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Considering gender in cannabinoid research: A step towards personalized treatment of marijuana addicts

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Addiction is a complex disorder with interacting factors, including environmental factors, drug-induced neurobiological changes, comorbidity, personality traits and stress responsivity. Numerous genetic variants that affect these factors may work in concert to affect vulnerability and severity of addiction. Traditionally, abuse of illicit drugs, including cannabis, was considered to be primarily a problem specific to men but the recent focus on drug addiction in women has brought attention to numerous sex differences in the central effects of these drugs, epidemiology of abuse-related disorders, etiologic considerations and psychiatric comorbidity. Gender is now recognised as a major factor in the modulation of the pharmacological effects of drugs of abuse, and sex differences have been reported in various phases of the addiction cycle in both humans and animals. Recently, important gender-dependent differences have been detected in the rates of initiation of marijuana smoking and in the frequency of use. Several animal studies, and in particular self-administration studies, confirmed the crucial role played by sex and gonadal hormones in determining higher sensitivity to marijuana's rewarding properties and vulnerability to cannabis addiction in females than in males. In general, women also show higher rate of relapse to drug use than men, likely due to divergent withdrawal experiences and increased reactivity to internal (emotional) and external (drug-associated) cues. According with this, craving for marijuana smoking and propensity to re-use cannabis after abstinence may also develop differently between the sexes and require distinct treatment approaches, thus highlighting the urgent need for gender-tailored prevention strategies and detoxification treatments.

Men and women in biomedical research

Men are from Mars, Women are from Venus is not only the title of the famous book by American writer John Gray (1992). It is also the epitome of the commonly recognized evidence that men and women have diverse brain anatomy and organization, different attitudes, skills and information processing when dealing with daily life, experiencing dissimilar emotions in response to similar stimuli, and being variably susceptible to stress and pathologies.

More than 20 years ago, the National Institutes of Health (NIH) set up an Office of Research on Women's Health (ORWH), to ensure the inclusion of women and minorities in clinical research, and to promote and support research on women's health. In 1993, President Bill Clinton signed the NIH Revitalization Act, which included in its provisions a statutory mandate for increasing female representation in clinical trials. Scientists and clinicians have subsequently shifted emphasis to include women in their studies and trials to such an extent that some people believe that bias has now shifted against men, and programmes and initiatives aimed at recruiting women for clinical trials are no longer necessary.[1] Yet, not all researchers and practitioners are persuaded that women and men are equally represented in biomedical research, and believe that gender disparities in clinical research continue to undermine patient care.

There are considerable differences in the frequency, symptoms, age at onset, and severity of many diseases between men and women. These include cardiovascular diseases, bone diseases (osteoporosis), chronic fatigue syndrome, asthma, several types of cancer, but also autoimmune diseases (rheumatoid arthritis, thyroiditis, systemic lupus erythematosus), neurological and muscular diseases (multiple sclerosis, fibromyalgia) as well as psychological (major depressive disorder, schizophrenia, autism, ADHS), and eating (obesity, anorexia nervosa, bulimia) disorders. It is quite easy to ascribe these differences to the genomic profile, since hundreds of genes in several tissues are expressed differently in males and females,[2] or to hormonal repertoire and fluctuations. Yet, though playing a leading role, genes and hormones cannot be the only response. Acknowledgment of gender-related differences is fundamental in medicine, as biological differences necessarily affect the way men and women respond to therapies and medications.[3–5] It has been well documented that sex influences pharmacokinetic and metabolic activity of drugs: but how many doctors take this into account while prescribing drugs? Could this explain, at least in part, why women are 1.5 times more likely than men to experience adverse reactions to prescribed drugs?[6]

> *Internists should be trained to provide comprehensive care to men and women based on an awareness of the influences of gender . . . on an individual's health.*[7]

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Male and female addicts show different drug use pattern

