Pharmacotherapy for Alcohol Use Disorder

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Disclosure

- I have no financial conflicts of interest

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Objectives

- At the end of the lecture, participants should be able to
  - Understand the prevalence of alcohol use disorders
  - Discuss the mechanism of action, evidence for, and potential adverse effects of FDA-approved medications used for the treatment of alcohol use disorders (AUD) and incorporate these medications into their practice.

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Alcohol Use Disorder

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Co-Morbid Alcohol Problems

- The third leading cause of death in the United States, behind tobacco, poor diet and physical inactivity (obesity)
- The second leading cause of disability and disease burden in the United States
- Associated with 41% of traffic deaths,
- 29% of suicides, which constitute the leading causes of death among persons aged 15 to 35 years.

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Alcohol and Health

- **Health risks:** Excessive alcohol consumption
- Cancer
  - pancreas
  - Mouth
  - Pharynx
  - Larynx
  - esophagus
  - Liver
  - breast cancer
- Pancreatitis
- Sudden death in people with cardiovascular disease
- Stroke
- Brain atrophy (shrinkage)
- Cirrhosis of the liver
- Miscarriage
- Fetal alcohol syndrome in an unborn child, including impaired growth and nervous system development
- Injuries due to impaired motor skills
- Suicide
- Heart muscle damage (alcoholic cardiomyopathy) leading to heart failure

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Alcohol's impact

- NSDUH 2016
  - 15.1 million adults (6.2%) had AUD
  - Approximately 6.7% percent of adults with AUD received treatment
- Alcohol is the 3rd leading preventable cause of death in the US.
    - 1st = tobacco
    - 2nd = poor diet and physical activity

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Co-Morbid Alcohol Problems

- 13.5% of the US population had experienced an alcohol disorder during their lifetime
- A third of those people have had at least one other psychiatric diagnosis, this number is even higher among women.
- 22% of mood disordered patients have an alcohol use disorder, 17.9% anxiety patients, 73.6% of antisocial patients.

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Alcohol and Health

- Health benefits: Moderate alcohol consumption
  - Reduce your risk of developing heart disease, peripheral vascular disease and intermittent claudication
  - Reduce your risk of dying of a heart attack
  - Possibly reduce your risk of strokes, particularly ischemic strokes
  - Lower your risk of gallstones
  - Possibly reduce your risk of diabetes

Problem drinking

- How much is "too much"
  - Causes or elevates the risk for alcohol related problems, or
  - Complicates management of other health problems
- There are increased risks for alcohol-related problems for…
  - Men who drink more than 4 standard drinks in a day or more than 14 in a week
  - Women who drink more than 3 standard drinks in a day or more than 7 per week.

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Problem drinking

- About 3 in 10 adults drink at levels that elevate health risks
- Among heavy drinkers, 1 in 4 has alcohol abuse or dependence.
- All heavy drinkers have a greater risk of hypertension, gastrointestinal bleeding, sleep disorders, major depression, hemorrhagic stroke, cirrhosis or the liver, and several cancers.

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Problem drinking

- Heavy drinking often goes undetected
  - Patients with alcohol dependence received the recommended quality of care only about 10 percent of the time.

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Screening and Brief Intervention

- Patients are likely to be more receptive, open, and ready to change than you expect
  - Most patients don't object to being screened for alcohol use by clinicians and are open to hearing advice afterwards
  - Most primary care patients who screen positive for heavy drinking or alcohol use disorders show some motivational readiness to change
  - Those who have the most severe symptoms are often the most ready to change.

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Screening and Brief Intervention

- Brief interventions can promote significant, lasting reductions in drinking levels in at-risk drinkers who do not have alcohol use disorder

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Screening and Brief Intervention

- Screening
  - A single question about heavy drinking days to use during a clinical interview
    - Do you sometimes drink beer, wine or other alcoholic beverages
      - How many times in the past month have you had 5 (man), 4 (woman) drinks in a day?
    - A standard drink is 14 grams of or alcohol
      - 12 oz beer
      - 5 oz wine
      - 1.5 oz liquor

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What's a drink?

