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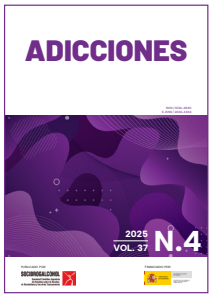

ORIGINAL

The influence of sex and gender factors on the modulation of vulnerability to addictions: A narrative review

La influencia de los factores de sexo y género en la modulación de la vulnerabilidad a las adicciones: Una revisión narrativa

Cristina Rius*,**; Rut Lucas-Dominguez*,**; Judit Tirado-Muñoz***,****; Lydia Garcia- Gomez**; Laura Prieto-Arenas*****; Antonio Vidal-Infer*,**,****.

*Department of History of Science and Information Science, School of Medicine and Dentistry, University of Valencia, Valencia, Spain.

**UISYS, Joint Research Unit, University of Valencia, Valencia, Spain. Associated Unit Research Institute for Higher Education and Science (INAECU) UC3M-UAM, Spain.

***Department of Psychology, Faculty of Biomedical and Health Sciences, Universidad Europea de Madrid, Madrid, Spain.

****Research Network in Primary Care of Addictions (RIAPAd), Spain.

*****Unidad de Salud Mental. Hospital General Obispo Polanco de Teruel, Spain.

Abstract

This narrative review identifies the sex- and gender-related factors that influence individual vulnerability to developing addictive disorders. Addiction arises from the complex interaction between neurobiological and psychosocial factors. Sex-based brain dimorphisms, shaped by genetic, hormonal, and epigenetic influences, lead to differences in neural circuits involved in reward, emotional regulation, and executive functioning. Pharmacokinetic differences, such as higher blood alcohol levels, faster nicotine metabolism, and slower μ-opioid receptor internalization in women, contribute to earlier medical complications and faster addiction progression. Gender, understood as a system of socially constructed roles and expectations, further modulates these vulnerabilities. Traditional masculine norms are associated with higher substance use, while certain aspects of femininity may increase risk (e.g., emotional repression or partner dependence) or serve as protective factors through help-seeking behavior. Sexual and gender minorities experience the most significant disparities. Lesbian and bisexual women show the highest rates of substance use disorders; gay and bisexual men report greater illicit drug use; and bisexual individuals consistently display the highest overall risk. Transgender and non- binary populations exhibit increased prevalence of tobacco, stimulant, and chemsex-related substance use, often as a response to minority stress and exclusion from cisnormative care systems. Psychiatric comorbidity affects 50–80% of cases. Women show higher rates of anxiety, trauma histories, and adverse clinical outcomes. Many face "triple stigma" due to their gender, mental health condition, and substance use. Addressing these disparities requires an intersectional, gender-informed, and culturally competent approach to prevention, diagnosis, and treatment.

Keywords: vulnerability, sex differences, gender norms, substance-use disorder, dual diagnosis, sexual and gender minorities

Resumen

En este trabajo se ha realizado una revisión narrativa que identifica los factores asociados al sexo y al género que influyen en la vulnerabilidad frente al desarrollo de un trastorno adictivo. Las adicciones surgen de la interacción entre factores neurobiológicos y psicosociales. Los dimorfismos cerebrales según el sexo, mediados por factores genéticos, hormonales y epigenéticos, generan diferencias en los circuitos implicados en la recompensa, la regulación emocional y las funciones ejecutivas. Las diferencias farmacocinéticas, como mayores niveles sanguíneos de alcohol, metabolismo más rápido de la nicotina y una internalización más lenta de los receptores μ-opioides en mujeres, contribuyen a una progresión más rápida y a la aparición más temprana de complicaciones médicas. El género, entendido como un sistema de roles y normas socialmente construidos, modula estas vulnerabilidades. Las normas masculinas tradicionales se asocian a mayor consumo, mientras que algunos aspectos de la feminidad pueden actuar como factores de riesgo o protección. Las minorías sexuales y de género presentan las mayores disparidades. Las mujeres lesbianas y bisexuales tienen las tasas más elevadas de trastornos por uso de sustancias; los hombres gays y bisexuales informan mayor consumo de drogas ilícitas; las personas bisexuales muestran el mayor riesgo global. Las poblaciones trans y no binarias presentan prevalencias más altas de consumo de tabaco, estimulantes y sustancias asociadas al chemsex, muchas veces como respuesta al estrés de minoría y a sistemas de salud cisnormativos. La comorbilidad psiquiátrica afecta al 50–80 % de los casos. Abordar estas desigualdades requiere un enfoque interseccional, sensible al género y culturalmente competente.

