



Hormonal Differences Between Women and Men, Their Consequences on Addiction to Substances and Considerations on the Therapeutic Approach

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Accepted: 24 March 2022

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Abstract

Purpose of the review A search of scientific papers has been carried out to investigate sex differences in drug abuse and to understand the underlying biological and psychosocial causes of these differences. Based on the anatomical and neurochemical differences of the male and female brain, the difference in skills, and the possible importance of evolutionary factors, the reasons for the differential characteristics of addictions in men and women as well as the sex bias in the concurrent neuropsychiatric disorders are reviewed. The importance of sex hormones in these differences is also reviewed, as well as the influence of psychosocial conditioning factors associated with gender in addiction. Finally, the main features that differentiate the treatment of drug abuse in men and women are reviewed.

Recent findings The results obtained indicate that there is a close link between the differential biological characteristics of the male and female brain and sex hormones, which explain the specific characteristics of drug abuse according to sex.

Summary These differences exist in the reward circuit, in metabolism, and in the different phases of the addictive process—acquisition, escalation of consumption, abstinence, and relapse—as well as in the associated neuropsychiatric disorders; all of them are modulated by psychosocial gender particularities. Finally, the need for separate sex-specific treatments, especially indicated in the presence of coexisting psychological or psychiatric disorders, is assessed.

Keywords Gender differences · Neuropsychiatric disorders · Sex hormones · Sex differences · Therapeutic approach

Introduction

This work is an update of the existing scientific knowledge that explains the biological differences between men and women, in relation to substance use disorder (SUD, following the nomenclature proposed by the *Diagnostic and Statistical Manual of Mental Disorders* [5th edition]). The need to incorporate the gender perspective into social research in general, and in the field of study of drugs in particular, has been evident since 1985, after the III World Conference of the United Nations about women [1].

Sex is defined based on the organic differences between women and men and gender is based on the socially determined role, which can vary according to different cultures and times [2]. The brain develops throughout the life of each individual through a combination of genetic, hormonal, and environmental factors as well as sociocultural experiences [3] [4]. Social researchers have routinely attributed cognitive differences between men and women to educational and cultural aspects, and to the consequences of lived experiences during development. However, we now know that some of these differences appear in early stages, before disparate experiences occur, and arise in distant cultures, with different activities socially assigned to men and women [5].

There is now convincing evidence of sexual dimorphism in the structural, chemical, and functional characteristics of the brain, in cognition and in people's behaviour [6] [7]. For example, men and women use different neural circuits and molecular mechanisms during memory-related tasks [8]. Men and women differ in learning processes regarding language development and the way they solve intellectual problems,

This article is part of the Topical Collection on *Gender and Addiction*.

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without relation to the general level of intelligence [3]. The aforementioned differences also contribute to the sex-dependent differences in the approach to drugs and their effects.

The objective of this work has been to organise and present the most recent scientific studies that have advanced significantly the knowledge of the biological and psychosocial differences between men and women in drug use, with the intention of also assessing whether sex-specific treatments could or should be an informed and recommendable option.

Method

A search for scientific articles on sex differences in SUD has been carried out to try to understand the biological and psychosocial foundations linked to these differences. For the search, the Google Scholar and Web of Knowledge tools were used, employing the following keywords: ‘human brain’, ‘sex differences’, ‘addiction’, ‘gender differences’, ‘drug abuse’, ‘substance use disorders’, ‘treatment outcomes’, and ‘sex dimorphism’. The inclusion criteria were articles published between January 2000 and January 2020 that provide updated, important, or novel information. Each article, as well as its included references, was reviewed in depth. For this work, the collaborative book edited by Shansky [9] has been especially important. The most important aspects and conclusions have been organised in corresponding headings in the ‘Results’ section of this work.

After this review was completed, a coincident paper was published [10] that ostensibly meets the inclusion criteria, but the authors did not cover the basic biological characteristics of the brain or the importance of evolutionary factors, nor did they carry out a detailed analysis of the importance of performing more effective sex-specific treatments.

Results

Brain Anatomical Differences Between Men and Women

Although the brain structure of men and women is similar in many respects, there are also important differences. Even taking individual variations into account, on average, men have approximately 9% larger brains [6]. There are differences in the volume of some specific parts. The largest brain regions in men are found mainly in the bilateral limbic areas and in the left posterior cingulate gyrus. In women, the largest regions are the language-related areas of the right hemisphere, in addition to various limbic structures, such as the right insular cortex and the anterior cingulate gyrus [11]. Regional sex-related differences in tissue volume and density include the amygdala, hippocampus, and insula [11]. Men have a larger

amygdala and hypothalamus, while women have a larger caudate nucleus [12]. In several species of rodents, the hippocampus, a region thought to be involved in spatial learning, is larger in males than in females [13]. Magnetic resonance imaging (MRI) studies have shown that women have 23% larger Broca’s area and 13% larger Wernicke’s area compared with men; these are two important speech-related regions [3].

In most people, the left hemisphere of the brain is critical for speech and the right hemisphere is critical for certain perceptual and spatial functions. The left and right hemispheres of the brain are more asymmetrically organised in men than in women [13]. The corpus callosum, a major neural system connecting the two hemispheres, as well as the anterior commissure, is larger in women, allowing for better communication between the two hemispheres [6] [13].

Sexual orientation and gender identity have been linked to anatomical variation in the hypothalamus, which is the region of the brain that regulates reproductive behaviour. This small structure, located at the base of the brain, connects to the pituitary. In rats, it has been shown that a part of the hypothalamus is visibly larger in males than in females and that this difference in size is subject to hormonal control. In humans, some parts of the interstitial nucleus of the anterior hypothalamus are larger in men than in women [13].

