The Substance Use Disorders in Women

Grace Chang, MD, MPH

Professor and Chair, Harvard VA Boston Psychiatry

September 2020

Disclosures

- FDA approved medications and applications
- Up to Date royalties

Participant Poll Question

Which of the following best describe the nature of the substance use disorders?

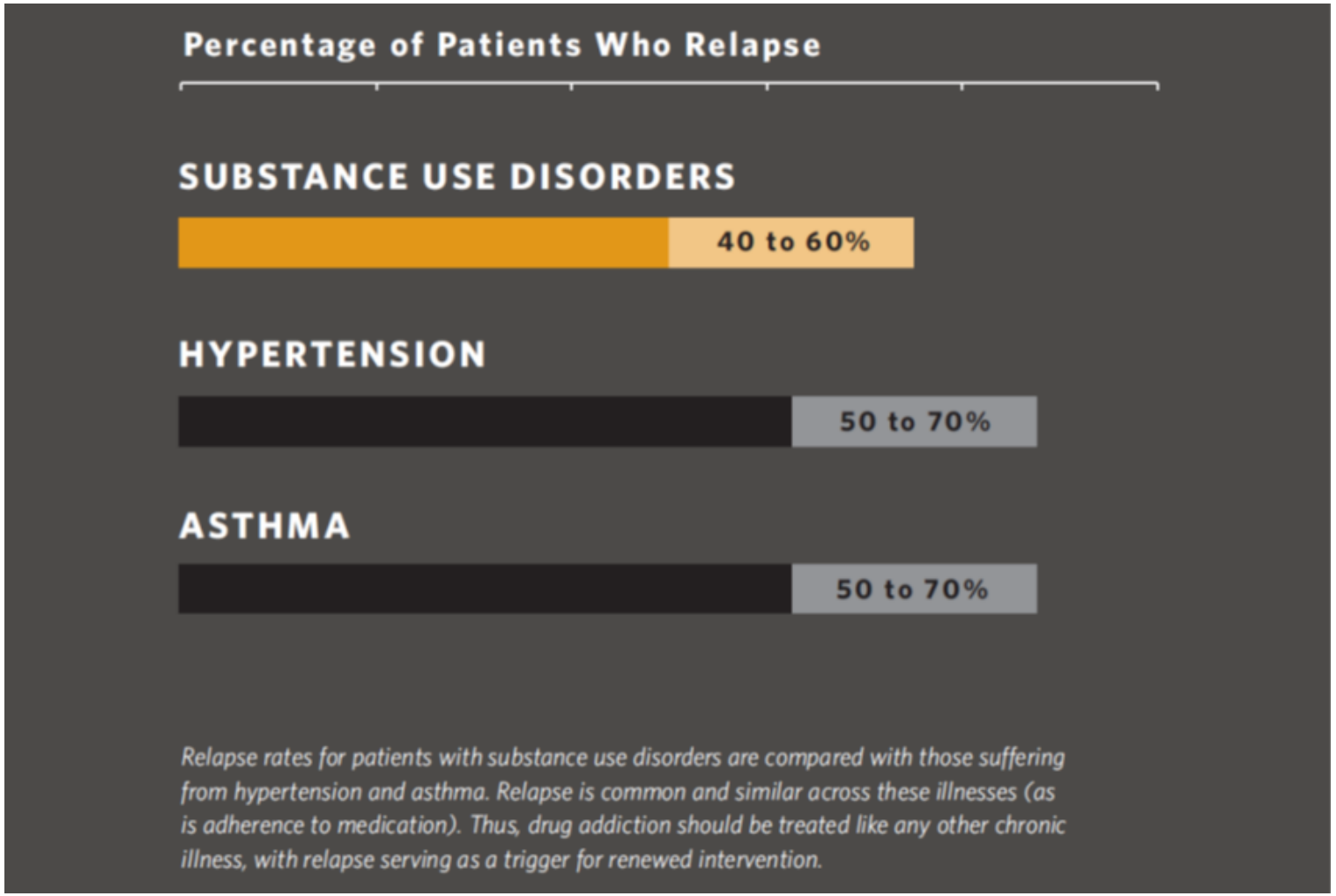
a. They are best treated with acute strategies such as detoxification only
b. There are effective medications for nicotine, alcohol, and cocaine dependence
c. Treatment outcomes are comparable to those for other chronic medical diseases
d. Men and women have similar rates of SUD treatment

The Substance Use Disorders

- Chronic diseases
  - Usually treated with acute strategies
    - Detoxification
  - Compared to Type 2 Diabetes, Hypertension, and Asthma
    - Genetic heritability
    - Personal choice
    - Environmental factors

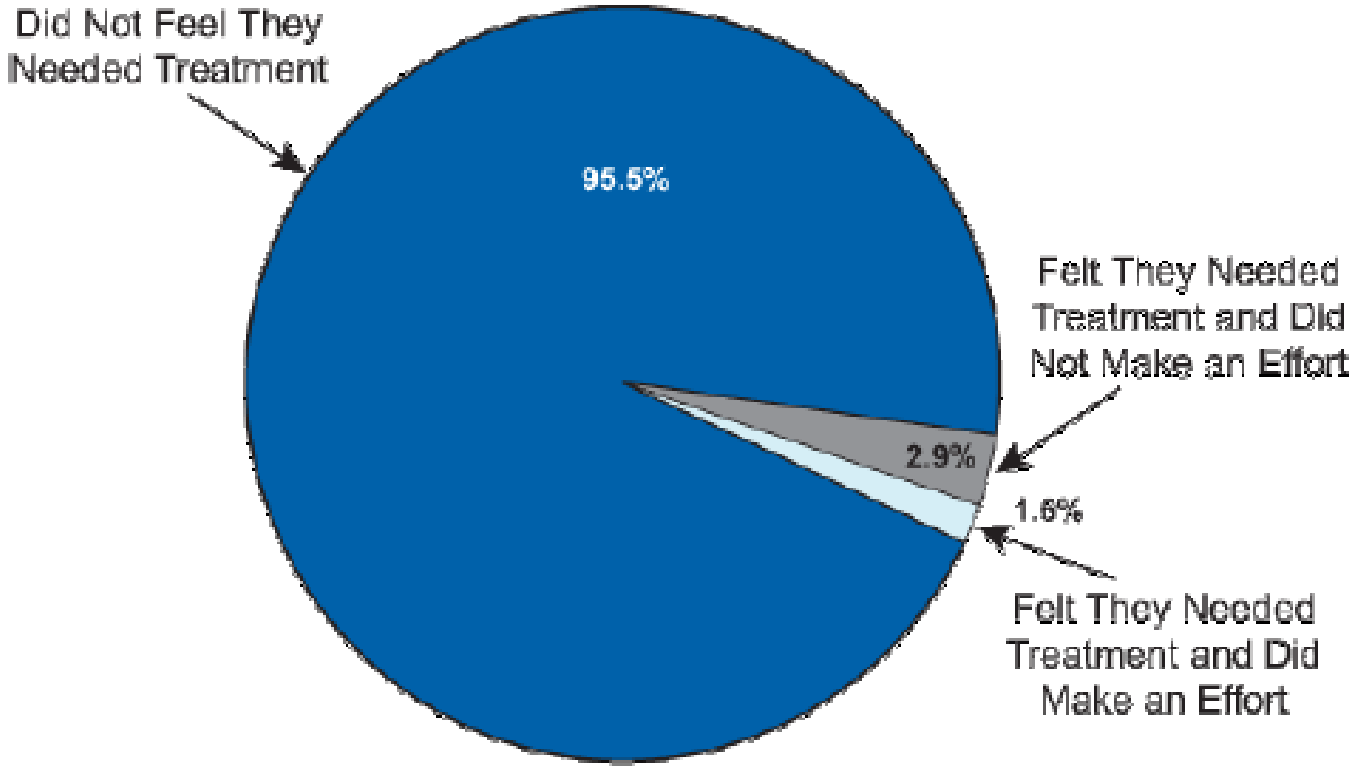
Chronic Disease Model

- Significant and lasting changes in brain chemistry and function
- Effective medications for nicotine, alcohol, and opiate dependence
- Comparison to other diseases
  - Type 1 Diabetes, < 60% adherent
  - Asthma & Hypertension, <40% adherent
  - <30% adherent to dietary, lifestyle, and behavioral changes