Palabras clave: vulnerabilidad, diferencias según el sexo, normas de género, trastorno por consumo de sustancias, patología dual, minorías sexuales y de género

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■ **Send correspondence to:**
Antonio Vidal Infer. Department of History of Science and Information Science, School of Medicine and Dentistry, University of Valencia. Avda. Blasco Ibañez, 15, 46010. Valencia (Spain). Email: Antonio.Vidal-Infer@uv.es

Addiction is a complex phenomenon shaped by biological, psychological, and social factors. Within this framework, vulnerability emerges as a key concept for explaining why some individuals develop pathological dependence while others do not, even with similar patterns. This transition is mediated by individual characteristics such as impulsivity, sensation-seeking, or the presence of affective and anxiety disorders.

These traits can predispose individuals to use substances as a means of regulating negative emotions, coping with stress, or meeting unmet psychological needs.

Biological sex and socially constructed gender profoundly shape the responses of brain and body to addictive stimuli. Incorporating these dimensions into research is therefore essential for accurately pinpointing risk factors and crafting truly effective prevention and treatment strategies. Informed by a targeted search of the scientific literature from the past two decades in Web of Science and Scopus, this article delineates the principal sex/gender related determinants of vulnerability, ranging from biological and social factors to specific concerns, such as abuse, trauma, gender-nonconforming populations and co-occurring disorders (dual diagnosis).

Modulation Of Vulnerability To Addictions By Sex And Gender From A Biological Perspective

Scientific literature has shown sexual dimorphisms in the nervous system (NS) that can influence vulnerability to addictions. Specifically, genetic, epigenetic, and hormonal differences during brain development and organization lead to variations in the neural circuits involved in reward processing, emotion, and executive functions in men and women (McHugh et al., 2018), triggering divergent responses to the same substances of abuse.

At the neuroanatomical and functional level, neuroimaging studies in people with substance-use disorder (SUD) reveal alterations in regions such as the striatum —particularly the nucleus accumbens (NAc), which integrates pleasure and motivation— the amygdala (associates stimuli with reward or punishment), the hippocampus (contextual memory of rewarding experiences), the insula (regulates craving), and the corpus callosum (connects the cerebral hemispheres, integrating cognitive and emotional functions). These alterations differ between sexes, although further research is needed to refine these findings (Cornish & Prasad, 2021; Rando et al., 2013), and they also vary depending on the substance consumed. In alcohol-use disorder (AUD), men show volume reductions in these areas compared with healthy controls, whereas women with AUD exhibit enlarged volumes (Sawyer et al., 2017; Sawyer et al., 2018; Zahr et al., 2020). Studies of heavy alcohol consumption in adolescence and early adulthood likewise reveal sex-specific imaging differences in the prefrontal, striatal, and medial-temporal regions: young women drinkers have greater volumes than healthy women, while men show the opposite pattern with volume loss (Kvamme et al., 2016; Morris et al., 2019; Pfefferbaum et al., 2016). Similarly, Nie et al. (2021) found that male chronic methamphetamine users in abstinence had smaller hippocampi than healthy men, whereas no such structural effects were observed in women. Conversely, significant gray-matter reductions were detected in women with stimulant addiction, cocaine and/or amphetamines, after prolonged abstinence, but not in men (Regner et al., 2015). Collectively, these findings suggest sex-specific neuroplastic adaptations that may underlie the differing clinical manifestations of addiction (Cornish & Prasad, 2021).