Early studies investigating the neural mechanisms underlying the rewarding effects induced by drugs of abuse led scientists to conclude that these drugs employ or hijack the same neural circuits that reinforce the basic necessities of survival (i.e. eating, having sex, nurturing).[8] Drug addiction relapses in both men and women, and gender differences have been documented in biological and behavioural effects of drugs of abuse[9]; however, research investigating the neural systems underlying the effects of drugs of abuse on the 'pleasure brain pathway' has mainly focused on male brain functioning. Men and women abuse the same drugs, but not always in the same ways. For example, women who smoke cigarettes usually take shorter and fewer puffs, and experience improvements in mood not typically experienced by males. Nora Volkow, Director of National Institute on Drug Abuse (NIDA, USA) warned about recent statistics which show that adolescent girls have ca. a 60–70% higher rate of abuse of stimulant medications than adolescent boys, as they take stimulant medications to improve cognitive performance, to study for an exam, or to lose weight.

Recently, advances in understanding sex differences in drug-induced effects involved a variety of animal models. Although addictive behaviour displayed by female rodents differs considerably from female human addictive behaviour, these experiments have been useful in guiding clinical trials that test pharmacological treatments for drug dependence.[9] Thanks to animal research, much progress has been made in defining sex-related differences in cocaine, heroin, nicotine and alcohol abuse[10]; however, the gender gap in marijuana smoking and cannabis dependence is still largely unexplored.

Sex-dependent differences in cannabinoid addiction

According to United Nation Office on Drugs and Crime, cannabis is by far the most widely used illicit drug, consumed by between 125 and 203 million people worldwide in 2009, corresponding to an annual prevalence rate of 2.8–4.5%.[11] Marijuana and cannabis derivatives are generally believed to have only mild addictive potential, especially when compared with nicotine or heroin. However, some users do become dependent on cannabis, showing compulsive smoking and a number of clinical symptoms after cessation of frequent drug consumption. Importantly, marijuana-related cues increases self-reported craving and activates the reward brain pathway including the ventral tegmental area, thalamus, anterior cingulate, insula, and amygdala.[12]

Factors determining vulnerability to cannabis dependence have proven difficult to untangle in human studies, although several genes have shown to have critical roles in determining the vulnerability to cannabis use.[13–16] Marijuana withdrawal after abstinence and cue-elicited craving have been associated with two single nucleotide polymorphisms (SNPs) within two genes involved in regulating the endocannabinoid system, cannabinoid receptor 1 (CNR1) and fatty acid amide hydrolase (FAAH).[17]

Recently, sex has been identified as another important factor strongly influencing the proclivity towards cannabis use.[18] In Europe, males outnumber females among drug users, clients attending drug treatment services, and 15–16-year-old students who use cannabis.[19] Male marijuana smokers experience greater cardiovascular and subjective effects,[20] more evident withdrawal symptoms[21] and have higher circulating levels of THC[22] than female smokers. Male high-school students who smoke marijuana report poor family relationships and problems at school more often than age-matched female students,[23] while adult men smoke marijuana to a greater extent than women[24] and display a higher prevalence of panic attacks and personality disorders.[25] In apparent contrast with the human subjects, female rats were found to intravenously self-administer more cannabinoid than males[26] and to exhibit higher cannabinoid-seeking reinstatement than males when abstinent.[27] Notably, cannabinoid self-administration proved to depend not only upon sex (intact female rats being more sensitive than males to the reinforcing properties of cannabinoids) but also upon oestrous cycle, as ovariectomized female animals are less responsive than cycling females.[26,27] In this regard, cannabis acts as other drugs of abuse, since even when cocaine or heroin infusions are made contingent upon increasingly higher numbers of bar presses, female rats make substantially more presses than males, and their level of cocaine self-administration varies as a function of oestrus cycle.[9] Importantly, in a human study, increased marijuana use has been associated with premenstrual dysphoria[28]; during the premenstruum, female subjects reported significantly greater depression, anxiety, mood liability, anger, irritability and impaired social functioning.