Regarding the differences at the cellular level, women have a higher density of neurons in the area of the temporal lobe responsible for processing and understanding language [7]. Microglia and astrocytes are also sexually dimorphic in the brain, a phenomenon that can be attributed to the presence of sex hormones [14].

Proportion of Grey and White Matter According to Sex

Grey matter, present in the brain and spinal cord, is made up of the bodies of neurons, while white matter is made up of nerve fibres covered with myelin sheaths. Grey matter is associated with the processing of information, while white matter acts as a transmitter, coordinating communication between different regions of the brain. The volumes of grey and white matter are different depending on sex, with women having a higher percentage of grey matter and men having a higher percentage of white matter [6]. Compared with men, women have 12.8% more grey matter in the superior temporal gyrus and 23.2% more in the dorsolateral prefrontal cortex [15].

Different cortical and subcortical regions have been identified in the brain that are sexually dimorphic. Women have a larger volume or greater density of cellular packing in the areas related to language, such as Broca’s and Wernicke’s areas [16], as well as in the frontal, temporal, parietal, and occipital lobes; the cingulate gyrus; and the insula [12]. Men have a larger neuronal volume or greater density in the medial frontal cortex, amygdala, hypothalamus, medial

temporal lobes, paracingulate gyrus, cerebellum, hippocampus, insular cortex, globus pallidus, putamen, and cloister [11] [16].

In the male brain, there is a pattern of increased local connectivity and decreased connectivity between the hemispheres. In the female brain, there is greater connectivity between the cerebral hemispheres [6]. Men seem to think with their grey matter, made up mostly of active neurons, while women seem to think with their white matter, consisting of more connections between neurons. These connections can allow a woman's brain to function faster than a man's brain [3].

In adult men and women, grey matter decreases with age, but this decrease is more pronounced in men. It seems that female sex hormones could act as protectors [12].

The Effect of Hormones on the Sexual Dimorphism of the Brain

Numerous studies have shown the important role sex hormones play in brain dimorphism. During the development of the foetus, the sex hormones that bathe the brain cause its anatomical organisation to be different in boys and girls [12] [13]. The levels of exposure to these hormones during a very early critical period permanently alter brain function [16] [17]. More recent research suggests that the organising action of steroid hormones on brain morphology could continue even after puberty [16].

Female oestrogens are critically involved in the sexual differentiation of the brain, contribute to differences in its morphology and neurochemistry, help direct its organisation during development, and influence the structure and neuronal density of various regions [12] [18]. The direct effect of testosterone on the male foetal brain produces sex differences in neural structure and function and is responsible for gender identity and sexual orientation [18]. Enzymes for oestrogen synthesis and oestrogen receptors have been located in the hippocampus, while androgen receptors are more common in the amygdala [12].

Sex-specific differences in dopaminergic, serotonergic, and GABAergic markers indicate that male and female brains are also neurochemically different [12]. Testosterone and oestradiol modulate serotonergic and GABAergic transmission and increase dendritic spine formation [6].

Oestrogens and testosterone affect learning and memory processes and contribute to differences between women and men in neuronal processing and cognitive ability. They also influence the specific vulnerabilities of each sex to certain psychiatric and neurological diseases [16], as we will see later.

Testosterone and its metabolites possess anxiolytic properties, reduce behaviours of anxiety, and improve cognition in male rodents. Men with low testosterone conditions have

a higher risk of developing anxiety and stress-related disorders, and this can be reversed with the administration of testosterone [19]. This is the reason why these types of disorders are more prevalent in women.

Differences Between Men and Women in Task Performance Skills

Men and women solve intellectual problems differently. Behavioural, neurological, and endocrinological studies have clarified the processes that give rise to these sex differences in the brain. Men and women show different abilities and capacities in certain intellectual functions, which are not related to differences in the general level of intelligence [20]. Women, on average, are faster than men in identifying matching elements (perceptual speed), in verbal fluency and memory, in speed of articulation, in arithmetic calculation, and in the retrieval of waypoints of a route. In addition, they are faster in certain manual precision tasks [20]. They also surpass men in recognising emotional nuances in others, in emotional and artistic expressiveness, in aesthetic appreciation, and in carrying out detailed and previously planned tasks [3]. Men, on average, outperform women on certain spatial tasks, on tests that require the subject to imagine rotating or manipulating an object, and on tests of mathematical reasoning. They seem to learn routes faster but cannot remember landmarks as easily as women, relying preferentially on spatial cues, such as distance and direction. They are most accurate in target-directed motor skill tests, such as guiding or intercepting projectiles [3] [20]. It has been found that, in rodents, males and females also solve spatial problems differently: female rats also have a greater tendency to use landmarks in spatial learning tasks [13].

Elevated oestrogen levels are associated with an improvement in tasks related to speech and manual skills and with a decrease in spatial abilities. For this reason, as oestrogen levels change in the menstrual cycle, the performance of these tasks also varies. Testosterone levels are also related to men's spatial ability, and seasonal fluctuations have been observed [5] [13].

In the male and female brains, the two hemispheres function differently in some cognitive tasks. When men solve spatial problems, there is greater activation of the right hemisphere. However, no relationship has been found between lateralisation and cognitive performance in women [3]. In memory tests with an emotional component, men and women show differences in the lateralisation of the amygdala, and women also show greater use of the hippocampus [8]. The male brain separates language in the left hemisphere and emotions in the right, while in the female, both hemispheres intervene in emotions. This difference may explain why men tend to have more difficulties expressing their feelings [3]. Faced with stress, there are also differences: women

are more resistant to chronic stress but less resistant to acute stress than men [7].