Regarding neurochemical sex differences in reward, the mesocorticolimbic dopaminergic system is most prominent, with the ventral tegmental area (VTA) as the main source of dopaminergic neurons. Dopamine (DA) release in the NAc is central to reward; drugs inhibit its reuptake as an artificial reinforcement. Human and rodent studies reveal that men and women activate dopaminergic reward circuits differently, not only in magnitude but also neuroanatomically, with distinct responses in the ventral NAc versus dorsal striatum (Copenhaver & LeGates, 2024; Cosgrove et al., 2014; Gillies et al., 2014). This neural pattern may underlie the sex difference in escalation of use leading to addiction. Cosgrove et al. (2014) showed that men activate the ventral striatum more intensely when smoking, consistent with cigarette reinforcement, whereas women smoke more for emotional regulation and cue-reactivity. PET imaging further demonstrated that men exhibit a rapid, consistent dopaminergic response in the ventral striatum, while women respond more rapidly in the dorsal striatum (putamen). In cocaine addiction, women tend to progress faster to habitual use, partly due to lower DA release in the ventral striatum, prompting higher intake to achieve similar effects. Enhanced dopaminergic activity in the dorsolateral striatum may, in turn, facilitate the transition to compulsive use in women (Becker & Chartoff, 2019).

About the effects of sex on the endocrine system and how this influences vulnerability, there is extensive literature that examines how estradiol interacts with the mesolimbic reward circuit to heighten women's vulnerability to drug addiction. Sex hormones, such as estrogens, progesterone, and androgens, strongly modulate brain and behavior, including reward responses. Estradiol enhances drug reinforcement by increasing drug-induced DA release in mesolimbic and striatal pathways. Consequently, female rats display stronger drug-motivated behaviors when estradiol levels are high (proestrus/estrus, analogous to late follicular/ovulation in women) (Becker, 2016). Hormonal fluctuations across the

estrus/menstrual cycle can alter both the rate of addiction acquisition and the strength of drug reinforcement (Kokane & Perrotti, 2020; Sardari et al., 2024). Estradiol elevates the rewarding, reinforcing properties of opioids, cocaine, and amphetamines, thereby affecting vulnerability (Kokane & Perrotti, 2020). By contrast, progesterone often counters estradiol. In women who use cocaine, high progesterone levels and it derivates such as allopregnanolone (e.g., during the luteal phase or with certain contraceptives) associate with reduced craving and consumption (Peart et al., 2022). These findings have spurred research into progesterone analogues as potential relapse-reduction treatments for female psychostimulant users: progesterone has shown efficacy in lowering cocaine craving and arousal in women, though not in men (Fox et al., 2013).

Hormonal modulation extends to drug metabolism. Estrogens and progestogens partly account for higher peak plasma cocaine levels in women than in men given the same dose (Peart et al., 2022). Conversely, women metabolize nicotine more rapidly, particularly those on oral contraceptives (Allen et al., 2019; Berlin et al., 2007). Such pharmacokinetic variations contribute to sex differences in addiction vulnerability (Thibaut, 2018). Women also reach higher blood-alcohol concentrations than men after equivalent consumption due to lower lean body mass and reduced gastric alcohol-dehydrogenase activity (Komáreková et al., 2013). Consequently, women may suffer alcohol-induced hepatic and cardiac damage at lower doses and shorter durations—a "clinical telescoping" effect (McHugh et al., 2018). Many medical complications of addiction —neuropathy, alcohol-related cognitive decline, cardiomyopathy, cirrhosis, and substance-induced mood disorders— appear earlier and after lower cumulative exposure in women (Trillo et al., 2012). With opioids, morphine shows slower μ-opioid-receptor activation and clearance in women, often necessitating higher doses and making them more prone to hyperalgesia and rapid tolerance, potentially requiring larger opioid doses for equivalent analgesia (Fullerton et al., 2018).

