



# **MEN ARE FROM SOMERSET, WOMEN ARE FROM ST GEORGES: GENDER/SEX DIFFERENCES IN ADDICTION**

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# DISCLOSURE

- No disclosures or conflicts

# AGENDA

- Gender differences in addiction, age as a moderator
- Gender differences – what we know from animal studies
- Gender Barriers and Strengths

# RESEARCH ON SEX DIFFERENCES

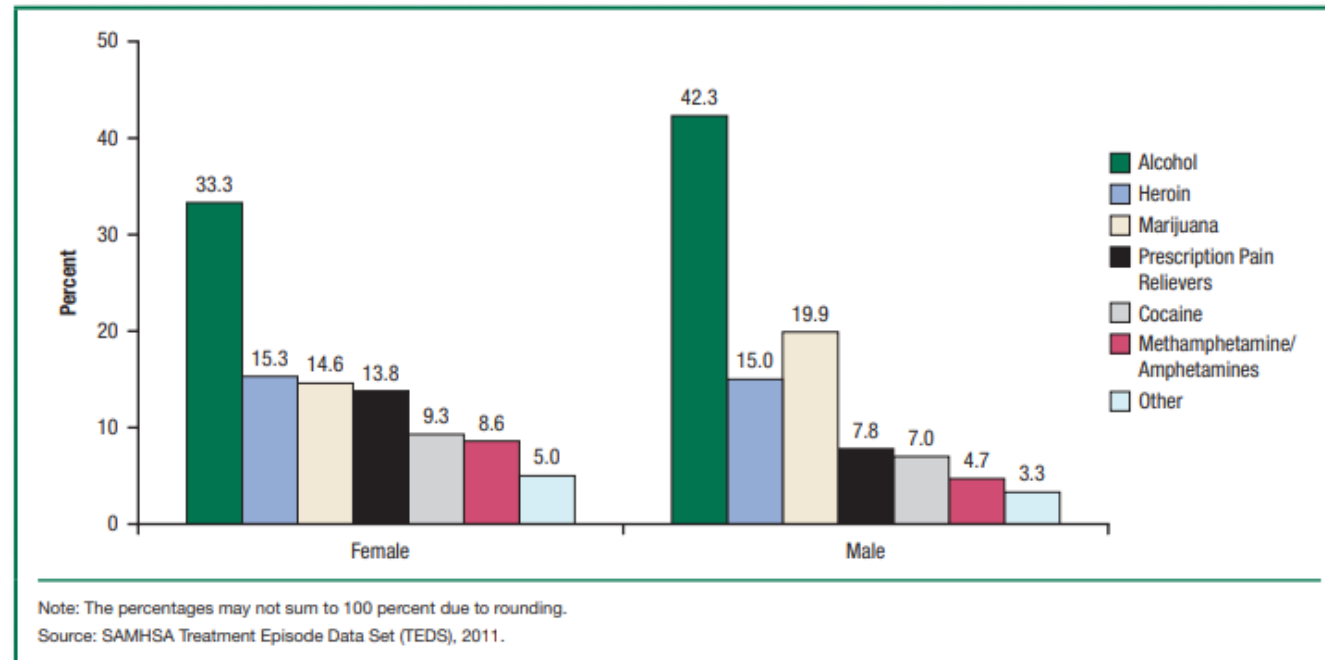
- Addiction research has historically neglected women
- Results generalized to women
- Sex differences in drug use
  - Vulnerability to drug use and to drug abuse
  - Progression from recreational drug use to dependence
  - Role of underlying brain mechanisms
  - Role of hormones

# GENDER AND AGE DIFFERENCES IN ADDICTION

- In general males more likely than females to report marijuana and alcohol use
- In general females more likely than males to report nonmedical use of prescription drugs
- BUT data vary further when we examine differences in age
  - Data from 2011 National Survey on Drug Use and Health show men 18 years and older have almost 2x rate of substance dependence as adult women (but the gap is narrowing!)
  - Youths aged 12-17, rate is the same for both genders (around 6.9%)
- The Treatment Episode Data Set (TEDS), from SAMHSA, USA
  - Collect data on admissions to substance abuse treatment facilities across the US

