ALCOHOL & ALCOHOL USE DISORDERS

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CONFLICT OF INTEREST DISCLOSURE

I, Thomas Meeks, MD have nothing to disclose. Off-label use of gabapentin and baclofen for treatment of alcohol use disorder/withdrawal will be discussed in this presentation.

Special thanks to Dr. Lori Karan, Professor of Internal Medicine & Preventive Medicine, Program Director of the Addiction Medicine Fellowship at Loma Linda University, who made significant improvements in this presentation at the 2021 CSAM Annual Meeting.

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EDUCATIONAL OBJECTIVES

After attending this presentation, participants will be able to:

1. Summarize assessment tools & diagnostic aides useful in identifying and treating unhealthy alcohol use and alcohol use disorder.

2. Explain the epidemiology, prevention, and illness course of alcohol use disorder.

3. Describe the effects of alcohol on the human body, including intoxication, withdrawal, and long-term health effects.

4. Demonstrate knowledge about effective pharmacological and psychosocial treatments for alcohol use disorder.

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ALCOHOL: NEED TO KNOW

- Epidemiology of alcohol use & alcohol use disorder
- Prevention, including USPSTF Screening Recommendations & SBIRT
- Differentiate between unhealthy drinking, mild/moderate/severe AUD
- Neurobiology/pharmacology of intoxication, chronic use, and withdrawal
- Laboratory evaluation related to AUD
- Pharmacokinetics & pharmacodynamics of alcohol ingestion
- Evidence-based treatments, pharmacological & otherwise, for intoxication, withdrawal, & AUD
- Medical sequelae of unhealthy alcohol use, including FASD

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QUESTION #1:

A 36 year-old woman came in for her annual physical. She works full-time as a software designer and reports stopping after work for a glass of wine with a group of friends just about every night. On weekends, she goes out to clubs to dance and drink, and she may have up to 4-5 drinks/night. She denied any negative consequences from alcohol use. Her father quit drinking when she was a teenager and continues to attend AA meetings. **You recommend that she:**

a) Abstain from alcohol and start naltrexone

b) Limit her drinking to 3 drinks/day and 7 drinks/week

c) Limit her drinking to 4 drinks/day and 14 drinks/week

d) Just not to increase her alcohol use any further

QUESTION #1

Answer: b) Limit drinking to 3 drinks/day and 7 drinks/week

NIAAA defines at-risk drinking, as occurring above the following limits:

	Maximum drinks/day	Maximum drinks/week
Women	3	7
Men	4	14

SAMHSA defines heavy alcohol use as **binge drinking (women ≥4 and Men ≥5 drinks within 2 hours) on at least one day in the past 30 days**. This pattern of use usually results in BAC of 0.08 g/dL or higher.

Other recommendations, including the USDHHS and US Dept Agriculture, Dietary Guidelines for Americans 2020-2025, have more stringent recommendations (same weekly cap but no more than 2 drinks/day for men & no more than 1 drink/day for women).

QUESTION #2:

Which of the following is a reason that the previously described recommended drinking limits are lower for women than for men?

a) Gastric alcohol dehydrogenase levels are higher for women than for men.

b) Women are less likely than men to stop alcohol use once drinking 4 or more drinks in a single occasion.

c) Women have a lower volume of distribution for alcohol than men.

d) Women have lower rates of hepatic alcohol metabolism than men.

QUESTION #2

Answer: c) Women have a lower volume of distribution for alcohol than men.

When women and men drink the same amount of alcohol, women generally have a **higher BAC**. This is **not** thought to be primarily due to substantial differences in hepatic metabolism vs men (which is about 0.15 g/dL/hr in non-dependent adults).

Women absorb more alcohol from the gastric lumen because they **have less gastric alcohol dehydrogenase (ADH)** than men. ADH breaks down alcohol in the gastric lumen before it can be absorbed. Less ADH means less pre-absorption alcohol breakdown, i.e. a higher degree of alcohol absorption.

QUESTION #2

Answer: c) Women have a lower volume of distribution for alcohol than men.

Women also on average **have a lower volume of distribution**. On average, they weigh less. Women also on average have higher body fat% and lower lean body mass% than men.

Alcohol is water-soluble, not fat-soluble, and can only distribute to lean body mass. When there is less lean body mass, the bodily compartment over which alcohol is distributed shrinks, which causes the concentration of anything dissolved in that compartment to increase.

