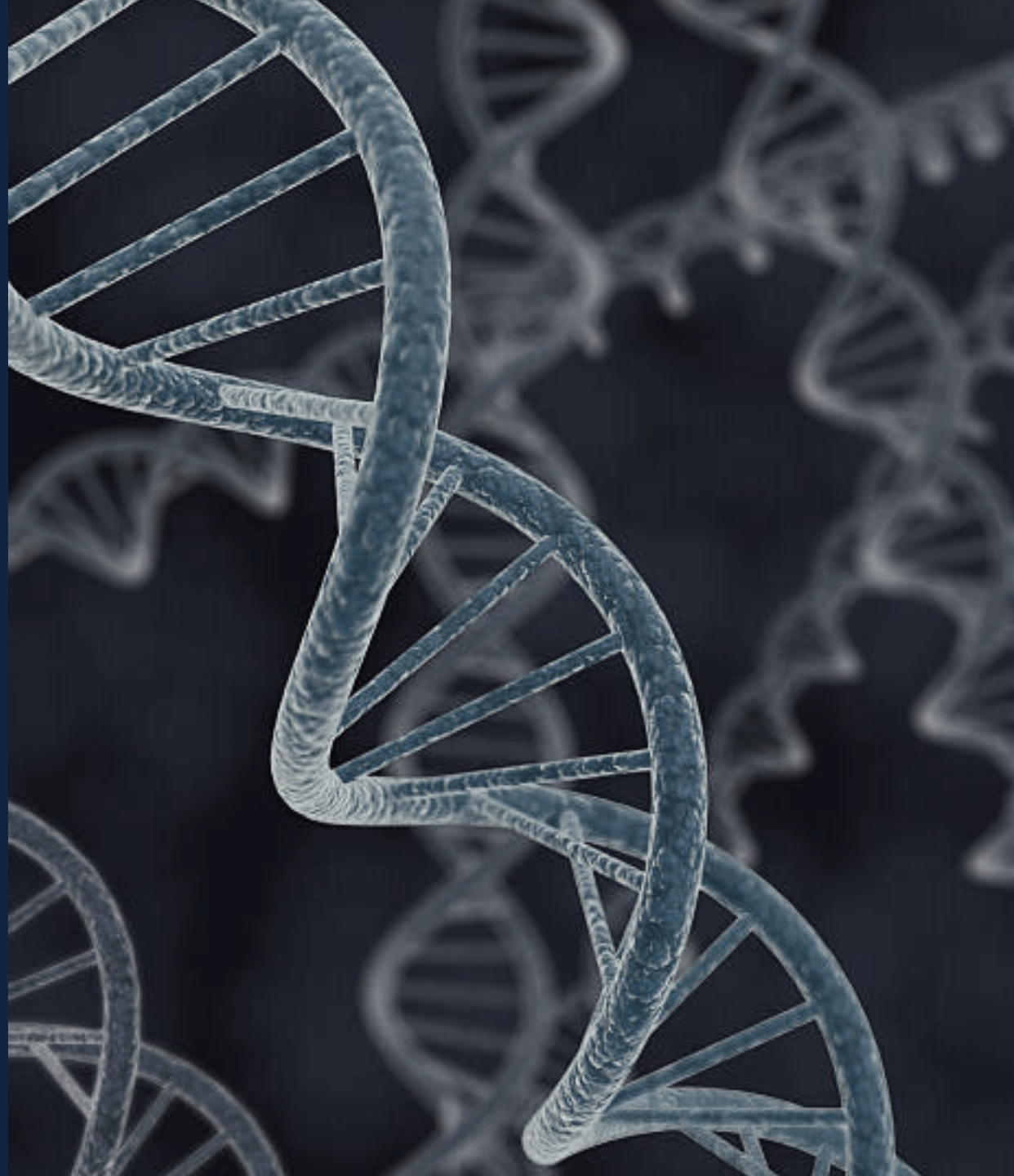




ASAM REVIEW COURSE 2026

Genetics and Gender: Impacts on Diagnosis and Care

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Financial Disclosure

Leslie Hayes, MD

- No relevant disclosures

Genetics and Substance use disorder

- Overview
- Pharmacogenetics
 - Pharmacokinetics
 - Pharmacodynamics
- Epigenetics
- Polygenic risk scores

Disclaimer for genetics portion of talk

- Almost all the research done on addiction and genetics has been done on persons of European ancestry.