In men, a more stable androgen-dominated hormonal profile exists, and its influence on addictive behavior is less studied than that of estrogens and progesterone. Testosterone and derivatives can modulate dopaminergic and glutamatergic transmission, and some evidence links high androgen levels to greater risk-taking and sensation-seeking, facilitating initiation of use. However, direct testosterone effects on drug reinforcement are less clear and appear subtler than estrogen's impact in women (Bawor et al., 2015). In opioid-use disorder, any opioid intake markedly reduces or suppresses testosterone in men but not in women (Bawor et al., 2015), underscoring sex-specific regulation of the hypothalamic–pituitary–gonadal axis and its hormones GnRH, LH, and FSH (Katz & Mazer, 2009). Resulting mood, stress reactivity, aggression, and libido changes tied to testosterone fluctuations can therefore trigger markedly different responses in male versus female opioid users (Börjesson et al., 2011; Fullerton et al., 2018; Smith & Elliott, 2012).

Understanding the biological determinants of vulnerability to addiction can be very useful in developing psychoeducational programs and interventions aimed at prevention and treatment. Although biological factors help explain some of the differences in addiction vulnerability, a comprehensive understanding of why certain individuals initiate and sustain substance use is possible only when psychosocial determinants are also taken into account.

Sex, Gender, And Social Expectations

Over the past decades, substance-use disorder research has moved toward a more holistic perspective that, in addition to biological determinants, also considers psychological and social factors to understand vulnerability to addiction. Within this framework, sex and gender emerge as essential analytical categories for explaining the differences seen in epidemiological trends, patterns of use, clinical presentations, and access to treatment (Becker & Koob, 2016; Fonseca et al., 2021; Greenfield et al., 2010). Sex differences refer to genetically determined biological characteristics, whereas gender refers to the socially constructed and variable roles, norms, expectations, and behaviors associated with men, women, and non-binary people (Kaufman et al., 2023; World Health Organization, 2011). These norms are deeply embedded in social structures and have evolved over time. In the realm of addiction, gender expectations play a crucial role in vulnerability to substance use and in the development of alcohol-use disorder, influencing both the decision to consume and access to treatment.

According to the World Health Organization (2011), gender norms affect not only people's emotional and social experiences but also their mental and physical health. Social pressures linked to gender roles may therefore lead men and women to experience exposure to substances, the progression of use, and treatment responses differently (Harris et al., 2022). Historically, substance use has been more prevalent among men, which has led to addiction services, research, and policies that are male-centered or "gender-neutral," leaving the specific needs of women and other gender identities unaddressed (Fonseca et al., 2021; Harris et al., 2022; Meyer et al., 2019; Torrens-Melich et al., 2021). Scientific literature indicates that the gender gap in SUDs is narrowing for certain substances and age groups, an alarming trend when psychosocial and clinical settings do not adequately recognize or meet differentiated needs.

Beyond the biological-sex vulnerabilities described in the previous section, social expectations grounded in gender shape consumption behaviors. Social dynamics, especially interpersonal relationships and community

contexts, strongly influence men's and women's patterns of use, because traditional norms assign specific roles to each gender. Men are typically linked to protection and provider roles within the family, characterized by competitiveness, confidence, and persistence; women, to reproductive, caregiving, and emotional-support roles, with traits such as dedication, expressiveness, and empathy (Sánchez-López, 2013; Sánchez-López & Limiñana-Gras, 2017).

Conformity to these norms, however, varies with contextual and individual factors, producing different degrees of adherence or resistance (Sánchez-López et al., 2014).