QUESTION #3:

A 32 year-old man reports drinking 4 beers per day. Before charting that he drinks 4 standard drinks per day, you think to ask what the % alcohol-by-volume (ABV) of the beer is and how many ounces of beer are in each beer container. The patient states “It’s a triple IPA, so I think it’s about 10% [ABV] and each one is 22 ounces.” **Approximately how many standard drinks per day is he actually consuming?**

a) 6

b) 8

c) 10

d) 15

STANDARD DRINKS

A standard drink (US) is defined as 0.6 fluid ounces or 14 grams of pure alcohol:

12 fluid ounces of regular beer (5% alcohol).	12 x 0.05 = 0.6 fluid ounces = 1 standard drink
5 fluid ounces of wine (12% alcohol)	5 x 0.12 = 0.6 fluid ounces = 1 standard drink
1.5 fluid ounces of spirits (40% alcohol, 80- proof)	1.5 x 0.40 = 0.6 fluid ounces = 1 standard drink

QUESTION #3:

Answer: d) 15

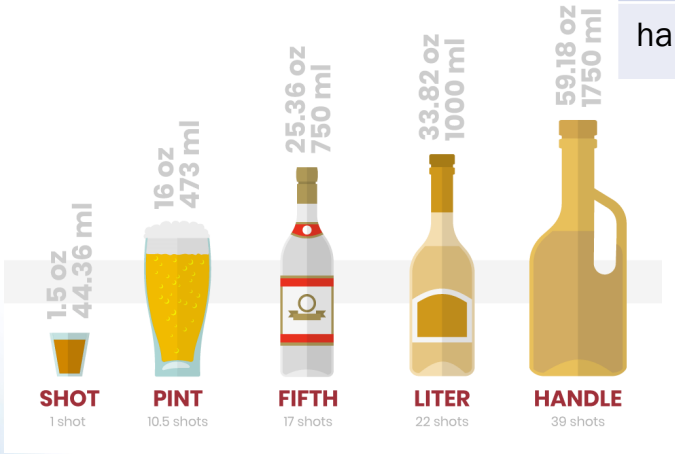
For beer, the traditional ABV% is 5% and a standard 12-ounce beer with this ABV% contains 14 gm (0.6 fl oz) of alcohol, i.e., one standard drink). The patient in this situation however is consuming four 22-ounce, 10%ABV beers per day.

Since the ABV is double a standard drink, we can convert 4 std drinks to 8 std drinks.

Since the beer volume is almost double as well (22 vs 12 oz), we can again double from 8 to ~16 std drinks to guess the best answer. More precisely, we can multiply 8 x 22/12 = 8 x 1.83 = 14.6 std drinks.

STANDARD DRINKS:

Name	Standard Drinks	Ounces	Milliliters
shot	1	1.5	44.36
pint	10.5	16	473
fifth	17	25.36	750
liter	22	33.82	1000= 1 liter
magnum	34.15	50.7	1.5 liters
handle	39	59.18	1.75 liters



QUESTION #:4

A 63 year-old man is drinking a fifth of liquor daily. His doctor advised him that his drinking was making it difficult to control his blood pressure, diabetes mellitus and acid reflux, as well as putting him at risk for many more adverse health consequences. He presents stating that he cannot imagine stopping alcohol altogether but is open to reducing his alcohol use. He requests a medication to help. Recent lab values are below. **What medication would have the best combination of safety & effectiveness in this case?**

Total Bilirubin	1.4 mg/dL	normal 0.3-1.2 mg/dL
Aspartate aminotransferase	100 U/L	normal < 45 U/L
Alanine aminotransferase	59 U/L	normal < 35 U/L
Estimated glomerular filtration	30 mL/min	normal 60-111 mL/min

a) Acamprosate

b) Disulfiram

c) Gabapentin

d) Naltrexone

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QUESTION #:4

Answer: d) Naltrexone

Disulfiram would not be appropriate for someone looking merely to reduce alcohol use.

Of the remaining medications, **naltrexone has the best evidence for harm reduction outcomes among someone who plans to still consume alcohol**.

Although naltrexone is relatively contraindicated in severe liver disease, it is believed to be safe for elevations of liver transaminases below 3-5 times the upper limit of normal when there is no evidence of advanced liver disease, as in this case.

The renal impairment evident in the reduced glomerular filtration rate is more concerning for exclusively renally cleared medications (e.g. gabapentin, acamprosate) than the mild liver enzyme elevations are for use of naltrexone in this case. The patient had the top two risks factors for chronic kidney disease: hypertension & diabetes mellitus.

