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Sex and Gender Differences in Substance Use Disorders

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Abstract

The gender gap in substance use disorders (SUDs), characterized by greater prevalence in men, is narrowing, highlighting the importance of understanding sex and gender differences in SUD etiology and maintenance. In this critical review, we provide an overview of sex/gender differences in the biology, epidemiology and treatment of SUDs. Biological sex differences are evident across an array of systems, including brain structure and function, endocrine function, and metabolic function. Gender (i.e., environmentally and socioculturally defined roles for men and women) also contributes to the initiation and course of substance use and SUDs. Adverse medical, psychiatric, and functional consequences associated with SUDs are often more severe in women. However, men and women do not substantively differ with respect to SUD treatment outcomes. Although several trends are beginning to emerge in the literature, findings on sex and gender differences in SUDs are complicated by the interacting contributions of biological and environmental factors. Future research is needed to further elucidate sex and gender differences, especially focusing on hormonal factors in SUD course and treatment outcomes; research translating findings between animal and human models; and gender differences in understudied populations, such as those with co-occurring psychiatric disorders and gender-specific populations, such as pregnant women.

Keywords

women; female; gender differences; risk factors; treatment outcomes; substance use disorders

Historically, research on substance use disorders (SUDs) has disproportionately focused on males. However, there are numerous biological, psychological and social differences

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Author Disclosures

Contributors

Dr. McHugh, Ms. Votaw, and Dr. Sugarman conducted the literature review and wrote the first draft of the manuscript. Dr. Greenfield participated in the conceptualization and critical revision of the manuscript for relevant intellectual content. All authors have contributed to and approved the final manuscript.

Conflict of Interest

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between men and women that may affect the development, maintenance and treatment of SUDs (Greenfield, Brooks, et al., 2007). Accordingly, with increased attention to the importance of research on sex and gender in health over the past 20 years (Mazure & Jones, 2015), research has begun to identify key differences in SUDs between males and females (Becker & Koob, 2016; Brady, Back, & Greenfield, 2009). This research is particularly critical in light of the narrowing gender gap in the prevalence of SUDs, characterized by an increasing representation of women (Keyes, Grant, & Hasin, 2008; Seedat et al., 2009a). In this manuscript, we provide a critical overview of sex and gender differences in SUDs, with a focus on human research. For readers interested in the growing preclinical literature on sex differences in SUDs, this has been recently reviewed elsewhere (Becker & Koob, 2016).

In this article, we will review studies of sex and gender differences, as well as literature that addresses topics specific to females (e.g., ovarian hormones, pregnancy). We will use the definitions of sex and gender provided by the National Institutes of Health Office of Research on Women's Health: *sex* is defined as biological differences between females and males and *gender* is defined as socially determined roles that vary across cultures and over time (National Institutes of Health, n.d.). Although we will cover the range of types of SUDs, where possible, we will attempt to disentangle findings across drug classes (e.g., alcohol, opioids). Search terms and methods for this review were adopted from a review previously published by our group that examined sex and gender differences in SUD treatment entry, retention, and outcome (Greenfield, Brooks, et al., 2007); a full description of study methods is available in the original review. Our search terms included: g*ender, sex, sex factors, gender identity, female, male, gender differences, sex, sex differences, women, gender-specific, substance-related disorders, substance-induced disorders, substance abuse treatment centers, drug users, prescription drug misuse, alcohol-related disorders, alcohol-induced disorders, alcoholism, alcohol drinking, and opioid-related disorders.* We expanded our methods to include a brief overview of biological sex differences and the epidemiology of SUDs. This current review of gender differences in the prevalence and incidence of substance use includes recent government publications reporting data from population-based surveys. In our review sex and gender differences in the etiology of substance use, as well as substance use in pregnancy, we also included seminal manuscripts published before 2007. On the topic of treatment, we only included manuscripts published since 2007 (through April, 2017) in order to highlight the most recent findings. This yielded a total of 517 papers, which were reviewed for relevance to the current review.

Biological Sex Differences in Substance Use

A number of biological differences exist between males and females in the acute and long-term effects of alcohol and other drugs. These differences reflect sexual dimorphisms in brain, endocrine (e.g., ovarian hormones), and metabolic systems, among others. Among the most consistent findings in this area is that females and males metabolize alcohol differently. Females exhibit lower levels of alcohol dehydrogenase (the enzyme that metabolizes ethanol) activity in the gastric mucosa relative to males. Combined with lower total body water relative to males, this results in higher blood alcohol concentrations in women, even after consumption of equivalent quantities of alcohol (Baraona et al., 2001; Chrostek, Jelski, Szmitkowski, & Puchalski, 2003). This metabolic difference results in greater intoxication

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for females relative to males when the same amount of alcohol is consumed. Sex differences in the metabolism of other substances have not been consistently demonstrated. However, there is some evidence that females metabolize nicotine more rapidly than males (Benowitz, Lessov-Schlaggar, Swan, & Jacob, 2006; Berlin, Gasior, & Moolchan, 2007) and exhibit higher peak plasma levels of cocaine (Lukas et al., 1996), which may be modulated by ovarian hormones. Substantial heterogeneity *within* sexes in metabolic processes, as well as the contribution of multiple metabolic pathways to the clearance of substances may obscure sex differences in drug metabolism (DeVane, 2009). Nonetheless, findings to date suggest that the metabolism of substances (and, accordingly their effects) cannot be assumed to be consistent for males and females.

Research on sex differences in the acute subjective effects of substances has yielded equivocal results. For example, several studies of sex differences in the rewarding effects of substances (e.g., self-reported “good drug effect”) have found no difference between males and females (e.g., oxycodone; Zacny & Drum, 2010), with others finding greater subjective effects in males (e.g., morphine [Comer et al., 2010]; *d*-amphetamine [Vansickel, Lile, Stoops, & Rush, 2007]) or greater effects in females (e.g., THC [Z. D. Cooper & Haney, 2014]; oxycodone [Lofwall, Nuzzo, & Walsh, 2012]). Heterogeneity in study methodology, such as dosing and study population, might contribute to mixed results. Low doses of THC (5 mg) and *d*-amphetamine (8–10 mg) have demonstrated greater abuse liability among females, whereas malesmen appear to be more sensitive to the rewarding and reinforcing properties of these substances at higher doses (15 mg for THC; 16–20 mg for *d*-amphetamine; Fogel, Kelly, Westgate, & Lile, 2017; Vansickel, Stoops, & Rush, 2010). One study enrolling participants with and without frequent marijuana use found that males without frequent marijuana use produced greater subjective ratings of THC abuse liability (compared to their female counterparts), whereas there were no sex differences among frequent marijuana smokers (Haney, 2007).