Femininity and masculinity thus play a significant role in addiction vulnerability. Femininity encompasses the culturally defined traits, behaviors, and roles considered proper for women, shaping expectations about how they should think, feel, and act (Mahalik et al., 2005). In Western societies, normative femininity idealizes, among other qualities, caregiving, emotional expressiveness, and concern with appearance (Levant et al., 2007; Mahalik et al., 2005). Adherence varies across racial and cultural groups: for example, Latin culture values subordination and self-sacrifice; the "strong Black woman" stereotype emphasizes resilience; Asian hyper-femininity prizes docility and reliability (Castillo et al., 2010; Donovan & West, 2014). These norms shape behavior and can create differential risks for substance use (Kulis et al., 2008); understanding vulnerability therefore demands an intersectional approach that integrates gender, ethnicity, and cultural expectations.

A recent systematic review showed that femininity significantly influences within-group variations in women's substance use: 74 % of the studies (n = 17) found that endorsement of feminine norms accounted for a unique portion of variance in consumption (Brady et al., 2016). Although substance use has traditionally been linked to masculinity (Van Gundy et al., 2005), recent research also connects feminine norms to use (Iwamoto et al., 2016). Engaging in stereotypically masculine behaviors such as drinking can be associated, for many women, with empowerment, pleasure, and peer approval (Lyons & Willott, 2008). While femininity often promotes health-seeking behaviors (e.g., getting help) (Shakya et al., 2019), some traits today may increase risk (Kaya et al., 2016). Examining how femininity shapes consumption is essential, as women frequently use substances to manage emotional distress (Dragan, 2015) and are vulnerable to gender-role stress; they often turn to substances to cope with emotional or physical pain and to self-medicate mental-health problems, frequently in response to traumatic experiences (National Institute on Drug Abuse, 2020; Stone et al., 2021).

Additionally, women are at greater risk than men of being introduced to drug use by their partners, suggesting an initiation pattern shaped by intimate relationships and co- dependence (Mburu et al., 2019). Rigid adherence to feminine norms can generate dissatisfaction, devaluation, and shame, raising the likelihood of substance use as a coping strategy (Efthim et al., 2011; Hoffman, 2001). Conversely, a strong identification with traditional femininity may deter some women, as substance use conflicts with expected "proper" behavior (Iwamoto et al., 2018).

Research on substance use often focuses on how femininity or minority identities (e.g., women, LGBTQ+ individuals) shape vulnerability, while the influence of masculinity norms remains underexplored. However, many men engage in substance use to align with ideals of toughness, suppress emotions, or respond to social pressures tied to hegemonic masculinity (Klingemann & Klingemann, 2023). Overlooking this perspective limits the understanding of substance use among men. Integrating gender roles into interventions may enhance both their effectiveness and contextual relevance

Social factors and expectations can also act as protective elements. Women are generally less exposed than men to drug- or alcohol-centered social environments and tend to form close, supportive relationships, which foster psychological resilience (McHugh et al., 2018). Caregiving responsibilities, that sometimes become barriers, can likewise motivate treatment seeking, particularly efforts to maintain or regain child custody (Greenfield et al., 2007; Sword et al., 2009).

Finally, stigma is a key factor that profoundly shapes experiences and outcomes, especially for women. Women with addictions face dual stigma: for their dependence and for violating gender norms of self-control and responsibility (Howard, 2015). This stigma can prompt concealment or delayed help-seeking.

Regarding people whose sexual orientation is non-normative (gay, lesbian, and bisexual individuals), recent evidence indicates that substance-use risk is patterned by sexual identity rather than by sex alone. Lesbian and bisexual women display elevated rates of alcohol- and drug-related disorders, whereas gay and bisexual men are more likely to use illicit drugs and encounter related problems (Green & Feinstein, 2012).

These disparities appear to be shaped by sociocultural factors, such as affiliation with gay culture or HIV status, and are not mitigated by demographic characteristics like female sex or older age (Green & Feinstein, 2012). In fact, bisexual orientation is consistently linked to the highest substance-use risk: bisexual women engage in more forms of use than lesbian or gay women, and no substance-use domain shows lower risk for bisexuals (Schuler & Collins, 2020; Schuler et al., 2018).