> *The effects of marijuana use on neuropsychological processes may differ by sex.*[29]

Biological (sex) and socio-cultural (gender) factors

Many of the gender differences observed in drug use and misuse are determined by sex differences in the brain, which in turn differentially influence behavioural and neurochemical responses of males and females to drugs. Though macroscopically indistinguishable on the exterior, male and female brains are anatomically different. The average male and female brain sizes are different (roughly 1.5 and 1.2 kg, respectively, in adult individuals), but sexual dimorphism is clearly evident also in terms of brain functional and neuroanatomical organization. Different areas of the brain, including forebrain and midbrain structures, work together to sustain the multifaceted addictive behaviour. THC, the main psychoactive component in marijuana, targets cannabinoid type 1 (CB1) receptors within the brain, lungs, liver and kidneys, and cannabinoid type 2 (CB2) receptors primarily in T-cells and macrophages. Within the central nervous system, CB1 receptors are differently expressed between males and females. Importantly, human and animal studies have widely demonstrated that limbic brain regions, often referred to as the 'emotional brain', are particularly vulnerable to chronic marijuana use.[16,30]

The limbic brain has evolved to respond to natural rewards, but drugs of abuse also affect these same circuits. Studies on interactions between drug rewards and natural rewards have led us to a better understanding of motivation in general. Addictive potential of drugs of abuse is believed to be based on its motivational properties.[31] Motivation for a drug may significantly vary between sexes, and in this sense behavioural animal studies have provided in part a rational basis for how

males and females differ in efforts made to gain a reward. More specifically, male and female animals showed different propensity to abuse drugs, different vulnerability to develop drug dependence, and different susceptibility to relapse when abstinent.[32,33] Female laboratory animals typically self-administer more caffeine,[34] cocaine,[35,36] heroin,[37] morphine,[38,39] and fentanyl[40] than males. Ethanol consumption is greater in female rats,[41] mice,[42] and vervet monkeys[43] than in males. Such sex differences in ethanol intake are the opposite of those found in humans, where daily average ethanol intake by men is about double than that for women after adjusting for body weight and body water. Thus, while men drink alcohol and smoke marijuana more often than women, female animals consistently appear more vulnerable than males to positive reinforcing effects of alcohol and cannabinoids and more motivated to obtain them.

What can explain such an apparent discrepancy between epidemiological human data and animal studies? Societal factors are likely to contribute to this divergence, for example, a higher social disapproval of smoking marijuana by girls and women. This does not necessarily imply that females find cannabis less rewarding than males, but it can explain why female animals (unaffected by socio-cultural factors) usually display higher drug intake.

Environmental factors and stress

Previous studies have identified a variety of factors that enhance vulnerability to initiate drug self-administration and accelerate the rate of acquisition of drug-reinforced responses in laboratory animals. Among these, environmental and/or stress factors, such as reduced access to food[44,45] or history of restricted feeding,[46] subjective individual differences, such as impulsivity[47] and enhanced spontaneous motor activity in a novel environment[48,49] have all been well documented. In humans, increased risk taking and novelty-seeking behaviours during adolescence may increase the tendency to experiment with drugs of abuse.[50] Notably, sexually-dimorphic effects of THC on anxiety-related behaviours and locomotor activity has been recently described in adolescent rats.[51]

Among chronic users of marijuana, stress has been recognized as a significant factor in regular use; marijuana users expect relaxation and tension reduction from using cannabis.[52] Stress relief is the most commonly reported benefit from smoking marijuana, and stress-related factors such as negative life events or trauma have been demonstrated to be associated with marijuana use. Thus, a different response to traumatic episodes by men and women could account, at least partly, for the observed gender differences in the amount and frequency of marijuana use. The study of biological responses to stress has historically focused on the major neuroendocrine stress response system of mammals, the hypothalamic-pituitary-adrenocortical (HPA) axis, but other systems, such as the mesolimbic dopamine system, are also involved. Neuroscientists have clearly demonstrated that the female brain uses a different innate strategy and activates different neuronal (limbic) circuitries than the male brain to handle stressful situations.[53] While males are typically in line with the classical 'fight-or-flight' response, the female brain tends to adopt the 'tend-and-befriend' approach as defined by Taylor *et al.*[54]

