



ASAM REVIEW COURSE 2024

# Genetics and Gender: Impacts on Diagnosis and Care

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# Financial Disclosure

Leslie Hayes, MD

- No relevant disclosures

# LEARNING OBJECTIVE

**Describe** genetic and gender differences impacting the assessment and treatment of substance use disorder.

# Presentation Outline

Genetics and  
substance use  
disorder

Gender differences in  
substance use  
disorder

# 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 individuals differently

Epigenetics affects which genes are expressed

# Twin Studies

- Both the Swedish and Vietnam twin studies showed significantly higher concordance rates for substance use disorder in monozygotic twins than in dizygotic twins.<sup>1,2</sup>

<sup>1</sup>Gelernter et Kranzler. Chapter 2. Genetics of Addiction in Galanter et al. Textbook of Substance Abuse Treatment. The American Psychiatric Publishing 2015 pp. 26-45

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

# Genetics of substance use disorder

- SUD is likely polygenic. Multiple genes, each having a small effect contribute to risk of developing SUD.<sup>1</sup>
- Environment has stronger influence on initiation, whereas genetic factors are more important in progression and development of SUD.<sup>2</sup>

1. *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*

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



# Pharmacogenetics

- Pharmacogenetics can be further divided into two different categories:
  - Pharmacokinetics: how the body metabolizes the drug
  - Pharmacodynamics: how the drug affects the body

# Pharmacokinetics

- Metabolism of alcohol



# 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.<sup>1</sup>
  - More common in person of South Asian descent and those of Jewish ancestry.
  - Homozygotes nearly completely protected from alcohol use disorder.

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

# Pharmacokinetics

- Opioids are mainly metabolized by the cytochrome P450 (CYP450) or by UDP-glucuronosyl-transferase (UGT) in the liver.
- Some opioids are pro-drugs and need to be converted into an active metabolite to be active. (Codeine to morphine, oxycodone to oxymorphone, hydrocodone to hydromorphone, tramadol to P-desmethyl-tramadol)
- Other opioids are already active and will be converted to inactive metabolites. (morphine, methadone)

# Pharmacokinetics

- CYP2D6 is characterized by extreme variability.
  - 4 phenotype groups: ultra-rapid metabolizer (UM), normal metabolizer (NM), intermediate metabolizer (IM), and poor metabolizer (PM)
- UM can have severe or even lethal effects when treated with prodrugs, whereas poor metabolizers experience decreased analgesia after prodrug administration

# Pharmacogenetics of Medication Therapy of OUD

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



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

# Pharmacodynamics

- The mu-1 opioid receptor (OPRM1) gene 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.
  - Some studies have suggested it may be involved with response to morphine.

# 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.



# FDA Approves First Test to Help Identify Elevated Risk of Developing Opioid Use Disorder

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**FOR IMMEDIATE RELEASE**

**Dec. 19, 2023**

*The following is attributed to Jeff Shuren, M.D., J.D., director of the FDA's Center for Devices and Radiological Health*

Today, the U.S. Food and Drug Administration approved the first test that uses DNA in assessing whether certain individuals may have an elevated risk of developing opioid use disorder (OUD). As part of a clinical evaluation, the AutoGenomics, Inc. AvertD test is intended to be used prior to first exposure to oral opioid pain medications in patients being considered for a 4-30 day prescription for the treatment of acute pain, such as in patients scheduled to undergo a planned surgical procedure.