As for gender-nonconforming individuals, the determinants are somewhat more complex and will be explained in the next section.

Vulnerability In Gender-Nonconforming Individuals

Among gender-nonconforming people, that is, individuals whose gender identity differs from their sex assigned at birth, sex and gender issues become fundamental and even defining when it comes to vulnerability to addiction. Recent studies show that transgender and non-binary (TNB) individuals have higher prevalence rates of alcohol, tobacco, cannabis, and psychostimulant use, as well as greater involvement in chemsex practices, than their cisgender peers (Cotaina et al., 2022; Scheim et al., 2017). For instance, Scheim et al. (2017) estimated in a Canadian sample that 12 % of TNB people had used at least one high-risk drug in the preceding year, particularly cocaine and amphetamines, a proportion higher than in the general population. Likewise, a recent meta-analysis determined that identifying as TNB roughly doubled the odds of tobacco and drug use compared with cisgender individuals, although no significant differences were found for alcohol use (Cotaina et al., 2022). In addition, analysis of thousands of U.S. medical records revealed higher rates of nicotine, alcohol, and drug-abuse diagnoses in TNB patients than in cis patients (Kidd et al., 2023). Collectively, these data underscore that TNB people bear a disproportionate burden of problematic substance use relative to the cisgender population, making them more vulnerable.

Research has often focused on transgender women, those assigned male at birth, particularly in socially vulnerable contexts and has confirmed high prevalence of methamphetamine and cocaine use (Reback & Fletcher, 2014). In transgender women engaged in sex work, many reported recent methamphetamine or other stimulant use to prolong and enhance sexual encounters (Santos et al., 2014). Continuing the theme of substances used for sexual purposes, chemsex is especially relevant among TNB individuals and reveals differences even within this group; clinical data show stimulant-use rates up to ten times higher in transgender women than in transgender men (Gómez-Gil et al., 2012). However, a recent U.S. study by Kidd et al. (2023) concluded that there were no significant differences between transgender men and women regarding problematic substance use.

Why is this vulnerability higher? Several studies indicate that substance use among TNB people often serves as a coping strategy for chronic stress arising from discrimination, rejection, and trauma (Hendricks & Testa, 2012). TNB individuals frequently face stigma and prejudice in family school, workplace, and healthcare settings, as well as transfobic violence throughout life, all of which contribute to sustained experiences of social exclusion and chronic stress. Empirical evidence shows that transgender people who report higher levels of discrimination also present significantly elevated rates of recent substance use and lifetime substance use disorders, highlighting the cumulative impact of chronic exposure to stigma and exclusion (Wolfe et al., 2021). Faced with insecurity, emotional stress, and perceived lack of support, substance use may emerge as self-medication (Bockting et al., 2013; Kidd et al., 2023). For example, transgender women with a history of sexual trauma or violence have significantly higher odds of using drugs like cocaine to cope with psychological pain (Budhwani et al., 2017). Similarly, in a U.S. study of 600 adult trans people, those who experienced frequent transfobic discrimination showed much higher rates of recent use, lifetime substance-use disorders, and likelihood of having needed treatment (Wolfe et al., 2021). These findings confirm that continual exposure to rejection and violence increases the risk of turning to psychoactive substances to manage stress and emotional distress (Hughto et al., 2021; Klein & Washington, 2024).