Subjective drug effects may be further influenced by variation in ovarian hormones, which are often not measured and thus may present a source of variability among females that obscures true sex differences. Studies of menstrual cycle phase have found that the follicular phase is associated with greater reports of drug liking and pleasant subjective effects relative to the luteal phase (S. M. Evans, Haney, & Foltin, 2002; Justice & de Wit, 1999), although other studies have not detected fluctuations in subjective effects across the menstrual cycle (Holdstock & de Wit, 2000; Kouri, Lundahl, Borden, McNeil, & Lukas, 2002). Findings on the association between menstrual cycle phase and drug consumption (DeBon, Klesges, & Klesges, 1995; Mello, Mendelson, & Lex, 1990) and craving (Franklin et al., 2015; Gray et al., 2010) have been inconsistent. Equivocal findings highlight the importance of refined examination of menstrual cycle phases (i.e., sub-phases) that better characterize fluctuating levels of both estrogen and progesterone, rather than the broad luteal vs. follicular phase distinction (A. M. Allen et al., 2016).

Indeed, studies that have involved the exogenous administration of ovarian hormones have yielded more consistent results than studies of naturally occurring fluctuations. Progesterone administration is associated with acute decreases in craving, including cue-induced cocaine craving (Fox, Sofuoglu, Morgan, Tuit, & Sinha, 2013; Milivojevic, Fox, Sofuoglu, Covault,

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& Sinha, 2016) and nicotine craving (Sofuoglu, Babb, & Hatsukami, 2001). Among postpartum women, progesterone treatment has been associated with less cocaine relapse (Yonkers et al., 2014), and initial evidence of less nicotine relapse in a small pilot study (S. S. Allen, Allen, Lunos, & Tosun, 2016).

Neuroimaging research has identified a number of sex differences in brain volume and function in response to various substances; however, many studies have not detected sex differences, have not tested sex differences, or were insufficiently powered (Lind et al., 2017).

Structural neuroimaging studies suggest that there may be sex-specific neural consequences of substance use. For example, both females and males with cocaine use disorder exhibited lower gray matter volume relative to controls; but the regions exhibiting these volumetric differences varied (Rando, Tuit, Hannestad, Guarnaccia, & Sinha, 2013). Similar findings have been reported in smokers (Franklin et al., 2014). Moreover, females may be more susceptible to the negative effects of chronic cocaine (Ide et al., 2014) and alcohol use (Mann et al., 2005) on brain volume; however, not all studies have reported these differences (Demirakca et al., 2011) and causality cannot be established in these cross-sectional designs.

Research examining neural response to substance-related cues (e.g., images of drugs) has identified some sex differences. For example, women demonstrate greater neural activation to cocaine cues relative to men (Volkow et al., 2011), and men and women differ in regional activation in response to alcohol cues (Seo et al., 2011). A study of stress- and cue-induced cocaine craving found greater neural reactivity to stress cues in women and drug cues in men (Potenza et al., 2012). Striatal dopamine release–which is reflective of activation of the brain reward pathways–is higher in men relative to women in response to stimulants (Munro et al., 2006), alcohol (Urban et al., 2010), and nicotine (Cosgrove et al., 2014). Although further research is needed to fully understand the impact of these volumetric and functional differences, these studies provide an initial indication of neural correlates of observed sex gender differences in SUDs, such as greater stress-related vulnerabilities in women (see below). Of note, these differences may be attributable to biological as well as gender-related differences (e.g., neurobiologic differences between sexes as well as environmental cues related to gender).

Taken together with the extensive preclinical evidence for biological differences between males and females, these data suggest that sex differences in the biology of substance use are evident, but may be subject to key moderators (e.g., ovarian hormones, type of drug, dose, history of drug exposure). Prospective studies designed to clarify whether differences are present prior to drug exposure are needed to better understand the drivers of these differences as well as their functional consequences. Moreover, these findings suggest that sex differences are complex and cut across multiple systems ranging from metabolism and substance effects to brain structure and function. Accordingly, research attempting to disentangle the effects of sex on substance use must consider these multiple levels of analysis to better understand the nature of these differences and their implications for men and women. Nonetheless, this body of research clearly suggests that we cannot assume that

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males and females will respond similarly to substances, and therefore inclusion of both sexes in research on this topic is essential.

Gender Differences in Substance Use Disorders

Prevalence and Incidence

The historical gap in SUD prevalence between men and women (characterized by higher prevalence in men) is narrowing worldwide (Keyes et al., 2008; Seedat et al., 2009b; Steingrimsson, Carlsen, Sigfusson, & Magnusson, 2012). The epidemiology of SUDs varies internationally, and is affected by culture and policies that influence the access to and acceptability of using substances. Data from the World Health Organization World Mental Health Surveys found that lower gender role traditionality (defined by variables such as women's representation in the workforce, access to contraception, etc.) is associated with a smaller male to female gap in SUDs (Seedat et al., 2009b). Although there is significant variation across cultures, in general, men are more likely to have access to substances relative to women; this difference in access appears to account for much of the gender difference in the prevalence of substance use. In other words, when controlling for access, the likelihood of substance use does not differ between men and women (Caris, Wagner, Rios-Bedoya, & Anthony, 2009; Delva et al., 1999; Van Etten & Anthony, 1999). Given international variability, we will focus on the prevalence and incidence of substance use and SUDs in the U.S. Unless otherwise specified, all prevalence estimates are from the National Survey on Drug Use and Health, an annual, population-based survey of US citizens ages 12 years and older.