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QUESTION #5:

A 63 year-old man with unstable diabetes mellitus and severe coronary artery disease recently completed inpatient treatment for alcohol withdrawal and is abstinent now for 7 days. He presents requesting a medication that might help him abstain from alcohol. His lab results are below. You notice on physical exam some spider angiomas and lower extremity edema. Given the below test results, **What medication would have the best combination of safety & effectiveness in this case?**

Albumin	2.8 g/dL	normal 3.5-5.4 g/dL
Total Bilirubin	4.9 mg/dL	normal 0.3-1.2 mg/dL
INR	2.5	normal 0.8-1.2
Estimated GFR	78 mL/min	normal 60-111 mL/min

a) Acamprosate

b) Disulfiram

c) Gabapentin

d) Naltrexone

QUESTION #5:

Answer: a) Acamprosate

The patient in this case has some relative contraindications to use of naltrexone & disulfiram. **Naltrexone contraindications** include:

- **Severe liver disease** (e.g. liver enzymes 3-5x ULN, clinical signs of decompensated cirrhosis or significant bilirubin or INR elevation). He had physical exam findings consistent with cirrhosis and markedly elevated INR & bilirubin, which are concerning even if his transaminase levels were normal.
- Pregnancy
- Taking or likely to soon need opioids

Disulfiram relative contraindications include:

- **Unstable medical illness** (e.g., cardiovascular disease, diabetes mellitus)
- Pregnancy
- Taking paraldehyde, metronidazole, or any alcohol containing product
- Treatment goal is not abstinence from alcohol
- Psychosis

QUESTION #5:

Answer: a) Acamprosate

Both **gabapentin** and **acamprosate** can be safely used in severe liver disease, as they both are cleared **renally**, but there is more evidence supporting efficacy for acamprosate in AUD, especially for abstinence outcomes. Acamprosate is more effective if, as in this case, the person is already abstinent. Gabapentin has several positive trials for AUD and alcohol withdrawal, though the largest RCT for AUD failed to demonstrate efficacy.

The medication with the most RCTs for AUD in alcohol-related liver disease is actually baclofen, but there are safety concerns and the results have been mixed. Neither gabapentin nor baclofen is FDA-approved for the treatment of alcohol use disorder.

QUESTION #6:

Which of the following public health interventions has the most robust evidence for reducing excessive alcohol use and its associated harms?

a) Increased prices/taxes for alcohol purchase

b) Privatization of alcohol sales

c) Project DARE

d) School programs promoting resilience among students

QUESTION #6:

Answer: a. Increased prices/taxes for alcohol purchase

Meta-analysis across multiple studies in many different locations has demonstrated **increasing alcohol prices and/or taxation robustly reduces overall alcohol use**, heavy alcohol use and lowers alcohol related MVCs & all-cause + liver-related mortality.

Many preventive interventions targeting children and adolescents in school have been tried. One of the most well-known was **Project DARE** (Drug Abuse Resistance Education), which centered around uniformed police officers educating elementary school children about how to resist peer pressure to use alcohol/drugs. Despite substantial financial investment and widespread implementation, it **failed to demonstrate benefits** for substance use outcomes.

QUESTION #6:

Answer: a) Increased prices/taxes for alcohol purchase

A somewhat more successful approach to school-based interventions to prevent substance use has involved programs to **build emotional resilience among the students**. A recent meta-analysis showed **these can reduce drug use** but they did not clearly reduce alcohol or tobacco use.

Privatization of alcohol sales leads to an increase in alcohol sales outlet density, which **is associated with increased alcohol use/alcohol-related harms.**

Other interventions that may reduce alcohol use/harm include reduction in sales outlet density, enhanced enforcement prohibiting sales to minors, and holding businesses that sell alcohol liable for failure to take action to limit inappropriate sale/service of alcohol.

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QUESTION #7

You are designing an intake questionnaire for a primary care clinic. You want to screen for problematic alcohol use. **If you were to include only one question, what should you use?**

a) Are you able to stop drinking if you want to?

b) Have you ever felt guilty about drinking?

c) How many drinks containing alcohol did you have on a typical day when you were drinking last year?

d) How many times in the past year have you had more than four drinks (for women) or five drinks (for men) in a day?

QUESTION #7

You are designing an intake questionnaire for a primary care clinic. You want to screen for problematic alcohol use. **If you were to include only one question, what would you use?**

a) Are you able to stop drinking if you want to? MAST

b) Have you ever felt guilty about drinking? CAGE

c) How many drinks containing alcohol did you have on a typical day when you were drinking last year? AUDIT-C

d) How many times in the past year have you had more than four drinks (for women) or five drinks (for men) in a day? Single Alcohol Screening Question (SASQ)

QUESTION #7

Answer: d) How many times in the past year have you had more than four drinks (for women) or five drinks (for men) in a day?