The AvertD test, a prescription-use only genetic laboratory test for patients 18 years and older, is to be used only with patients who consent to the test and have no prior use of oral opioid analgesics. The test is administered by a health care provider by swabbing the cheek of a patient to collect a DNA sample that will be used to determine if a patient has a combination of genetic variants that may be associated with an elevated risk of developing OUD. This information should be used as part of a complete clinical evaluation and risk assessment; it should not be used alone to make treatment decisions. The test is not intended to be used in patients being treated for chronic pain. AvertD may help patients who are concerned about being treated with an opioid for acute pain make better informed

# 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

- General differences
- Sex hormones and SUD
- Special health risks for women with alcohol
- LGBTQ community and alcohol
- Incarceration
- Sex work
- Violence
- Treatment

# Gender differences and substance use disorder

- Men are more likely than women to use almost all types of illicit drugs.<sup>1,2</sup>
  - Women use prescription drugs at greater rates than men and have higher rates of prescription drug use disorder.<sup>2</sup>
  - Otherwise, men have higher rates of drug use disorder.<sup>2</sup>
- Men have higher rates of alcohol use, including binge drinking, than women<sup>1,2</sup>, except for teens, where rates were similar until recently.
- Men are more likely to engage in riskier types of drug use that elevate mortality, including taking greater amounts of drugs, using more lethal drugs, and sourcing drugs from riskier sources and unvetted dealers.<sup>3</sup>

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. *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>

3. *J. Ho. Cycles of Gender Convergence and Divergence in Drug Overdose Mortality. Population And Development Review 46(3): 443–470 (September 2020)* 4

# Most recent study of teens showed higher rate of drug and alcohol use among girls

<b>Behavior/Substance – current use</b>	<b>Male 2019 (%)</b>	<b>Male 2021 (%)</b>	<b>Female 2019 (%)</b>	<b>Female 2021 (%)</b>
<b>Alcohol</b>	26.4	18.8	31.9	26.8
<b>Marijuana</b>	22.5	13.6	20.8	17.8
<b>Binge drinking</b>	12.7	9.0	14.6	12.2
<b>Prescription opioid misuse</b>	6.1	4.0	8.3	8.0

*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.<sup>1</sup>

<sup>1</sup> 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.<sup>1</sup> Men are more likely to use prescription opioids for experimentation or to get high.<sup>2</sup>
- 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.<sup>3</sup>

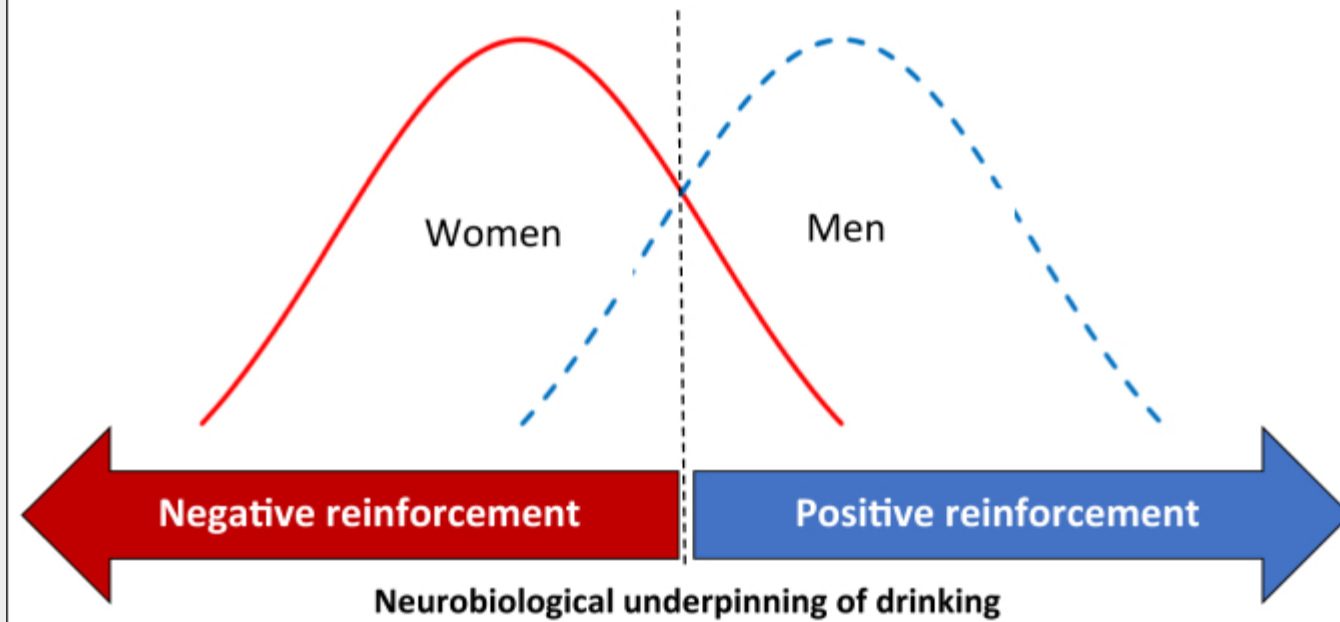
<sup>1</sup> *Final Report: Opioid Use, Misuse, and Overdose in Women.. Office on Women's Health. July 19, 2017*