In 2015, an estimated 47.4% of females ages 12 and older reported past-month alcohol use, compared to 56.2% of males. Women also displayed lower rates of binge drinking (i.e., four or more drinks on the same occasion in the past-month for women, five or more drinks for men; 20.5%), heavy drinking (i.e., binge drinking on at least 5 days in the past month; 4.2%), and alcohol use disorder (4.1%) than men (29.6%, 8.9%, 7.8%, respectively) (Center for Behavioral Health Statistics and Quality [CBHSQ], 2016). Although a greater proportion of adult men tend to use alcohol, and display problematic use (i.e., binge drinking, alcohol use disorder) compared with women, recent data indicate that this gender gap is not present among adolescent boys and girls. For example, data show no gender differences among adolescents (i.e., ages 12–17) for both current alcohol use (9.9% of girls vs. 9.6% of boys) and binge drinking (5.8% of both genders) (CBHSQ, 2016). This gap also appears to be closing for older adults in the U.S. with data from the National Interview Surveys between 1997 and 2014 demonstrating that binge drinking increased 3.7% annually among U.S. women but demonstrated no change among U.S. men over the age of 60 (Breslow, Castle, Chen, & Graubard, 2017)

Nicotine dependence is present in 52.3% of women who are current smokers and 9.7% of women overall (CBHSQ, 2016). However, tobacco use prevalence has declined among both males and females over the past decade (CBHSQ, 2016). Across this period, women have consistently displayed lower rates of tobacco use than men (CBHSQ, 2016). In 2015, 18.5% of women ages 12 and older reported past month use of tobacco products, compared to 22.5% of women in 2007. Decreases in past-month tobacco use have been particularly rapid

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among adolescents, with 4.9% of girls reporting past-month tobacco use in 2015, compared to 10.7% in 2007 (CBHSQ, 2016). The decrease in use of tobacco products has been accompanied by an increase in other forms of nicotine administration. For example, electronic cigarette use is now more prevalent among adolescents than tobacco use. According to Monitoring the Future Study in 2016, 9.1% of 12th grade girls reported past-month electronic cigarette use, a rate significantly lower than boys of the same age (16.1%) (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2017). Large-scale data on electronic cigarette use is not yet available among adults.

Illicit drug use is significantly more prevalent among men than women (CBHSQ, 2016). In 2015, 7.9% of women and 12.5% of men ages 12 and older reported past-month illicit drug use; corresponding rates of illicit drug use disorders were 2% and 3.8%. However, 8.8% of adolescents (i.e., ages 12–17) of both genders reported past-month illicit drug use (CBHSQ, 2016). This gender parity among adolescents appears to be driven by prescription drug misuse, with adolescent girls reporting higher rates of past-month use than boys (2.3% of girls vs. 1.7% of boys) (CBHSQ, 2016). Among adults, prescription drugs are among the only substance class for which past-month prevalence of misuse is similar in adults of both genders (2.2% of women vs. 2.7% of men).

Recent trends in illicit drug use differ by drug class. Rates of heroin use have increased in adults of both genders from 2002–2013 (Centers for Disease Control and Prevention [CDC], 2015). Although men displayed higher rates of heroin use across this time, women have had a greater overall increase in heroin use during this time period (100% increase in women vs. 50% increase in men) (CDC, 2015). Likewise, rates of past-year marijuana use have increased in both genders from 2007–2014. However, this increase has been greater among men, thus widening the gender gap in marijuana use (+4.4% for men vs. +2.7% for women; reflecting past-year prevalence of 16.9% and 10.1% in 2014, respectively) (Carliner et al., 2017).

Course of Illness

The peak risk period for onset of substance use is late adolescence (Vega et al., 2002). On average, women initiate substance use at a later age than men (Greenfield, Pettinati, O'Malley, Randall, & Randall, 2010; Keyes, Martins, Blanco, & Hasin, 2010). A number of studies have suggested that, relative to men, women may have an accelerated course of substance use, progressing more rapidly from initiation of substance use to problems with substances, and from problems with substances to treatment-seeking (Hernandez-Avila, Rounsaville, & Kranzler, 2004). This progression is referred to as a "telescoping" course of illness and has been replicated in alcohol (Diehl et al., 2007; Randall et al., 1999), marijuana (Khan, Okuda, et al., 2013; Lewis, Hoffman, & Nixon, 2014), cocaine (Haas & Peters, 2000) and prescription opioid use (Lewis et al., 2014). However, this has not been demonstrated for all substances (e.g., heroin; Lewis et al., 2014; Stoltman, Woodcock, Lister, Greenwald, & Lundahl, 2015), and one large, population-based analysis examining alcohol use trajectories failed to replicate the telescoping effect (Keyes et al., 2010). This discrepancy may reflect cohort differences, with some evidence that telescoping is not evident in younger cohorts (P. B. Johnson, Richter, Kleber, McLellan, & Carise, 2005); however, other studies have not

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found evidence for the telescoping effect across cohorts (Keyes et al., 2010). A previous review posited that equivocal findings might be explained by differences in study population (Becker, McClellan, & Reed, 2017). Specifically, the telescoping effect has primarily been identified among women who are already in treatment, and likely represent those with more severe SUDs, whereas population-based surveys have failed to replicate the telescoping effect. Thus, this effect might be present only among women who are vulnerable to more severe SUDs, with mitigation of this effect when simultaneously examining women who represent the wide range of substance use severity. In other words, a subset of women may be vulnerable to a rapid progression to severe SUDs.

There is also variation by substance type in the likelihood of transition from use to dependence (i.e., dependence liability); this also varies modestly by gender, with evidence for greater dependence liability of nicotine and lower dependence liability of marijuana in women relative to men (Lopez-Quintero et al., 2011; Wagner & Anthony, 2007). For many illicit substances, such as heroin, cocaine, and methamphetamine, use is characterized by a chronic course (i.e., persistent regular use) in both men and women (Hser, Huang, Brecht, Li, & Evans, 2008). Receipt of treatment is associated with more favorable course of illness in both genders, particularly when treatment is initiated early and sustained over time (E. Evans, Li, Grella, Brecht, & Hser, 2013).

