



ASAM REVIEW COURSE 2023

Genetics and Gender: Impacts on Diagnosis and Care

Leslie Hayes, MD
Family Physician and Addiction Medicine
El Centro Family Health
Española, NM





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LEARNING OBJECTIVE

Describe genetic and gender differences impacting the assessment and treatment of addiction in women and list evidence-based treatment strategies for pregnant patients and newborns.

Genetics and Substance Use Disorder



Three ways that genetics influences substance use disorder

Direct effect of genes on susceptibility to substance use disorder

Pharmacogenetics affects how drugs affect an individual

Epigenetics affects which genes are expressed

Genetics of substance use disorder

- Nature vs nurture better phrased as nature and nurture for substance use disorder. A person's likelihood of developing substance use disorder is a result of a dynamic interaction between genes and the environment. ¹
- SUD is likely polygenic. Multiple genes, each having a small effect, contribute to risk of developing SUD. ²

1. *Genetics and Epigenetics of Addiction*. in *DrugFacts*. <https://www.drugabuse.gov/publications/drugfacts/genetics-epigenetics-addi>

2. *Prom-Wormley EC, Ebejer J, Dick DM, Bowers MS. The genetic epidemiology of substance use disorder: A review. Drug Alcohol Depend. 2017 Nov 1;180:241-259. doi: 10.1016/j.drugalcdep.2017.06.040. Epub 2017 Aug 1. PMID: 28938182; PMCID: PMC5911369*

Genetics of substance use disorder

- Environment has stronger influence on initiation, whereas genetic factors are more important in progression and development of SUD.¹
- Heritabilities of SUD's range from 0.39 for hallucinogens to 0.72 for cocaine.²



1. Deak JD, Johnson EC. Genetics of substance use disorders: a review. *Psychol Med*. 2021 Oct;51(13):2189-2200. doi: 10.1017/S0033291721000969. Epub 2021 Apr 21. Erratum in: *Psychol Med*. 2022 Mar 02;:1. PMID: 33879270; PMCID: PMC8477224.

2. Bevilacqua and Goldman. *Genes and Addictions*. *Clin Pharmacol Ther*. 2009 April; 85(4) pp 359-361

Pharmacogenetics

- Both the ADH1 B2-His47 ARG allele of Alcohol Dehydrogenase 1B and ALDH-Glu487 Lys allele of Aldehyde Dehydrogenase 2 can cause flushing, nausea, and headache with alcohol, due to accumulation of acetaldehyde.¹
 - More common in person of South Asian descent and those of Jewish ancestry.
 - Homozygotes nearly completely protected from alcoholism.

Pharmacogenetics of medication therapy of OUD

- The A118G SNP (single nucleotide polymorphism) of the opioid mu receptor (OPRM1) enhances the therapeutic response to naltrexone for alcohol dependence.¹
 - A118G is also much more common in people with heroin use disorder.²
- Increased length of stay and increased need for pharmacotherapy in Neonatal Opioid Withdrawal Syndrome have recently been observed among neonates with variations in the A118G SNP in the mu opioid receptor OPRM1 gene and various SNP's in the COMT (Catechol-O-methyltransferase – enzyme that degrades dopamine, norepinephrine, and epinephrine.)³

¹ Haile et al. Pharmacogenetic Treatments for Drug Addiction: Alcohol and Opiates, *The American Journal of Drug and Alcohol Abuse*, 34:4, 355-381

² Ibid

³ Wachman et al. Association of OPRM1 and COMT single-nucleotide polymorphisms with hospital length of stay and treatment of NAS. *JAMA* 2013;309(17):1821-

Pharmacogenetics of Medication Therapy of OUD

- Methadone is metabolized in part by CYP2D6.
 - Ultrarapid metabolizers do not do well on methadone.¹

Epigenetics

- Epigenetics is the study of epigenomes which are markers that turn genes on or off or express them more or less strongly.
 - Changes to the epigenomes can be passed down anywhere from 2-12 generations.
 - Environmental factors like diet, stress, and prenatal drug use can cause epigenetic changes which predispose to substance use disorder.

