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Review: Sex-based Differences in Treatment Outcomes for Persons with Opioid Use Disorder

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Abstract

Background and Objectives: In order to address the current opioid crisis, research on treatment outcomes for persons with OUD should account for biological factors that could influence individual treatment response. Women and men might have clinically meaningful differences in their experience in OUD treatment and might also have unique challenges in achieving successful, long-term recovery. This review summarizes and synthesizes the current literature on sex-based differences in OUD treatment outcomes.

Methods: Relevant literature was identified via automated and manual searches using the terms “opioid treatment outcome sex [or gender] differences” and “opiate treatment outcome sex [or gender] differences”. Search methodology was consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and were conducted within the PubMed electronic database during March and April of 2018.

Results: The initial PubMed search yielded 241 manuscripts; 31 original research articles that met inclusion/exclusion criteria were synthesized in this review. Several important trends emerged, including findings that women are more likely than men to present to treatment with co-occurring mental health conditions such as depression, and that women might respond particularly well to buprenorphine maintenance.

Discussion and Conclusions: While much of the literature on this topic is subject to potential cohort effects, interventions that address co-occurring mental health conditions and psychosocial stress might improve treatment outcomes for women with OUD.

Scientific Significance: Funding agencies and researchers should focus attention toward human laboratory studies and clinical trials that are prospectively designed to assess sex-based differences in OUD recovery.

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Introduction

In 2016, approximately 12.5 million people in the United States misused an opioid and 2.1 million people met criteria for opioid use disorder (OUD)[1]. Moreover, heroin use disorder tripled between 2002–2016[2], leading to increased infectious disease transmission and unprecedented levels of death from opioid overdose[1,3,4]. Persons with OUD face significant challenges and there is limited research regarding individual differences in OUD treatment response. This is further complicated by the fact that there are several treatment approaches for persons with OUD, including medication-assisted treatments that utilize different mechanisms of action such as full μ-opioid receptor agonists (methadone), partial μ-opioid receptor agonists (sublingual or extended-release buprenorphine), and μ-opioid receptor antagonists (oral or extended-release naltrexone). Individual differences in human physiology are likely associated with differential risk for negative treatment outcomes[5]. In an effort to delineate these differences, the National Institutes of Health (NIH) now requires preclinical and human research to evaluate key biological variables, including sex. This directive is aimed at improving the scientific understanding of how sex and gonadal hormones influence outcome measures related to health, and is particularly relevant for drug misuse and addiction. It also addresses the historical bias toward male subjects, particularly in preclinical research, and allows for greater understanding of and generalization to diseases and conditions affecting both sexes.

Sex may be one of the most obvious potential biological predictors of disease, and there is growing recognition that men and women respond to drugs in a way that is qualitatively different and clinically meaningful. There is evidence from preclinical literature that sex hormones confer sex-based differences in opioid-based effects[6], and animal studies suggest females are more vulnerable to the positive reinforcing effects of opioids that underlie acquisition of OUD and the negative reinforcing effects of opioids that promote dysregulation, escalation, and relapse that might also exacerbate the pace of OUD progression[7]. In the clinical literature, sex-based differences has been well characterized for stimulants, for which there is clear evidence that women's subjective experience to stimulants such as cocaine varies as a function of the menstrual cycle phase[8]. Preclinical and clinical research has also shown that gonadal hormones, pharmacokinetic, and other social factors, influences sex-based differences in response to nicotine/tobacco [9] and alcohol[10–12].

However, the role of sex in individual response to opioids is not as well characterized; the majority of investigations on this topic have focused on outcomes related to opioid-based analgesia[13,14], and there is a paucity of empirical data available regarding sex-based differences in OUD treatment outcomes. Understanding how sex may influence these outcomes could inform new methods for combatting the opioid crisis and lead to more refined intervention strategies, better patient matching to OUD treatments, the development of new pharmacotherapies, and ultimately a precision medicine approach to the treatment of OUD. This review aims to summarize and synthesize the current literature on human clinical studies that focused on sex-based differences in OUD treatment outcomes.

Methods

The scope of this literature review was limited to manuscripts focused on sex-based differences in OUD treatment outcomes. The terms “sex” and “gender” have often been used interchangeably in human studies, although sex is a biological variable based on genetics and genitalia, and gender refers to societal roles and lived experiences in persons who identify as men or women. Sex, as a biological variable, is likely to have greater influence on response to pharmacotherapies or other physiological outcomes, while gender is more likely to influence psychosocial outcomes. This review will utilize the term “sex” to bridge preclinical and clinical literature on this topic, however the treatment outcomes reviewed here span both biological and psychosocial factors that contribute to the human experience of OUD recovery.

Relevant literature was identified via automated and manual searches for original investigations published in peer-reviewed journals. Systematic searches were consistent with the guidelines for systematic reviews outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15], and were conducted within the PubMed electronic database during March and April of 2018. Key words including sex and opioid/opiate treatment were present in the title and/or abstract of all reviewed literature. The following search terms were used: “opioid treatment outcome sex differences”, “opiate treatment outcome sex differences”, “opioid treatment outcome gender differences”, and “opiate treatment outcome gender differences”.