Adverse Consequences and Co-occurring Psychiatric Disorders

Relative to men, women in SUD treatment consistently report more severe functional impairment in domains such as employment, social/family, medical and psychiatric functioning (Foster, Li, McClure, Sonne, & Gray, 2016; Hernandez-Avila et al., 2004; McHugh et al., 2013; Sherman et al., 2017; Wu et al., 2010), as well as poorer overall quality of life (Griffin et al., 2015). Although findings are somewhat mixed regarding gender differences in the legal consequences of substance use, a number of studies indicate greater legal problems in men (Sonne, Back, Diaz Zuniga, Randall, & Brady, 2003; Westermeyer & Boedicker, 2000).

SUDs are associated with significant mortality. Despite reductions in smoking over time, it remains the leading preventable cause of death in the U.S. (CDC, 2017) and women's risk of dying from smoking-related causes more than tripled since 1964, and was equal to that of men in 2014 (U.S. Department of Health and Human Services, 2014). Heavy drinking is also associated with increased mortality (Plunk, Syed-Mohammed, Cavazos-Rehg, Bierut, & Grucza, 2013); mortality among women with alcohol use disorders was four times that of the general population (E. M. Smith, Cloninger, & Bradford, 1983). Drug overdoses–currently predominated by the epidemic of opioid overdose–continue to escalate in the U.S. (Rudd, Seth, David, & L., 2016). Although overdose death is more common among men, the rate of increase in overdose death is rising more rapidly in women relative to men, and accordingly this gender gap is narrowing (CDC, 2013). Deaths from prescription opioid overdoses among women increased 400% since 1999 compared with 265% among men (CDC, 2013). Among those in SUD treatment, mortality remains elevated relative to gender- and age-matched population estimates, with women exhibiting a 5-fold greater mortality rate relative to the general population compared with 3-fold greater mortality in men; however

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this difference was not statistically significant (Lindblad et al., 2016). Accordingly, further research is needed to understand relative mortality risk in men and women with SUDs.

Moreover, substance use is associated with myriad negative health consequences, such as liver, cardiovascular, and gastrointestinal disease, among others (National Institute on Alcohol Abuse and Alcoholism, 2010). Both smoking and heavy alcohol use have been linked to breast cancer (W. Y. Chen, Rosner, Hankinson, Colditz, & Willett, 2011; Gaudet et al., 2013). Substance use increases risk for both perpetration (Shorey, Stuart, McNulty, & Moore, 2014) and victimization (Krebs, Lindquist, Warner, Fisher, & Martin, 2009) of sexual violence in both men and women. Binge drinking has been associated with sexual assault (McCauley, Calhoun, & Gidycz, 2010; Stappenbeck & Fromme, 2010), unintended pregnancy, and sexually transmitted disease in women (Wechsler, Davenport, Dowdall, Moeykens, & Castillo, 1994). Similarly, illicit drug use is associated with sexual victimization and sexual risk behaviors in women (Brooks et al., 2010; Jessell et al., 2015; Walsh et al., 2014)

There are also gender differences in other co-occurring psychiatric disorders among those with SUDs, with higher rates of anxiety and depressive disorders in women and higher rates of other externalizing disorders such as conduct disorder and antisocial personality disorder in men (Conway, Compton, Stinson, & Grant, 2006; Khan, Okuda, et al., 2013). Women are more likely to report experiencing a traumatic event and posttraumatic stress disorder onset prior to the onset of an SUD (Compton, Cottler, Phelps, Ben Abdallah, & Spitznagel, 2000; Sonne et al., 2003). Women also report more frequent use of substances to reduce negative affect (Lehavot, Stappenbeck, Luterek, Kaysen, & Simpson, 2014; McHugh et al., 2013). Co-occurring psychiatric disorders can complicate SUD treatment outcomes especially with respect to treatment entry and post-treatment clinical outcomes (Greenfield et al., 2009). Because co-occurring psychiatric disorders are more prevalent among women with SUDs than their male counterparts, psychiatric comorbidity may be an especially critical treatment target for women with SUDs (Greenfield, Brooks, et al., 2007).

Treatment of Substance Use Disorders in Women

Results of our 2007 review of gender and SUD treatment entry, retention and outcome (Greenfield, Brooks, et al., 2007) suggested that women, in general, were less likely to seek treatment for SUDs relative to men but the majority of studies also found that women and men did not differ with respect to treatment retention or outcomes. Nonetheless, a number of key prognostic variables–such as co-occurring psychiatric disorders–disproportionately affect women, and such subgroups may benefit from targeted interventions (e.g., treatment of PTSD and SUDs concurrently; Hien et al., 2009a). Below, we provide a brief update on the research on gender differences in the treatment of SUDs published over the past 10 years. Our discussion will first focus on studies comparing men and women, followed by studies of gender-responsive treatments and treatment for pregnant women.

Treatment Seeking

There is some evidence that women present to treatment more quickly after substance use initiation and disorder onset (see above; Alvanzo et al., 2014; Blanco et al., 2013; Lewis &

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Nixon, 2014). Among adolescents with alcohol use disorder, girls are more likely to receive treatment than boys (Haughwout, Harford, Castle, & Grant, 2016). Nevertheless, population-based and treatment admission data suggest that many women with SUDs do not receive treatment. In 2015, of the estimated 7.9 million women in the U.S. who needed treatment for an alcohol or drug use disorder, only 10.4% received treatment, compared to 11.1% of men (CBHSQ, 2016). Treatment underutilization is particularly notable among adult women with alcohol use disorder (Alvanzo et al., 2014; Cohen, Feinn, Arias, & Kranzler, 2007; Khan, Okuda, et al., 2013). Additionally, men are more likely to receive specialized SUD treatment (e.g., self-help groups, specialized outpatient treatment, etc.), whereas women with SUDs are more likely to seek treatment at mental health treatment settings (Edlund, Booth, & Han, 2012).