Gender Differences in Substance Use Disorder

A word about terminology

- None of the studies I found looking at gender and substance use disorder specified cis- or trans-gender.
- I have generally used the terms (female/male or woman/man) the study did.

Gender differences and substance use disorder

Men are more likely than women to use almost all types of illicit drugs.¹

- Women probably use prescription drugs at greater rates than men.²
- Men are 1.9 times more likely to have drug dependence.³

Men have higher rates of alcohol use, including binge drinking, than women, except for teens, where rates are similar.⁴

¹*Substance Use in Women Research Report Sex and Gender Differences in Substance Use*
<https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/sex-gender-differences-in-substance-use> Accessed 2/18/2021

²*Greenfield et al. Substance Abuse in Women. Psychiatr Clin Nort Am. 2010 June; 33(2): 339-355*

³*Ibid*

⁴*Substance Use in Women Research Report Sex and Gender Differences in Substance Use*
<https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/sex-gender-differences-in-substance-use> Accessed 2/18/2021

Gender differences and substance use disorder

- Women are more likely to be introduced to injection drug use by their male sexual partner, whereas men are more likely to be injected by a friend.¹

¹ Greenfield et al. Substance Abuse in Women. *Psychiatr Clin Nort Am.* 2010 June; 33(2): 339-355

Gender differences and substance use disorder

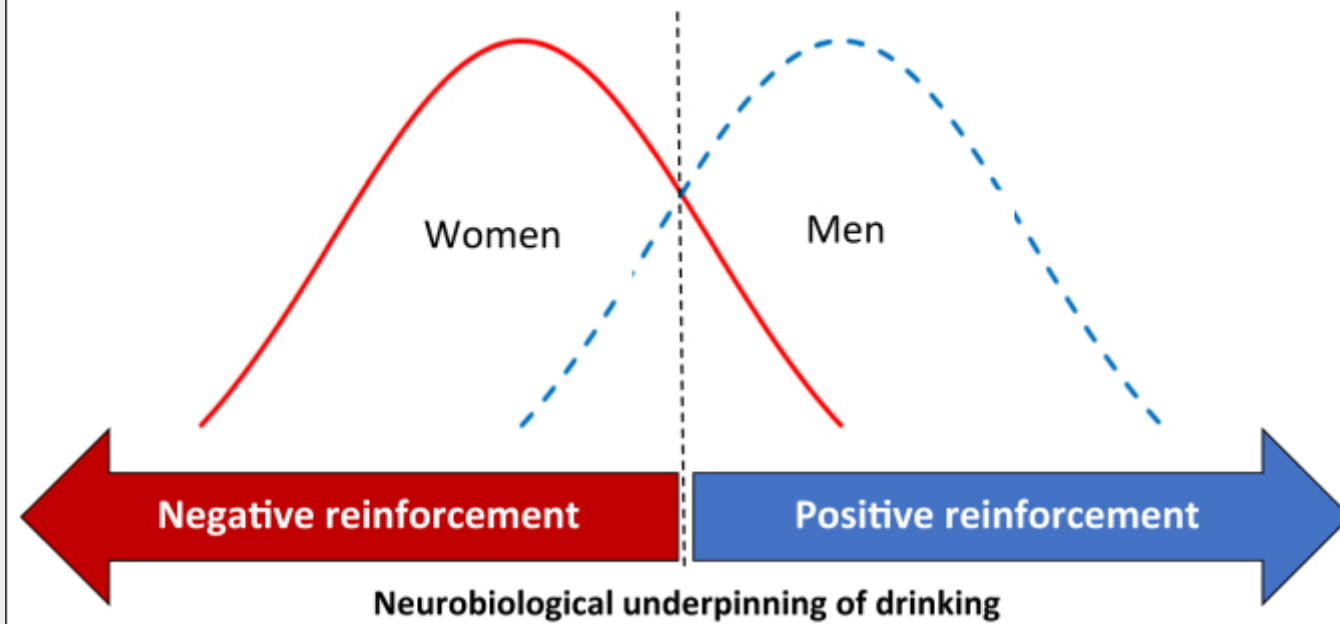
- Women are more likely to use prescription opioids to self-medicate for anxiety or stress.¹ Men are more likely to use prescription opioids for experimentation or to get high.²
- Women are more likely to drink in response to stress and negative emotions whereas men are more likely to drink to enhance positive emotions or conform to a group.³