Inclusion/Exclusion Criteria

Manuscripts were included in this review if they (1) included a study abstract, (2) were published in English, (3) were a peer reviewed, original research article, (4) were published between the years of 1990 – March, 2018, (5) focused on outcome measures relevant to OUD treatment (e.g., continued drug use, comorbidities), (6) reported data that statistically compared outcomes as a function of sex, and (7) were conducted in human subjects. Manuscripts were excluded if (1) the primary outcome measures were pain, analgesia, and/or antinociception, or (2) only described results for one sex.

In order to conduct a robust and inclusive literature review, no restrictions were placed on the type of treatment outcome measure evaluated, the age of participants, or the country or population of the study. All three authors reviewed the titles and abstracts of studies identified via PubMed search to determine initial relevance. The manuscript was directly evaluated for inclusion in cases where the title and abstract did not provide sufficient information. The original terms and concepts utilized by the primary authors of literature reviewed remain intact whenever possible to ensure accurate representation of the various outcomes [16,17].

Results

Summary

The initial PubMed search yielded 241 manuscripts, and 31 original research articles were deemed by the authors to meet inclusion/exclusion criteria and are reported in Table 1 and in the Results section.

Treatment Outcomes and Sex-based Comparisons

The study of sex-based differences in human clinical samples is challenging because of the numerous potential outcomes and treatment modalities evaluated. Studies in this review treated OUD in many ways, including treatments common across substance use disorders (e.g., counseling, residential treatment, and 12-step groups) and medication-assisted treatments (e.g., methadone, buprenorphine, and extended-release [ER] naltrexone) that are specific to OUD (with the majority of data collected from methadone maintenance treatments [MMT]). These differences are likely to impact treatment outcomes independent of sex.

In addition, “sex” and “gender” were used indiscriminately in many of these studies. For consistency, the following studies are all described in the context of sex, regardless of whether the original study reported results as a function of sex or gender. The available literature consists primarily of secondary outcomes and retrospective chart review evaluations that were categorized into four domains, 1) sex-based differences in treatment presentation; 2) sex-specific issues experienced while undergoing treatment; 3) OUD treatment outcomes (retention, opioid relapse) and 4) response to different OUD treatment modalities. Retention and relapse to opioid use are reported as they were the most common OUD treatment outcomes. Due to variations in definitions, this review used the original source document’s definition of retention, and any outcome pertaining to the resumption of opioid use during or after treatment was operationalized as “opioid relapse” for the purpose of this review.

Sex-based Differences in Presentation to Treatment

Studies that examined qualitative differences between men and women as they enter OUD treatment suggest that significant between-sex differences exist, though the specific characteristics upon which men and women differ are not consistent.

Several studies suggest that women present to treatment with higher rates of psychiatric comorbidities. One retrospective chart review (N=96) reported that young women in a community treatment center for OUD presented with more co-occurring mental health and substance-use related issues than men, including co-occurring use of psychotropic medication, benzodiazepines, and cocaine; men were only more likely to have co-used marijuana[18]. Likewise, a large Italian cohort study (N=10,454) of OUD patients reported that women entered treatment with a higher prevalence of HIV, unemployment, use of sedatives, and depression than men, but had lower concurrent use of alcohol[19]. Another Italian cohort study (N=1,052) found that women were more likely than men to enter

treatment with co-occurring depression, anxiety disorders, and also more likely to be prescribed psychopharmacotherapies[20].

Additional studies suggest that women may present to treatment with greater life instability, albeit less risky substance use. One cohort study of methadone-maintained individuals in Iran (N=260) found that women were more likely than men to be unemployed and have addicted spouses or other family members, and that men were more likely than women to present to treatment with polysubstance use, report injection drug use, and initiated opioid use at a younger age [21]. Another review of 2004–2013 national treatment admissions in the US (N=1,260,151) found women to be less likely than men to escalate their route of prescription opioid administration from oral to injection, intranasal, or combustible[22] . A chart-review conducted among methadone maintenance (MMT) patients (N=435) found that women presented to MMT with more family dysfunction and were more likely to report seeking OUD treatment because of ongoing psychosocial problems than men[23]. In addition, a phase III randomized trial of OUD pharmacotherapies for harm reduction (N=202) reported that women were significantly more likely than men to be younger, using crack cocaine, and to report prior month sex work upon treatment presentation[24]. Finally, a 7-year longitudinal study of a buprenorphine-maintenance program that included a work requirement and educational training (N=170) also reported that women presented to treatment with more psychiatric conditions than men but this difference absolved by the seven-year follow-up[25].

Evidence also suggests that women develop problems related to OUD more quickly than men. For instance, one evaluation of patients enrolled in MMT (N=246) reported that women progressed from mild to severe levels of OUD more rapidly than men[26,27]. This is supported by the results of a retrospective chart review (N=103) that found women presented to treatment with significantly higher opioid withdrawal scores (e.g., muscle twitch, vomiting, depression, and poor appetite) compared to men, suggesting they did not seek treatment until their physical dependence was more severe[28]. Similarly, another cohort study (N=343) of older adults in MMT reported that psychological distress and chronic health problems developed at a younger age among the female versus male patients[29].