According to the empathising-systemising (E-S) theory of psychological sex differences, there is stronger systemising in men and greater empathising in women [6]. Systemising is the impulse to analyse a system in terms of the rules that govern it. Empathising is the ability to identify the mental states of others and respond to them with an appropriate emotion.

We know from observations in both humans and animals that young males engage in rougher play than females and that females display more eating behaviours [13], and these observations imply that toy preferences in children are at least partly the result of innate biological differences [7].

Importance of Evolutionary Factors in the Differences by Sex

As we have noted, the finding of consistent—and in some cases substantial—sex differences suggests that men and women may have different interests and abilities, regardless of social influences [20]. This divergence, as well as anatomical differences in the male and female brain, probably arose as a consequence of selective pressures during evolution [7]. The brain is essentially like that of our ancestors 50,000 years ago, and we can get an idea of the differences between the sexes by studying the different roles that men and women have played during evolutionary history. Men hunted and defended the group against predators and enemies, as well as preparing and using weapons. Women collected food near the home, prepared food and clothing, and cared for young children. This specialisation has been able to exert different selective pressures on men and women [13].

Social interactions are a crucial component for most vertebrate species. Although there is considerable diversity in social behaviour among species, certain characteristics of social behaviour are deeply ingrained. This may explain why there is an interconnected network of evolutionarily conserved nuclei in the hypothalamus and limbic system that modulate social behaviours (reproduction, aggression, associative behaviour, etc.). Important neuroanatomic and neurochemical sex differences have been identified at various nodes within this neural network of social behaviour. Most of these nuclei contain receptors for sex steroid hormones, both androgens and oestrogens. These receptors have important effects on behaviour, both during development and in the adult brain.

Furthermore, the sexual dimorphism of the social behaviour network has been conserved strongly in a wide range of mammals with different social systems. Motivational systems, and particularly the mesolimbic dopaminergic system, can also generate important sex differences in behaviour [21], and as we will see below, they have great importance

in the biological and psychosocial differences of addictions between men and women.

Biological Differences Between Men and Women in Substance Use Disorder and Mechanisms of Action

Genetic differences, personality traits, the degree of social support, experiences or traumas during development, and also biological sex contribute to the possibility of developing compulsive behaviours associated with an addiction [22].

Differential Biological Characteristics Between Sexes in Addiction

Very similar sex differences have been found in humans and animals, and this suggests that there are some basic biological differences between women and men that influence how each sex responds to drug addiction [4] [22]. Differences in the brain can influence the response to drugs of abuse, both in experimental or occasional use, and in the development of addiction [22]. Male and female animals also differ in their behavioural, neurological, and pharmacological responses to drugs [23]. For this reason, any reference in this matter must incorporate the sex perspective [2]. However, manuals that incorporate the gender perspective do not usually contemplate biological sex differences.

Oestrogens play an essential role in the existence of sex differences in drug abuse [23], because they can intensify the response in women, but this effect is masked in the presence of progesterone [24]. Oestradiol enhances the psychostimulant-induced increase in dopamine in the striatum in women but not in men [25]. For this reason, the phases of the menstrual cycle and the release of associated hormones can affect drug behaviour because the ovarian hormones oestradiol and progesterone have free access to the brain [22].

Sex Differences Related to the Effect of Drugs on the Reward Circuit

Drugs produce their effects because they cause changes in neurotransmitter function that increase neuronal activity in the reward circuit, and there are sex-related differences in this regard [4]. The dopaminergic reward system is one of the systems that mediates these ‘vulnerable’ behavioural traits. In humans, non-human primates, and rodents, differences in this system have been found to be involved in individual variability in sensitivity to drugs of abuse [25].

The nucleus accumbens (NAc), the dorsomedial striatum (DMS), and the dorsolateral striatum (DLS) are believed to be crucial points in the reward system involved in the transition from initiation of use to compulsive drug seeking. The first two (NAc and DMS) are important for drug use

initiation, while the DLS is believed to be involved in binge use. When drug use changes from sporadic to compulsive, there is an improvement in the release of dopamine in the DLS [25]. Therefore, there is a reduction in the release of dopamine in the NAc that is believed to be what allows the dorsal striatum to assume control of the addict's behaviour, thus transforming sporadic drug use into compulsive behaviour, which it is what we properly consider addiction [23].

There is a difference in the response to dopamine in the NAc depending on the sex, which may be the basis for the sex difference in the escalation of drug use that leads to addiction. Women appear to be more vulnerable than men to the reinforcing effects of psychostimulants, opiates, and nicotine during many phases of the addiction process [4] [22] [24].

Metabolic Differences

The metabolism of drugs, and consequently their effects, are not the same for men and women, although the participation of several different metabolic pathways complicates the interpretation of these differences [2]. For example, the ingestion of equal amounts of alcohol produces a greater intoxication in women than in men. There is also some evidence that women metabolise nicotine more quickly than men and exhibit higher plasma levels of cocaine, which can be modulated by ovarian hormones [2].

Sex hormones influence also nicotine metabolism. This metabolism is faster in women than in men and is faster in women taking oral contraceptives compared with those who are not. Accelerated nicotine metabolism appears to be a result of oestrogen and sex-related differences in nicotine clearance could affect smoking behaviours [26].