The most commonly used brief screening tools to assess for possible unhealthy alcohol use are the **AUDIT-C** (Alcohol Use Disorder Identification Test, the first 3 questions) and **CAGE** (cut back, annoyed, guilty, eye opener). **AUDIT-C is more sensitive than CAGE in detecting at-risk alcohol** use that is not yet an alcohol use disorder.

An even briefer **SINGLE ALCOHOL SCREENING QUESTION** has been developed with a modified version of question 3 from the AUDIT-C, which incorporates a sex-specific definition of binge drinking and the NIAAA recommended limit of drinks/day for lower-risk alcohol use. Any response other than 0 is considered a positive screen.

The Michigan Alcohol Screening Test and CAGE are more specific for alcohol use disorder than the AUDIT-C or single item screening question

QUESTION #7

Test		Sensitivity (Hazardous drinking)	Specificity (Hazardous drinking)	Sensitivity (AUD)	Specificity (AUD)
AUDIT-C	men	0.86	0.72	0.79	0.56
	women	0.66	0.94	0.80	0.87
CAGE ≥1 HD ≥2 AUD	all	0.47	0.87	0.71	0.90
	Primary care	0.49	0.75	0.85	0.78
Brief-MAST* ≥6 HD ≥13 AUD		0.35	0.97	0.50	0.98
Single Item		0.84	0.78	0.88	0.67

QUESTION #8

Which of the following statements about Screening and Brief Intervention (SBI) is correct?

a) SBI for alcohol use in primary care is recommended with an evidence grade of B by the US Preventive Services Task Force

b) SBI is more effective for alcohol use disorder than for risky alcohol use.

c) SBI is more effective for reducing opioid use than for reducing alcohol use.

d) The setting with the most robust evidence supporting the efficacy of SBI for alcohol use disorder is the emergency department

QUESTION #8

Answer: a) SBI for alcohol use in primary care is recommended with an evidence grade of B by the US Preventive Services Task Force (USPSTF)

An evidence grade of B by the USPSTF means either that (1) there is high certainty for a moderate net benefit or (2) there is moderate certainty for a moderate to substantial net benefit. This was the grade assigned to SBI in primary care per latest USPSTF guidelines https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics

Decades of research on SBI for alcohol use in primary care settings support the above statement/grading. More specifically the recommendation to conduct SBI for alcohol use in primary care is for those with **risky or hazardous alcohol use**. The efficacy for those with alcohol use disorder is not as well established. Also, the **recommendation is specific to adults aged 18 or more**—the evidence was deemed insufficient in adolescents.

While one review found some small short-term benefits of SBI for alcohol use in the **ED**, overall, the **evidence is less consistent than in primary care**.

There is **insufficient evidence to recommend routine use of SBI** for drug use, including opioids, per USPSTF guidelines.

QUESTION #9

Which of the following correctly describes hazardous, harmful, and unhealthy alcohol use as defined by the American Society of Addiction Medicine (ASAM)?

a) Harmful and hazardous alcohol use are both forms of unhealthy alcohol use

b) Harmful alcohol use is synonymous with at-risk alcohol use.

c) Hazardous alcohol use is a subtype of harmful alcohol use.

d) Unhealthy alcohol use implies that an individual has experienced direct harm to their health as a result of alcohol use.

QUESTION #9

Answer: a) Harmful and hazardous alcohol use are both forms of unhealthy alcohol use

Category of alcohol use	Subcategory	Organization responsible	Definition
Lower risk use		**ASAM**	**Consumption below amount identified as hazardous and in situations not defined as hazardous**
Risky/at-risk use		NIAAA	Consumption above the daily/per occasion & weekly amounts that does not meet criteria for AUD
Unhealthy use	Hazardous	**ASAM**	**Use that increases risk for adverse health consequences but no such consequences yet**
	Hazardous	WHO	Use that increases risk of harmful consequences; risk is relevant to prevention more than treatment
	Harmful	**ASAM**	**Use adversely affecting health in the absence of addiction**
	Harmful	WHO	Use that results in adverse physical or mental health consequences; ICD-10 Alcohol Abuse included
AUD		DSM-5	2+ of 11 criteria within a 12 month period causing clinically significant distress or impairment