In sum, there are many sex-based differences in presentation to treatment that could be targeted for developing sex-specific treatments. These sex-based differences include greater co-occurring mental health issues and greater substance co-use issues among women compared to men. Women are also more likely to seek OUD treatment because of ongoing psychosocial problems than men, and women may develop problems related to OUD more quickly than men.

Sex-based Differences During Treatment

A limited number of studies have reported on sex-based differences among patients who are currently undergoing OUD treatment, and those studies have generally focused on the physiological side effects of OUD medications. One chart-review study (N=96) reported that women in MMT gained more weight than men over an approximate 2-year period[30] . An additional multi-site trial in Canada (N=231) reported that men receiving MMT had lower levels of testosterone than healthy non-MMT males, and that testosterone levels were

negatively correlated with methadone dose; there were no significant findings regarding testosterone levels in females in this study[31]. A study in Taiwan (N=411) found that higher methadone doses in women was positively correlated with higher levels of estradiol[32]. Finally, a retrospective chart review of medical records from a publicly-funded treatment center (N=465) reported that women experienced more total adverse events, and specifically headaches, than men following treatment with the opioid antagonist/relapse prevention medication extended-release naltrexone[33]. Notably, patients in this study were categorized based upon whether they were receiving naltrexone for either OUD or alcohol use disorder, and no sex-based differences with regard to opioid cravings were reported.

Research therefore suggests that women and men experience differences during and as a result of treatment. Women, for example, may be more likely to gain weight, and male testosterone levels may decrease with higher methadone doses to a greater extent than female testosterone levels. Women may also be more likely to experience adverse events compared to men. These findings should be considered when developing treatments tailored to the sexes.

Sex-based Differences in Treatment Retention Outcomes

Much of the research on sex-based differences on treatment outcomes has focused on treatment retention among patients utilizing opioid-maintenance therapies, and the results of these studies are not always consistent. Some evidence suggests that women are more likely than men to be retained in treatment. For instance, both a large cohort study conducted among heroin users in Italy (N=10,454) and a 7-year follow-up of men and women receiving buprenorphine treatment (N=170) reported that women were more likely than men to stay in maintenance therapy[19]. A large retrospective chart-review study conducted among participants of an office-based buprenorphine treatment (N=1,237) also found women to be 55% more likely than men to remain in treatment[34]. Another retrospective chart-review study (N=720) further reported that young men who entered treatment as daily heroin users *and* were also unemployed and unmarried had the highest risk of dropping out of MMT compared to all other demographics evaluated[35].

Conversely, two retrospective chart reviews have suggested that women were less likely than men to be retained in treatment. The first (N=96) found that female young adults attending a community-based program dropped out of treatment at a higher rate than young men[18], and a second study (N=246) found that women were more likely to be involuntarily discharged from MMT than men[26], although this study did not observe sex-based differences in overall treatment retention.

Several additional studies have reported no sex-based differences in retention outcomes. A 1-year follow-up of MMT treatment outcomes (N=290) reported no association between sex and treatment retention[36], and a clinical trial comparison of buprenorphine induction in prison versus in the community (following incarceration) (N=211) reported no differences in buprenorphine induction rates as a function of sex[37].

Concurrent use of non-opioid drugs is also reviewed here because it may affect treatment retention. One recent study of 58 OUD treatment clinics in Canada (N=644) found

concurrent cannabis use to be associated with decreased treatment retention in patients undergoing opioid maintenance therapy. While this effect was true in both sexes, treatment retention was poorer among men who used cannabis regularly during treatment, relative to men who did not continue to use regularly[38]. A retrospective chart review study (N=503) of patients undergoing compulsory treatment for heroin in China also found that men experienced higher rates of "negative treatment outcomes" (defined as incarceration, treatment readmission) than women when they endorsed polysubstance use at treatment entry[39].

The literature regarding sex-based differences in treatment retention suggests that sex is commonly associated with treatment retention, though the direction of the effect varies across studies, with some showing an advantage for women and others showing an advantage for men. Although retention, as it is reviewed here, is highly influenced by differences in the definition of retention employed by the reviewed studies, the consistency with which sex emerges as a valuable predictor of retention supports more focused research on this topic to understand the specific challenges faced by each sex to improve retention in treatment.

Sex-based Differences in Relapse to Opioids

Similar to retention, the data regarding opioid relapse risk as a function of sex are inconclusive. Several studies have suggested relapse varies as a function of sex, though once again the direction of effects varies. One study that used ecological momentary assessments to monitor opioid craving and relapse (N=114) found that women reported higher cue-elicited craving and feelings of guilt following opioid relapse than men[40]. A survey study conducted in China (N=178) reported that women undergoing MMT were more likely than men to relapse to heroin if they had a family member who also used heroin[41]. However, a 7-year study of patients receiving buprenorphine for OUD (N=170) reported that women were significantly less likely to relapse to opioids than men[25].