Differences in Perceived Effects and Acquisition

Women may experience more pleasant responses to drugs (cocaine, amphetamines) and are more prone to self-medication. Precisely in animals, female rats learn to self-administer drugs more easily than males, and this phenomenon happens with all types of drugs studied [22]. Short-term oestradiol ingestion in female rats increases the acquisition and escalation of consumption as well as the motivation for compulsive seeking [4].

Differences in Escalation

One of the most notable differences in addiction is that women progress to dependence at a faster rate than men [2] [25] [27]. This trend is also observed in female compared with male rodents [4] [22] and this shows that, although there are sociocultural factors that influence addiction in humans, biological processes contribute in a fundamental

way to the differences observed between the sexes [25]. This progression is known as a 'telescopic' disease course and has been replicated for alcohol, cannabis, and cocaine; however, it has not been shown for other substances, such as heroin [2].

There is greater dependence on nicotine and less dependence on cannabis in women compared with men [2]. For other substances, such as heroin, cocaine, and methamphetamine, use is characterised by a chronic course (i.e., persistent regular use) in both men and women [2].

Hormones associated with the menstrual cycle may act as reinforcers during the acquisition stage and contribute to a more rapid escalation in drug use in females, but once addictive behaviour is established, hormones no longer continue to play an important role, neither in humans nor in rodents [25] [22]. As noted above, oestradiol is believed to facilitate this transition in women by enhancing the release of dopamine in important brain regions, such as the dorsal striatum, which is involved in regulating drug-seeking behaviour [7] [22]. Differences in susceptibility to stimulants, such as cocaine and amphetamines, could explain why women may be more vulnerable to the effects of these drugs, and why they tend to progress more rapidly from initial use to dependence [7]. Once the addictive behaviour has developed, men stabilise their consumption at a lower dose and women also have more unwanted effects [22].

Differences in the Abstinence Period

During attempts to quit drug use, women tend to have more unpleasant symptoms than men [22]. Women smokers experience greater stress during withdrawal, while men experience worse symptoms when quitting alcohol consumption [4] [22].

Differences in Relapse

Men maintain longer abstinence periods and women are more prone to relapse [4] [22]. Women increase consumption more quickly after a relapse [25]. As we have seen, rats exhibit these same sex differences in addiction [25].

In both animals and humans, relapse can be precipitated by internal cues (such as exposure to a booster dose of a substance) or external cues (such as drug-associated locations and paraphernalia). Women are more likely to attribute relapse to external drug-related cues, a stressful event, or depression [22] [23]. In addition, there is the hormonal influence: in rodents, short-term oestradiol intake in female rats increases the occurrence of relapse-like behaviours [4]. However, these differences are not determined solely by biology because contextual and sociocultural factors also differentially affect men and women. As we will see later, the existence of more barriers to seeking treatment and the

lack of social support prevent the recovery of women to a greater degree than men [22].

Differences Between Men and Women for Nicotine, Alcohol, and Cocaine Use

Nicotine During nicotine withdrawal, women experience more severe symptoms in mood, anxiety, and stress [4] [22], and this varies depending on the phase of the menstrual cycle [23]. Progesterone administration is associated with a decrease in nicotine craving [2]. On the other hand, the release of dopamine in the ventral striatum in response to stimulant drugs, such as alcohol and nicotine—a phenomenon that reflects the activation of reward pathways in the brain—is greater in men [2] [25]. Internal nicotine signals modulate both maintenance and relapse in smoking behaviour in men, while external signals are more influential in women [23].

As we have seen, women metabolise nicotine faster than men do and this could affect women's smoking behaviour. The rate of nicotine passage through the body was significantly higher for women than for men and was also higher in women who were using oral contraceptives compared with those who were not. Nicotine persisted in the body longer in men (132 min) than in women not taking oral contraceptives (118 min) and in women who were taking oral birth control (96 min) [26].

Alcohol A number of genetic, social, and environmental factors have been proposed to explain the sex differences observed in alcoholism and its medical consequences. Many of the sex differences have been shown to be determined by differences in the brain, which influence behavioural and neurochemical responses, both in the acute and long-term effects of alcohol and other drugs. There are also important differences produced by the metabolic systems and the endocrine system (e.g., ovarian hormones) [28].

As we have noted above, women and men metabolise alcohol differently. Women have lower levels of activity of alcohol dehydrogenase, the enzyme that metabolises ethanol in the gastric mucosa. In addition, they have less body water than men; hence, women have higher concentrations of alcohol in the blood, even after consuming equivalent amounts of alcohol [2].

Neurochemical and behavioural data suggest that many of the effects of alcohol (anxiolytic effects, anaesthetic effects, and alterations in motor coordination) occur through the enhancement of the activity of brain GABA receptors [28]. In addition, steroid hormones are neuroactive (neurosteroids) and interact with GABA receptors, which is why they can have an important influence on the effects of alcohol on the activity of these receptors. For this reason, sex differences in the levels and activity of neurosteroids are partly responsible for the differences in responses to alcohol that have

been observed in women and men [28]. Neurosteroids are also dependent on factors such as age, developmental stage, menstrual cycle, and stress [28]. Women tend to drink more alcohol during the premenstrual phase [22] and have greater urges to drink and smoke in response to negative mood [23].

Excess levels of corticosterone, which are released in response to stress and alcohol and drug use, can be metabolised as neurosteroids that have the ability to increase the activity of GABA receptors in the brain. On the other hand, elevated levels of GABA activity decrease memory and learning. For this reason, alcohol, by increasing the activity of GABA receptors, interferes with the neural processing of memory and learning [28].