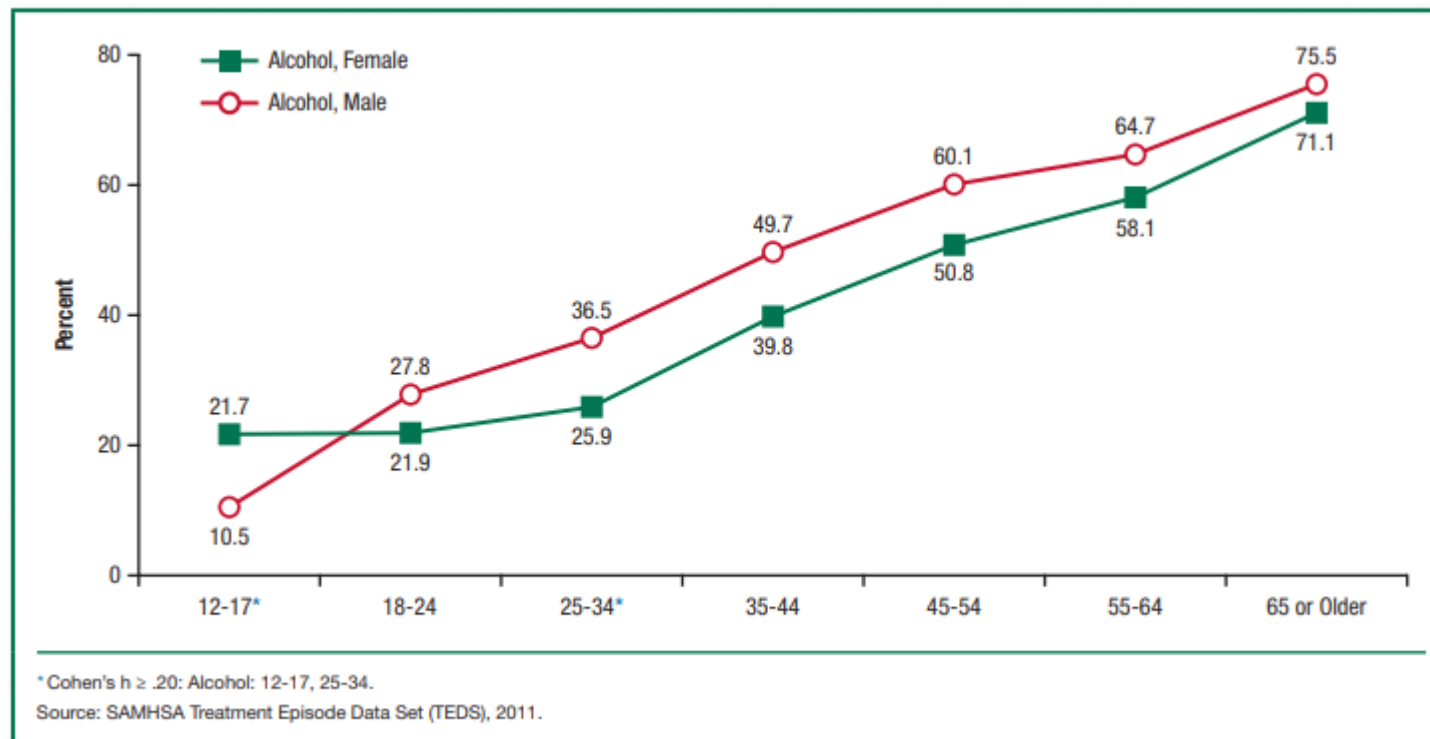
# TREATMENT ADMISSION BY SEX AND DRUG TYPE

Figure 1. Substance Abuse Treatment Admissions Aged 12 or Older, by Gender and Primary Substance of Abuse: 2011