Four studies have suggested no sex-based differences in relapse risk. The first was a prospective, nonrandomized evaluation of men and women receiving MMT for OUD (N=91) which reported no sex-based differences in the number of relapses to opioids that occurred over 6 months, though women in this study were significantly more likely than men to experience a "significant" relapse (generally to heroin)[42]. Two retrospective chart review studies of MMT patients (N=290 and N=435) reported no sex-based differences in overall relapse to opioids, though one study did note that women in the study were more likely to relapse if they had a history of sexual victimization[36]. The final trial evaluated outcomes following buprenorphine induction in prison or in the community (N=211) and reported no sex-based differences in opioid relapse[37].

In summary, data regarding relapse to opioids among men and women provides mixed results. Some studies have suggested that women are at heightened risk for opioid relapse, whereas other studies suggest that men are at heightened risk for opioid relapse. Four direct comparisons also found no sex-based differences in relapse. Given the methodological differences across studies, it is not possible to draw strong conclusions regarding sex-based differences in relapse risk from the available data.

Sex-based Differences in Response to Different OUD Treatment Modalities:

Several double-blind, randomized, controlled trial evaluations of different OUD treatment pharmacotherapies or approaches have suggested treatment response may vary as a function of participant sex. The following results collapse across retention and relapse outcomes to demonstrate the breadth of effects as a function of treatment type. The first study (N=202) compared methadone and diacetylmorphine (heroin) for OUD treatment and reported women assigned to diacetylmorphine were more likely to be retained in treatment, have greater reductions in illicit drug use, and demonstrated improved psychological health than women assigned to methadone. Within the diacetylmorphine arm, men reported greater increases in quality of life and physical health than women[43].

A second clinical trial comparison of buprenorphine, lavacetylmethadol (LAAM), and methadone (N=165) reported no sex-based differences in retention, with men and women assigned to methadone demonstrating higher retention relative to participants assigned to LAAM (buprenorphine did not differ from either group)[44]. Women were less likely than men to relapse to opioids when assigned to buprenorphine. Women assigned to buprenorphine were also less likely than women receiving methadone to relapse to opioids, with no differences reported in women assigned to LAAM. However, men assigned to LAAM were less likely to relapse to opioids than men assigned to buprenorphine, with no differences reported in men assigned to methadone[44].

A third clinical trial (N=116) that compared buprenorphine to methadone found that women assigned to buprenorphine had higher treatment retention and lower rates of opioid relapse than men assigned to buprenorphine[45].

Additional secondary outcomes have been reported from the Prescription Opioid Addiction Treatment Study (POATS), a large-scale randomized controlled trial that compared outpatient supervised withdrawal with buprenorphine to extended buprenorphine maintenance among primary prescription opioid users (N=653)[46]. These analyses have reported that, relative to men, women entered the POATS study with higher levels of functional impairment and psychiatric severity and were also more likely than men to attribute opioid relapse to efforts to cope with negative affect and pain[47]. Men and women also displayed similar levels of opioid withdrawal during the study[48].

To summarize, sex-based differences could arise in response to different pharmacological OUD treatments including methadone, diacetylmorphine, buprenorphine and levacetylmethadol. Data from these clinical trials suggest that women who were assigned to diacetylmorphine had better responses than those assigned to methadone, though it should be noted that poor response to methadone is often a requirement for diacetylmorphine treatment. Another study found no sex-based differences in retention in methadone treatment, but instead found that women were less likely than men to relapse to opioids when assigned to buprenorphine. Taken together, these data suggest that the OUD treatment modality type could play a fundamental role in treatment outcomes including retention, and these results appear to vary by sex.

Discussion

This review evaluated sex-based differences in presentation to OUD treatment, the onset of treatment-specific issues, treatment retention and relapse rates, and relative efficacy of different OUD treatment types. Although the direction of effects did not consistently suggest that men or women had better or worse outcomes in any of these elements, the majority of studies reviewed did identify a specific effect of sex on one or more outcomes, suggesting that sex is an important contributor to OUD treatments. Several notable trends emerged, including sex-based differences in presentation to treatment (which might affect outcomes) (Table 2), factors that might drive negative treatment outcomes, and treatment response to OUD pharmacotherapies, particularly buprenorphine (Table 3). Importantly, the vast majority of treatment outcome studies reviewed here were not originally designed to and/or powered to formally evaluate the contribution of sex on outcomes, so results concerning sex-based differences are secondary in nature. As can be observed in Table 1, treatment outcome studies also tended to enroll more men than women, further undermining the ability to draw firm conclusions from these data.

In general, women appeared to present to treatment with more psychiatric comorbidities and life instability. When compared to men, women presenting to OUD treatment generally had more psychosocial issues[23] including mental health conditions such as depression[18,19] (Table 2). They also appeared to be sensitive to the effects of the treatment medications, evidenced by more serious weight gain, hormone fluctuations, and side effects. Women had variable levels of retention across the studies and it is notable that several studies suggested they relapsed more than men because their partners were using opioids, as this reflects the trends in treatment presentation. In general, men were more likely than women to present to treatment with ongoing drug use and other risky drug -related behaviors and also demonstrated hormone-related effects to chronic treatment. Retention and relapse outcomes in men varied, with some studies reporting that ongoing drug use undermined both efforts, which also reflects differences in how men generally presented to treatment.

