

Sex Related Factors in Substance Use & Addiction

Sex related factors are observed in almost every aspect of addiction, yet most existing biological research employs generic approaches, using males as the norm. Increased inclusion of both male and female research subjects is reducing this disparity, and accumulating evidence reinforces the need for the inclusion of sex (and gender) in research.¹ The examination of sex in addiction research means better science and is critically important when translating research findings to inform treatment and health policy.

Sex is a multidimensional construct that encompasses anatomy, physiology, genes, and hormones that together create a human “package” that affects how we are labelled. Common conceptualizations of sex usually employ the female/male binary; however, in reality, individuals’ sex characteristics exist on a continuum that reflects variations in anatomy, physiology, genes and hormones. All of these differences can affect the way that bodies respond to alcohol, drugs and therapeutics. It is important to note that while sex differs from gender it interacts with it and ideally, both concepts are considered in research.

Additional Resources

Test your knowledge of sex in the following online courses:

CIHR Sex and gender in biomedical research: <http://www.cihr-irsc-igh-isfh.ca/?lang=en>

Gendered innovations: Sex and gender methods for research: <https://genderedinnovations.stanford.edu>

DID YOU KNOW?

Differences in behaviors relating to addiction are partly due to sex related factors in the reward pathway, and include increased risk-taking and poor impulse control among males, whereas females exhibit increased: use of drugs to self-medicate, reactivity to drug-related cues, and propensity for relapse. Several neurochemical systems in addition to dopamine (e.g., norepinephrine, opioids, acetylcholine) are key to mediating the effects of drugs and risk for addiction, yet very little research exists on sex related influences in these systems, and their implications for addiction.

Sex related factors influencing substance use:

Neurobiology. We are learning more about the neurobiology underlying addiction. The neural circuitry mediating positive reinforcing effects (e.g., reward) of addictive drugs has been relatively preserved across evolution and species.^{1,2} Dopamine function in the ‘reward pathway’ is implicated in essential behaviors, such as eating, reproduction, and social play: all of which differ in important ways between sexes.¹ Following drug use, greater dopamine release and inhibition of dopamine reuptake is observed in female compared to male rats.³ In males, basal dopamine tone remains relatively stable, whereas females experience fluctuations based on their hormonal context and are more sensitive to drug-related decreases.²

Hormones. In humans, the rewarding subjective effects of stimulant use varies as a function of menstrual cycle in females with subjective effects being rated higher with high estradiol, and rated lower with high progesterone.² Brain regions involved in processing emotions are differentially activated during the follicular versus luteal phase.⁴ For males, different regions of the brain are activated than females when they anticipate rewards.⁴ Very little research on interactions between testosterone and the reward pathway exists, yet is needed to further understand sex related factors in addiction. Stress hormones can activate the reward pathway. Females experience greater negative states following chronic drug use, and are more sensitive to stress-induced craving and relapse compared to males, partly because they have higher stress hormone levels.¹

Genetics. An individual's risk for addiction can also be influenced by their genetic predisposition. For example, certain genetic variants can impact the metabolic rate of drug.⁵ Twin studies have demonstrated a high genetic component for addiction, where heritability estimates for alcoholism range from 0.50 to 0.61 (out of 1.0). Twin studies on addiction among males consistently find strong heritability, whereas similar studies among females have mixed results.⁶ Thus, more research on sex differences in the molecular mechanisms of how genetic risk translates into behavior is needed. It is possible that genetic risk isn't as straight forward in females compared to males because females have two X chromosomes, and their genes are being expressed within a more variable hormonal context compared to males.

Mental Health. Mental health problems often co-occur with addiction and overlapping brain regions of the reward pathway have been found to be implicated in vulnerability to mental health problems. Stress/trauma occurring in childhood predicted susceptibility to addiction to a greater extent in women than men.⁷ It is possible that heightened stress reactivity in females leads to increased sensitivity of the reward pathway, resulting in increased susceptibility to a range of mental health problem.¹ Gender has also been shown to influence the intersections between addiction and mental health and should also be considered.

Implications for:

Research: Inclusion of both males and females in all levels of research is essential for understanding the complexities of addiction. Inclusion of females requires more multifaceted research designs and hypotheses. Theories of addiction must withstand a range of genetics (XY, XX or other variants) and fluctuating hormonal conditions, yet the majority of research occurs in XY males who have more static basal dopamine tone and hormonal contexts across days relative to females.

Treatment: Pharmacological or behavioral treatments need to consider sex-specific dysregulation of the reward pathway and interactions with stress systems, as well as co-morbid psychopathologies. Understanding that stress acts on the reward pathway to increase vulnerability to addiction, and may do so to a greater extent in females, strongly suggests that stress should be a main focus in addiction treatment. Treatments that reduce stress may be beneficial², particularly among individuals who have experienced chronic and/or intense stress. Further, a woman's stage of menstrual cycle may impact her propensity for use and relapse, and this information could be used to inform optimal timing of treatment initiation, or increased intervention during particularly vulnerable time points.

Health Policy: As inclusion of both males and females is more expensive, inclusion may need to be mandated to ensure that addiction research that attends to sex is being conducted at the basic, pre-clinical and clinical levels.

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