The SUDs versus Other Chronic Diseases

Substance Use Treatment is Infrequent



20.2 Million Needing But Not Receiving Treatment for Illicit Drug or Alcohol Use

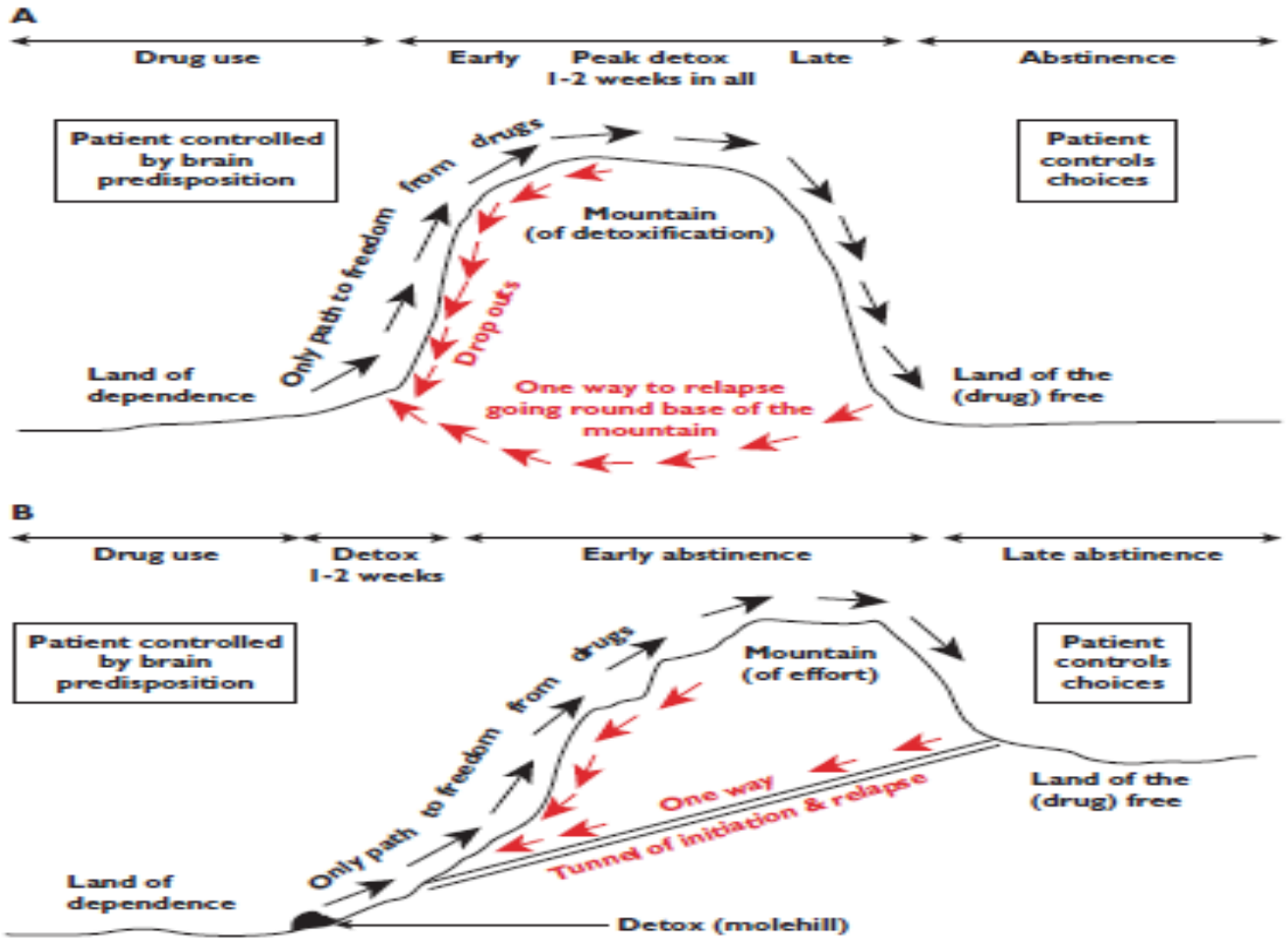


Figure 1

Perception is an issue. Patients, their families and staff frequently have a belief that detoxification is the key issue, whereas in fact this is a small part of the much longer road to abstinence. The figure is in two parts, subheading for each: (A) The fantasy: How patients (and staff) perceive progress in addiction treatment. (B) The reality: The road to abstinence

Women experience more barriers to Substance Use Treatment

- Examples of barriers
  - Low perception of need for treatment
  - Guilt and shame
  - Co-occurring disorders
  - Employment, economic, and insurance disparities
  - Childcare responsibilities
  - Fear of child protective services

Corey Foster, 34, retired as an Army sergeant. “Standing in line at the registration desk, I was getting comments from the male patients behind me, looking me up and down,” she said, describing a visit to her local Veterans Affairs medical center. “It was a major source of discomfort.” Erin Schaff/The New York Times

Consequences of Treatment Barriers

Less likely to access treatment

- Greater problem severity at admission
- More complex psychological, social and service needs

Surmounting the barriers

- Women only programs
- On-site childcare and/or prenatal care
- On-site psychological care
- Supplemental social services

Prevalence of the Substance Use Disorders among Women

CDC, Health, United States 2018

Some definitions

Any illicit drug use

- Marijuana, cocaine, heroin, hallucinogens, non-medical use of prescriptions

Non-prescription use of medications

- Greater amounts, more often, longer than prescribed

Binge drinking

- For men, 5 or more drinks on the same occasion
- For women, 4 or more drinks on the same occasion