Cocaine In the case of cocaine, women undergo a more accelerated transition from sporadic use to compulsive consumption patterns, and they enter treatment programmes after a shorter period of use [23]. In addition, women have shorter periods of abstinence from cocaine, and during these periods they experience symptoms that are more unpleasant, including greater anxiety and depressive symptoms [4] [23]. The differences between the sexes reflect differences in the underlying neural mechanisms involved in the response to the drug [4]. Research examining the neuronal response to external cues (e.g., drug images) associated with cocaine use has shown greater neuronal activation and increased desire in women compared with men [2] [23].

Oestradiol has been shown to enhance the behavioural response to cocaine and amphetamines, so its effects can vary throughout the menstrual cycle [4]. The subjective effects of cocaine and amphetamines tend to be more intense during the follicular phase, when oestradiol levels rise, relative to the luteal phase, when both oestradiol and progesterone levels rise [22]. The administration of progesterone is associated with a decrease in craving for cocaine induced by signals and with a lower rate of relapses [2].

On the other hand, structural neuroimaging studies indicate that there may be sex-specific neural consequences of drug use. For example, women and men with cocaine use disorder have a smaller volume of grey matter than controls, but the regions in which this decrease occurs are different for each sex. Similar results have been found in smokers [2]. The separate and combined effects of alcohol, tobacco, cocaine, and cannabis in reducing the thalamic volume of grey matter can trigger cognitive deficits among users of these substances [29].

Linkage of Addictions to Neuropsychiatric Disorders and Differences Between Men and Women in Psychiatric Conditions

Addiction to any type of substance and neuropsychiatric disorders are linked closely; these constitute a risk factor for having an addictive disorder and, conversely, patients

with addiction are at risk of experiencing mental illness, a factor that complicates their evolution and prognosis [30]. Structural and functional sex differences in the brain, along with changes in the levels of sex hormones and their receptors, can increase the vulnerability and prevalence of certain types of neuropsychiatric disorders [12] [18]. Regional differences in the brain linked to sex include the amygdala, hippocampus, and insula, which are areas involved in sex-biased neuropsychiatric conditions [11].

Although there are common characteristics that are a direct consequence of addiction, certain concurrent psychiatric disorders (comorbidity) occur more frequently in women than in men [2]. The conditions with the highest incidence in women include depression, anxiety disorder, and anorexia nervosa [11] [30]. Examples of disorders more prevalent in men include autism, attention deficit hyperactivity disorder, and specific language deficits such as dyslexia [11].

Sex differences have been documented in the levels of the neurotransmitters: serotonin, dopamine, and GABA [12]. Serotonin production is higher and occurs at a faster rate on average in men, and this could explain why women are more prone to depression, a disorder commonly treated with medications that increase serotonin levels [7].

The differences between the sexes in the regulation of body weight are well documented [31]. As with drug addiction, the aetiology of eating disorders is complex, involving a number of disorders: biological (e.g., neurotransmitters and hormonal disorders), psychological (e.g., personality and state traits mood), sociocultural, and environmental (e.g., pressure to achieve thinness). Information collected from animal studies and in humans suggests a significant biological contribution to the risk of eating disorder differentiated by sex [32]. Ovarian hormones (oestradiol and progesterone) can act on the central nervous system and increase the risk of eating disorders in women, while testosterone can exert protective effects that reduce the risk of this eating disorder in men [33].

There are also sex differences in three of the major brain disorders: stroke, multiple sclerosis, and epilepsy, in which gonadal steroids, which have many effects on the central nervous system and the immune system, also appear to play an important role [32].

In general, we can say that the associated medical, psychiatric, functional, and psychosocial consequences tend to be more serious in women [2], and the levels of impairment and prevalence of psychiatric and psychological disorders and comorbidity are also more severe [34].

Differential Psychosocial Characteristics in Drug Abuse Between Men and Women and in Their Therapeutic Approach

As we have seen so far, many of the differential characteristics between men and women related to drug abuse have their origin

in purely biological and in some way innate aspects, but there are psychosocial factors, fundamentally linked to stereotypes, mandates, or roles of gender, which influence not only the type of drugs used, but also the process of initiation, maintenance, the evolution of use, and the motivations by both sexes. Gender roles are also manifested in drug use contexts [35] [36]. Many of the differences that exist between men and women in relation to SUD are rooted in gender conditioning factors, and some of its variations can also be explained by historical or political factors, the social moment, social class, ethnicity, or age. The social mandates and expectations towards each sex are distinct and cause differences not only in the effects, but also in the meaning of consuming psychoactive substances.

Differences in the Type of Drugs Used by Each Sex and Psychosocial Consequences

The use of psychoactive substances predominates in men, except in the case of sedative-hypnotics, the use of which is significantly higher in women. In general, women mainly consume legal drugs, while the consumption of illegal drugs occurs in a higher proportion in men [37]. This reality seems to be clearly related to the social mandates directed at men to reaffirm their masculinity, such as taking risks or avoiding expressing emotions [38]. Likewise, the fact that the drugs most consumed by women are sedative-hypnotics is justified by these mandates, because their effects are more aligned with the qualities most expected and valued in them, such as calm, silence, or the lack of initiative in general, and more compatible with the roles of care, love, dedication, and beauty [39].