The fact that women present with higher rates of psychiatric comorbidity is consistent with other studies that described higher rates of psychosocial issues[23, 47], including mental health conditions such as depression[18,19] and suicidal ideation in women compared to men enrolled in a general substance use treatment program[49]. Since treatment presentation impacts subsequent treatment approach and outcomes, this finding represents an important and actionable sex-based difference. Comorbid mental health conditions are inherently difficult to assess in an OUD population because opioid use directly impacts mental health, however resolution of mental health conditions over time appears to be associated with positive OUD treatment outcomes in women[25].

There are additional sex-specific issues that may impact outcomes in men and women differently. Women compared to men, are more likely to be victims of physical and sexual violence[19,49], which has been associated with poor treatment outcomes[36]. Women are also more likely than men to report that relapse to opioids was associated with negative affect (which is consistent with depressive symptoms)[47], and to report guilt associated with

relapse[40]. There is also preliminary evidence that women may experience more severe opioid withdrawal symptoms than men[28,50].

Several studies support the use of buprenorphine in women (Table 3). Among the various treatment modalities described in this review, sex-based differences in treatment outcomes during buprenorphine maintenance were relatively consistent; women on buprenorphine maintenance relapsed at a lower rate than women on methadone maintenance[44], and women in buprenorphine treatment tended to relapse to opioids at a lower rate than men[45] and be retained in treatment longer than men[34,45]. It is possible that the antidepressant effects of buprenorphine[51] are particularly advantageous in women given the high rate of women presenting to OUD treatment who also endorse depressive symptoms.

Much of the literature reviewed here is consistent with sex/gender differences in other substance use disorders (SUDs). Women with comorbid SUDs and posttraumatic stress disorder are more likely to experience early life sexual trauma and physical abuse[52], are more likely to present to treatment with co-occurring mental health conditions, and are more likely to relapse to avoid thoughts of sexual trauma or physical abuse; whereas men are more likely to relapse for the purpose of sensation seeking[53,54]. Women who smoke are more likely than men to have co-occurring mental health conditions[55] and relapse due to stressful life events[56]. There are many sex and/or gender-based factors that could universally predispose individuals to SUDs, however the psychosocial experiences of men and women that put individuals at risk for OUD, and hormonal differences that might affect response to opioids and response to OUD treatment are not well characterized in human subjects research.

This review has several limitations. Few studies were prospectively designed to differentiate the role of sex on treatment outcomes. The fact that men and women may enter treatment with different psychosocial issues and varying levels of OUD severity further these comparisons. For instance, differences in familial circumstances that may vary as a function of sex, such as living with someone else that uses heroin or having primary childcare responsibilities, have been independently associated with different treatment outcomes[41,57]. A broader array of treatment outcomes, such as quality of life, should also be assessed since the limited studies investigating sex-specific effects have been inconclusive[58]. Finally, evidence of sex-based differences in opioid withdrawal and extended-release naltrexone induction [28,59] supports more focused research on sex-specific physiological effects of OUD medications.

Future Directions

Research on sex-based differences in OUD could have an immediate impact on improving treatment outcomes, which is important given the increasing prevalence of OUD and opioid overdose deaths[1,4]. Future clinical trials should be prospectively powered to examine sex-based interactions and to ensure adequate enrollment of women, which will allow for more powerful evaluations of OUD outcomes than simply including sex as an analytical covariate. Likewise, understanding whether the success of different treatments varies as a function of sex will support a precision medicine approach to OUD treatment. The results of this review suggest that treatment approaches tailored to stress and psychosocial issues in women may

be warranted, and also that women might respond particularly well to buprenorphine treatment. There is also a notable lack of human laboratory studies examining sex-based differences in the abuse potential or subjective effects of opioids. Given the results of this review, back-translation to preclinical work might include examination of pharmacotherapeutic approaches as a function of sex-hormones. Such studies could provide valuable links between preclinical and human clinical trials because they can examine the role of hormones on opioid-induced effects by evaluating effects in women across their cycle and/or collecting biochemical samples for gonadal hormone analyses.

Conclusions

Whereas several studies have examined sex-based differences in treatment outcomes for persons with OUD, much of literature on this topic is secondary in nature. Women appear more likely than men to present for treatment with comorbid mental health issues, though studies examining opioid relapse and treatment retention did not report consistent trends, with the exception that buprenorphine treatment might be particularly efficacious for women. Prospectively designed clinical trials and human laboratory studies that shed light on the role of sex on outcomes across the various forms of OUD treatment are warranted. Understanding whether there are sex-specific responses to treatment due to biology (e.g. hormones) or psychosocial factors (e.g. sexual abuse in women), will help in developing tailored treatments to improve OUD outcomes and ultimately advance a precision medicine approach to combat the opioid crisis.

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Table 1.