In the United States, a "standard" drink is any drink that contains about 0.6 fluid ounces or 14 grams of "pure" alcohol. Below is the approximate number of standard drinks in different sized containers of

regular beer (5% alc/vol)	malt liquor (7% alc/vol)	table wine (12% alc/vol)	80-proof distilled spirits (40% alc/vol)
12 fl oz = 1 16 fl oz = 1⅓ 22 fl oz = 2 40 fl oz = 3⅓	12 fl oz = 1½ 16 fl oz = 2 22 fl oz = 2½ 40 fl oz = 4½	750 ml (a regular wine bottle) = 5	a shot (1.5-oz glass/50-ml bottle) = 1 a mixed drink or cocktail = 1 or more 200 ml (a "half pint") = 4½ 375 ml (a "pint" or "half bottle") = 8½ 750 ml (a "fifth") = 17
Although the "standard" drink amounts are helpful for following health guidelines, they may not reflect customary serving sizes. In addition, while the alcohol concentrations listed are "typical," there is considerable variability in alcohol content within each type of beverage (e.g., beer, wine, distilled spirits).			

https://www.rethinkingdrinking.niaaa.nih.gov/How-much-is-too-much/What-counts-as-a-drink/How-Many-Drinks-Are-In-Common-Containers.aspx

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Screening and Brief Intervention

- The AUDIT – a self report instrument
  - 10-question Alcohol Use Disorders Identification Test (AUDIT), may be used to obtain more qualitative information about a patient's alcohol consumption.
  - Research shows that the AUDIT may be especially useful:
    - Most populations including women, minorities, adolescents and young adults; there is little research in older patients.
    - The AUDIT includes questions of
      - Quantity
      - Frequency
      - Binge drinking
      - Dependence symptoms
      - Alcohol-related problems
  - Positive Screening ($\geq$ 8 for men, $\geq$ 4 for women)

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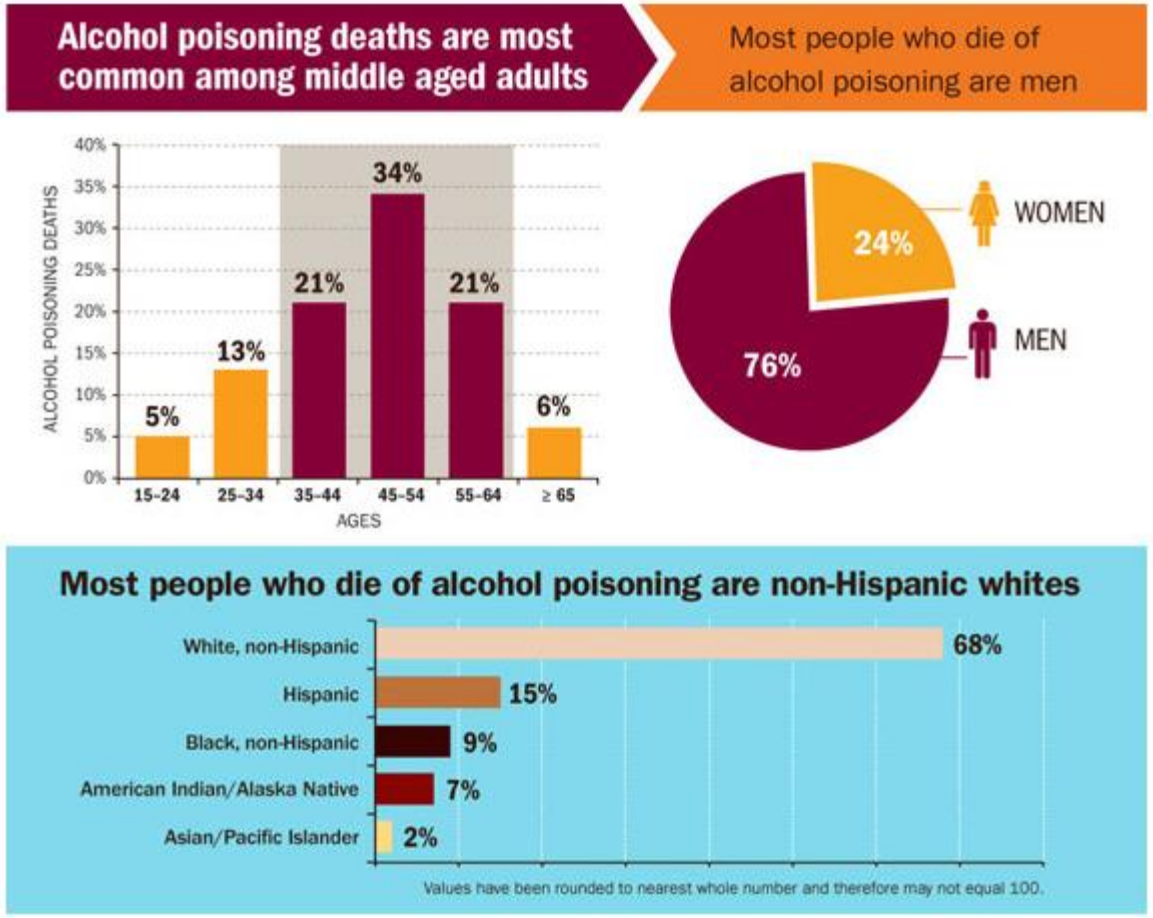
Alcohol's impact