Second disclaimer for genetics portion of talk

- December 2024 SAMHSA Advisory:
- Genetic testing should be used only as part of a comprehensive evaluation, and practitioners need to be aware of the limitations and risks.

Genetics of substance use disorder

Nature vs nurture better phrased as nature and nurture for substance use disorder. 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: PMC5911366*

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.

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

Twin studies – direct effect of genes

- Both the Swedish and Vietnam twin studies showed significantly higher concordance rates for substance use disorder in monozygotic twins than in dizygotic twins.^{1,2}

Pharmacogenetics

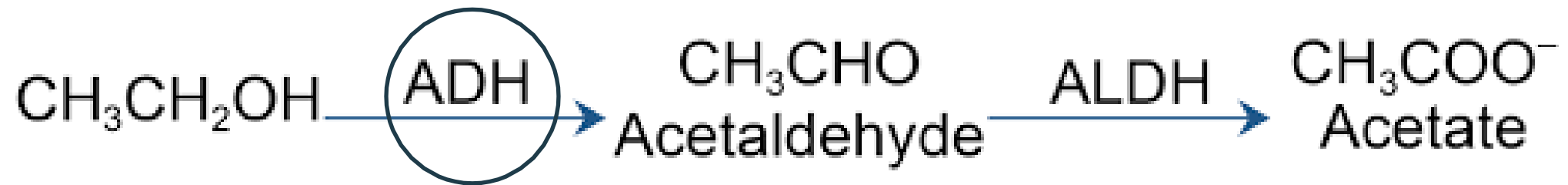
Pharmacokinetics

- Metabolism of alcohol



Pharmacokinetics

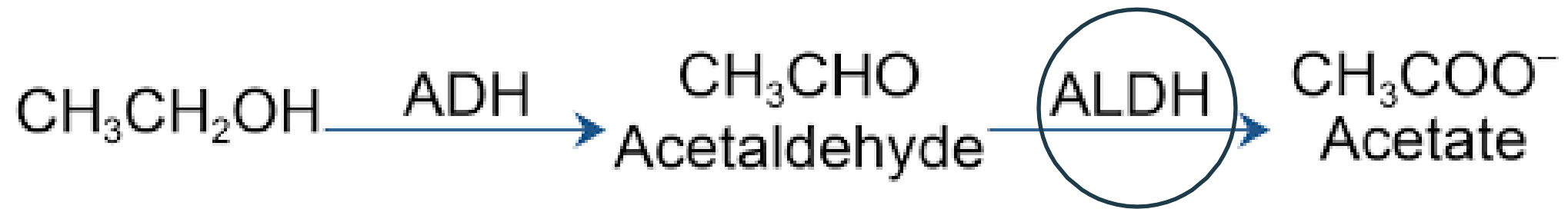
- Metabolism of alcohol



Alcohol dehydrogenase that metabolizes rapidly will cause high levels of acetaldehyde

Pharmacokinetics

- Metabolism of alcohol



Acetaldehyde dehydrogenase that metabolizes too slowly will lead to high levels of acetaldehyde