Treatment entry for illicit drug use disorders displays more gender parity. In an analysis of illicit drug use disorders, gender was not associated with past-year treatment utilization (Compton, Thomas, Stinson, & Grant, 2007). Studies have found no gender differences in treatment entry for prescription opioid use disorder (Blanco et al., 2013; Kerridge et al., 2015) and cannabis use disorder (Khan, Secades-Villa, et al., 2013) among adults, however, adolescent boys with cannabis use disorder are more likely to receive treatment than girls (Haughwout et al., 2016). Women represent approximately half of treatment admissions for prescription drug use disorders. Of those presenting to treatment for a primary prescription opioid use disorder in 2014, 46.8% were women; comparable rates were observed for tranquilizers (e.g., benzodiazepines; 46.5% women) and sedatives (e.g., barbiturates; 58.2% women) (CBHSQ, 2015).

Historically, women have faced specific barriers to SUD treatment entry, such as greater perceived stigma, childcare responsibilities, and lack of family support (Greenfield, Brooks, et al., 2007). Two recent population-based surveys indicate that women with alcohol use disorder are more likely to perceive stigma as a barrier to treatment (Khan, Okuda, et al., 2013; Verissimo & Grella, 2017). However, other population-based surveys indicate few gender differences in barriers to SUD treatment (Khan, Okuda, et al., 2013; Khan, Secades-Villa, et al., 2013; Zemore, Mulia, Ye, Borges, & Greenfield, 2009). These findings might be attributable to methodological features of these surveys, including failure to assess barriers related to pregnancy, childcare, and attitudes of family members. Although women with SUDs are more likely than men to have a co-occurring depressive or anxiety disorder (Khan, Okuda, et al., 2013; Khan, Secades-Villa, et al., 2013), access to care for co-occurring disorders remains severely limited (Gordon et al., 2008; Lambert-Harris, Saunders, McGovern, & Xie, 2013).

Treatment Outcome

Differences between men and women in treatment outcomes may emerge from the effects of gender (e.g., barriers to treatment access such as child care responsibilities) or sex (e.g., differences in the pharmacokinetics or pharmacodynamics of medications that impact medication bioavailability). Understanding the common and unique needs of men and women has significant implications for treatment decisions, such as selecting the optimal

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first-line treatment, medication dosing, and identifying needed complementary social services.

Available studies of gender differences in treatment outcome have yielded mixed results; however, most large-scale randomized clinical trials have not found evidence of gender differences in treatment outcome. This has been shown for varied substances, including large randomized trials of pharmacotherapy for alcohol dependence (N=1,226; 31% women; Greenfield et al., 2010) and prescription opioid dependence (N=653, 40% women; McHugh et al., 2013).

The exception to this pattern of findings is the treatment of nicotine dependence, for which outcomes are worse in women relative to men (P. H. Smith et al., 2015), and evidence for gender differences in response to pharmacological treatment is accumulating. A large randomized study found better response to nicotine replacement in men relative to women (Perkins & Scott, 2008), and a meta-analysis of randomized trials found better response to varenicline in women relative to men (McKee, Smith, Kaufman, Mazure, & Weinberger, 2016). In a meta-analysis of 32 smoking cessation trials (N=14,389, 51% women), the efficacy of varenicline relative to placebo was comparable in men and women; however, women had greater benefits of varenicline relative to both nicotine replacement (transdermal nicotine) and buproprion (P. H. Smith et al., 2017). Moreover, there is some evidence for differences in response to naltrexone, with men exhibiting greater reductions in smoking (King et al., 2012), whereas women exhibit less weight gain (King, Cao, Zhang, & O'Malley, 2013).

Gender differences in treatment response to other pharmacotherapies have not been consistently demonstrated. Women have shown poorer response to disulfiram for cocaine dependence (DeVito, Babuscio, Nich, Ball, & Carroll, 2014); however, this has not been reported in trials of disulfiram for alcohol dependence, perhaps because of the significant underrepresentation of women in these studies (e.g., 1.2%; see Agabio, Pani, Preti, Gessa, & Franconi, 2016). Findings on gender differences in response to naltrexone for alcohol dependence have been mixed, with some studies concluding that men responded better to naltrexone under certain dosing conditions (Kranzler et al., 2009; Pettinati et al., 2008), but others finding no difference (Baros, Latham, & Anton, 2008), including the COMBINE Study, a seminal multi-site trial (Greenfield et al., 2010). Studies of opioid agonist therapies have also not indicated significant gender differences, including studies of both buprenorphine (McHugh et al., 2013; Potter et al., 2013) and methadone maintenance (Potter et al., 2013). Women have worse outcomes than men to buspirone treatment for cannabis (McRae-Clark et al., 2015) and cocaine dependence (Winhusen et al., 2014); in both trials, buspirone did not outperform placebo in either gender.

Behavior therapy studies have generally found that women and men respond similarly to these treatments across a wide array of treatment types and substances, including cognitive-behavioral therapies, contingency management, and behavioral couples therapy (Burch, Rash, & Petry, 2015; Campbell et al., 2015; DeVito et al., 2014; Rash & Petry, 2015). The use of mutual-help groups, such as Alcoholics Anonymous, has been shown to help both

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men and women without evidence of significant differences (Ammon, Bond, Matzger, & Weisner, 2008).

In general, there are not substantive differences between women and men in treatment retention. For example, an aggregation of 24 clinical trials from the National Institute on Drug Abuse Clinical Trials Network (N>11,000) found no differences in clinical trial retention between men and women (Korte, Rosa, Wakim, & Perl, 2011). Likewise, an analysis of over 1.7 million SUD treatment episodes nationally did not find evidence for a difference in treatment completion between men and women, with the exception that women were less likely to complete detoxification (Bornstein, Longinaker, Bryant-Genevier, & Terplan, 2015).

Notably, most of these studies have identified reductions in substance use (or abstinence) and treatment retention as primary outcomes of interest. Given that women and men differ substantively in negative health and psychosocial effects of substance use, future studies should explore gender differences in the effects of treatment on other outcomes of interest (e.g., quality of life, measures of mental and physical health).