Focusing specifically on alcohol, during adolescence and the first stage of youth, there is a normalisation and generalisation of abusive alcohol consumption in both sexes [40]. A clear influence of gender roles is observed in the consumption patterns of this substance and the feminisation of alcohol consumption seems to reveal changes in traditional gender roles at present [40].

Males and females may differ in factors that maintain tobacco smoking or nicotine self-administration in animals and humans, and the identification of specific factors responsible for these sex differences may lead to improved interventions for smoking cessation and other substance abuse in women [41]. In women, the influence of nicotine on smoking reward and reinforcement is enhanced by accurate verbal information about the cigarette's nicotine dose. These results are consistent with the notion that the smoking behaviour of women may be more responsive to nonpharmacological factors, relative to men [42].

Psychosocial Differences Between Men and Women in Addiction

Accessibility to drugs is a powerful predictor of drug use [43]. The difference in relation to the 'self-perception' of

accessibility between men and women seems to explain a large part of the sex difference in the prevalence of drug use, so that when this factor is controlled for, such differences hardly exist. Although there is significant variation among cultures, in general men obtain drugs more easily than women. Men present a higher degree of risk behaviours, in part due to peer pressure [22]. Women maintain greater prevention against the risk, a factor that protects them from more abusive and harmful consumption [44]. The period of greatest risk for the initiation of substance use is late adolescence, however, women, on average, initiate substance use at a later age than men [2].

In relation to education level and work experience, women addicted to drugs have lower degrees than men addicted to drugs [36], and their work experience either does not exist or is linked to low-income jobs; therefore, they tend to be economically dependent on their partner [45]. From the socio-family point of view, in general, women find less support to seek treatment—they may even experience opposition from their partner or family [46], from which they tend to soon disengage [47]. This early disengagement increases their vulnerability to violence and external aggressions [48]. In addition, the existence of a history of SUD in the family environment is greater and it seems to have a greater influence on women than on men [27]. Taking all of this into account, it is not difficult to assume that drug use by women may constitute an escape route in adverse circumstances [35] [36].

The first consumption by women usually occurs in the company of male consumers, whether or not they are partners, and the progression in consumption is also linked to them [49]. The probability that a woman with drug dependency has suffered physical and sexual abuse during childhood before initiating drug use is very high [48], and the presence of sexual problems and menstrual disorders is also frequent [50]. Women resort to prostitution to buy drugs and for subsistence to a greater extent than men [34].

Regarding the social valuation of drug use, women experience greater rejection and social disapproval, stigmatisation, and exclusion [23] [51]. This circumstance causes, in general, a significant deficit of self-esteem and intense feelings of guilt and inferiority [46].

Adolescents, especially girls, report starting to smoke and continuing with the habit for purposes of weight control and weight loss. The more common the dieting habit becomes, the greater the risk of initiating the smoking habit. Young adults who are trying to lose weight are 40% more likely to smoke cigarettes [52] [53]. Another study demonstrate weight gain associated with smoking cessation among women prisoners, and the authors suggest smoking cessation interventions that address postcessation weight gain, as a preventative measure may be beneficial in improving health and reducing the high prevalence of smoking in prisoner populations [54].

Differences in the Therapeutic Approach

Motivations Used by Both Sexes and the Therapeutic Modality Women tend to enter drug addiction treatment centres for different reasons than men, and they are more likely to seek such treatment in mental health centres [23]. This may be due to the high rates of comorbidity between SUD and psychiatric disorders in women [23]. In fact, women with drug dependency are more likely than men to experience a concurrent depressive or anxiety disorder, as well as affective-emotional disturbances, a lower capacity for autonomy and initiative, and a feeling of inferiority, which also act as factors of risk associated with a possible relapse [2] [23] [51]. Other studies have indicated that women may show greater motivation for treatment than men [55]; however, they are less present in therapeutic centres and show lower rates of permanence [56] [57].

For all drugs, women generally decide to seek treatment due to problems related to parenting, while men are more likely to seek treatment due to consequences related to their work [23] [58]. On the other hand, men tend to have more legal problems with the courts [51].

Accessibility Historically, women have more difficulties accessing treatment because of pregnancy, responsibility for child care, lack of family support, lack of funds and resources, and greater social stigmatisation [2] [23] [51]. For this reason, women, in general, have more difficulties accessing treatment compared with men. However, women and men do not differ with respect to their temporal continuity in treatment or its results [2].

Group Versus Individual Therapy Between men and women, there are also different ways of relating that are manifested in their therapeutic preferences. A woman with drug dependency has a more individual way of relating—and has less sense of belonging to a group—and this makes it difficult for her to integrate into it [51]. For women with drug addiction, personal ties and relationships are very important and can put the needs of others before their own.

Types of Therapy and Therapeutic Responses Studies of behavioural therapy have found that women and men respond similarly to these therapies in a wide range of treatment types and substances, including cognitive behavioural therapy and couples behavioural therapy. The use of self-help groups has been shown to benefit both men and women, with no evidence of significant differences between the two [2]. During treatment, women seem to express their emotions and feelings more easily than men [56], which may be an advantage for them. A man with drug dependency is more disciplined and better follows the instructions, guidelines, and functional measures, while a woman with drug

dependency could require additional explanation and could engage in arguments [51].

Ambulatory Versus Residential Treatment One or the other has not been shown to have more satisfactory results for women. However, treatment must include a gender perspective and be sensitive to the needs and the most unfavourable situations of women [49] [59].

Therapist's Sex and Therapeutic Style Women attach great importance to the relationship with the professional [60] [61]. The sex of the therapist does not seem to affect the treatment of addictions in women, as long as the therapist knows how to manage emotional distance properly [51]. The confrontational style, excessive control, and a non-continuous therapeutic relationship are not advised [50].