Pharmacokinetics

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

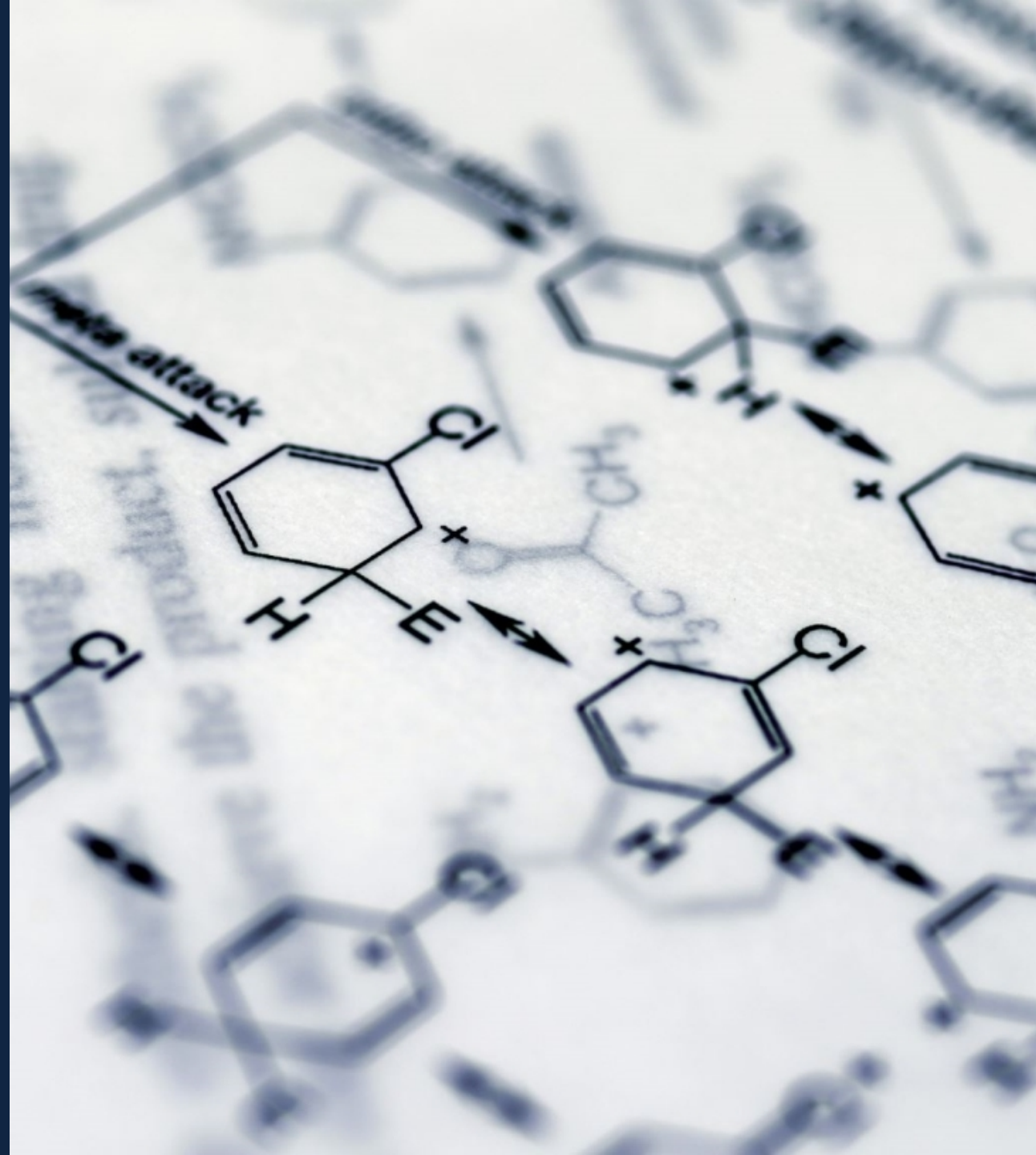
More common in person of South Asian descent and those of Jewish ancestry.

Homozygotes nearly completely protected from alcoholism.

¹Zajicek and Karan. *Pharmacokinetic and Pharmacodynamic Principles in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019. p. 97-98*