Gender-Specific and Gender-Responsive Treatments

Recognition of gender differences in SUDs led to the development of separate treatment programs for women with SUDs in the 1980's; particularly to address the needs of pregnant women and women with children (Greenfield & Grella, 2009; Grella, 2008). The term "gender-responsive" emerged in the 1990s, and refers to treatment that addresses factors that are more prevalent in women that may affect their treatment outcomes, including exposure to trauma, co-occurring psychiatric disorders (e.g., depression, anxiety, and eating disorders), relationships with children and intimate partners, and physical health issues (Greenfield & Grella, 2009).

A review of data from 43 SUD treatment programs found that women in women-only programs, despite having higher levels of substance use and psychiatric severity, had better drug use treatment outcomes than women in mixed-gender programs (Niv & Hser, 2007). Women-only treatment has also been associated with better outcomes with respect to criminal activity and incarceration following treatment (Hser, Evans, Huang, & Messina, 2011; Prendergast, Messina, Hall, & Warda, 2011). This is consistent with other studies that have found better outcomes (albeit, modest in magnitude, with the exception of psychiatric problems) among women in women-only relative to mixed-gender treatment (Orwin, Francisco, & Bernichon, 2001). However, a retrospective analysis of a residential treatment facility that switched from mixed to single-gender programming did not find any evidence that single-gender programming produced better treatment outcomes (Bride, 2001). Of note, the treatment program did not make any changes to the treatment such as including gender-responsive services or staff training; thus, simply providing a women-only environment may not be sufficient for improving outcomes.

Participation in gender-specific treatment is also associated with greater satisfaction, enhanced comfort, and feelings of safety among women (Greenfield, Cummings, Kuper, Wigderson, & Koro-Ljungberg, 2013), and increased continuity of care following discharge

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(Claus et al., 2007). Qualitative data from the WRG study found higher rates of verbal affiliation in women in the WRG compared to those in mixed-gender drug counseling (Greenfield, Kuper, Cummings, Robbins, & Gallop, 2013; Sugarman et al., 2016); thus, gender-specific treatments may create an environment of enhanced affiliation, which may in turn lead to better outcomes.

Results of several randomized controlled trials provide support for gender-specific treatments with specific subpopulations of women, such as: women with children (Slesnick & Erdem, 2013; Slesnick & Zhang, 2016), women with co-occurring psychiatric disorders (Hien et al., 2009b; Linehan et al., 1999; Najavits, Weiss, Shaw, & Muenz, 1998), and women in the criminal justice system (Nena Messina, Calhoun, & Warda, 2012; N. Messina, Grella, Cartier, & Torres, 2010). In addition, Greenfield and colleagues (Greenfield, Trucco, McHugh, Lincoln, & Gallop, 2007) developed the Women's Recovery Group (WRG), a gender-specific group therapy for women heterogeneous with respect to SUD type, age, trauma history, and co-occurring psychiatric disorders. When delivered in a closed group format, women in the WRG had greater reductions in substance use 6 months following treatment completion, compared to those in mixed-gender group drug counseling (Greenfield, Trucco, et al., 2007). Results of a larger randomized trial showed that when delivered in a rolling group format typical of community SUD treatment, women in the WRG had clinically meaningful reductions in substance use during treatment and post-treatment, and the WRG was as effective as mixed-gender drug counseling in reducing substance use (Greenfield et al., 2014; Greenfield, 2016).

Treatments have also been developed to address the association between intimate relationships and relapse in women with SUDs (Walitzer & Dearing, 2006). For example, behavioral couples therapy is an efficacious treatment for women with alcohol use disorder and other SUDs (McCrady, Epstein, Cook, Jensen, & Hildebrandt, 2009; O'Farrell, Schumm, Murphy, & Muchowski, 2017).

Studies of mixed-gender treatments targeting co-occurring disorders are somewhat limited, and most are characterized by small sample sizes that preclude gender-based analyses. In a large (N=353) multi-site trial in women comparing a behavioral group therapy for co-occurring PTSD and SUDs (Seeking Safety) (Najavits, Weiss, Shaw, & Muenz, 1998) to a psychoeducational comparison treatment, women exhibited significant reductions in substance use and PTSD symptoms in both conditions (Hien et al., 2009a). Notably, those with greater reduction in PTSD symptoms exhibited more substance use improvement, highlighting the importance of addressing co-occurring psychiatric disorders (Hien et al., 2010). In a secondary analysis, Seeking Safety was associated with more rapid improvement, which was associated with reductions in cocaine and alcohol use (Morgan-Lopez et al., 2014). There remains a significant need for trials of treatments for co-occurring mood, anxiety, eating, posttraumatic stress, and personality disorders in women.

Substance Use in Pregnancy

Although substance use is less common in pregnant compared with non-pregnant women, a substantial proportion of pregnant women use substances. The National Survey on Drug use

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and Health found that an estimated 4.7% of pregnant women used illicit drugs in the previous month, 13.9% used tobacco products, and 9.3% used alcohol (including 4.6% and 0.8% with heavy use); 21.7% of pregnant women reported using any substance in the prior month (CBHSQ, 2016). Marijuana is the most frequently used illicit drug in pregnant women, followed by prescription opioid analgesics (CBHSQ, 2016). Rates of SUDs are lower in pregnant women relative to women who are not pregnant; approximately 3.6% of pregnant women meet diagnostic criteria for alcohol use disorder and approximately 1.6% meet diagnostic criteria for a drug use disorder (Vesga-Lopez et al., 2008). Pre-pregnancy alcohol, nicotine and illicit drug use is a robust predictor of substance use during pregnancy (Harrison & Sidebottom, 2009; Ward, Weg, Sell, Scarinci, & Read, 2006), with higher frequency of pre-pregnancy use representing the highest risk for prenatal substance use (Harrison & Sidebottom, 2009).