Another potentially decisive determinant of TNB vulnerability is the healthcare environment. Living in a cisnormative care system means that mental-health and addiction services were built on the premise that being cisgender is the norm and that being trans was historically classified as a disorder. Consequently, interventions were designed only for cisgender men or women, and even today many programs lack affirmative protocols for TNB people; only a few are specifically geared to the LGBTIQ+ population (Williams & Fish, 2020). A direct outcome of this binary approach is the lack of visibility of the non-binary community: non-binary individuals show poorer mental health than binary trans people, presumably because of the added stress of being invalidated or ignored by the healthcare system, and they report higher anxiety, depression, and risk behaviors than their binary peers (Klein & Washington, 2024; Reisner & Hughto, 2019; Thorne et al., 2019). Moreover, non-binary people have been excluded from many substance-use studies (Connolly & Gilchrist, 2020), further reinforcing their invisibility. A qualitative study in Argentina highlighted that the lack of trans-health education among providers is a main obstacle to appropriate care (Cordero & Saletti-Cuesta, 2025). Likewise, recent work by Jessani et al. (2024) noted insufficient preparation of healthcare teams to recognize and address the needs of transgender and gender-diverse people, especially outside major urban centers. In the face of this training deficit, various authors call for cultural-competence training and affirmative-practice models to improve care quality and reduce biases linked to underdiagnosis and undertreatment (Hughto et al., 2015; Korpaisarn & Safer, 2018), as repeated discrimination is associated with greater psychological distress, risk of depression, and substance abuse, factors that drive many TNB individuals away from formal services and lead to self-medication and self-care as survival strategies (Johnson et al., 2019; Schechner et al., 2025).

All these factors that heighten the vulnerability of TNB people to addiction mean that interventions must be adaptable to this population and attentive to its specificneeds.

Sex, Gender And Dual Diagnosis

Psychiatric comorbidity among individuals with substance-use disorders is remarkably high, with prevalence estimates ranging from 50% to 80%, depending on the population studied (Andersson et al., 2023; Díaz-Fernández et al., 2023; Fernández-Miranda et al., 2024; Szerman et al., 2022). The simultaneous presence of a SUD and another mental disorder is referred to as dual diagnosis (DD) (Fernández-Artamendi et al., 2024; Szerman et al., 2022). The explanation with the strongest scientific backing is that both conditions share common neurobiological bases and genetic risk factors, while the toxic substances consumed alter many neurotransmission systems involved in the pathogenesis of these other mental disorders (Szerman et al., 2022). Determining the primary diagnosis in DD cases is often complex. Most studies have focused on linking substance use to the development of psychiatric disorders; far fewer examine the reverse relationship, and fewer still incorporate a gender perspective.

The limited studies that do consider sex and gender as variables indicate that anxiety and affective disorders are more prevalent among women with DD (Díaz-Fernández et al., 2023; Szerman et al., 2015). Anxiety is a significant risk factor for substance use, especially alcohol and cannabis (Prieto-Arenas et al., 2022). For instance, a study on social anxiety found a stronger association between this condition and alcohol-related problems in women than in men (Buckner et al., 2023). Similarly, panic disorder has been linked to a greater risk of developing alcohol dependence, about twice as high in women as in men (Chang et al., 2020). Gender differences have also been identified in patterns of psychiatric comorbidity and in the use of health services prior to the onset of alcohol dependence. Among young people, cannabis use has been described as a coping strategy for anxiety and low distress tolerance (Morris et al., 2024). Low distress tolerance is significantly associated with heavier cannabis use and related complications. Although women tend to report lower overall consumption, their use is more often motivated by the management of psychiatric symptoms (Arranz et al., 2020; Leadbeater et al., 2019).

Gender disparities are likewise evident in the comorbidity between psychotic disorders and SUDs. Patients with schizophrenia face a three-fold higher risk of developing cannabis-use disorder than the general population (Kozak et al., 2021). Even though women with schizophrenia display a lower substance-use prevalence (Gómez-Sánchez-Lafuente et al., 2022; Novick et al., 2016), substance misuse seems to have more detrimental long-term effects for them (Casanovas et al., 2023; van der Meer et al., 2015). Women with schizophrenia and cannabis-use disorder typically experience more severe symptoms, more hospitalizations, and poorer treatment outcomes (Miquel et al., 2013) and are less likely to reduce cannabis use over time, worsening illness trajectory (Calakos et al., 2017; Casanovas et al., 2023).