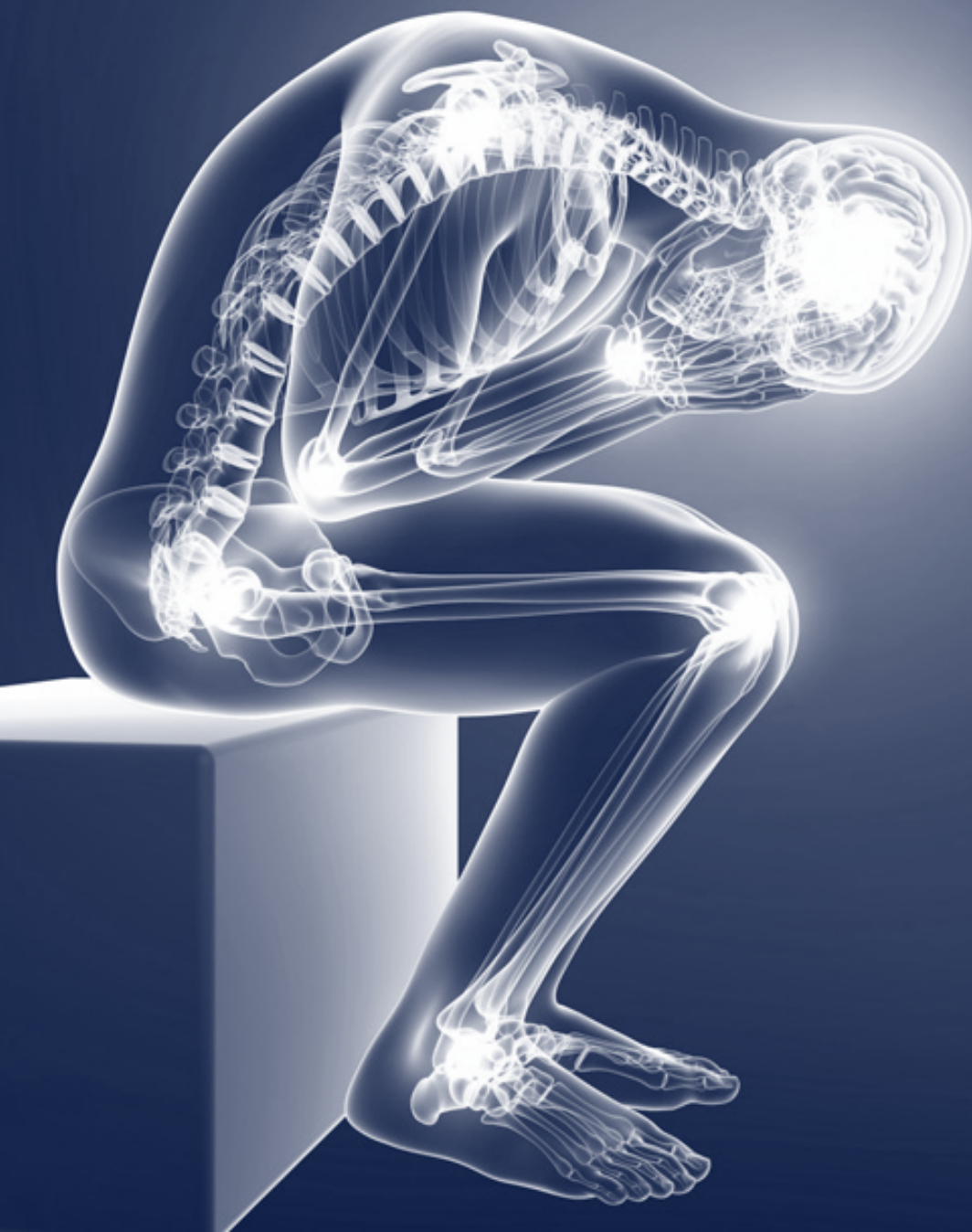
Pharmacodynamics

Genes that code for the receptor for various substances can affect the likelihood of substance use disorder for that substance



Pharmacodynamics -- Nicotine

- CHRNA and CHRNA = family of genes that encode subunits of nicotinic acetylcholine receptors
- The gene cluster encoding the neuronal acetylcholine receptor (CHRNA3-CHRNA5-CHRNA4) seems to be closely related to quantity and frequency of cigarette use.



Pharmacodynamics – opioid receptor

- The mu-1 opioid receptor gene (OPRM1) codes for the mu opioid receptor.
 - The G allele of the OPRM1 is related to a lower pain threshold and higher opioid consumption in the post-op period.
- The catechol-O-methyltransferase (COMT) gene regulates the expression of the mu-opioid receptor.

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.