¹ *Final Report: Opioid Use, Misuse, and Overdose in Women.. Office on Women's Health. July 19, 2017*

² *Greenfield et al. Substance Abuse in Women. Psychiatr Clin Nort Am. 2010 June; 33(2): 339-355*

³ *Ibid*

Sex differences in positive and negative reinforcement drinking



Peltier MR, Verplaetse TL, Mineur YS, Petrakis IL, Cosgrove KP, Picciotto MR, McKee SA. Sex differences in stress-related alcohol use. *Neurobiol Stress*. 2019 Feb 8;10:100149. doi: 10.1016/j.ynstr.2019.100149. PMID: 30949562; PMCID: PMC6430711.

Menstrual cycle and substance use disorder

- Women who attempt to quit smoking during the luteal phase of their menstrual cycle had more favorable outcomes than women who attempted to quit during the follicular phase.¹
- Response to stimulants, such as cocaine and methamphetamine, is higher in the follicular than the luteal phase.²

¹ Allen et al. Menstrual phase effects on smoking relapse. *Addiction*. Volume 103. Issue 5. April 14, 2008.

² Terner et al. Menstrual cycle phase and responses to drugs of abuse in humans. *Drug Alcohol Depend*. 2006 Sep 1;84(1):1-13.

Testosterone and substance use

- Testosterone levels in men are suppressed by both alcohol¹ and opioids.²

¹ Malabanan and Jack. *Endocrine and Reproductive Disorders Related to Alcohol and Other Drug Use. The ASAM Principles of Addiction Medicine. Sixth Edition. Wolters Kluwer 2019 p. 1298*

² Bawor et al. *Testosterone suppression in opioid users: A systematic review and meta-analysis. Drug and Alcohol Dependence 149 (2015) 1–9*

Women and alcohol

- Women get drunker faster than men:
 - Decreased body weight ¹
 - Decreased alcohol dehydrogenase²
 - Decreased volume of water compartment distribution²
 - Less muscle than then men

Health risks for women with substance use disorder

- Women have “telescoped course” for alcohol use disorder.¹
- They develop pathologic effects of alcohol more rapidly.
- Women have a 50-100% higher death rate from alcohol use disorder, including deaths from suicide, alcohol-related accidents, heart disease, stroke, and liver damage.²

¹ Zweben. *Special Issues in Treatment: Women in Miller et al. The ASAM Principles of Addiction Medicine, Sixth Edition.* Wolters Kluwer 2019 p. 529

² *Substance Use in Women Research Report Sex and Gender Differences in Substance Use*
<https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/sex-gender-differences-in-substance-use> Accessed 2/18/2021

CDC guidelines for risky drinking¹

- Excessive drinking (or risky drinking or at risk drinking) is defined as the following:
 - Binge drinking, the most common form of excessive drinking, is defined as consuming
 - For women, 4 or more drinks during a single occasion.
 - For men, 5 or more drinks during a single occasion.
 - Heavy drinking is defined as consuming
 - For women, 8 or more drinks per week.
 - For men, 15 or more drinks per week.
- Most people who drink excessively are not alcoholics or alcohol dependent.
- 2020 commentary by Lowik et al in the Journal of Addiction Medicine discussed whether adjustments are needed for these guidelines.²

¹ <https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm> accessed 2/17/2021

²Lowik et al. *Where is the Science? A Critical Interrogation of How Sex and Gender are Used to Inform Low-Risk Alcohol Use Guidelines.* *J. Addict Med* Vol 14, No. 5, Sept/Oct 2020

Incarceration and substance use disorder

- A population-based study showed that 22% of patients with substance use disorder had been incarcerated before.
- 10.6% of the general population reported a history of incarceration.