Differences in Treatment Results Treatment is associated with a favourable outcome in both sexes, particularly when treatment is started early and is maintained over time [2]. However, the exception to this pattern is the treatment of nicotine dependence, whose results are worse in women compared with men [2] [23]. In a study on gender differences in the treatment of opiate dependence, men also showed a better prognosis due to cultural factors related to gender, demonstrating that these factors cause different evolution in therapy [62].

Some studies indicate that women are more likely to abandon treatment [63], and the reasons for doing so tend to be different. The causes of women dropping out are related to interpersonal conflicts with colleagues or therapists, fear of losing their relationship or their children, difficulty finding their own space, or reaching a point in the process where they begin to work on issues such as self-esteem or autonomy. In men, the main causes of abandoning treatment are linked to a lack of freedom and relapses.

Differences Regarding Social Reintegration and Integration There are also differences regarding social reintegration according to sex. Women find more difficulties in this area, due to reasons similar to those already mentioned, related to greater social marginalisation, less capacity for autonomy, emotional and affective dependence, less cultural training, not having a defined profession, and a higher percentage of unemployment or access to low-paying jobs, as well as children, which can make it difficult to work, due to conciliation problems [51].

Centres for Women Versus Mixed Centres We have already mentioned that, until recently, there were more male than female addicts seeking treatment, and therefore the situation of women in treatment centres has been precarious, because the established centres had been designed to accommodate men [51]. As we have seen, there are numerous differences

between women and men in the progression towards drug dependence and abuse, in the mechanisms that underlie these differences, in the difficulties to access treatment, in the treatment itself, and in social integration. Therefore, different prevention and treatment strategies may be required for men and women [23].

The lack of sex-specific treatment facilities and research studies on success rates means there has been little information on how to resolve this circumstance [23]. In the 1980s, however, recognition of differences in gender in addictions led to the development of separate treatment programmes for women, particularly to address the needs of pregnant women and women with children [2]. A scientific review concluded that women in treatment programmes designed exclusively for them, despite having more serious diagnoses and worse psychiatric status, had better results than mixed programmes [2].

Furthermore, participation in gender-specific treatment is associated with greater satisfaction, comfort, and feeling of security among women and greater continuity of care after discharge [2] [51]. Kaskutas et al. [64] indicate that there are few studies that suggest the effectiveness of programmes directed towards women. The authors distinguish between those oriented to women, or exclusively for women and adapted to their needs, from the mixed ones. They point out that when men participate in group therapy, some women do not feel they are in a suitable environment to discuss their problems about drug use, relationships, or sexuality.

Therefore, gender-specific treatments can create an environment of enhanced affiliation, leading to better results [2]. Treatment for women only has also been associated with better outcomes regarding criminal activity and incarceration after treatment [2]. However, this approach requires a different therapeutic style, which incorporates specific activities aimed at affective restructuring and the adequate expression of emotions and which encourages the acquisition of personal autonomy [51].

In addition, in mixed centres, there are therapeutic failures due to the formation of couples, and the problem is that both members of the new couple divert attention—which is essential to focus on their recovery—towards the relationship, which usually leads to abandonment and possible subsequent relapse [51]. It has also been proven that the presence and interaction with men undergoing treatment is not recommended in the early stages of treatment, but rather at a later time [65].

Conclusions

This review presents the conclusions of the most recent scientific work that has significantly advanced the knowledge of the biopsychosocial differences between men and women in

relation to SUD. For this, the anatomical and structural differences of the male and female brain have been described. Next, the importance of sex hormones in brain differences and in drug addiction has been reviewed, and the associated neuropsychiatric problems have been explained. Finally, the important role played by psychosocial conditioning in SUD has been analysed. Figure 1 represents the most important interrelationships between the different spheres of knowledge obtained in this work.

Any reference in this matter must incorporate the sex perspective [2]. However, gender perspective guides do not usually address biological differences. In this sense, this work represents a necessary bridge between disciplines. The role of gender, defined environmentally and socioculturally, contributes to the initiation and evolution of addiction, and the associated adverse medical, psychiatric, and functional consequences are usually more serious in women [2]. There are also sex differences in the reasons for seeking treatment and in the difficulty of accessing it [23].

Taking into account that the problem associated with SUD has historically been a male phenomenon and that consumption by women has been invisible or doubly penalised, it is easy to understand that the perspective on drug addiction treatment has been essentially masculine, and women, even in rehabilitation centres, are victims of gender stereotypes. In fact, many treatment centres and

especially therapeutic communities reproduce basic social and family structures in controlled environments to favour training, modelling, and acquisition of new skills, and the contamination by socially dominant gender roles is highly probable, both by professionals and the therapeutic structure.

The incorporation of the gender perspective has been an important step towards equality between men and women, although it has not necessarily translated into differential approaches, which would be necessary. This perspective must be based not only on stereotypes, but also on existing biological differences, which must be incorporated as an essential starting point. This approach should oblige us to review the operation of rehabilitation and reinsertion programmes, to adapt and promote positive discrimination against women in treatment centres, taking into account that the general consequences of SUD are more serious in women.

Considering the results of this work, we present below some points that should be considered when planning the specific psychotherapeutic intervention with women with a substance addiction problem.

- **Humour and state of mind.** Mood fluctuations are especially important in women and are related to their menstrual cycle. Knowledge of hormonal function and its implications can help prevent SUD and act knowingly.