Polygenic risk scores for alcohol use disorder

- Polygenic risk scores were useful for showing a predisposition.
 - In a recent JAMA study, the 5% of samples with the highest polygenic risk score were approximately twice as likely to develop AUD as the rest of the sample (OR 1.96, [95% CI, 1.78-2.16] ¹
 - The 5% of samples with the lowest polygenic risk score were approximately twice as likely to develop AUD as the rest of the sample (OR 0.57 [95% CI, 0.39-0.84] ¹
- Another study showed an increase in psychological distress in people as score increased, but also an increased likelihood to engage in follow-up behaviors such as seeking additional information, talking to a healthcare provider, and reducing drinking behaviors.²

Lai D, Zhang M, Abreu M, et al. Alcohol Use Disorder Polygenic Score Compared With Family History and ADH1B. *JAMA Netw Open*. 2024;7(12):e2452705. doi:10.1001/jamanetworkopen.2024.52705

Driver MN, Kuo SI, Dron JS, Austin J, Dick DM. The impact of receiving polygenic risk scores for alcohol use disorder on psychological distress, risk perception, and intentions to reduce drinking. *Am J Med Genet B Neuropsychiatr Genet*. 2023 Jul-Sep;192(5-6):93-101. doi:10.1002/ajmg.b.32933. Epub 2023 Mar 1. PMID: 36856135

Gender and Substance use disorder outline

Gender differences
in presentation of
substance use
disorder

Differences in
medical problems
for males and
females

LGBTQ and SUD

Incarceration and
SUD

Sex work and SUD

Differences in
treatment for SUD

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. I have also used the terms for substance use disorder (addiction, dependence, SUD) from the study.

Social stigma and substance use disorder

- Women are less likely to develop problems as a results of substance use because they are less likely to use substances. However, because of this, when they do develop problems, they deviate more from the female norm compared with a man with an addiction.

Different presentations of Substance Use Disorder in Men and Women

Gender differences and substance use disorder

Men are more likely than women to use almost all types of illicit drugs.^{1,2}

- Women use prescription drugs at greater rates than men and have higher rates of prescription drug use disorder.²
- Otherwise, men have higher rates of drug use disorder.²

Men have higher rates of alcohol use, including binge drinking, than women^{1,2}, except for teens and young adults, where rates were similar until recently.

- Female teens currently use more alcohol than males.³
- Young adult women binge drink more than young adult men.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

Center for Behavioral Health Statistics and Quality. (2023). Results from the 2022 National Survey on Drug Use and Health: Detailed tables. Substance Abuse and Mental Health Services Administration. <https://www.samhsa.gov/data/report/2022-nsduh-detailed-tables>

Hoots BE, Li J, Hertz MF, et al. Alcohol and Other Substance Use Before and During the COVID-19 Pandemic Among High School Students — Youth Risk Behavior Survey, United States, 2021. *MMWR Suppl* 2023;72(Suppl-1):84–92. DOI: <http://dx.doi.org/10.15585/mmwr.su7201a10>