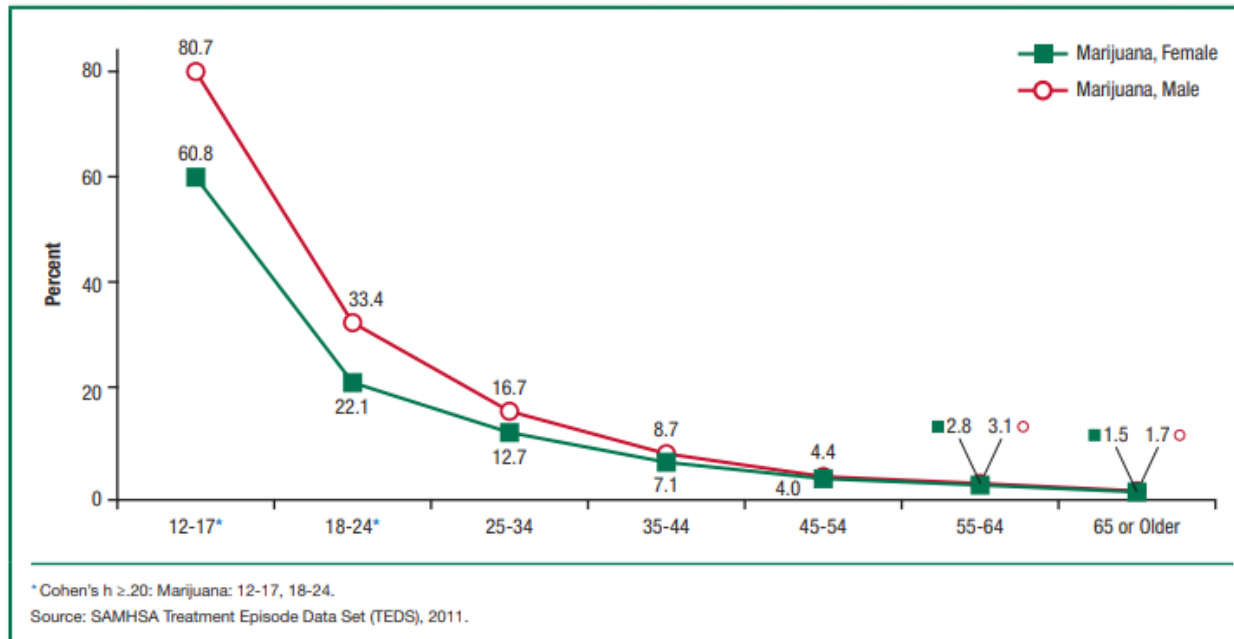
# ALCOHOL BY SEX AND AGE

Figure 2. Alcohol as the Primary Substance of Abuse among Substance Abuse Treatment Admissions Aged 12 or Older, by Gender and Age: 2011



# MARIJUANA BY SEX AND AGE

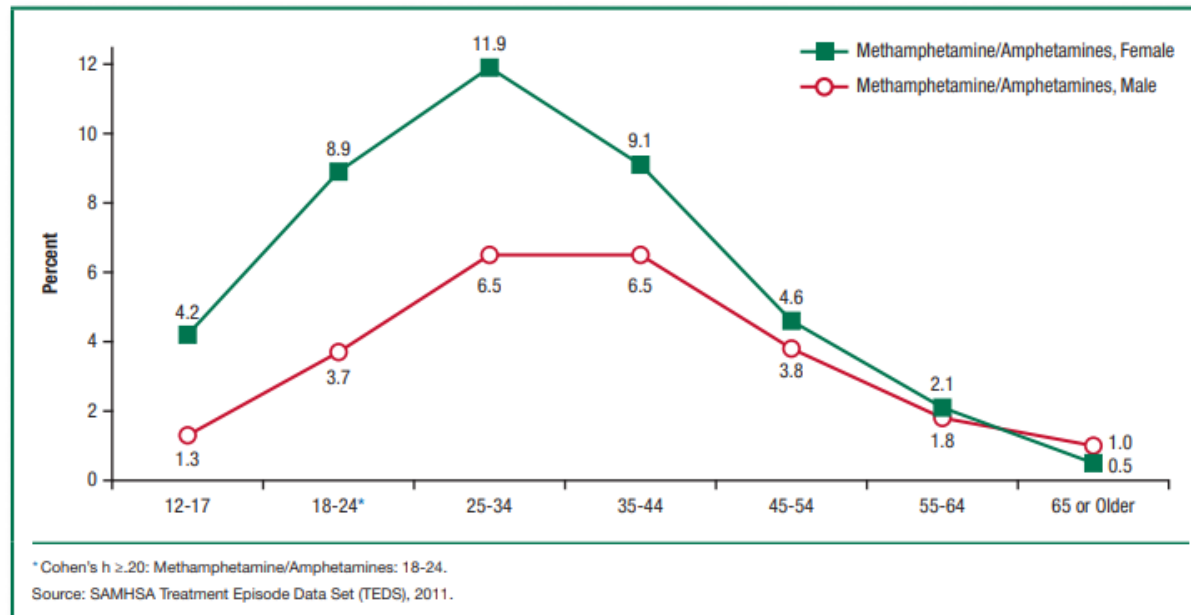
Figure 3. Marijuana as the Primary Substance of Abuse among Substance Abuse Treatment Admissions Aged 12 or Older, by Gender and Age: 2011