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

<sup>3</sup> *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.

# Special health risks for women from alcohol



# Women and alcohol

- Women get drunker faster than men:
  - Decreased body weight<sup>1</sup>
  - Decreased alcohol dehydrogenase<sup>2</sup>
  - Decreased volume of water compartment distribution<sup>3</sup>

<sup>1</sup> Zweben. *Special Issues in Treatment: Women in Miller et al. The ASAM Principles of Addiction Medicine.* Wolters Kluwer 2019 p. 529

<sup>2</sup>*Ibid*

<sup>3</sup>*Ibid*

# Health risks for women with substance use disorder

- Women have “telescoped course” for alcohol use disorder.<sup>1</sup>
  - 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.<sup>2</sup>

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

<sup>2</sup> *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 drinking<sup>1</sup>

- 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, or men over 65, 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.<sup>2</sup>

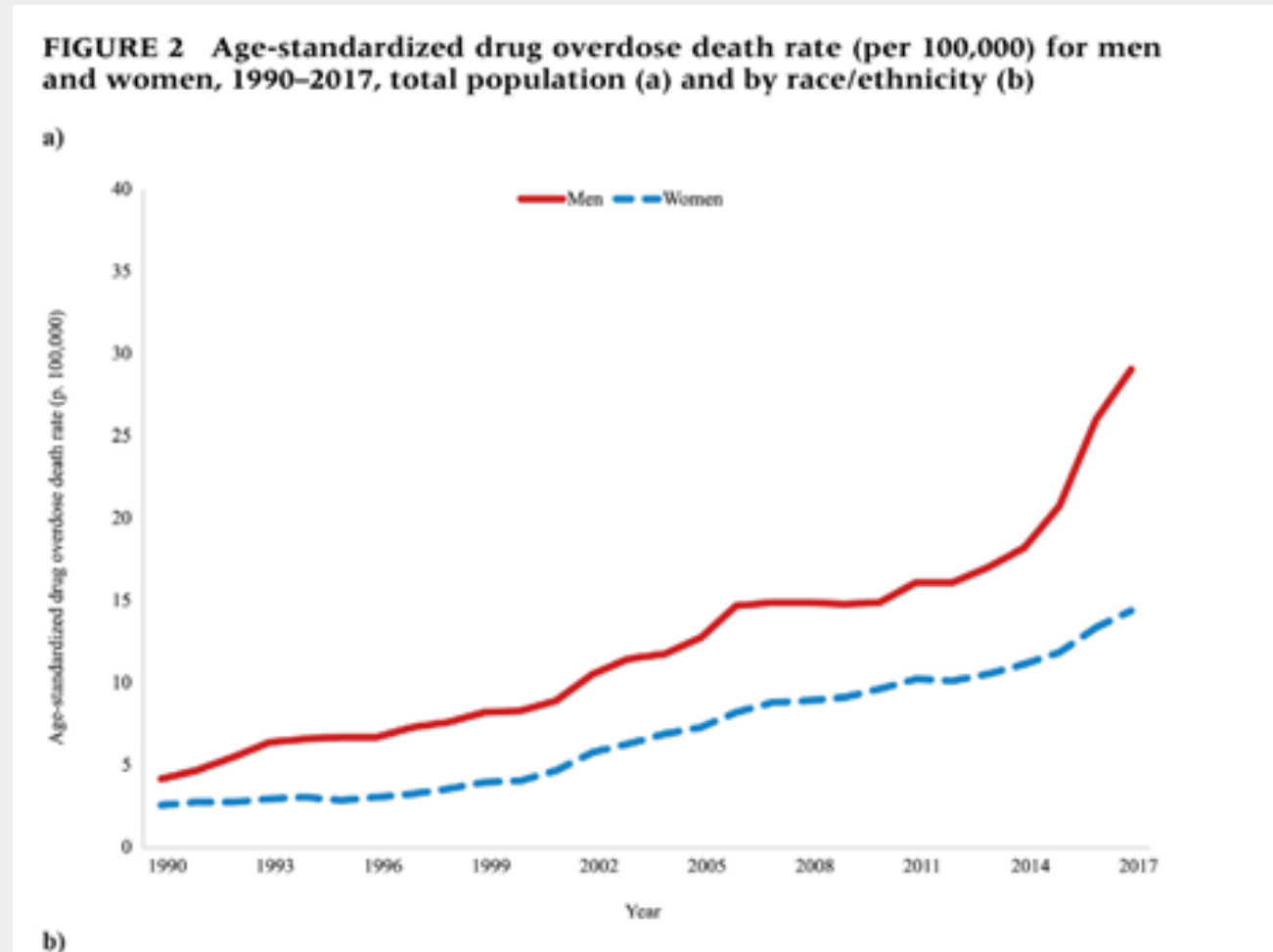
<sup>1</sup> <https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm> accessed 2/17/2021

