescriptions were more likely to have children with suicide attempts relative to matched controls (at a rate of 2.25 per 1000 children), independent of child sex, age, or parental history of suicide attempt [73•]. Moreover, children of parents who had OUD specifically (10.3%) were also significantly more likely to have OUD and depression relative to controls [73•].

Unplanned Pregnancy and Family Planning

Stress related to introducing a child into the household may be elevated when the pregnancy was unplanned. Indeed, persons who have OUD are much more likely than the general population to experience an unintended pregnancy (85% versus 33–45%, respectively) [74–77], and pregnancy often occurs at a young age (mean age 20) [77]. Evaluations of women from the Millennium Cohort Study ($n = 12{,}462$) and an internet survey ($n = 1078$) both provide evidence that having a child as a result of an unplanned pregnancy in the general population can lead to significant psychological distress that is enhanced among persons who have preexisting depression, mental health disorders, or SUDs [78, 79]. Conversely, women who choose to not have the child via abortion are still prone to poor outcomes. An examination of abortion within the National Longitudinal Study of Adolescent to Adult Health (Add Health) ($n = 3935$) found that the relative risk of having an abortion was higher among persons who had an SUD and that abortions themselves increased the risk of affective problems by 43% relative to women who had the child [80].

These outcomes emphasize the potential value of family planning education for women with OUD, which is of particular interest following a recent systematic review ($n = 66$ articles) that confirmed contraceptive use is both safe and effective for use in women who are receiving opioid medications [81]. A recent survey of women receiving methadone treatment for OUD ($n = 100$) found that 70% did not want to be pregnant and 66% were trying actively to avoid pregnancy, yet the majority were relying on oral contraceptives (88%) and condoms (98%) rather than long-acting forms of contraception protection (54%) [77]. This is not surprising given the results of a recent cross-sectional survey of women receiving OUD treatment ($n = 200$) that found 38% of women were uninformed about long-acting contraceptive methods [82], suggesting a key opportunity for intervention. Another survey of women ($n = 91$) enrolled in OUD treatment reported that 97.8% had previously been pregnant and 52.8% had a previous unwanted pregnancy. The majority (60%) of these women were currently trying to avoid pregnancy but most (75.8%) reported that concerns about adverse effects, provider stigmatization, problems attending appointments, and prohibitive costs served as barriers to them accessing effective contraception [76]. An additional interview study with women who had OUD ($n = 31$) found that issues with transportation and childcare were significant barriers to women receiving contraceptive care [83].

Impact of Maternal Use on Children and Family Members

Ongoing maternal substance use may present significant risk to their children and perpetuate a continued cycle of problematic substance use. For instance, a qualitative interview ($n = 14$) reported that many of the mothers who were struggling with OUD and homelessness reported that their own parents had used opioids and introduced them to substances, which they believed normalized their use [62]. An assessment of 35,000 parent-child (aged 12–17) dyads from the NSDUH found that nonmedical use of opioids among parents was highly correlated with adolescent use, and that this effect was stronger among mothers relative to fathers [84]. Moreover, adolescent substance use was more likely to be present when there was low parental monitoring or high parent-child conflict [84]. A recent analysis of hair samples from 141 parent-child dyads found that 96% of families had one or more substances detected in family hair samples and that over 60% of children showed evidence of direct (not secondary) exposure to methadone and heroin [85]. A longitudinal evaluation of mothers ($n = 457$) and fathers ($n = 368$) found that maternal (but not paternal) alcohol and opioid use were both independently associated with greater adolescent substance use at 5 years [86]. Finally, a population-based, nested case control study found that children ($n = 103$) who presented to the hospital for an opioid overdose were primarily below the age of 2 and were significantly more likely than matched controls ($n = 412$) to have a mother who was being prescribed opioids and antidepressants [87].

OUD also exerts collateral impact on additional family members and this can serve as a source of stress that is unique to female family members. For instance, an interview survey of persons who had OUD and their healthy relatives ($n = 50$) found that relatives had significantly higher ratings on the Zarit Burden Interview assessment of caregiver burden and poorer physical, psychological, social, and environmental quality of life ratings on the World Health Organization Quality of Life measure, relative to matched healthy control family dyads [88]. Quality of life ratings decreased as the duration of OUD increased, and corresponded to increases in ratings of caregiver burden [88]. Another qualitative interview study ($n = 8$) with family members of persons who had OUD revealed they were concerned about the health of their loved one, struggled with helping their family member seek treatment and avoid relapse, experienced conflict over a perceived expectation that they love the individual unconditionally despite being confronted with problematic and disrespectful behaviors, and felt stigma towards them and their family member when they discussed their family member's substance use openly with support networks [89]. Finally, a qualitative interview study of grandparents ($n = 15$) who were serving as primary caretakers for their grandchildren as a result of their child's SUD or recent overdose found the caregiver role imposed significant legal, financial, and support burdens on them [90].