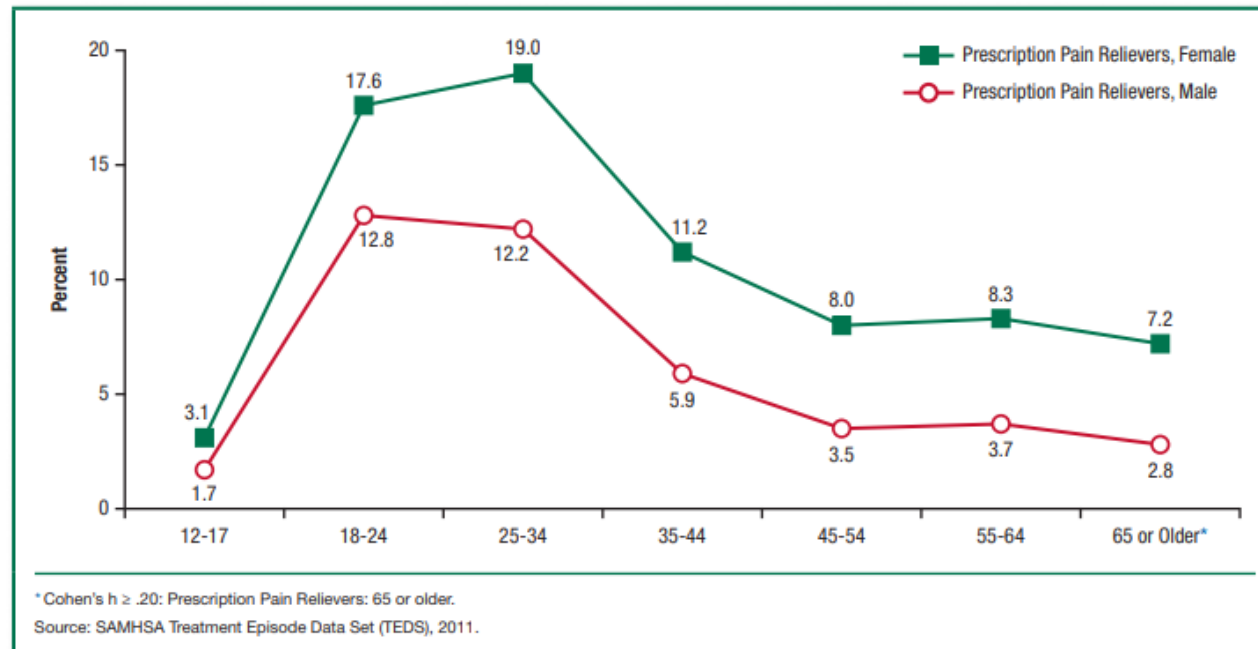
# METHAMPHETAMINE / AMPHETAMINES BY SEX AND AGE

Figure 4. Methamphetamine/Amphetamines as the Primary Substance of Abuse among Substance Abuse Treatment Admissions Aged 12 or Older, by Gender and Age: 2011



# PRESCRIPTION PAIN RELIEVERS BY SEX AND AGE

Figure 5. Prescription Pain Relievers as the Primary Substance of Abuse among Substance Abuse Treatment Admissions Aged 12 or Older, by Gender and Age: 2011