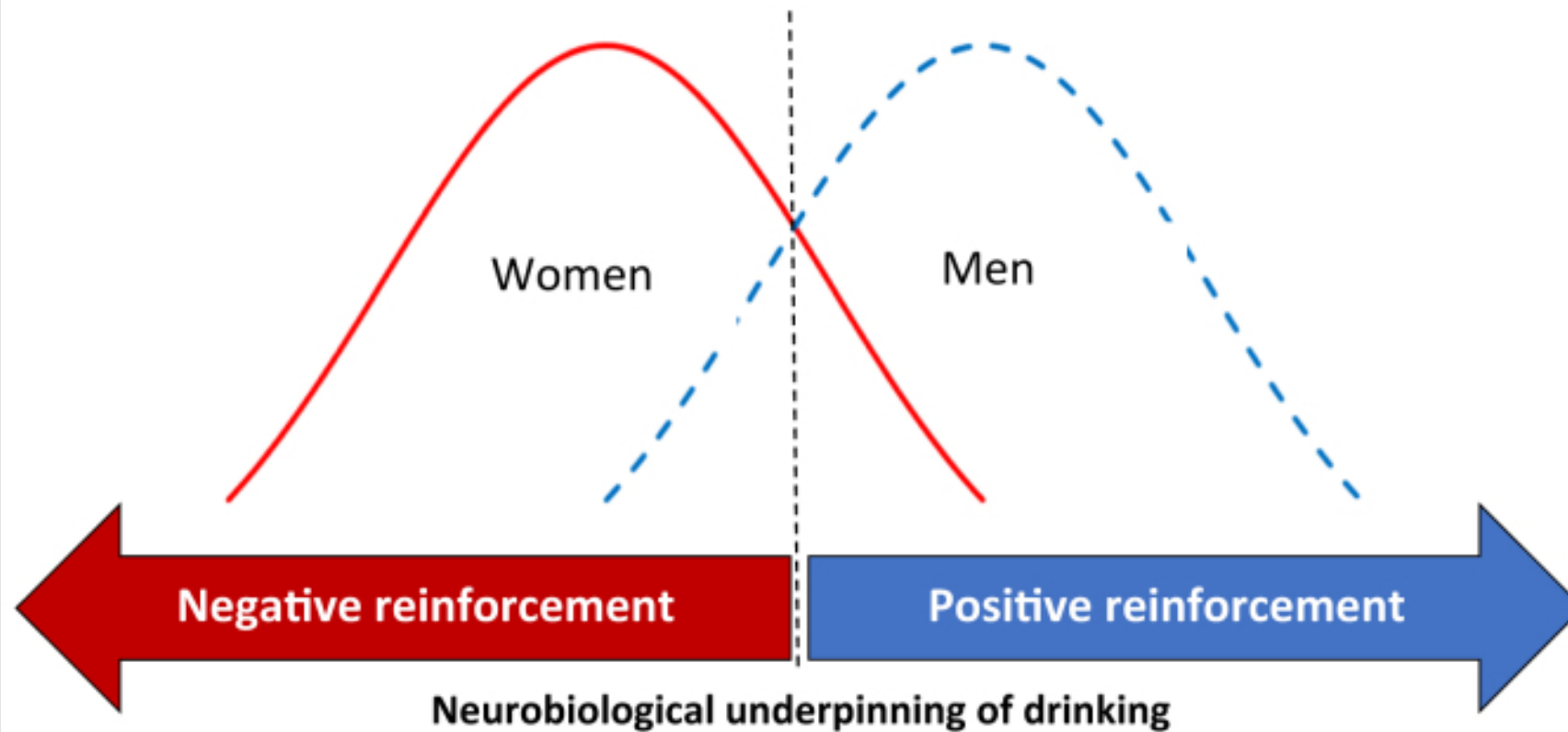
Gender differences and substance use disorder

- 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

Gender differences and substance use disorder

- Women are more likely to use prescription opioids ¹ and to drink² to self-medicate for anxiety or stress.
- Men are more likely to use prescription opioids for experimentation or to get high.² Men are more likely to drink to enhance positive emotions or conform to a group.³

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.

Mental illness and substance use disorder

- Men and women have different co-occurring mental illness with substance use disorder

Mental illness and substance use disorder

	No alcohol use disorder or substance use disorder	Alcohol use disorder only	Substance use disorder +/- alcohol use disorder
Past year depression-- males	5.7%	10.2%	21.4%
Past year depression-- females	11.9%	21.2%	35.9%
Past year antisocial personality d/o --males	4.5%	11.6%	22.0%
Past year antisocial personality d/o -- females	1.7%	5.8%	13.2%
Lifetime suicide attempt -- males	2.7%	5.5%	11.8%
Lifetime suicide attempt-- females	5.6%	11.1%	24.7%

Women have increased levels of mortality at lower levels of intake

- A 2023 systematic review and meta-analysis of 107 cohort studies involving more than 4.8 million participants found a significantly increased risk of all-cause mortality among female drinkers who drank 25 or more grams per day and among male drinkers who drank 45 or more grams per day.
- They also have a “telescoped” course and develop the effects more rapidly.

1. Zhao J, Stockwell T, Naimi T, Churchill S, Clay J, Sherk A. Association Between Daily Alcohol Intake and Risk of All-Cause Mortality: A Systematic Review and Meta-analyses. *JAMA Netw Open*. 2023;6(3):e236185.

doi:10.1001/jamanetworkopen.2023.6185

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



Men die at higher rates than women from alcohol

- Despite the higher risk for alcohol-related problems for women if they do drink, men still have much higher death rates from alcohol because they drink at higher rates
- A study from 2023 of alcohol-related deaths in the United states showed that the mortality burden was higher among male individuals than female individuals, with male individuals being 2.88 (95% CI, 2.86-2.89) times more likely to die compared with female individuals.