Articles on Sex-based Differences in OUD Treatment Outcomes

Author Names	Year of Publication	Sample Size	Article Type (e.g. Observational; Randomized Controlled Trial [RCT])	Primary Outcome Measure	Primary Drug of Choice based on Inclusion/Exclusion Criteria	Reported Results
Bawer et al.	2014	100 women; 131 men	Observational	Testosterone levels	Heroin/Prescription Opioid	Mean testosterone was significantly lower in male MMT patients compared to healthy controls. Testosterone reduction associated with methadone dose in males.
Chatham et al.	1999	135 women; 300 men	Treatment Outcome	Self-report of family dysfunction, drug use, criminal involvement, and further treatment.	Heroin/Prescription Opioid	Women reported more family dysfunction compared to men. Women were more likely to seek addiction treatment for psychosocial problems than men. No sex-based differences in drug use.
Chiang et al.	2017	Cohort 1: 67 women; 254 men Cohort 2: 24 women 66 men	Treatment Outcome	Methadone dosing and metabolism as a function of sex and estrogen levels.	Not reported	Women required higher doses of methadone compared to males. Greater levels of estradiol were associated with greater methadone dose in women.
Cox et al.	2013	80 women; 166 men	Observational	Voluntary and Involuntary discharge from methadone treatment	Prescription Opioid	Women had a higher rate of involuntary treatment discharge compared to men.
Fenn et al.	2014	35 women; 61 men	Observational	Weight gain	Heroin/Prescription Opioid	Women experienced more weight gain than men over the course of ~1.8 years methadone treatment.
Franklyn et al.	2017	138 women; 178 men	Observational	Treatment retention (1 year) in MMT in baseline cannabis users (positive at first assessment) versus heavy cannabis users (several positive screens)	Heroin/Prescription Opioid	Baseline females and heavy use males had increased risk of dropout.
Ghaderi et al.	2017	120 women; 140 men	Observational	Participant demographics and drug use behaviors upon admission to MMT	Heroin/Prescription Opioid/Opium	Men were more likely than women to present to treatment with polysubstance use, report injection drug use, and initiate opioid use at a younger age. Women were more likely to be unemployed and have addicted spouses or other family members than men.
Giacomuzzi et al.	2005	38 women; 65 men	Observational	Lancashire Quality of Life Profile, opioid use, opioid withdrawal	Heroin	Upon treatment entry, women displayed lower quality of life scores on self-esteem, physical health, and law and security than men. Women also displayed higher opioid withdrawal scores on muscle twitch, vomiting, depression, and poor appetite compared to men.

Author Names	Year of Publication	Sample Size	Article Type (e.g. Observational; Randomized Controlled Trial [RCT])	Primary Outcome Measure	Primary Drug of Choice based on Inclusion/Exclusion Criteria	Reported Results
Gordon et al.	2017	63 women; 148 men	RCT of buprenorphine induction in prison versus in community after prison	Treatment retention, heroin use, cocaine use, criminal activity	Heroin	No sex differences found. Buprenorphine induction in prison versus in community associate with treatment retention but not reduced opioid use, cocaine use, or criminal activity
Grella & Lovinger	2012	152 women; 191 men	Treatment Outcome	Self-report from longitudinal cohort study	Heroin	Women reported more chronic health problems and psychological distress than men.
Haifeng et al.	2015	265 women; 238 men	Treatment Outcome	Incarceration or readmission to treatment	Heroin	Men experienced a higher rate of negative outcomes compared to women.
Herbeck et al.	2016	17 women; 39 men	Observational	Adverse events and craving for individuals maintained on extended release naltrexone	Opioid/Alcohol	Women reported more adverse events to extended-release naltrexone. Women with alcohol use disorder reported greater reduction in craving; no gender difference in craving reduction for OUD.
Hser et al.	1990	328 women; 379 men	Treatment Outcome	Treatment retention	Heroin	Young men who were daily drug users, unemployed, and unmarried were at the highest risk of dropping out of methadone maintenance
Ignjatova & Raleva	2009	31 women; 60 men	Treatment Outcome	Relapse, frequency of relapse, type of substance use	Heroin/Prescription Opioid	No significant difference in relapse rate or injection drug use but women were more likely to relapse to heroin specifically relative to men.
Jones et al.	2005	61 women; 104 men	RCT buprenorphine, LAAM, and methadone	Drug use and treatment retention	Heroin	Women in buprenrophine treatment relapsed less than women in methadone treatment. Men in LAAM treatment relapsed less than men in buprenorphine treatment.
Jones et al.	2017	590,633 women; 669,518 men	Observational from national database of U.S. treatment admissions	Route of administration	Prescription Opioid	Men more likely than women to change the route of administration of prescription opioids to injection, intranasal, or combustible.
Kennedy et al.	2013	42 women; 72 men	Treatment Outcome	Drug cue and random prompt measures of craving	Heroin and Cocaine	Women had higher cue-elicited craving relative to men. Women also reported higher levels of guilt following drug use and reported using despite trying not to.
Leone et al.	2017	260 women; 792 men	Observational in methadone and buprenorphine treatment entry	Psychiatric disorders and treatment needs	Heroin/Prescription Opioid	Women were more likely than men to enter treatment with depression and anxiety disorders, to require psychopharmacotherapy, and required higher stabilization doses of buprenorphine