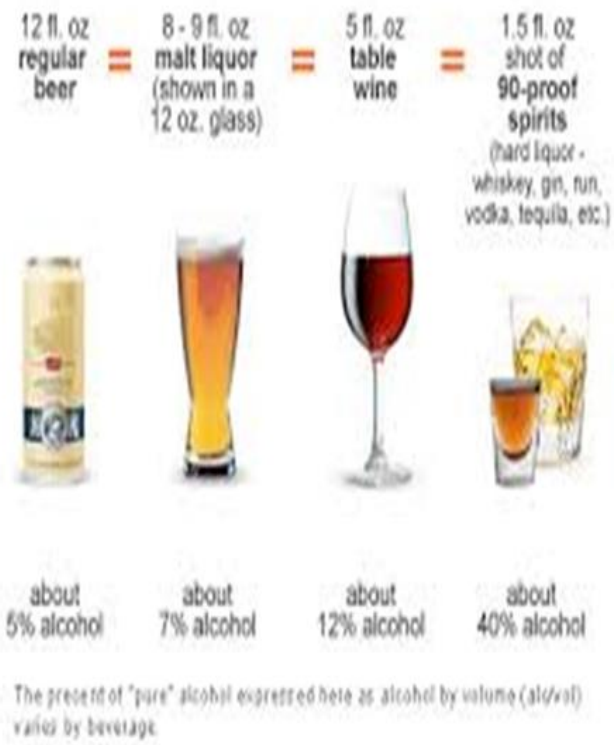
Heavy drinking

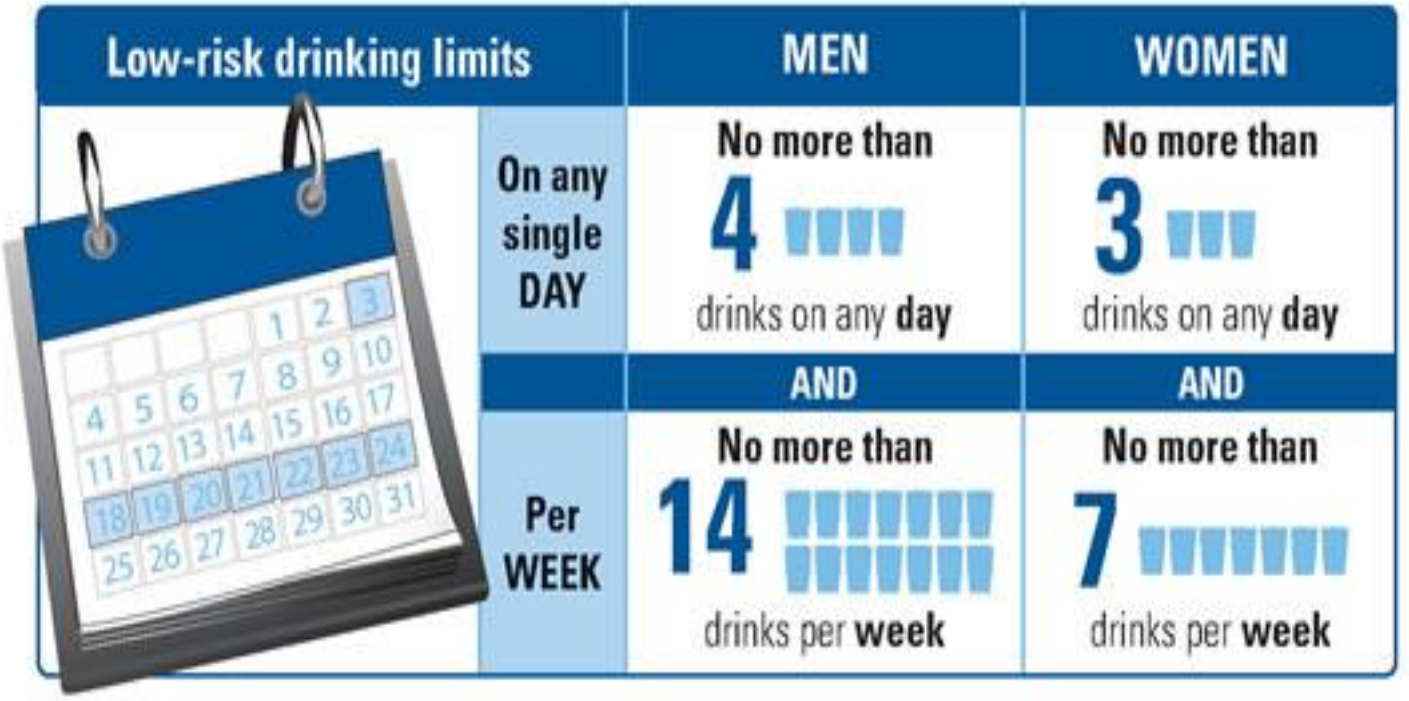
- Binge drinking on 5 or more days per month

Past month use

	Male	Female
Any Illicit Drug	13.7%	8.8%
Marijuana	11.9%	7.3%
Non-medical use of prescriptions	2.5%	1.9%
Alcohol use	55.5%	48.1%
Binge alcohol use	28.8%	20.4%
Heavy alcohol use	8.3%	4.1%

Sensible drinking limits for adults





The Opioid Crisis

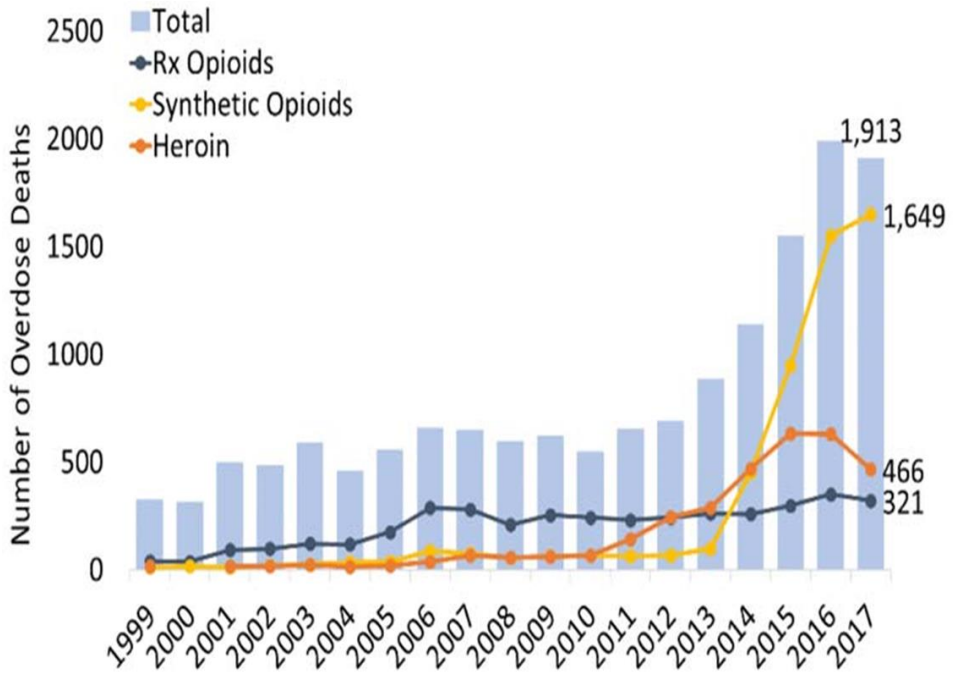
The opioid epidemic has affected everyone from birth to death

Opioid Related Births

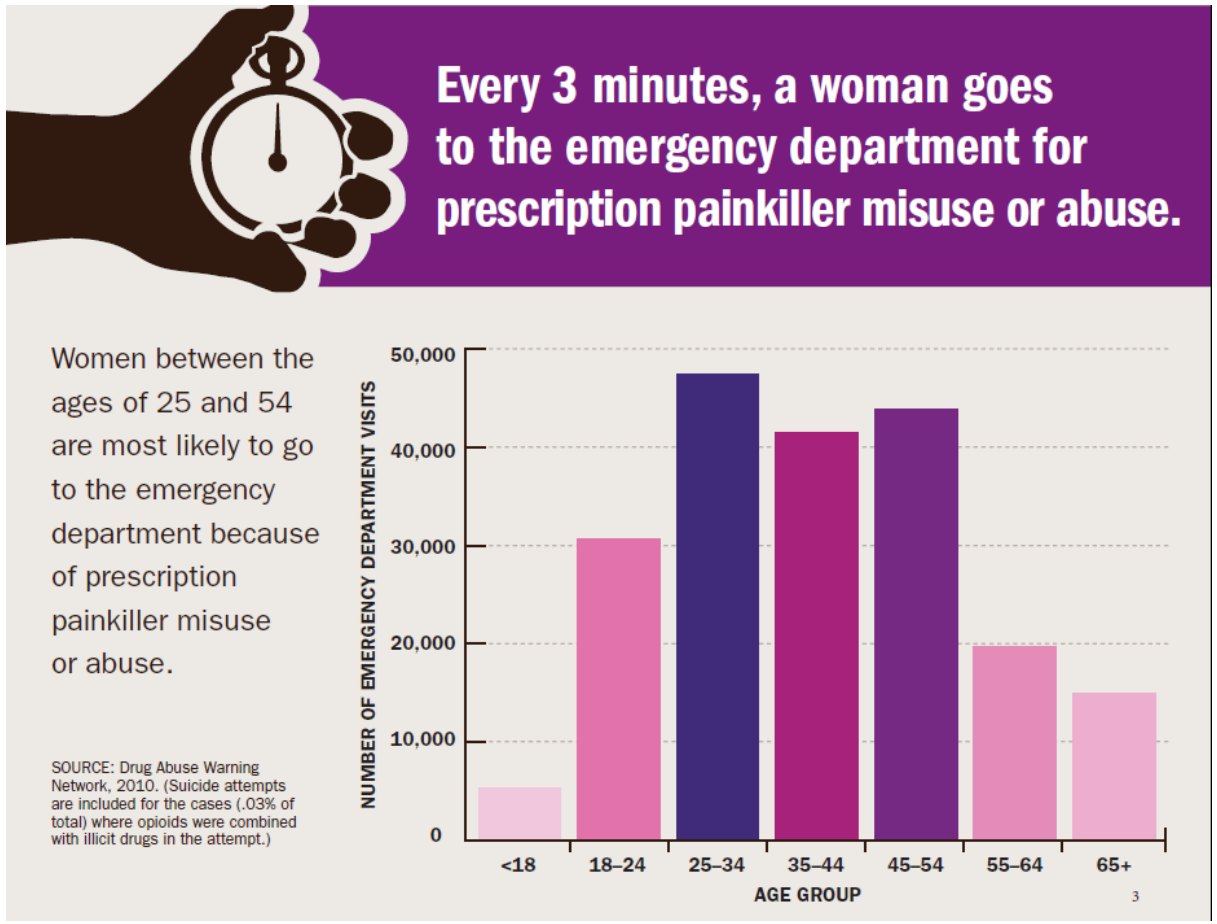
- Neonatal abstinence syndrome/Neonatal opioid withdrawal syndrome may occur when a when a woman uses opioids while pregnant
- Fivefold increase in the incidence between 2004 and 2014
  - 1.5 to 8.0 cases per 1,000 hospital births
- In other words, there is one baby born with NAS/NOWS every 15 minutes in the US
- In Massachusetts, the rate was 14.5 cases per 1,000 births