CDC guidelines for risky drinking



- 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.

CDC guidelines for risky drinking

- Excessive drinking (or risky drinking or at risk drinking) is defined as the following:
- Heavy drinking is defined as consuming
 - For women or men > 65, 8 or more drinks per week.
 - For men < 65, 15 or more drinks per week.



LGBTQ Persons and Substance Use

LGBTQ People have higher rates of SUD

- Data from the 2020 National Survey on Drug Use and Health (NSDUH) suggest sexual minority adults report increased consumption and substance use disorders compared to heterosexual adults.
 - (In this survey, sexual minority adults include individuals who describe themselves as lesbian, gay, or bisexual.)
- Sexual minority adults had roughly double the rate of marijuana use, misuse of opioids, and alcohol use disorder compared to heterosexual adults.

This rate is high for LGBTQ youths, especially if they are not accepted

- Youths experiencing “conversion therapy,” or physical harm due to their LGBTQ identity have higher rates of drug and alcohol use.¹
- Rates are higher for LGBTQ youth overall.²

<https://www.thetrevorproject.org/research-briefs/substance-use-and-suicide-risk-among-lgbtq-youth-jan-2022/> Accessed 11/12/2023

Hoots BE, Li J, Hertz MF, et al. Alcohol and Other Substance Use Before and During the COVID-19 Pandemic Among High School Students — Youth Risk Behavior Survey, United States, 2021. *MMWR Suppl* 2023;72(Suppl-1):84–92. DOI: <http://dx.doi.org/10.15585/mmwr.su7201a10>



Reasons for increased substance use and misuse among LGBTQ persons

- High levels of stress
- Lack of cultural competency and health care discrimination in the medical community
- Targeted marketing efforts by alcohol and tobacco companies
- Discrimination in employment
- Discrimination in housing

Sex Hormones and Substance Use Disorder

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

Testosterone and substance use

- Testosterone levels in men are suppressed by both alcohol¹ and opioids².

Gender differences in incarceration and substance use disorder

Incarceration and substance use disorder

- An estimated 65% percent of the United States prison population has an active SUD.
- Another 20% percent did not meet the official criteria for an SUD, but were under the influence of drugs or alcohol at the time of their crime.

Incarceration and substance use disorder

- Men with substance use disorder are much more likely to have a history of incarceration than women with substance use disorder. Both are more likely to have a history of incarceration than persons without substance use disorder.

Incarceration and substance use disorder

	No history of alcohol or substance use disorder	Alcohol use disorder without other substance use disorder	Any substance use disorder +/- alcohol use disorder
History of incarceration -- females	4.9%	13.9%	27.5%
History of incarceration -- males	15.5%	28.1%	45.5%



Rhee TG, Rosenheck RA. Gender Differences in Psychiatric and Behavioral Health Burden Among Adults With Alcohol and Other Substance Use Disorders in the United States. *J Addict Med.* 2022 May-Jun 01;16(3):295-302. doi: 10.1097/ADM.0000000000000890. PMID: 34310435.

Incarceration and gender differences

- 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.¹

1. <http://www.drugpolicy.org/resource/drug-war-mass-incarceration-and-race-englishspanish> Accessed 11/15/19

Sex work and substance use disorder

There is a significant correlation between sex work and substance use disorder

- A 2021 meta-analysis looked at 86 studies in 46 countries¹
 - Most studies reported lifetime drug use among female sex workers (32 studies from 20 countries), and pooled prevalence in this sub-group was 29% (95% CI 24–34%).
 - There was insufficient data for estimates for male and transgender sex workers.
- A 2008 cross-sectional, secondary data analysis of 1606 women and 3001 men entering substance use treatment in the United States found a high incidence of sex work among people entering treatment.²
 - 50.8% of women and 18.5% of men reported prostitution in their lifetime. 41.4% of women and 11.2% of men reported prostitution in the past year
 - Women who engaged in prostitution had far more episodes than the men did.