Stigma

Stigma towards persons who have OUD and/or are receiving OUD treatment is a well-documented phenomenon [91] and recent data suggests that many women also report significant perceived stigma related to their status as an opioid-using parent. This perception is likely grounded in their lived experience. A recent survey of pediatric medical students found that the large majority did not believe that mothers being treated for OUD could be actively involved in managing their infant's care, though the majority did believe the women would be good mothers [92]. Another qualitative survey of new mothers of opioid-exposed infants ($n = 25$) found that many felt highly stigmatized by hospital staff and believed staff were not acknowledging their concerns and were showing bias against them and their infants [93]. Another survey of mothers ($n = 157$) receiving treatment for OUD suggested many (38%) did not believe their healthcare worker respected them [5]. There are also legal concerns for new mothers with OUD. A survey of 52 representatives from 42 state departments of health and family services found that 30% of states

required toxicology screening for mothers and infants most or all of the time, with 64% of those states requiring mandated reporting of an infant-positive screen and 38% defining prenatal opioid exposure as evidence of child abuse or neglect [94]. An analysis of children aged 0–1 who were in the Adoption and Foster Care Analysis and Reporting system ($n = 320{,}986$) found that 30% of child welfare admissions are related to maternal substance use [95], and data suggest that removals associated with substance use have decreased likelihood of reunification relative to non-SUD removals [96].

These mandates likely contribute to the documented fear held by many women who are using opioids that their children will be removed from their custody [76]. A longitudinal assessment of new mothers who were receiving OUD treatment suggests this may be a somewhat rare occurrence, with the majority (81%) of women in that study retaining custody of their child at a 10-year follow-up [97]. Conversely, an evaluation of women who had "near-miss" overdoses ($n = 60$) or family members of women who had a fatal overdose ($n = 39$) found that losing custody of their child placed the woman at greater risk for experiencing an opioid relapse and fatal/nonfatal overdose [42]. Although having a child could serve for some women as a transformative moment that prompts treatment entry, an evaluation of the Sobriety Treatment and Recovery Team (START) child welfare-based program ($n = 596$) found only 9.2% of new parents had entered treatment for OUD. However, those who did were more likely to retain their children and experienced a 10% greater likelihood of their family remaining intact for every additional month they stayed in treatment [63].

Stigma is likely to impact other elements of the parenting experience. For instance, a qualitative interview study of new mothers who were maintained on methadone ($n = 8$) reported their willingness to breastfeed was heavily impacted by the perceived stigma they felt from others [98]. This is unfortunate, as there is clear consensus that breastfeeding for infants who were treated for neonatal abstinence syndrome and/or among mothers being treated for OUD is beneficial and of low risk to the infant. Though rates of breastfeeding initiation among women receiving treatment for OUD are relatively high (75–82%), mothers who have OUD are significantly more likely to discontinue breastfeeding by 2–6 months (23–50%) relative to controls (53%) [99, 100]. A survey study of women ($n = 40$) found those who are continuing to breastfeed did so because they believed it improved their infant's health (85%) and bonding (45%). The largest cited reason for not breastfeeding was concern about passing on medications or other substances through breastmilk (35%) [100]. Data from this study also suggested that infants who received treatment for NAS may be significantly less likely to be breastfed, suggesting opportunities for targeted intervention. Pharmacokinetic studies of mother-infant pairs suggest that levels of methadone passed to infants through breastmilk are negligible and do not affect neurobehavioral outcomes [101].

Conclusions and Actionable Improvements to OUD Treatment for Women

The literature reviewed here suggests that women who have OUD may face several unique challenges relative to men that could complicate their treatment initiation and retention. These include differences in physiological/hormonal factors that affect physical dependence to opioids [17, 20, 23•], increased prevalence of comorbid psychiatric conditions [44, 45], higher likelihood of history of trauma including IPV [53, 56], and parenting issues including stress associated with childcare and maternal depression that may culminate in higher substance use in the children of mothers with OUD [67, 72, 86]. Moreover, mothers who have OUD with young children may feel stigmatized by the medical and social support systems that are supposed to treat them [94–96]. Taken together, these findings suggest several areas of opportunity to improve medical care for women with OUD.

A recent commentary by Springer and colleagues identified several actionable steps to improve OUD treatment for women, including (1) improving access to treatment for women, including medications for OUD (MOUD), (2) removing laws that punish women seeking treatment for OUD, (3) providing wrap-around services that address the unique needs of women with OUD, (4) childcare and transportation assistance, and (5) programs that address life skills including financial literacy and gaining/maintaining employment [3••]. Research by our group and others further supports the finding that MOUDs—specifically buprenorphine—might be particularly effective in women with OUD [4, 102]; however, access to buprenorphine and other MOUDs remains an issue, especially in states that were resistant to expanding Medicaid under the Affordable Care Act [103, 104]. Furthermore, buprenorphine and methadone might improve certain physiological outcomes, for instance sleep and/or viral suppression in women with human immunodeficiency virus, and be particularly effective in minority women [105–107]. At the same time, behavioral- and technology-based interventions might further optimize other important outcomes including social functioning and reduction of harms associated with trauma [108, 109].

This review demonstrates that, although there is a growing body of literature regarding the unique challenges that women might face in seeking treatment for OUD, methods to improve treatment delivery for women with OUD are sorely needed. Many previous large-scale treatment outcome studies and clinical trials have heavily skewed recruitment towards men. Large intervention studies to improve relapse outcomes, mental health outcomes, and psychosocial outcomes in women are

warranted and should be a priority in an overall effort to address the opioid crisis.

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