Incarceration and substance use disorder

- Men with SUD were found to be more likely to have a history of incarceration as women with SUD. ¹
- Blacks and Latinos are far more likely to be incarcerated for drug law violations than whites, even though rates of drug use and drug selling are similar.²

¹Tsai, J., Gu, X. Utilization of addiction treatment among U.S. adults with history of incarceration and substance use disorders. *Addict Sci Clin Pract* **14**, 9 (2019).

²<http://www.drugpolicy.org/resource/drug-war-mass-incarceration-and-race-englishspanish> Accessed 02/16/2021

Women and violence and SUD

- Girls with a history of childhood sexual abuse are 3 times as likely to develop an addictive disorder as girls without that history.¹
- One study showed lifetime intimate partner violence victimization was reported by 46.7% of women and 9.5% of men entering SUD treatment.



¹ Zweben. *Special Issues in Treatment: Women in Miller et al. The ASAM Principles of Addiction Medicine.* Wolters Kluwer 2019 p. 532

² Schneider et al. *Violence and Victims*, Volume 24, Number 6, 2009 744 © 2009 Prevalence and Correlates of Intimate Partner Violence Victimization Among Men and Women Entering Substance Use Disorder Treatment

Medications for tobacco use disorder

- For women, varenicline was found to be more efficacious than transdermal nicotine or bupropion¹
 - Neither nicotine or bupropion increased quitting in women
- For men, all three medications were found to be effective, and there was no statistical difference between them¹
- Women have more difficulty maintaining long-term abstinence than men do²

1 McCrady BS, Epstein EE, Fokas KF. Treatment Interventions for Women With Alcohol Use Disorder. *Alcohol Res.* 2020 Jul 30;40(2):08. doi: 10.35946/arcr.v40.2.08. PMID: 32742894; PMCID: PMC7384374

2 Smith PH, Bessette AJ, Weinberger AH, Sheffer CE, McKee SA. Sex/gender differences in smoking cessation: A review. *Prev Med.* 2016 Nov;92:135-140. doi: 10.1016/j.ypmed.2016.07.013. Epub 2016 Jul 26. PMID: 27471021; PMCID: PMC5085924.

Medications for opioid use disorder

- Women using buprenorphine had greater treatment retention and less opioid use compared to men.^{1,2}
- Females receiving buprenorphine were less likely to relapse than females receiving methadone, whereas males receiving LAAM were less likely to relapse than males receiving buprenorphine^{1,3}
 - Retention in treatment was longer for both sexes receiving methadone versus LAAM.
- All three medications benefit both sexes.³

¹ McCrady BS, Epstein EE, Fokas KF. Treatment Interventions for Women With Alcohol Use Disorder. *Alcohol Res.* 2020 Jul 30;40(2):08. doi: 10.35946/arcv.v40.2.08. PMID: 32742894; PMCID: PMC7384374

² Schottenfeld RS, Pakes JR, Kosten TR. Prognostic factors in Buprenorphine- versus methadone-maintained patients. *J Nerv Ment Dis.* 1998 Jan;186(1):35-43. doi: 10.1097/00005053-199801000-00006. PMID: 9457145.

³ Jones HE, Fitzgerald H, Johnson RE. Males and females differ in response to opioid agonist medications. *Am J Addict.* 2005 May-Jun;14(3):223-33. doi: 10.1080/10550490590949569. PMID: 16019973

Transgender persons and substance use disorder

- 5 Recent studies indicate that transgender individuals have high rates of alcohol use (estimates up to 72%), marijuana (estimates up to 71%), other illicit drug use (estimates up to 34% [including intravenous drug use]), and nonmedical use of prescription drugs (estimates up to 26.5%) and show more severe misuse of these substances compared with non-transgender persons.



In Summary



1


There is a substantial genetic component to substance use disorder.

2

Women are less likely than men to use drugs and alcohol but have worse outcomes when they do.



Get in Touch

 301.656.3920

 education@asam.org

 www.asam.org