

# Genetics and Gender - Hayes

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## SUMMARY KEYWORDS

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 00:01

This presentation is entitled Genetics and Gender: Impacts on Diagnosis and Care. I will now turn it over to Dr. Leslie Hayes to begin our presentation.

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Hi, I'm Dr. Leslie Hayes,

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I'm going to be speaking on genetics and gender, the impacts on the diagnosis and care of patients. I have no disclosures.

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Learning objectives are to describe the genetic and gender differences impacting the assessment and treatment of substance use disorder. We'll talk about genetics first. There's three different ways that genetics actually influence substance use disorder. The first is a direct effect of the genes on a person's susceptibility to substance use disorder. The second is pharmacogenetics, which is how your body interacts with the drugs. And it affects how the drugs actually affect an individual. And the third is a field called epigenetics. And epigenetics actually affects which genes are expressed. So you may be more or less likely to express genes that would predispose you to substance use disorder.

 01:07

So, we talk a lot about nature versus nurture, how much is your genetic background, and how much is your environmental? For substance use disorder, it's better phrased as nature and nurture. There's really no way you can develop a substance use disorder without being exposed to the substance. So environment is obviously important. But on the other hand, your genetic background is also significant for your risk of developing a substance use disorder. So the likelihood of developing it is a

result of an interaction between both your genes and the environment. And substance use disorder is almost certainly polygenic, meaning multiple genes are going to affect your risk. There are dozens if not hundreds of genes that have been found that have an effect on your risk of developing substance use disorder, and almost all of them have just a very small effect. And overall, they contribute to the risk of developing substance use disorder.

 02:03

Environment has a very strong effect on- or very strong influence on your likelihood of initiating substance use, which makes sense if you're in a household where people are using alcohol or using cocaine, or if your friends are using fentanyl, you're going to be much more likely to start using. However, once you have started using genetic impact factors play a much stronger effect on the risk of progression to substance use disorder. Heritability is a term that means how likely something is caused by a genetic. And for instance, speaking Spanish has a heritability of zero, that's entirely environmental. Whether you speak Spanish or not, there are no genes for speaking Spanish. However, blood type is has a heritability of one. So that is entirely determined by your genes, your environment does not matter at all for your blood type. So, and the heritability of substance use disorders range from 0.39 for hallucinogens up to 0.72, for cocaine, so somewhat affected by your genes, but definitely not as much as other things are.

 03:14

Pharmacogenetics is how your body interacts with the drugs. And I think this is the most likely place that we're going to find actual clinical applications. And this is where you're more likely to get one strong gene affecting things. The one that we have all heard of is the effect of the alcohol dehydrogenase and these are common in South Asian descent and people of Jewish ancestry.

 03:40

The ADH1, B2-His47 ARG allele of alcohol dehydrogenase 1B, and ALDH-Glu-487 Lys allele of the aldehyde dehydrogenase 2 can cause flushing, nausea, and headache with alcohol. People accumulate acetaldehyde because they do not break it down as well. I wouldn't necessarily remember the exact genes but I do think it's useful to remember this pathway. Homozygotes for these these- genes are nearly completely protected from alcoholism, just because it is almost impossible for them to drink because they become so very sick.

 04:22

And pharmacogenetics also significantly affect medication therapy for opioid use disorder. The one that's had the most researched and seems to have the most effect is the A118G single nucleotide polymorphism, which is also called the SNP or snip. And this is a variant of the opioid mu receptor. And the opioid mu receptor you may see abbreviated OPRM1 and it enhances the therapeutic response to naltrexone for alcohol dependence. So if somebody has this gene, they're much more likely to respond to naltrexone. Interestingly, they're also much more likely to develop heroin use disorder to begin with.

 05:04

They have also found for babies who have developed neonatal opioid withdrawal syndrome, that they have significant variations in the A118G SNP, that really affects how long they're going to need to be treated and how effective the pharmacotherapy is going to be for them. In addition, various SNPs in the catechol-o-methyltransferase enzyme that helps to degrade dopamine, norepinephrine and epinephrine, also affect how they're going to respond to therapy for the neonatal opioid withdrawal.

 05:40

Pharmacogenetics also affect our treatment. Methadone in particular is rapidly metabolized by CYP2D6, and ultra rapid metabolizers just don't do well on methadone, because they would need to be dosed so often, that we can't do it in a methadone clinic.

 05:57

Epigenetics is a really interesting phenomenon that has only really come up in the last 10 to 20 years. And it's the study of epigenomes, and these are markers that turn genes on or off or express them more or less strongly. So changes to the epigenomes can be passed down anywhere from two to 12 generations. And interestingly, diet, stress and prenatal drug use can all cause these genes to turn on or off. And so the epigenetics changes affect which genes are going to be affected. And if you get a gene that is more likely to have you develop substance use disorder expressed then it's going to have a significant effect on that.

 06:42

We're going to move on now to gender differences in substance use disorder. And I just want to mention terminology real quick. None of the studies I found looking at gender and substance use disorder specified cis or transgender, I have assumed that they are looking at cisgender. But it- I really can't say from the studies because none of them specified. And in general, I've used the terms either female or male or woman or man that the study did when I put them in.

 07:13

So men are much more likely than women to use almost all types of illicit drugs. Women probably misuse prescription drugs at greater than men- greater rates than men do. But overall, men are 1.9 times more likely to have a drug dependence. Men in general have higher rates of alcohol use, including binge drinking than women, except for teens, and the rates are similar in teens. And we don't know if this is because of societal shifts, where females are more likely to do these risky behaviors than males, or females are more likely to do these risky behaviors than females were, say 20 years ago, or is it just because teens are more likely to engage in risky behavior, and 20 years from now, these female teens will be using less alcohol than the males at that time.