1. Iversen J, Long P, Lutnick A, et al. **Patterns and Epidemiology of Illicit Drug Use Among Sex Workers Globally: A Systematic Review.** 2021 Apr 29. In: Goldenberg SM, Morgan Thomas R, Forbes A, et al., editors. *Sex Work, Health, and Human Rights: Global Inequities, Challenges, and Opportunities for Action* [Internet]. Cham (CH): Springer; 2021. Chapter 6. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK585687/> doi: 10.1007/978-3-030-64171-9_6

2. Burnette ML, Lucas E, Ilgen M, Frayne SM, Mayo J, Weitlauf JC. **Prevalence and Health Correlates of Prostitution Among Patients Entering Treatment for Substance Use Disorders.** *Arch Gen Psychiatry.* 2008;65(3):337–344.

There is a significant correlation between sex work and substance use disorder

- It is often assumed that women who use drugs and participate in sex work began sex work to pay for drugs, but it is often the other way around, that they began using drugs to cope with the trauma of sex work.¹
 - A study in Chicago that interviewed 222 women doing sex work found that women on the streets, in drug houses, and in hotels reported high rates of forced sex and physical violence, with almost one-fourth of women in drug houses being raped more than 10 times.
- Sex workers who are sexually assaulted do not get good support from the medical system, the legal system, or family and friends.
 - It is often believed that they deserve sexual assault because of their work.
 - It is also commonly believed that they are not traumatized by sexual assault because of their work.

<https://www.caase.org/mental-health-impacts-of-sex-trade/> accessed 12/9/2023

Raphael J. and Shapiro D. Sisters speak out: the lives and needs of prostituted women in Chicago a research study Center for Impact Research. www.impactresearch.org August 2002

Natalie West with Tina Horn. We Too. Essays on Sex Work and Survival. Feminist Press. 2021

Relationship of violence to Substance Use Disorder

“Trauma is both a risk factor for and a consequence of substance use.”

Substance Abuse and Mental Health Services Administration. (2021). Addressing the Specific Needs of Women for Treatment of Substance Use Disorders. Advisory. Publication No. PEP20-06-04-002

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

Gender Differences in Treatment

Treatment Differences

- Women have been found to do better in treatment programs that reduce barriers to treatment or address women's needs.
 - Provision of childcare
 - Prenatal care
 - Treatment for co-occurring mental health problems
 - Comprehensive approach to treatment
 - Supplemental services that address women-focused topics
- Actual treatment for substance use disorder probably doesn't vary

Gender Differences in Treatment – Different Responses to Medication

- Male smokers have been found to respond better to nicotine replacement therapy than female smokers.
- Women may respond less favorably to bupropion for tobacco.
- Naltrexone was found to reduce the stimulating effects of alcohol in women but not men.

Take Home Messages:

- Genetic risk for substance use disorder is usually polygenic.
- Some of the genes that may affect risk include the genes affecting metabolism of alcohol to aldehyde to acetate, the genes affecting the receptor (CHRNA and CHRNA and OPRM1) and epigenetic changes

Take Home Messages:

- Women are less likely to use substances or have a substance use disorder, but when they do, the consequences are usually more severe.
- Be aware of the correlation between violence and substance use disorder.
- Recognize that women with SUD may have substantially different co-morbidities and social factors than men do, and address those. There may not be much difference in actual substance use disorder treatment.

Which of the following is true about genetics and substance use disorder?

- A. Some alleles of the ADH2 gene will cause flushing and nausea with alcohol ingestion. People who are homozygous for these alleles are protected against alcohol use disorder
- B. There has been one gene found that completely determines the likelihood of developing SUD
- C. Genetic factors influence whether people start using drugs, whereas environment influences how likely they are to continue.
- D. Epigenetic changes affect only the individual and are not passed down.

Which of the following is true regarding gender differences with respect to substance use disorder?

- A. Men are less likely to use illicit drugs than women are
- B. Women are more likely to use drugs to celebrate, whereas men are more likely to use to cope with physical or emotional pain
- C. Women will suffer adverse effects from their use of similar levels of alcohol much sooner than men will
- D. Women with substance use disorder are more likely to have a history of incarceration than men are



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