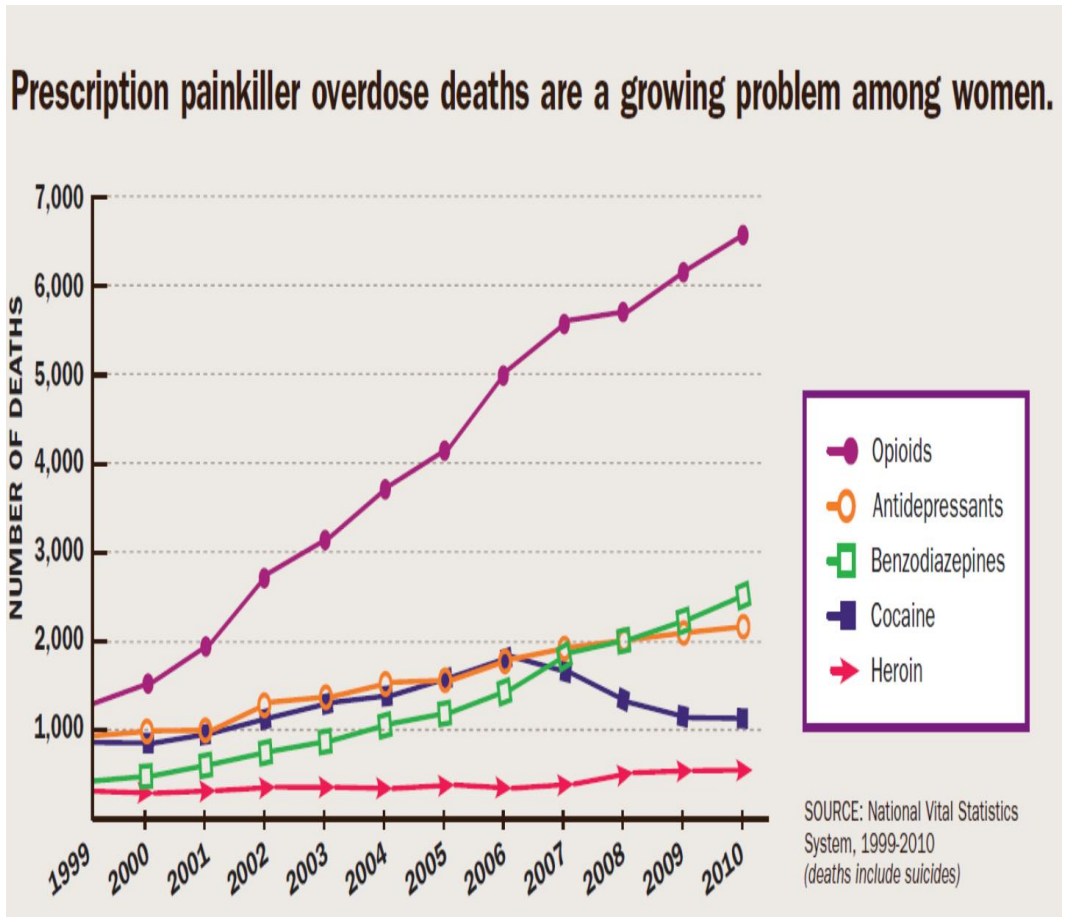
Opioid-Related Deaths

- The national death rate was 14.6 deaths per 100,00 in 2017
- Synthetic opioids are associated with the greatest increases in deaths



Prescription painkillers adversely affect women disproportionately





Women and the Substance Use Disorders

- Unique issues based on sex and gender
- Different patterns of use
  - Smaller amounts for less time, but greater problem severity
- Different responses to substances
  - Sex hormones
  - Increased physical consequences
- Co-morbid psychiatric conditions
  - Panic attacks, depression
- Childbearing potential
- Treatment barriers

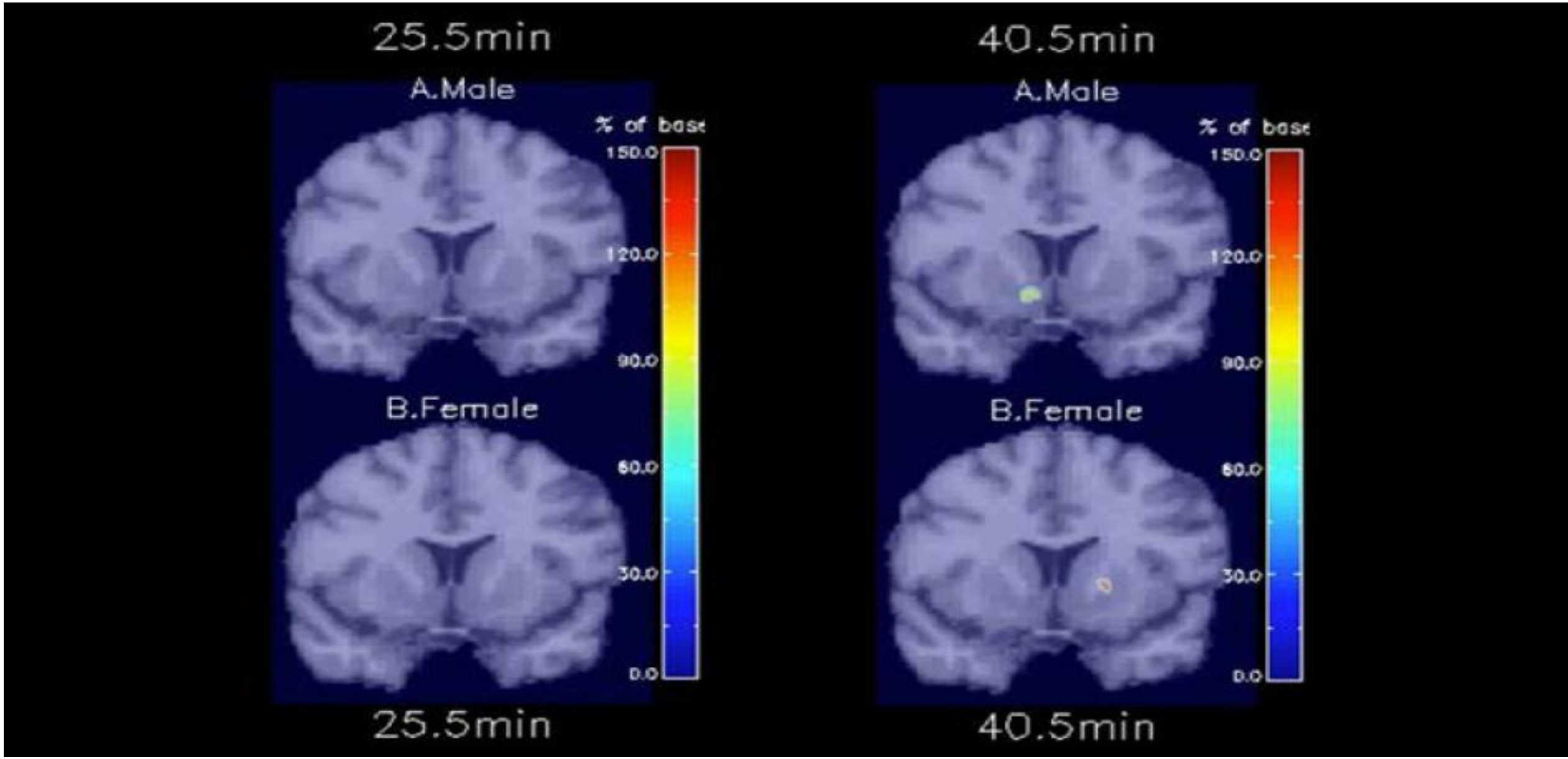
Sex and Gender Differences—the Smoking Example