# ANIMAL STUDIES

- Animal models are helpful as they allow for exploration without human ethical considerations
  - Both oral and intravenous self-administration paradigms to examine the phases of the addiction cycle
  - Self-administration: animals given opportunity to perform an action (lever press, nose to hole) to receive a contingent drug administration. (Addiction)
  - This allows for ethical research of the 'acquisition phase.'
  - Removals and pharmacological intervention can be useful in examining involvement of brain processes in addiction.
  - Also allows for examination of the role of estrous cycle-dependent effects

# PHASES OF ADDICTION – OPERANT CONDITIONING

## Phases of Addiction: Context Reinstatement

### 1. Acquisition



Context A



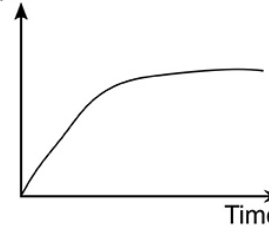
Cue

+



Alcohol

Responses



### 2. Extinction



Context B

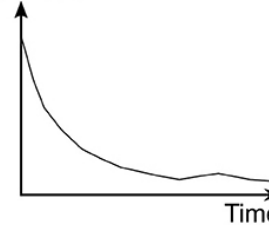


Cue



No alcohol

Responses



### 3. Reinstatement



Context A

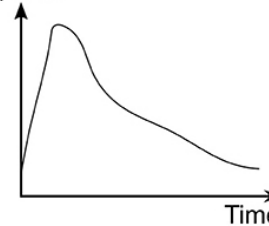


Cue



No alcohol

Responses



# ANIMAL STUDIES



# SEX DIFFERENCES IN RATS, META-ANALYSIS

**Table 1. Sex differences in female and male laboratory animals in drug self-administration, and influence of the estrous cycle on drug intake.**

Drug	Female versus male	Estrogen- and/or estrous cycle-dependent effects
Nicotine	F > M [14-16]	No significant effects [14]
Alcohol	F > M [17-19]    F < M [20]	No significant effects [21,22]
Cocaine	F > M [5,7,25]    F = M [26]	No significant effects [26] Significant positive effects [27-29,31,32] Significant negative effects [30]
Amphetamine	F > M [5,34]	Significant positive effects [35]
Opioids	F ≥ M [40]	Discordant data [41]
Cannabinoids	F > M [47]	Significant positive effects [47]
Caffeine	F > M [54]	Not known
Phencyclidine	F > M [56]	Not known

F: Female; M: Male.

- For self-administration, female rats **more** responsive during all phases of the addiction cycle
  1. Acquisition of drug self-administration
  2. Escalation of drug intake
  3. Reinstatement of extinguished drug-seeking behavior
- Compelling evidence for a key role of the estrous cycle
- Estrogen administration post ovariectomy associated with increasing and dampening operant behavior in female rats

# OTHER DATA FROM ANIMAL STUDIES

- Licit drugs (nicotine & alcohol)
  - Female rats acquire nicotine self-administration behavior more rapidly than males
  - Females show shorter latency to the first drug infusion and work more for the drug than males
  - Adolescent female rats consume more nicotine than adolescent male rats suggesting that they may be more sensitive to the effects of nicotine
  - Cue reactivity differences: females show more responsivity to cues
  - Female animals in general show more alcohol consumption than males (worse in adolescents, rats and velvet monkeys)
  - Females also maintain alcohol drinking over longer periods of time BUT males consume higher alcohol concentrations and reach higher blood alcohol levels than females.
    - In humans, males consume more alcohol than females
    - Implications for the role of the mediating factors of social, genetic, hormonal, environmental factors

## OTHER DATA FROM ANIMAL STUDIES

- Illicit drugs: cocaine, amphetamine & opioids
  - Female rats acquire cocaine self-administration more than male rats with fixed ratio schedules (same # lever presses for drug)
  - Female rats show reduction in levels of responding for cocaine with progressive-ratio schedules (increasing # lever presses for drugs)
  - Female rats and mice show greater reinstatement of extinguished cocaine-reinforced responses than males
  - Rats given estradiol showed enhanced acquisition of cocaine self-administration behaviors (in rats with ovariectomy).
  - For opioids, female rats acquire self-administration much faster than males, and self-administer more heroin and morphine.
  - In rats with ovariectomy given estradiol, faster acquisition of heroin admin behavior, no differences in self-administration.