<sup>2</sup>Lowik 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

# 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.

# Overdose death rate is higher in men



*J. Ho. Cycles of Gender Convergence and Divergence in Drug Overdose Mortality. Population And Development Review 46(3): 443–470 (September 2020) 4*

# 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.<sup>1</sup>
- Progesterone may protect against cigarette smoking and nicotine addiction, whereas estradiol may underlie enhanced vulnerability.<sup>2</sup>
  - When progesterone levels are high, nicotine self-administration is decreased.<sup>2</sup>

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

2. Wetherill RR, Franklin TR, Allen SS. Ovarian hormones, menstrual cycle phase, and smoking: a review with recommendations for future studies. *Curr Addict Rep*. 2016 Mar 1;3(1):1-8. doi: 10.1007/s40429-016-0093-z. Epub 2016 Feb 1. PMID: 27134810; PMCID: PMC4847745

# Testosterone and substance use

- Testosterone levels in men are suppressed by both alcohol<sup>1</sup> and opioids.<sup>2</sup>

<sup>1</sup> 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*

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

# 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.

# 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

# Gender Differences in Incarceration and Substance Use Disorder

# Incarceration and gender differences

- Men are far more likely than women to be incarcerated than women. 126/100,000 women were incarcerated in 2010 vs 1,352/100,000 men.<sup>1</sup>

# 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

- 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.
- Men with SUD were 2.61 times as likely to have a history of incarceration as women with SUD.

*Tsai, 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).*

# 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.<sup>1</sup>

# 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 countries 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%).<sup>1</sup>
  - 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 the incidence of sex work was 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<sup>2</sup>

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. doi:10.1001/archpsyc.65.3.337

# 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. Many began using drugs to cope with the trauma of sex work.<sup>1</sup>
- A study in Chicago that interviewed 222 women doing sex work found that almost one-fourth of women in drug houses being raped more than 10 times.<sup>2</sup>
- Sex workers who are sexually assaulted often do not get good support from the medical system, the legal system, or family and friends because of their sex work.<sup>3</sup>

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

2. 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](http://www.impactresearch.org) August 2002

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

# Violence and Substance Use Disorder



# Women, 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.<sup>1</sup>
- 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.

# Treatment Differences for SUD by Gender





# 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

# 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.

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

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- 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

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

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- 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. People who are ultra rapid metabolizers of methadone will get a better response to it.



# Get in Touch

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