Sex Differences

- Women have a harder time quitting
- Women metabolize nicotine faster than men
  - Men are more sensitive to nicotine's pharmacologic effects
  - NRT works better in men
  - Tobacco smoking induced upregulation of the B2-nicotinic acetylcholine receptors appear to be distinctly different in men and women, female sex hormones most likely play a role

Gender Differences

- Women may be more susceptible to non-nicotine factors
  - Sensory and social stimuli


25.5min
A.Male
% of base
150.0
120.0
90.0
B.Female
60.0
30.0
0.0
25.5min
40.5min
A.Male
% of base
150.0
120.0
90.0
B.Female
60.0
30.0
0.0
40.5min

Women and Alcohol

Alcohol has a greater impact on the US than opioids

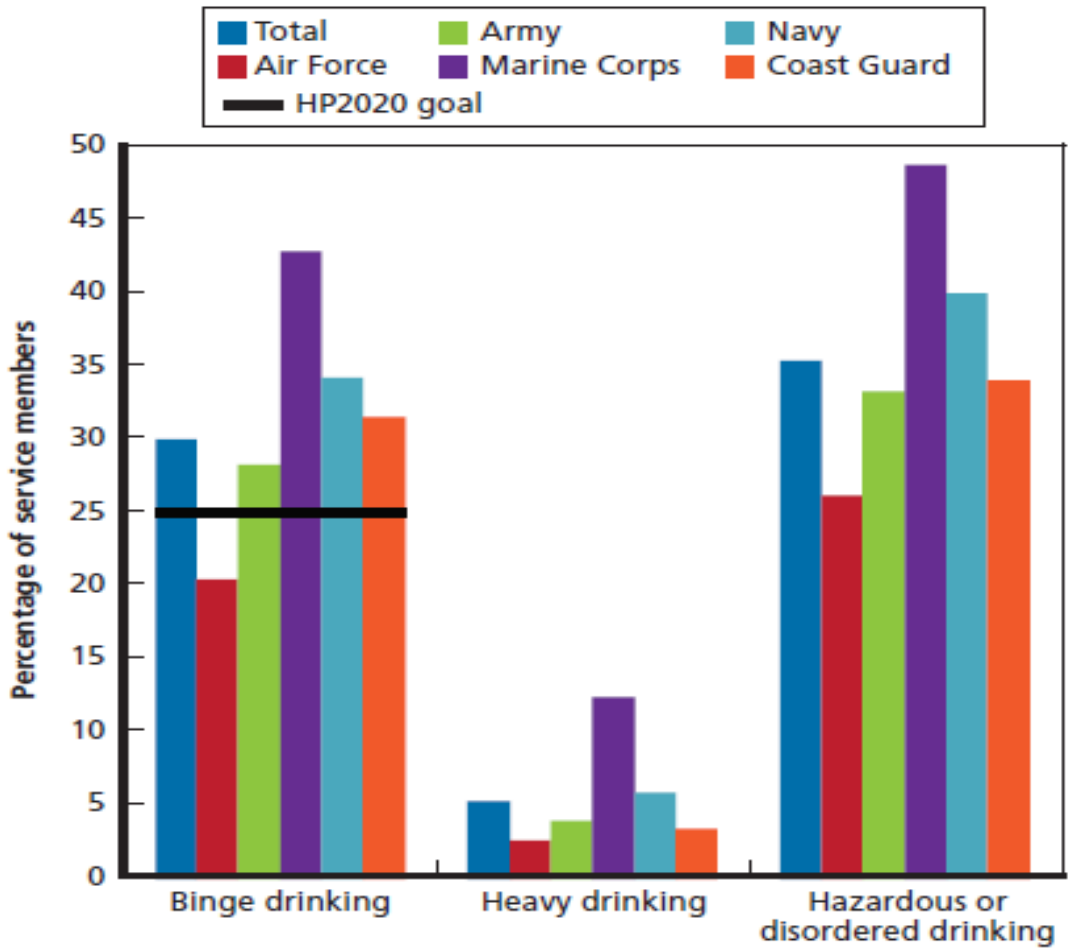
- 93,000 deaths each year
- 1 in 10 deaths among working adults
- Binge drinking
  - Accounts for 75% of the costs to America
  - Responsible for 50% of the deaths
- In 2010, excessive alcohol use cost the US $ 249 billion dollars
  - $2.05 per drink
  - $2 of every $5 is paid by the public
- *Women are the fastest growing segment of alcohol consumers in the United States*

US Active Duty Service Members

Binge, heavy, and hazardous drinking

- Varied by service and pay grade
- Higher among men than women

Figure 1
Alcohol Use, by Service Branch



Millennium Cohort Study

Among women military Service members	32% reported binge drinking 8% reported heavy weekly drinking 7% reported alcohol related problems
Among women in the US Army	15% engaged in binge drinking 9% engaged in unsafe drinking

Pooled National Survey on Drug Use and Health (NSDUH) Data Women Veterans, 2007-2012

- Alcohol use
  - 19% had past month heavy episodic drinking
  - 43% had past month heavy episodic drinking if aged 18-25
  - 5% met criteria for Alcohol Use Disorder (AUD)
  - 12% met criteria for AUD if aged 18-25
- Other drug use
  - 10% used illicit drugs in the past year
  - 7% used cannabis
  - 4% misused pain killers and 5% misused prescription prescriptions
- More common among younger women Veterans
- Rates are lower than among civilian women

Women and Alcohol: the Sex Differences

Alcohol metabolism

- Women who drink excessively develop more medical problems compared to men
- Biological [sex-related] factors
  - Differences in pharmacokinetics
  - Effect on brain function
  - Levels of sex hormones
  - Male/female differences in genetic factors predisposing to AUD
    - Strong predictors for AUD among women
      - Family history, early onset anxiety disorders, nicotine dependence
    - Strong predictors for AUD among men
      - Novelty seeking, conduct disorder, childhood sexual abuse, parental loss, neuroticism, low self-esteem, low marital satisfaction

Differences in Blood Alcohol Levels

Women absorb and metabolize alcohol differently than men

Have higher blood alcohol levels after consuming the same amount to drink

Explanations have included

- Women's smaller amounts of body water
  - Compared to dropping the same amount of alcohol into a smaller pail of water
- The activity of the alcohol metabolizing enzyme Alcohol Dehydrogenase (ADH) in the stomach is lower in women
  - A larger proportion of alcohol reaches the bloodstream

* ADH is located in the cytosol of stomach and liver cells and functions as the main enzyme for alcohol metabolism

Additional Explanations

Women have the same alcohol elimination rate as men

- Eliminate the same amount of alcohol per unit body weight per hour

Women have a higher alcohol disappearance rate

- Eliminate more alcohol per unit of lean body mass per hour

Smaller volume of distribution

- Lower proportion of body water
- Longer persistence of high ethanol blood levels

Participant Poll Question

Which of the following is not true about the medical consequences of the SUDS in women?

a. Alcohol is a modifiable risk factor for breast cancer
b. Alcohol is associated with an increased risk for end-stage liver disease in women
c. Alcohol use likely affects sleep systems differently in men and women
d. Alcohol in any amount is cardio-protective in women

Health Consequences of Alcohol

Breast Cancer

Liver Disease

Prenatal Exposure

Women, Alcohol, and Breast Cancer

More than 2 million new cases of breast cancer each year

- US has 496,000 new cases annually

World-wide prevalence is 6.8 million

Many risk factors are not modifiable (5-7%, age, genetic factors)

Alcohol consumption is modifiable

- Consistent evidence based on hundreds of thousands of women
- Intake of < 10-15 grams of alcohol per day is associated with increased risk of breast cancer
  - 4%, if <0.5 drink per day
  - 9%, if 1.0 drink or less per day
  - 13% if 1-2 drinks per day

Mechanisms for Alcohol's Effects

Complex process, risk does not differ with type of alcohol consumed

Potential mechanisms

- Oxidative stress
- Cell proliferation
- Effects on hormones, particularly steroid hormones
- Effects on one-carbon metabolism