Emotion dysregulation

As THC activates both the HPA axis and the limbic dopaminergic transmission, could we link gender differences in cannabis abuse to the different way male and female brain responds to emotional stressors? A positive answer would be supported by the evidence that male and female brains also show different emotional traits such as anxiety and depression, which are both more evident in women than in men. The effects of marijuana frequently resemble symptoms of depression (attention deficits, psychomotor retardation, anhedonia), and may lead to emotion dysregulation like mood disorders and anxiety, especially in teenage marijuana users. Women may be particularly vulnerable to the use of substances like marijuana to manage social anxiety. Girls with marijuana dependence, for example, have been found to exhibit higher anxiety compared to boys with marijuana dependence.[55] As a consequence, a better understanding of gender differences in response to cannabis smoking and underlying reasons will provide insight on how to tailor treatment programs to meet the needs of men and women.

> *When women are depressed, they eat or go shopping. Men invade another country. It's a whole different way of thinking.*
> *~ Elayne Boosler*

Brain anatomy and neurochemistry

The brain structure that assesses whether an experience is pleasurable or adverse, and that connects the experience with its consequences is the amygdala, a very small area in charge of the affective and emotional processing. Men and women differ in this critical brain area, as cannabinoid CB1 receptors density and efficacy differ between the two sexes, suggesting that male and female users smoke marijuana motivated by different reasons, in an attempt to achieve different effects. Not only brain anatomy but also brain neurochemistry and physiology may differ between males and females. For example, dopamine, serotonin, and GABA neurotransmission systems exhibit significant sex differences in their metabolism and activity.[56] Therefore, it is not surprising that THC, acting in these areas and through mechanisms involving these neurotransmitters, could trigger different responses in males and females. If males and females use different neural paths to reach the same behavioural endpoint, THC exposure may have different neuronal consequences on the male and female brain.

Detoxification and relapse

Women and men have been found to have different needs in maintaining health, coping with diseases and responding to treatment protocols and drugs. Women seem to be more responsive than men to treatment for drug abuse as well.[57] In 1998, Steven Stocker, a NIDA NOTES contributing writer, announced that while men reported more self-justification after initial use of drugs, women reported more help-seeking and are less likely than men to relapse after entering treatment. Before relapse into drug re-use, women also reported more unpleasant affect and interpersonal problems than men, suggesting that women might benefit more from techniques that enable them to deal more effectively with unpleasant emotions and interpersonal problems.

Conclusion

As with other drugs of abuse, many aspects of cannabis abuse are different for men and women, including the reasons for seeking support, response to treatment, and vulnerability to relapse. Men and women, for example, differ in their experience of craving for

marijuana as well as in the likelihood to relapse during abstinence, implying that different, sex-tailored relapse prevention strategies might be emphasized for male and female cannabis smokers. To strengthen this notion, women smoking marijuana have been found to be more likely than men to report physical withdrawal symptoms, especially upset stomach,[58] suggesting that attention to physical withdrawal symptoms in women may help promote abstinence. Women are more likely to speak about using marijuana, to maintain a social network, to remain abstinent after treatment, and to relapse in response to interpersonal problems and negative feelings. Marijuana female users also demonstrate greater craving than men in response to drug cues.

As we continue to pursue the questions of what neuroanatomical and neurochemical systems control male and female sensibility to THC exposure, we hope that progress will be made to provide treatment options for drug male and female smokers in the near future. The hope is that by understanding the motivational system that draws men and women to abuse cannabis and other drugs, we can develop gender-tailored detoxification treatments and provide the next step on the path to truly personalized healthcare.

Performing gender analyses is simply a matter of doing good science. ~ Cora Lee Wetherington, NIDA's Women's Health Coordinator

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