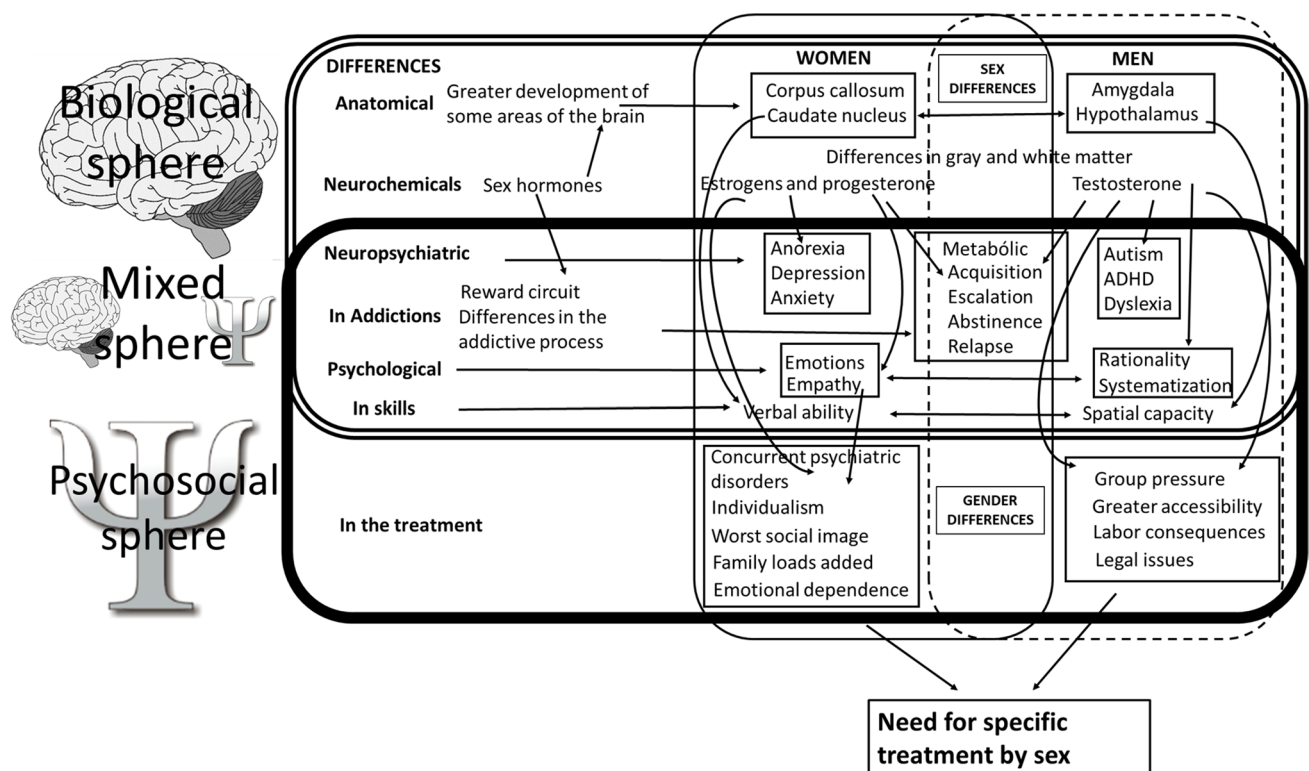


Fig. 1 Conceptual diagram with the most important results obtained in this work

- **Progress in consumption and relapse.** SUD in women develops more quickly, so early interventions are especially advisable.
- **Weight of family responsibilities.** For women, leaving home to enter a rehabilitation centre is very complicated. The design of actions that consider this variable is a good practice that increases accessibility to treatment.
- **Systemising and empathising.** Men have significant difficulties in identifying emotions and women have difficulties in managing them. Treatments must incorporate this variable and provide specific interventions that contribute to educate and balance these aspects in both sexes so that they can be managed adequately.
- **Psychosocial support structures.** The programmes must incorporate specific actions that strengthen said networks, such as protective factors in the process and subsequent reintegration.
- **Comorbidity in SUD and mental illness.** Comorbidity in women is very common and the diagnosis must be improved and weighed to align the intervention with the specific needs.
- Women need a comprehensive explanation to know and understand the therapeutic intervention.
- Episodes of violence and trauma are more likely in women and require an extremely careful approach.
- Gender mandates are not the only cause of the differences between men and women. The biological differences between the two sexes transcend these mandates and determine many of them.
- Training people involved in rehabilitation in biological specificity constitutes an advance towards equality from the knowledge and acceptance of differences and will improve the rehabilitation of women.
- Diagnostic manuals must incorporate biological differences between the sexes and disaggregate their diagnoses, criteria, and severity levels, because they do not usually consider the biological perspective as a factor causing cognitive-behavioural differences in relation to SUD.
- It is essential to understand the specific aspects of each sex and those shared by both, to identify the most effective individualised treatments and to optimise them for both men and women. Because women with addiction often have additional problems, it may be necessary to develop female-specific programmes to address more effectively the problems that women with addiction present, such as self-esteem or co-occurring psychiatric disorders (e.g., depression, anxiety, or eating disorders), without abandoning the traditional mixed programme [2] [7] [51].
- Prevention should work based on different strategies in men and women, also considering the sex differences for each type of substance.

The need and importance of applying differentiated treatments for each sex and the importance of a specific treatment for women are evidenced by the biopsychosocial peculiarities of women compared with men.

Author Contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by all authors. The first draft of the manuscript was written by all authors. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

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