Risk Awareness and Knowledge

Global data on breast cancer

- Alcohol accounts for 8.6% of all incidence and 7.3% of mortality

Awareness of the link between alcohol and breast cancer is limited

- 19% of women attending a breast screening clinic in the UK were aware
- 3.3% of respondents to a 23-nation survey were aware of alcohol as a risk

More research

- Roles of drinking pattern
- Breast cancer subtypes
- In utero exposure
- Interaction between alcohol and other risk factors

Liver Disease

- Certain populations are more susceptible to end-stage effects of alcohol-related liver injury
  - Women and those with genetic predispositions
  - 15% of people who drink heavily develop cirrhosis
- Increasing rates of alcohol-related liver disease among women
  - 2009 to 2015, 50% increase among women compared to 30% among men
  - Rates parallel increases in heavy alcohol consumption among women
    - 80% increase in heavy alcohol use among women compared to 30% increase among men
      - Comparing 2012-2013 to 2001-2002
    - Fourfold increase in alcohol consumption among women from 1968 to 1987 in Japan

Mechanisms and Implications

Gender differences in alcohol metabolism

- Increased susceptibility to injury
  - Increased blood alcohol levels
  - Reduced gastric alcohol dehydrogenase resulting in impaired first-pass metabolism

Estrogen increases the susceptibility of Kuppfer cells to endotoxin

- Leading to more severe hepatic injury and necrosis

Faster progression to cirrhosis

- 13.5 years for women versus 20 years for men in Australia, controlling for alcohol consumption
- Million Woman Study in the UK advised women to abstain from daily drinking which increased susceptibility to liver injury

Antepartum substance use

Substance Use by Pregnant Women

Substance use pattern	Past 12 months drinking†	Past 30 days (current) drinking
All pregnant females (N = 3,006*)		
Any alcohol use	64.7 (62.1–67.3)	9.8 (8.5–11.1)
Alcohol use only	37.7 (35.7–39.7)	6.0 (5.0–7.2)
Alcohol and ≥1 additional substance	27.0 (25.1–29.0)	3.7 (2.9–4.7)
Other substances used§		
Tobacco¶	19.6 (18.0–21.3)	2.7 (2.1–3.6)
Marijuana	14.2 (12.3–16.3)	2.0 (1.4–2.8)
Opioids**	4.5 (3.5–5.8)	—††
Other††	6.2 (5.0–7.7)	—††

Consequences of prenatal marijuana use

- Increased risk of preterm birth
- Secondary perinatal and neonatal outcomes
  - Small for gestational age
  - Placental abruption
  - Increased admission to the neonatal intensive care
  - < 5 minute Apgar scores

Consequences of prenatal cigarette exposure

19.6% of pregnant women smoke cigarettes

Pregnancy complications

- Ectopic pregnancy
- Placenta previa
- Prematurity
  - Decreased birth weight, birth length, head circumference
- Intrauterine death
  - Sudden infant death syndrome

Later effects associated with prenatal cigarette use

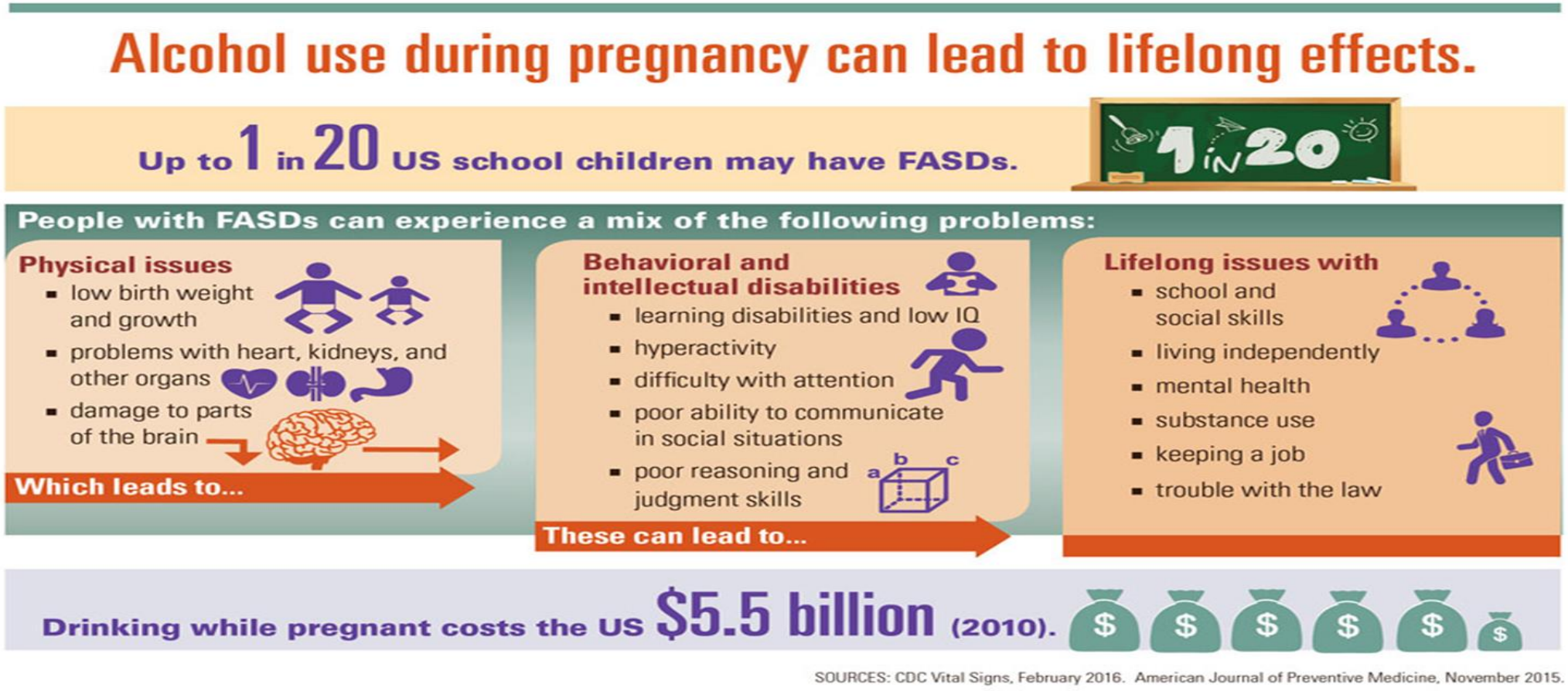
- Disturbed maternal infant interaction
- Excitability
- Hypertonia
- Stress abstinence signs
- Reduced IQ

- Aggression
- Conduct disorder
- Antisocial behavior
- Impulsivity
- ADHD
- Tobacco use and dependence

Alcohol Use by Pregnant Women

Characteristic	Past 12 months drinking*	Past 30 days drinking*	Past 30 days binge drinking*
Overall	**64.7 (62.1–67.3)**	**9.8 (8.5–11.1)**	**4.5 (3.7–5.4)**
Age group (yrs)			
<18	39.0 (27.3–52.1)	—†	—†
18–25	61.2 (58.0–64.3)	9.9 (7.9–12.2)	6.0 (4.5–8.1)
26–34	68.2 (64.2–72.0)	9.4 (7.6–11.5)	3.9 (2.9–5.3)
≥35	63.1 (55.5–70.1)	11.1 (7.3–16.6)§	—†
Race/Ethnicity			
White, non-Hispanic	74.9 (71.4–78.0)	9.9 (8.2–11.8)	4.0 (3.0–5.3)
Black, non-Hispanic	56.7 (51.0–62.3)	13.7 (9.8–18.9)	7.0 (4.6–10.9)§
Hispanic	48.0 (42.2–53.7)	7.0 (4.5–10.7)§	—†