 08:05

When women start using, they're much more likely to start using because of their male sexual partner. Studies have particularly shown this for injection injection drug use, men are much more likely to be injected by a friend, women are much more likely to start using because their male sexual partner is using. And women are much more likely to use for stress and anxiety, where men are more likely to use for friends or to get high, to have a good time.

 08:34

One study showed that women were more likely to use prescription opioids to self-medicate anxiety or stress, where men were experimenting are getting high. Women are also more likely to drink in response to stress and negative emotions. Men are more likely to enhance positive emotions, they're already having a good time or to conform to a group. And where I find this really shows up in treatment is for women, it's very important that we help them find other ways to deal with anxiety or stress. If we don't really help them to find other ways to deal with anxiety or stress, they're very likely to relapse. For men, this shows up that they may have difficulty making friends, when they get drug or alcohol free. I can't tell you the number of 40 and 50 year old men I have who stopped drinking in their 30s or 40s. And definitely feel like it was the right decision. But they have never had friends since that time. So helping men find other ways to have friends I think is a really important part of treatments.

 09:32

And obviously, there's significant overlap. There are definitely men who are drinking or using drugs to deal with stress. And there are plenty of women who were drinking or using drugs to be with friends or to have a good time. But if we look at it, women tend to be more on the negative reinforcement sides. And men tend to be more on the positive reinforcement side. Women are using too because it helps to get rid of negative emotions whereas men are more likely to be using seem to get the positive emotions or to get high.

 10:05

There's a lot of effects of the menstrual cycle and female hormones on substance use disorder. And I found this fascinating that women who attempt to quit smoking during the luteal phase, which is the first half of the menstrual cycle, actually are more likely to be able to quit smoking than women who tried to quit during the follicular phase or the second half. I haven't actually used this clinically much yet, but it's definitely worth paying attention to. Interestingly, if you use stimulants, stimulants such as cocaine or methamphetamine, you're gonna get higher in the follicular phase, which is the second half then you will during the luteal phase again, the first half.

 10:47

Testosterone levels in men are suppressed by both alcohol and opioids. This is common enough that I think it's worth checking testosterone levels in men who complain of erectile dysfunction who are either alcohol users or opioid users or on medication and treatments.

 11:04

Women get drunk faster than men. They have a decreased body weight, they don't have as much alcohol dehydrogenase. They have a decreased volume of water compartment distribution, and they have less muscle than men.

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Women also have what we call a telescoped course for alcohol use disorder, which means they develop the pathological effects of alcohol more rapidly. They have a 50 to 100% higher death rate from alcohol use disorder including deaths from suicide, alcohol related accidents, heart disease, stroke and liver damage. Even though they're less likely to drink, when they do drink, it has a much worse effect on them.

 11:38

CDC guidelines for risky drinking are different for men and women because of this. Binge drinking, the most common form of excessive drinking, is defined as consuming for women four or more drinks during a single occasion. And for men, it's five or more drinks during a single occasion. Heavy drinking is defined as consuming eight or more drinks per week for women and for men 15 or more drinks per week. And it's important to realize most people who drink excessively are not alcoholics or alcohol dependent, but it can still have a substantial effect on their health. There was actually a really great commentary in the 2020 Journal of Addiction Medicine by Lowik that's discussing maybe needing to adjust these guidelines. For the review, for the exam, I would just memorize the guidelines. But it might be worth looking at the commentary for actual clinical practice.

 12:29

Incarceration: A population based study showed that 22% of patients with substance use disorder had been incarcerated before compared to about 10% of the general population. So our patients with substance use disorder are substantially more likely to have been incarcerated.

 12:44

And this is much more true for men than women. I couldn't find a study that actually compared men versus women, this study did separate them out. But they didn't actually do the statistical analysis, but it was about 30% of men with substance use disorder had a history of incarceration versus about 10% of women. And just a reminder that blacks and Latinos are far more likely to be incarcerated for drug law violations than whites, even though the rates of drug use and drug selling are similar.

 13:13

And unfortunately, strong association between violence and substance use disorder. Girls with a history of childhood sexual abuse are three times as likely to develop an addictive disorder as girls without that history. And one study showed that the lifetime intimate partner violence victimization is

reported by almost half of women and actually about 10% of men entering SUD treatment. So it's more common in women, but we do want to screen men as well.

 13:39

Medications differ in their effects. Varenicline is found to be much more efficacious than transdermal nicotine or bupropion. Neither nicotine nor bupropion actually increased quitting in women so we might want to focus more on varenicline. For men, all three medications were found to be effective, no statistical difference between them. And women have more difficulty maintaining long term abstinence from tobacco than men do.

 14:03

Women using buprenorphine had greater treatment retention and less opioid use compared to men using buprenorphine, and females receiving buprenorphine were less likely to relapse than females using methadone. Men receiving long acting methadone were less likely to relapse than males receiving buprenorphine and retention in treatment was longer for both sexes receiving methadone versus LAAM. But I do want to make the point all three medications benefit both men and women.

 14:31

And transgender individuals have high rates of alcohol use- estimates up to 72%. Marijuana, use other illicit drug use, and non-medical use of prescription drugs- show more severe misuse of these substances compared with nontransgender persons, related to stigma. So in summary, there's a substantial genetic component to substance use disorder. And women are less likely than men to use drugs and alcohol, but they have worse outcomes if they do. And that is all I have.