Author Names	Year of Publication	Sample Size	Article Type (e.g. Observational; Randomized Controlled Trial [RCT])	Primary Outcome Measure	Primary Drug of Choice based on Inclusion/Exclusion Criteria	Reported Results
Levine et al.	2015	117 women; 173 men	Treatment Outcome	Treatment retention and opioid abstinence after one year of methadone treatment	Heroin/Prescription Opioid	Gender did not predict treatment outcome. In women, treatment retention was predicted by first month cocaine and marijuana negative urines and absence of history of sexual victimization.
Lewis et al.	2014	288 women; 255 men	Survey	Progression of drug use	Heroin/Polysubstance	Women reported greater use of prescription medications including opioids relative to men. Women also reported moving from regular to problematic opioid use more rapidly than men.
Li et al.	2012	61 women; 117 men	Treatment Outcome	Self-report and/or urinalysis positive heroin use in methadone patients in China	Heroin/Prescription Opioid	Women more likely to use heroin than men if they had a family member that also used heroin.
McHugh et al.	2013	261 women; 392 men	RCT of buprenorphine taper and maintenance	Drug use and reason for drug use	Prescription Opioid	Women relative to men reported greater functional impairment, psychiatric severity, and use of opioids to cope with negative affect and pain.
Morales-Manrique et al.	2014	80 women; 284 men	Treatment Outcome	Quality of Life Survey	Heroin and Cocaine	No gender difference in quality of life among heroin users.
Öhlin et al.	2015	35 women; 135 men	Treatment Outcome	Drug abstinence, retention, psychiatric symptoms, employment, criminal convictions	Heroin	Women had lower relapse rates and higher treatment retention and employment than men after 7 years. Women began treatment with more psychiatric conditions than men but there was no significant difference in this measure after 7 years.
Oviedo-Joekes et al.	2010	97 women; 154 men	RCT of diacetylmorphine versus methadone	Retention, substance use, health-related quality of life	Heroin	Women displayed higher retention and improvements in illicit drug use scores and psychological health in the diacetylmorphine arm compared to methadone. Men in the diacetylmorphine arm increased quality of life and physical health compared to women.
Palis et al.	2017	62 women; 140 men	RCT of harm reduction via hydromorphone vs diacetylmorphine	Illicit opioid use and other illicit drug use	Heroin	Women more likely to be sex workers and use crack at baseline. No sex differences in treatment outcome.
Schottenfeld et al.	1998	36 women; 80 men	RCT of buprenorphine versus methadone	Alcohol use, benzodiazepine use, treatment retention	Heroin/Prescription Opioid	Women in the buprenorphine group had greater treatment retention than men. Women in the buprenorphine group had lower rates of opioid relapse than men. Women had higher rates of cocaine use in the buprenorphine condition and lower rates in the methadone condition relative to men.

Author Names	Year of Publication	Sample Size	Article Type (e.g. Observational; Randomized Controlled Trial [RCT])	Primary Outcome Measure	Primary Drug of Choice based on Inclusion/Exclusion Criteria	Reported Results
Vigna-Taglianti et al.	2016	1,501 women; 8,953 men	Observational	Treatment retention in methadone maintenance and therapeutic community	Heroin	Women compared to men reported higher prevalence of HIV+, unemployment, higher use of sedatives, lower use of alcohol, higher rates of depression, self-injury, and suicide attempts. Women had higher retention in methadone treatment than men.
Vo et al.	2016	24 women; 32 men	Treatment Outcome	Treatment retention (30 days and 24 weeks), opioid negative urines	Heroin/Prescription Opioid	Young women dropped out of medication assisted treatment at a higher rate than young men.
Weinstein et al.	2017	472 women, 765 men	Observational	Treatment retention in office based buprenorphine	Heroin/Prescription Opioid	Women were 55% more likely to remain in treatment than men.

Table 2.

Studies on Sex-based Differences in Mental Health at Presentation to OUD Treatment