# OTHER DATA FROM ANIMAL STUDIES

- Cannabis
  - Sometimes difficult to demonstrate in animal models of addiction (due to addictive properties)
  - Voluntary cannabinoid intake and cannabinoid-seeking behavior following period of drug withdrawal seen in both rodents and squirrel monkeys
  - Female rats appear to be more sensitive to the rewarding effects of cannabinoids than males (faster acquisition and greater drug seeking behaviors), differs with estruses
  - Highlights the importance of estrogens in the perception of the motivating and rewarding value of cannabinoids
- Exposure to THC during gestation
  - Adult female rats born from mothers treated with THC during gestation and lactation showed significant increase in acquisition rate of morphine self-administration compared to females born to placebo-exposed mothers. (impact not seen in THC treated fathers)
  - Endocannabinoid system known to strictly interact with the endogenous opioid system in the reciprocal modulation of reinforcing / addictive effects.

# SEX DIFFERENCES IN ADDICTION AND HEALTH CONSEQUENCES

- Important difference in pharmacokinetics and pharmacodynamics between men and women
  - Established modulatory role of estradiol in decision making and its interplay with dopamine in modulating rewards, motivation, and cognitive processes
  - Using the same amount of alcohol as men, women have higher alcohol blood concentrations and increased health risks
  - Morphine has both slower onset and offset at opioid-receptors in women, therefore usually require higher doses to achieve and maintain a high
  - Nicotine metabolism is faster in women (and even faster if taking oral contraceptives) leading to heavier use
  - Men and women react differently to environmental triggers for relapse of drug taking
    - Potenza et al., reported sex differences in neural correlates of cocaine-induced craving
    - Corticostriatal-limbic hyperactivity was linked to stress cues in woman but to drug cues in men
    - Similarly, women are less sensitive to the reinforcing effects of nicotine but more sensitive to social cues

# SEX DIFFERENCES IN ADDICTION AND TREATMENT

- Treatment accessibility
  - Addiction stigma is an important barrier to access to treatment
  - For women with substance use disorders, they suffer more negative attitudes than men, receive more denigrating comments and experience more perceived stigma
  - Women tend to search less for treatment than men and face more factors that limit their access (childcare, pregnancy, risk of losing custody of children, partner violence, resistance from family members, greater exposure to physical and sexual abuse, psychiatric comorbidity)
- Treatment response
  - Women less likely to receive specialized treatment
  - Generally perform better in treatment, women take longer to relapse in heavy drinking but not in other drugs
  - Women relapse due to negative emotional state, men because of social pressure to drink

# GENDER BARRIERS AND STRENGTHS

## ➤ Barriers associated with recovery weaknesses

Men	Women
Justice related	Psychological health / dual diagnosis
	Domestic violence

## ➤ Predictors positively associated with increased growth in recovery strengths

Men	Women
Prosocial activities (further education)	Prosocial activities (further education)
Steady employment / volunteering	Daily life administration
	Better general health management

# SUMMARY

	<b><u>Acquisition</u></b> (Initial exposure to drug)	<b><u>Escalation</u></b> (increase in amount and frequency of use)	<b><u>Maintenance</u></b> (Addictive behavior is established and stable)	<b><u>Withdrawal</u></b> (symptoms when unable to get high)	<b><u>Relapse</u></b> (reestablishment of drug use behaviors)
<b>Women</b>	Women may experience more pleasurable response. Related to stressors or MH	More rapid in women than in men	Women stabilize at high dose of drug than males. Side effects of drug use are greater than for men	Females generally report more negative affect on withdrawal and experience a greater stress response	Women more likely to relapse than men and relapse more sporadically. Relapse associated with stressors and MH variants
<b>Men</b>	May take drug to engage in risky behavior or under social pressure	Slower escalation in men than in women	Males stabilize at a lower dose than females	Men exhibit greater physical symptoms of withdrawal than women	Men have longer period of abstinence than women. Relapse associated with social pressures

Adapted from Becker et al. (2017)

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## THANK YOU

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