Although ethical concerns limit the ability to test the impact of substance use on fetal development, evidence suggests that many substances cross the placenta. Teratogenic effects of alcohol (K. L. Jones, Smith, Ulleland, & Streissguth, 1973; Warren & Foudin, 2001) and nicotine (R. Chen, Clifford, Lang, & Anstey, 2013; Ko et al., 2013; Pollack, Lantz, & Frohna, 2000) are well-established. Fetal alcohol spectrum disorders, which result from alcohol use during pregnancy and occur in 2–5% of births (May et al., 2009), are associated with long-term developmental impairments (Bailey & Sokol, 2011; K. L. Jones et al., 1973; Streissguth et al., 2004). Moreover, alcohol use is highly prevalent among breastfeeding mothers (e.g., 36%; Breslow, Falk, Fein, & Grummer-Strawn, 2007), despite evidence that alcohol is passed on via breast milk (Lawton, 1985) and appears to inhibit lactation and interfere with feeding (Mennella, 1998, 2001). Although understudied, use of illicit drugs has also been associated with a wide array of negative neonatal outcomes, such as low birth weight, long-term cognitive deficits, and–for opioids–neonatal abstinence syndrome (Behnke & Smith, 2013; Goldschmidt, Richardson, Cornelius, & Day, 2004; Lester et al., 2002; Patrick et al., 2012). For example, a large multisite collaborative study found that risk for stillbirth was more than doubled among users of nicotine, marijuana, stimulants, and prescription opioids (Varner et al., 2014). It is important to note that studies examining neonatal effects of substance exposure during pregnancy can also be confounded by other important predictors of neonatal outcomes, such as smoking and the lack of consistent (or any) prenatal care, which are associated with negative neonatal outcomes.

Treatments for Pregnant Women

Treatment-seeking and entry is limited among pregnant women with SUDs, with only 8.7% receiving specialized treatment (Terplan, McNamara, & Chisolm, 2012). Despite the efficacy of medications such as buprenorphine and methadone in preventing relapse, treatment attrition, and neonatal abstinence syndrome (H. E. Jones et al., 2010; Klaman et al., 2017), a minority of pregnant women with opioid dependence gain access to such treatment (Martin, Longinaker, & Terplan, 2015; K. Smith & Lipari, 2013). Gaps in treatment-seeking among pregnant women with SUDs might be due to fear of prosecution (Roberts & Nuru-Jeter, 2010), stigma, as well as the shortage of access to evidence-based medication treatment (e.g., methadone or buprenorphine) and other programming for pregnant women (Substance Abuse and Mental Health Services Administration [SAMHSA],

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2017; K. Smith & Lipari, 2013). Women with children also face unique barriers to SUD treatment due to limited availability of childcare in SUD treatment settings (i.e., 6.8% provide childcare services) (SAMHSA, 2017).

The majority of studies on SUDs in pregnant women have focused on smoking cessation, given the well-established teratogenic effects of smoking (R. Chen et al., 2013; Ko et al., 2013; Pollack et al., 2000), and the significant benefits of smoking cessation to maternal and fetal health (Polakowski, Akinbami, & Mendola, 2009; Reichert et al., 2009). The U.S. Preventive Services Task Force recommends that tobacco use should be assessed in all pregnant women, with behavioral interventions identified as the first line of care (Siu, 2015). For example, contingency management (Tappin et al., 2015) and cognitive-behavioral therapy have demonstrated efficacy for smoking cessation in pregnant women (Lee et al., 2015). Notably, this task force also concluded that the literature was insufficiently developed to confidently draw conclusions about the risks and benefits of pharmacotherapy for smoking cessation in pregnant women. Indeed, large studies have not provided support for the efficacy of nicotine replacement in pregnant women (S. Cooper, Lewis, et al., 2014), although women receiving nicotine replacement in a large trial displayed some evidence of superior short-term cessation outcomes and infant developmental outcomes two years later (S. Cooper, Taggar, et al., 2014).

In general, both naturalistic (Meyer, Johnston, Crocker, & Heil, 2015) and randomized trials (H. E. Jones et al., 2010) support the efficacy of both buprenorphine and methadone for pregnant women with opioid use disorder, with some evidence for modestly better infant outcomes among those receiving buprenorphine. The Maternal Opioid Treatment: Human Experimental Research (MOTHER) Study, a seminal study on the use of opioid agonist therapies in pregnant women, randomized pregnant women with opioid use disorder to receive methadone or buprenorphine (H. E. Jones et al., 2010). This study found that the proportion of infants requiring neonatal abstinence syndrome treatment did not differ between the two medications; however, infants whose mothers received buprenorphine required less morphine for the treatment of neonatal abstinence syndrome and had shorter hospitalizations. There were also no differences in maternal outcomes, except that women receiving buprenorphine were more likely to discontinue treatment, consistent with the broader literature comparing buprenorphine to methadone (Hser et al., 2014).

The use of incentives for treatment attendance has been associated with significantly improved attendance among pregnant women with SUDs (Brigham, Winhusen, Lewis, & Kropp, 2010). However, the use of motivational enhancement to improve retention has not been successful among pregnant women with respect to retention or outcome (Winhusen et al., 2008). Studies of behavioral therapies for pregnant women have yielded mixed findings. For example, contingency management has displayed efficacy in reducing cocaine use (Schottenfeld, Moore, & Pantalon, 2011), but did not promote abstinence or treatment retention among opioid-dependent pregnant women (Small, Curran, & Booth, 2010)

Surprisingly, treatment for alcohol use disorder in pregnant women is an understudied area. Most notably, there is a paucity of research on the safety and efficacy of pharmacotherapies for alcohol use disorder (e.g., naltrexone, disulfiram, acamprosate) during pregnancy, as well

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as management of alcohol detoxification in pregnant women (DeVido, Bogunovic & Weiss, 2015). Nonetheless, brief interventions have demonstrated efficacy for reducing alcohol use during pregnancy (O'Connor & Whaley, 2007; Wilton et al., 2013), and might be as efficacious as behavioral therapy (i.e., motivational enhancement + cognitive behavioral therapy) in reducing drug and alcohol use among pregnant women (Yonkers et al., 2012). Similarly, computer-delivered brief interventions have been associated with positive outcomes, including greater likelihood of smoking abstinence during pregnancy relative to low-intensity contingency management (Ondersma et al., 2012), and better post-partum drug use outcomes relative to assessment only comparison conditions (Ondersma, Svikis, & Schuster, 2007; Ondersma, Svikis, Thacker, Beatty, & Lockhart, 2014).