Alcohol is a known teratogen



Effects of Prenatal Alcohol Exposure

Range of effects, mild to severe

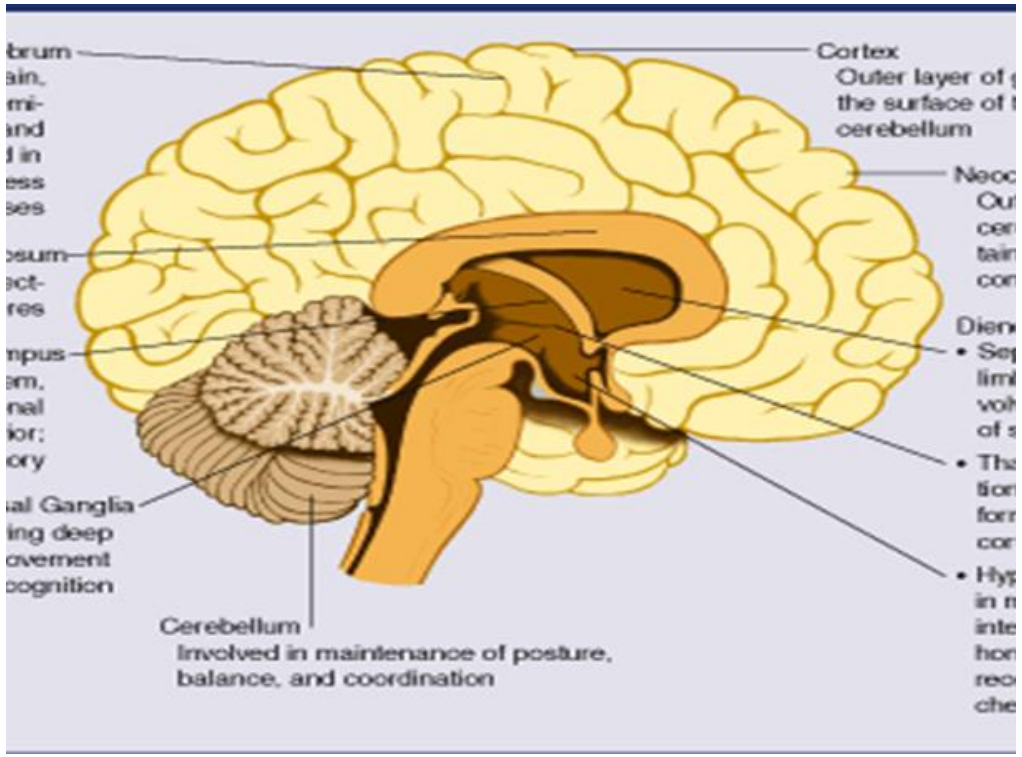
- Abnormal facial features
- Small head size
- Low body weight
- Poor coordination
- Hyperactive behavior

Persist for a lifetime

- Early intervention

Alcohol-Related Neurodevelopmental Effects

- Intellectual disabilities
- Problems with behavior and learning
  - School problems, difficulties with math, memory, attention, judgment, poor impulse control

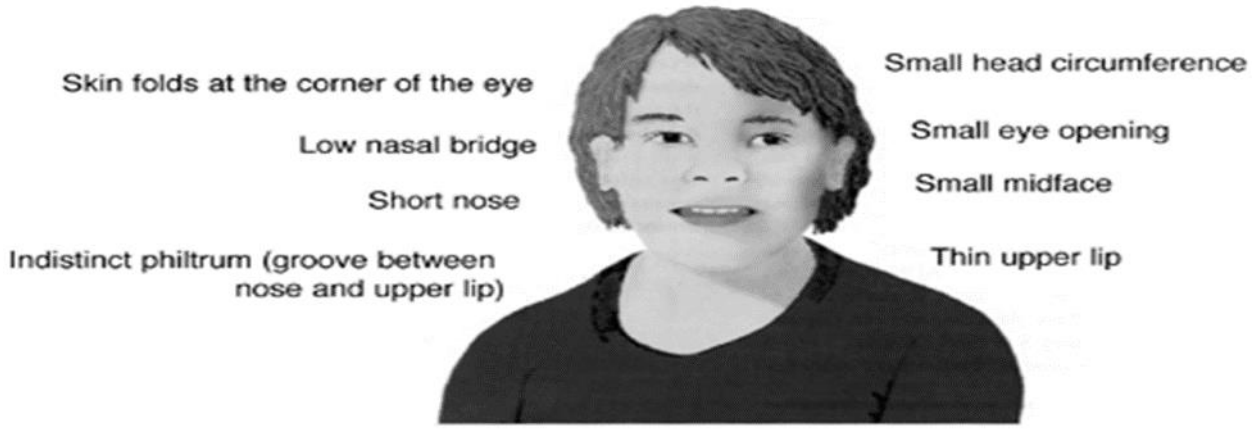


Fetal Alcohol Effects

- Problems with
  - Vision
  - Hearing
  - Heart
  - Kidneys
  - Bones

Fetal Alcohol Syndrome

- Classic triad
  - Abnormal facial features
  - Growth problems
  - CNS problems: learning, memory, attention span, communication, vision, hearing



Prevalence of Fetal Alcohol Syndrome

Prevalence rates

- FASD, three times the FAS rate
- 1 in 100 children are born with some exposure to alcohol

MMWR*[01-2015] FAS among children 7-9

0.3 per 1000 among children

- 0.3 per 1000 in Arizona
- 0.8 per 1000 in New York

Highest among Native American/Alaska Native

- 2.0 [CI=1.4-2.8] per 1000 children

Lowest among Hispanic children

- 0.2 [CI=.01-.02] per 1000 children age 7-9

* Morbidity and Mortality Weekly Report, Center for Disease Control

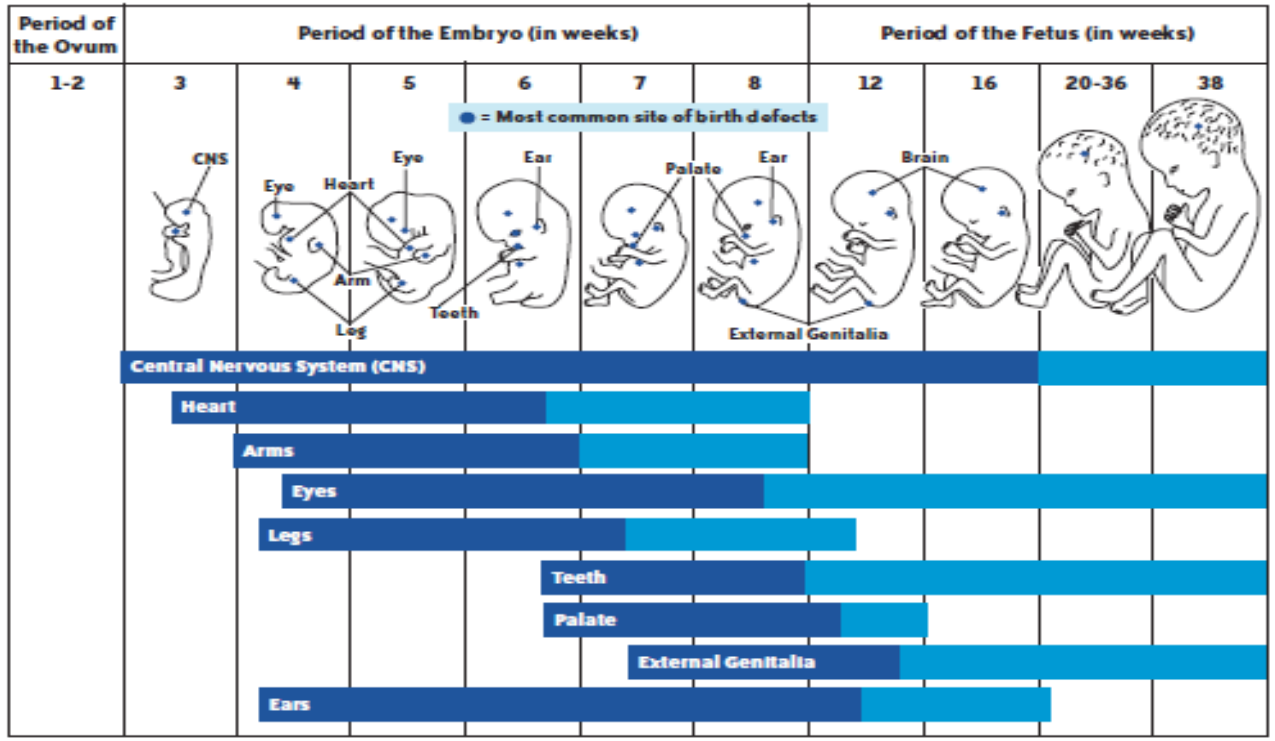
NO SAFE Time.