The co-occurrence of a psychiatric disorder and a SUD is linked to more severe clinical symptoms and greater psychosocial dysfunction than is usually seen in individuals with a single disorder (Andersson et al., 2023; Mangrum et al., 2006), and this is especially pronounced in women with dual diagnosis. These women face multiple, interconnected vulnerabilities that complicate both clinical and social care. The literature shows that, compared with men with similar diagnoses, they are disproportionately affected by histories of trauma, gender-based violence, and abuse, which increases the risk of relapse, non-adherence, and poorer health outcomes (Fonseca et al., 2021; Meyer et al., 2019; Tirado-Muñoz, 2018; Torrens-Melich et al., 2021). In addition, the interaction between psychiatric symptoms and substance use hinders timely diagnosis and contributes to a higher likelihood of social exclusion, unemployment, stigmatization, and limited access to gender-responsive integrated services (McHugh et al., 2018).

Women with DD also suffer from triple stigma: for being women, for having a mental disorder, and for experiencing a SUD. This compounded stigma may foster shame, guilt, and isolation, decreasing the likelihood of seeking or staying in treatment (Calderón Calvo, 2021). Many also lack strong social and family support networks, key elements in recovery. Both internalized and social stigma not only reinforce negative stereotypes and prejudices but directly affect how these women access, use, and benefit from health services (McCartin et al., 2022).

Although the small number of gender-focused studies hampers analysis of sex differences in dual diagnosis, the lack of data on sexual orientation and gender identity poses an even greater challenge to understanding disparities and designing tailored interventions for LGBTIQ+ populations (Flentje et al., 2015). In this regard, 56 % of LGBTIQ+ youths met criteria for at least one mental-health or substance-use disorder in the past year, compared with 29 % of their cis-heterosexual peers (Kingsbury & Findlay, 2024).

This group not only shows disproportionately high rates of substance use and SUDs but is also more susceptible to severe mental-health problems, such as higher levels of anxiety, depression, suicidal ideation, and greater exposure to trauma and PTSD (Marchi et al., 2023). They also face higher vulnerability to infections such as HIV and HCV, especially in the context of high-risk behaviors related to chemsex. Structural and interpersonal factors, like discrimination, stigmatization, harassment, and internalized homophobia, worsen psychological distress and act as significant barriers to adequate care (Kidd et al., 2019; Marchi et al., 2024; Silveri et al., 2022).

Thus, transgender and gender-diverse individuals face increased vulnerability to substance use disorders due to structural factors such as exclusionary public policies, limited access to inclusive healthcare services, and stigmatizing social norms (Poteat et al., 2023). Recent legislative frameworks specifically target LGBTQ+ youth, increasing their risk of academic underachievement, suicide, and discrimination. Policies that restrict access to gender-affirming care create ethical dilemmas for professionals by limiting their ability to provide safe, evidence-based treatment (Kline et al., 2023). These structural determinants significantly hinder effective prevention and treatment of substance misuse within LGBTQ+ populations (Phillips et al., 2025).

Conclusions

The evidence synthesized in this review indicates that gendered constructs, femininity, masculinity to non-binary identities, shape neurobiological, psychological, and social vulnerability to substance-use disorders (SUDs) and their frequent psychiatric comorbidities (DD). Rigid adherence to normative roles heightens risk behaviors, whereas incongruence between lived identity and societal expectations drives stress, trauma exposure, and maladaptive coping through substance use. These findings demand prevention and treatment strategies that explicitly account for gender identity, expression, and intersectional determinants such as class, race, and sexual orientation.

Only by dismantling binary, cisnormative assumptions in research design, diagnostic criteria, and service delivery, culturally informed interventions that target the mechanisms linking gendered stressors to addiction trajectories can be generated.

Conflict of interest

All authors declare that they have no conflicts of interest.

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