			Mental Health Factors	
Author Names	**Year of Publication**	**Treatment Setting**	**Depression or Depressive Symptoms**	**Other Mental Health Factors**
Chatham et al.	1999	Methadone maintenance treatment program	Women more likely than men to report depressive symptoms (51% v 35%, respectively, p<0.01)	Women more likely than men to report thoughts of suicide (35% v 16%, p<0.0001); previous attempted suicide (27% v 7%, p<0.0001).
Grella et al.	2012	Methadone maintenance treatment program	Women had greater scores on the Beck Depression Inventory (M=18.1) than men (M=13.0, p<0.001)	Women more likely than men to report history of suicidal thoughts (49.3% v 34.7%, p<0.01)/attempts 32.2% v 12.1%, p<0.001), and mental distress (35.5% v 26.0%, p<0.001)
Leone et al.	2017	Opioid maintenance treatment program	Women more likely than men to endorse depressive symptoms upon treatment entry (p<.001)	Women more likely than men to endorse somatization (p<0.001), obsession-compulsion (p<0.05), interpersonal sensitivity (p<0.001), phobic anxiety (p<0.001), paranoid ideation (p<0.01). No sex differences in anger-hostility, psychoticism and sleep.
Levine et al.	2015	Methadone maintenance treatment	NR	Women more likely than men to report lifetime interpersonal physical (35.9% v 12.7%, p<0.05), emotional (33.3% v 19.1%, p<0.05), sexual abuse (24.8% v 5.8%, p<0.05). No difference regarding DSM-IV non-drug Axis 1 Diagnosis (33.3% v 31.8%, ns).
McHugh et al.	2013	Substance abuse treatment facilities in the context of prescription opioid dependence	Women more likely than men to have been diagnosed with Major Depressive Disorder in lifetime (47.5% v 20.2%, p<0.001); Women had greater scores on the Beck Depression Inventory (25.5) than men (20.0, p < 0.001)	Women more likely than men to have a lifetime diagnosis of Post-traumatic Stress Disorder (11.9% v 5.4%, p < 0.001).
Ohlin et al.	2015	Treatment program with work/study requirement	Women more likely than men to be diagnosed with depression (27.3% v 18.3%, respectively, p value NR)	Women more likely than my to be diagnosed with borderline (51.5% v 40.0%, p<0.05), schitzotypal (42.4% v 35.7%, p<0.05), and/or obsessive personality disorder (39.4% v 26.1%, p<0.05). Men more likely than women to be diagnosed with narcissistic personality disorder (39.4% v 59.1 %, p<0.05).
Vigna-Taglianti et al.	2016	Public substance treatment centers	Pre-existing depressive symptoms occurred in 66% of women compared to 46% of men (p<0.05)	Women more likely than men to report self-damaging behaviors (29.0% v 11.6%, p<0.05), aggressive behaviors (31.8% v 26.7%, p<0.05), suicide attempts (20.9% v 4.3%, p<0.05), psychotic thinking/ hallucinations (7.4% v 4.9%, p<0.05), psychiatric hospital admissions (10.6% v 4.4%, p<0.05).
Vo et al.	2016	Community treatment program for young adults	NR	No significant difference in prevalence of psychiatric disorders

Results from studies examining sex-based differences in presentation to treatment. Not all articles reported percentages or p values. Percentages and p values reported when included in the primary article. DSM = Diagnostic and Statistical Manual of Mental Disorders; NR = not reported.

Table 3.

Studies on Sex-based Differences in Buprenorphine Treatment Outcomes

			Treatment Outcomes		
Author Names	**Year of Publication**	**Treatment Setting**	**Treatment Retention**	**Opioid Use/Relapse/Outcome**	**Other Drug Use**
Öhlin et al.	2015	Treatment program with work/ study requirement	After 7 years, 59% of women and 39% of men were retained in treatment (p=NR).	NR	Reduction in alcohol use for entire group (p<0.05); Women initially had higher alcohol consumption than men (p<0.05).
Vo et al.	2016	Community treatment program for young adults	Men compared to women were retained in treatment longer (p=NR).	Men compared to women had higher rates of opioid-negative weeks.	NR
Weinstein et al.	2017	Office-based buprenorphine	Women compared to men were 55% (p<0.05) and 44% (p<0.05) more likely to be retained in treatment at one and two years, respectively.	NR	NR
Franklyn et al.	2017	Opioid addiction treatment centers utilizing methadone and subsequent buprenorphine	Women positive for THC compared to negative for THC upon treatment entry were 76% more likely to drop out of treatment (p=NR). Men who were heavy compared to non-heavy cannabis users 45% more likely to drop out of treatment (p=NR).	NR	NR
Gordon et al.	2017	Buprenorphine induction before or after release from prison	No sex-based differences.	No sex-based differences.	NR
Jones et al.	2005	Clinical trial comparing buprenorphine, methadone, and levacetylmethadol (LAAM)	No sex-based differences.	Women compared to men had fewer opioid positive urine screens within the buprenorphine arm (p<0.05) and women receiving buprenorphine self-reported reduced illicit opioid use compared to women receiving methadone or LAAM (p<0.05).	No sex-based differences.
Schottenfeld et al.	1998	Clinical trial comparing buprenorphine to methadone	Women compared to men on 4mg buprenorphine had higher treatment retention (p<0.03).	Overall, women compared to men had higher rates of illicit opioid abstinence (50.0% vs. 27.5%; p <.02). Women compared to men on 4mg buprenorphine had lower rates of opioid-positive urine (63.7% vs. 83.6%; p <.001) and higher rates of illicit opioid abstinence (50% vs. 0%; p =.001).	Women compared to men on 12mg buprenorphine had higher rates of cocaine-positive urine screens the buprenorphine 12-mg group (81.7% *vs.* 53.8%; *p* <.02).
Back et al.	2011	Clinical trial comparing buprenorphine taper strategies for opioid withdrawal	No difference.	Women displayed elevated clinical opiate withdrawal scores (p=0.05) and opioid craving (p<0.01) during the opioid taper.	Women more likely than men to test positive for amphetamine, methamphetamine, and phencyclidine (ps<0.05). Men more likely than women to test positive for marijuana (p=0.03).

Results from studies examining sex-based differences in presentation to treatment. Not all articles reported percentages or p values. Percentages and p values reported when included in the primary article. NR = not reported; THC = Tetrahydrocannabinol.