Although substance use is less common in pregnant women relative to those who are not pregnant, the harmful effects of substances on both maternal health and fetal development is a significant public health concern. Several treatments for pregnant women have demonstrated efficacy, such as the use of opioid agonist therapies for opioid use disorder and contingency management approaches to enhance treatment engagement. However, much work is needed in this area, particularly with respect to improving treatments for alcohol and marijuana use in pregnant women.

Discussion

This review provided an overview of research on the biological, epidemiological and treatment outcome differences between men and women with SUDs. Although significant gaps remain in our understanding of the role of sex and gender in SUDs, a number of trends are beginning to emerge in the literature. In the U.S., the gender gap in prevalence of substance use and onset of substance use disorders has significantly narrowed over the past three decades. These trends suggest that much of the historical difference in the prevalence of both substance use and SUDs may have been attributable to social and cultural factors and not biological sex differences. Nonetheless, a wide array of differences have been identified that suggest that sexual dimorphisms–including, but not exclusively related to gonadal hormones–can impact the acute effects of substances, their long-term consequences, and the treatment of SUDs. These differences, when combined with social and cultural factors that disproportionately affect women and interact with SUD etiology and maintenance (e.g., child and elder care, risk for exposure to violence), highlight the critical importance of research aimed to disentangle sex and gender differences in SUDs to inform improved prevention and treatment efforts. Below, we highlight several consistent findings in the literature on sex and gender differences in SUDs.

First, both sex and gender clearly play a role in SUDs. Despite relatively consistent and replicable sex differences in animal models (Becker & Koob, 2016), these effects are much less robust in human models and may even conflict with preclinical findings, suggesting that both biological and social determinants play a significant role in substance use behaviors and effects. Indeed, the narrowing gender gap in SUD prevalence may reflect shifting environmental and cultural factors, characterized by cultural shifts away from more traditional gender roles (Seedat et al., 2009b).

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Functional consequences associated with SUDs tend to be more severe in women relative to men in treatment, even when SUD symptom severity is similar. These findings are particularly notable for psychiatric comorbidity, with women exhibiting significantly greater vulnerability than men. This vulnerability is reflected by not only greater overall prevalence of anxiety and depressive disorders among women, but also by a stronger link between these psychiatric symptoms and SUD symptoms. For example, women report that they are more likely to use substances to cope with mood disturbances and elevated anxiety symptoms are more strongly associated with substance use behaviors among women relative to men.

The literature on sex and gender differences in treatment response is limited. However, the available literature suggests that men and women do not substantively differ with respect to SUD outcomes across substances, with the exception of smoking cessation. Nonetheless, although most large-scale randomized trials now stratify treatment randomization by gender, many still do not conduct gender-specific analyses and women are underrepresented in clinical trials. Moreover, treatments that have been available for a longer duration of time were originally studied almost exclusively in men. Thus, the efficacy of treatments such as disulfiram for alcohol use disorder is unknown in women.

Significant improvements have been made in the inclusion of females in studies of SUDs; however, significant gaps in research remain (Wetherington, 2007). Filling these research gaps requires not only inclusion of both sexes, but also analytic plans that test specific gender-related questions with sufficient statistical power. For example, a review of structural neuroimaging studies in SUDs found that although the representation of women increased in research over time, almost three-quarters of the studies reviewed did not evaluate sex differences at all (Lind et al., 2017). Accordingly, studies should include evaluation of both main and interaction effects of gender and sex as standard reporting practice.

Additionally, this review identified an array of biological (e.g., impact of menstrual status), cohort (i.e., changes in SUD presentations over time), and social (e.g., cultural acceptance of substances) factors that have a significant impact on SUDs. Accordingly, research must take into account not only differences between men and women, but also differences among women (e.g., age, menstrual status). Furthermore, translational research bridging human and animal models has potential to rapidly advance our understanding of SUDs in women, and to disentangle the contributions of gender and sex (Chartoff & McHugh, 2016). However, much of the animal and human research occurs in isolation, where translation and back-translation remain understudied; the combination of the precision of animal models with the public health relevance of clinical models is needed to better understand sex and gender differences in SUDs. Finally, improved understanding of sex and gender differences by substance type is needed, and polydrug use in women is particularly understudied. It is not well known the degree to which gender difference findings vary across substance types, although several findings indicate that there may be substantive differences (e.g,. presence of a telescoping course of illness for some, but not other, substances).

Consideration of understudied populations, including older women, pregnant women, and women with co-occurring psychiatric disorders continues to be a key area of need (Greenfield, Brooks, et al., 2007). As highlighted in this review, these groups may critically

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differ from populations in which the predominance of research has been conducted. For example, although studies have begun to elucidate the role of ovarian hormones in the subjective effects of substances, substance craving, and SUD recovery, the implications of these findings for groups such as pregnant or postmenopausal women is not well-understood. Moreover, although not reviewed in detail in this manuscript, there are other key variables that interact with sex/gender, such as socioeconomic status (E. O. Johnson & Novak, 2009), age (Al-Otaiba, Epstein, McCrady, & Cook, 2012), race/ethnicity (Guerrero, Marsh, Cao, Shin, & Andrews, 2014; Montgomery, Burlew, Kosinski, & Forcehimes, 2011), and sexual orientation (Medley et al., 2016). Specifically, these groups differ with respect to access to substances, risk for problematic substance use, and access to substances; the nature of these differences and their implications for treatment are not yet well-characterized. A key next step in understanding these variables is increasing the representation of women in research to allow for examination of differences *among* women. The consideration of the intersection of sex, gender, and these variables will provide a richer view on the ways in which SUDs affect all women.

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Highlights

- Women and men exhibit differences in the acute and long-term effects of substances.
- Social and environment factors contribute to gender differences in substance use.
- Women report greater impairment, but have similar response to treatment.
- Some gender differences in response to pharmacotherapies have been detected.
- Gender differences in substance use disorders remain understudied.