NO SAFE Amount.

NO SAFE Alcohol during Pregnancy.

PERIOD.

Fetal Development Chart



Vulnerability of the fetus to defects during different periods of development. The dark blue portion of the bars represents the most sensitive periods of development, during which teratogenic effects on the sites listed would result in major structural abnormalities in the child. The lighte blue portion of the bars represents periods of development during which physiological defects and minor structural abnormalities would occur.

SOURCE: Adapted from Moore 1993.

National Organization on Fetal Alcohol Syndrome

Helping children & families by advocating for the prevention and intervention of Fetal Alcohol Spectrum Disorders, the leading known cause of mental retardation & birth defects in the United States.

Participant Poll Question

Strategies to improve the identification and treatment outcome of the SUDS in women include:

a. Offering gender-informed treatment
b. Focusing access to specialty clinics
c. Using screening techniques that have been validated in women
d. All the above
e. a and c

Identification and Intervention

The AUDIT-C

Q#1: How often did you have a drink containing alcohol in the past year?

- Never (0 points)
- Monthly or less (1 point)
- Two to four times a month (2 points)
- Two to three times per week (3 points)
- Four or more times a week (4 points)

Q#2: How many drinks did you have on a typical day when you were drinking in the past year?

- 1 or 2 (0 points)
- 3 or 4 (1 point)
- 5 or 6 (2 points)
- 7 to 9 (3 points)
- 10 or more (4 points)

Q#3: How often did you have six or more drinks on one occasion in the past year?

- Never (0 points)
- Less than monthly (1 point)
- Monthly (2 points)
- Weekly (3 points)
- Daily or almost daily (4 points)

Use a tailored cut-point?

- Score ranges from 0-12
- In general, the score is proportional to problematic alcohol use
- Positive cut-point
  - 4 or more for men
  - 3 or more for women
- *What is the VA cut-point?*

Identifying Substance Use

Bioassays

- Urine
- Blood
- Hair
- Breath

Questionnaires

- History: quantity and frequency questions
- Alcohol: AUDIT
- Substance Use Disorders

NIDA Quick Screen

Introduction (Please read to patient)

Hi, I'm _____, nice to meet you. If it's okay with you, I'd like to ask you a few questions that will help me give you better medical care. The questions relate to your experience with alcohol, cigarettes, and other drugs. Some of the substances we'll talk about are prescribed by a doctor (like pain medications). But I will only record those if you have taken them for reasons or in doses other than prescribed. I'll also ask you about illicit or illegal drug use—but only to better diagnose and treat you.

***Quick Screen* Question:** **In the past year, how often have you used the following?**	**Never**	**Once or Twice**	**Monthly**	**Weekly**	**Daily or Almost Daily**
Alcohol • **For men, 5 or more drinks a day** • **For women, 4 or more drinks a day**					
Tobacco Products					
Prescription Drugs for Non-Medical Reasons					
Illegal Drugs					

- If the patient says “NO” for all drugs in the Quick Screen, reinforce abstinence. Screening is done.
- If the patient says “Yes” to one or more days of heavy drinking, then she is an at-risk drinker
- If the patient says “Yes” to use of tobacco, follow the smoking cessation protocol.
- If the patient says “Yes” to the use of illegal or prescription drugs for non-medical reasons, then go to…

Q1. In your *LIFETIME*, which of the following substances have you ever used?	**Yes**	**No**
a. Cannabis (marijuana, pot, grass, hash, etc.)		
b. Cocaine (coke, crack, etc.)		
c. Prescription stimulants (Ritalin, Concerta, Dexedrine, Adderall, diet pills, etc.)		
d. Methamphetamine (speed, crystal meth, ice, etc.)		
e. Inhalants (nitrous oxide, glue, gas, paint thinner, etc.)		
f. Sedatives or sleeping pills (Valium, Serepax, Ativan, Xanax, Librium,Rohypnol, GHB, etc.)		
g. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, ecstasy, etc.)		
h. Street opioids (heroin, opium, etc.)		
i. Prescription opioids (fentanyl, oxycodone [OxyContin, Percocet], hydrocodone [Vicodin], methadone, buprenorphine, etc.) • Please record **nonmedical use only**: *Non-medical use refers to using a substance either not prescribed to the patient or used in ways or amounts not prescribed by their doctor.*		
j. Other – specify:		

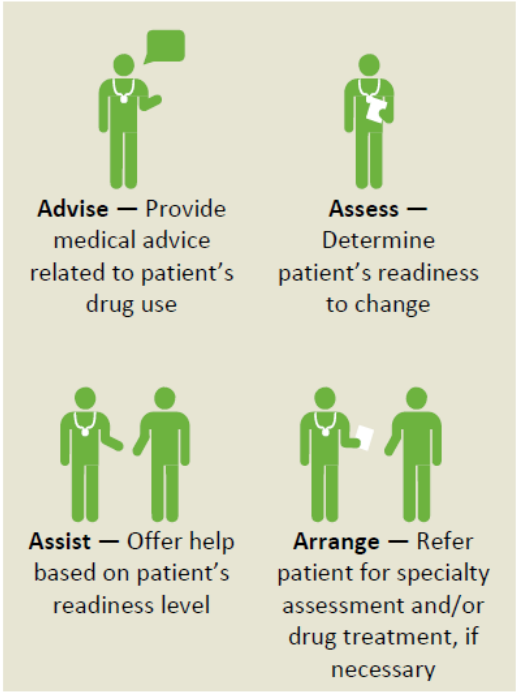
- The patient should say “Yes” to one of the questions
  - If she says no, remind her of her previous answer
- If the patient says “Yes” to any of the drugs, go to…

Name of the substance used: _____

Ask the following questions for each drug mentioned in Question 1:	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
Q2. *In the past 3 months*, how often have you used (insert name of drug)?	0	2	3	4	6
If the answer to Question 2 is "never", skip to Question 6. Otherwise, continue with Questions 3					
Q3. In the past 3 months, how often have you had a strong desire or urge to use (insert name of drug)?	0	3	4	5	6
Q4. In the past 3 months, how often has your use of (insert name of drug) led to health, social, legal or financial problems?	0	4	5	6	7
Q5. In the past 3 months, how often have you failed to do what was normally expected of you because of your use of (insert name of drug)?	0	5	6	7	8
Ask Questions 6 & 7 for all substances *ever used* (i.e., those mentioned in Question 1) :	NO	YES, but not in the last 3 months		YES, in the past three months	
Q6. Has a friend or relative or anyone else ever expressed concern about your use of (insert name of drug)?	0	3		6	
Q7. Have you ever tried and failed to control, cut down, or stop using (insert name of drug)?	0	3		6	
Instructions: Ask Question 8 if patient mentions ANY drug that might be injected, including those that might be listed in the 'Other' category (e.g., steroids). Circle appropriate response.					
Q8. Have you ever used any drug (including steroids) by injection? • Indicate you are referring to non-medical use only.	No, never	Yes, but not in the last 3 months		Yes, in the past 3 months	

Substance Involvement (SI) Score
(add all numbers circled in the questions)


High Risk
Score >27
Provide feedback on screening results
Advise, Assess, Assist
Arrange referral
Offer continuing support
Moderate Risk
Score 4-26
Provide feedback
Advise, Assess, Assist
Consider referral based on clinical judgment
Offer continuing support
Lower Risk
Score 0-3
Provide feedback
Reinforce abstinence
Offer continuing support


Advise — Provide medical advice related to patient's drug use
Assess — Determine patient's readiness to change
Assist — Offer help based on patient's readiness level
Arrange — Refer patient for specialty assessment and/or drug treatment, if necessary

Next Steps

Treatment for Women

Gender and Sex Differences

Informed treatment for women

- Recognizes sex and gender differences
  - Fastest growing group of alcohol users in the United States
  - Increased health risks
- Understands the types of trauma experienced by women
- Anticipates the additional needs and responsibilities of women
- Is evidence- based treatment
  - Most animal and human research based on male subjects
  - Sex based considerations and analyses are fundamental
    - Preclinical studies
    - Clinical studies