QUESTION #10

A 27 year-old woman who is 11 weeks pregnant presents for routine prenatal care. **Which of the following are the best validated screening tools for alcohol use during pregnancy?**

a) AUDIT, CRAFFT, TWEAK

b) AUDIT-C, T-ACE, TWEAK

c) CAGE, TWEAK, S-MAST

d) T-ACE, TWEAK, S-MAST

QUESTION #10

Answer: b) AUDIT-C, T-ACE, TWEAK

	AUDIT-C	T-ACE	TWEAK
Sensitivity	95%	69-88%	71-91%
Specificity	85%	71-89%	73-83%
Scoring	Same as in non-pregnant women	**Tolerance (>2 drinks): 2 pts** Annoyed: 1 pt Cut down: 1 pt Eye opener: 1 pt	**Tolerance: 2 pts** • "can hold" ≥ 6 drinks OR • takes ≥ 3 drinks to feel effects **Worried: 2 pts** Eye opener: 1 pt **Amnesia: 1 pt** **K(c)ut** down: 1 pt
Cut-off score	≥ 3	≥ 2	≥ 2

CAGE and S-MAST did not perform as well in pregnancy. CRAFFT is a substance use screening tool validated for use in adolescents.

QUESTION #11

A patient is 4 days post-operative from a total hip arthroplasty and starts to exhibit fever, tachycardia, waxing and waning confusion, visual hallucinations, and diaphoresis. **Without knowing additional details, which of the following are the most appropriate next steps in managing this case?**

a) Administer IV diazepam & thiamine, obtain blood cultures

b) Administer oral Gabapentin, IV folic acid, and IV haloperidol

c) Administer oral Oxazepam, IV thiamine, and place physical restraints

d) Administer IV Phenobarbital & folic acid, correct electrolyte derangements

QUESTION #11

Answer: a) Administer IV diazepam & thiamine, obtain blood cultures

Benzodiazepines are first line treatment for severe alcohol withdrawal.

Among benzodiazepines, **long-acting agents with active metabolites (e.g. diazepam or chlordiazepoxide) are preferred,** as they have a smoother coverage of symptoms, except in severe liver disease or older adults (when lorazepam and oxazepam are preferable). For severe withdrawal, **rapid onset is important, so IV administration is best**.

Nutritional supplementation is important, and among these options, **thiamine is the most important thing to replete first so that glucose in IVF can be administered without risk of precipitating Wernicke-Korsakoff syndrome**. Electrolyte imbalances should be assessed and corrected when needed. Folic acid is good to add, but not as vital in priority as thiamine.

QUESTION #11

Answer: a) Administer IV diazepam & thiamine, obtain blood cultures

Antipsychotics have limited benefit. They may worsen **lower seizure threshold, prolong QTc intervals, and impair thermoregulation**. Use in refractory agitation/hallucinations is sometimes helpful. Physical restraints may be needed due to the delirium if the patient is endangering themselves or others but should not routinely be initiated.

Anticonvulsants (e.g. gabapentin, divalproex, carbamazepine) may be helpful adjuncts to benzodiazepines or effectively treat/prevent mild alcohol withdrawal. Monotherapy as a 1st line treatment for severe withdrawal is not an accepted standard of care. **For refractory severe withdrawal, phenobarbital, propofol, or dexmedetomidine may be helpful** (usually in an ICU because mechanical ventilation is often needed on these meds). Of these, the best evidence is for phenobarbital.

Especially when one is not anticipating alcohol withdrawal (e.g., use was potentially under-reported pre-admission**), it is important to consider other causes**. Among various diagnostic tests, in a person with fever, tachycardia, confusion, and hallucinations, one should **rule out an infection** (e.g. order blood cultures).

QUESTION #12

For the condition treated in the prior question (question 11), about ___ % of persons with moderate-severe alcohol use disorder experience this during alcohol withdrawal (i.e., the incidence), and, of those who do, about ___ % die despite currently available interventions (i.e., the mortality rate). What are the most accurate values for the blanks above, respectively?

a) 1% incidence; 10% mortality rate

b) 5% incidence; <5% mortality rate

c) 10% incidence; 10% mortality rate

d) 15%incidence ; 25% mortality rate

QUESTION #12

Answer: b) 5% incidence; <5% mortality

The patient in questions #13/14 was experiencing **delirium tremens (DTs),** one form of complicated alcohol withdrawal characterized by delirium and autonomic hyperactivity. **Dopamine, norepinephrine, and glutamate excess and GABA deficiency** are associated with the symptoms of DTs. **The incidence is about 5%** during alcohol withdrawal. **Mortality** used to be above 20% but better detection and treatment have **lowered that to under 5%.** Causes of death in DTs may include cardiac arrhythmia and aspiration pneumonia. **Onset is typically 48 to 96 hours** post alcohol cessation

Generalized tonic-clonic seizures are another form of complicated withdrawal that occur **in about 10% of cases of alcohol withdrawal**. **Onset is typically 12-48 hours** post alcohol cessation.

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