Alcohol poisoning

- On average 6 deaths per day



https://www.cdc.gov/vitalsigns/alcohol-poisoning-deaths/index.html

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Estimated Economic Cost to Society Due to Substance Use and Addiction

	Healthcare	Overall	Year
Tobacco	$168 billion	$300 billion	2010
Alcohol	$27 billion	$249 billion	2010
Illicit Drugs	$11 billion	$193 billion	2007
Total	**$206 billion**	**$742 billion**	

https://www.drugabuse.gov/related-topics/trends-statistics accessed 5/16/18

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Medication Assisted Treatment

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Medication Assisted Treatment (MAT)

- One of many tools in the “recovery toolbox”
- Reduce cravings which can help stabilize and strengthen coping capacity
- Increase periods of abstinence and instill a sense of self-efficacy to help sustain recovery
- Allow patients to focus on behavioral therapies
- Improve clinical outcomes for patients and reduce impact on families/loved ones

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Underutilized Tool in Treatment of AUD

- Use of medications for AUDs has been limited
  - Lack of physician coverage in SUD programs
  - Not regularly used in primary care
  - Publicly funded programs less likely to prescribe medications for AUDs
  - Patients in private SUD programs more likely to receive psychiatric medications (70%), than medications for alcohol use disorder (24%)
  - Historically poor coverage by insurance
  - Program characteristics (e.g., 12-step oriented, funding, accreditation)

Mark et al., 2009;
Knudsen et al., 2011;
Roman et al., 2011;
Abraham et al, 2013

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Why Physicians Don't Prescribe MAT for AUD

- Believe AUD meds are not very effective
- Believe abstinence is best treatment
- Believe patients don't want meds for AUDs
- Patients are concerned about adverse effects
- Patients are concerned about acceptance in mutual support groups
- Cost of medications
- Lack of training in these medications

Mark et al., 2003;
Ponce Martinez et al., 2016;
Swift et al., 1998

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Medications for Alcohol Use Disorder

- FDA approved medications
  - Acamprosate
  - Disulfiram
  - Naltrexone
  - Naltrexone-XR

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Acamprosate

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Acamprosate

- Approved in 2004
- Mechanism
  - $GABA_A$ agonist, NMDA receptor antagonist
  - After chronic exposure to alcohol, upregulation of NMDA receptors to compensate for alcohol

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Acamprosate

- $T_{½}$ = 20-33 hrs
- Peak plasma concentration 3-8 hrs after administration
- Dose is
  - 333 mg, 2 tabs three times daily
- Not metabolized by the liver
- Excreted by the kidneys
- Adverse effects include: diarrhea, anxiety, headache, depression, fatigue, change in libido, dizziness, itching, suicidal ideation

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Acamprosate

- Cochrane review (Rosner et al., 2010), acamprosate reduced risk to return to any drinking by 14% and increased abstinence duration by 11%

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Table 1 Efficacy of acamprosate in randomized, double-blind, placebo-controlled trials in adults with alcohol dependence

Study (treatment period)	Regimen[a] (no. of pts)	Complete abstinence rate (% of pts)	Mean cumulative abstinence duration (days)	Percentage of alcohol-free days	Median time to first drink (days)
Short- to medium-term trials					
Berger et al. [29]	ACA (51)			NSTE[b]	
(≈3 months)	PL (49)				
Chick et al. [30]	ACA (289)	12[b]	77	43[c]	
(6 months)	PL (292)	11[b]	81	45[c]	
Geerlings et al. [31]	ACA (128)	25	61*[b]	34*	45[b]
(6 months)	PL (134)	13	43[b]	24	15[b]
Gual and Lehert [32]	ACA (141)	35	93**[b]	52**[c]	
(6 months)	PL (147)	26	74[b]	41[c]	
Higuchi [33]	ACA (163)	47*[b]	74	44[c]	
(≈6 months)	PL (164)	36[b]	74	44[c]	
Mason et al. [34]	ACA 2 g/day (253)			56[b]	
(≈6 months)	ACA 3 g/day (82)			61[b]	
	PL (257)			54[b]	
Pelc et al. [35]	ACA 1332 mg/day (63)	44*[b]	52*[b]	58*[c]	56**
(3 months)	ACA 1998 mg/day (63)	51*[b]	57*[b]	63*[c]	56***
	PL (62)	26[b]	34[b]	38[c]	15
Poldrugo [36]	ACA (122)	48*[b]	99**	55**[c]	151***
(6 months)	PL (124)	32[b]	70	39[c]	61
Tempesta et al. [37]	ACA (164)	58*[b]	110*[b]	61*	135**[b]
(6 months)	PL (166)	45[b]	89[b]	49	58[b]
Longer-term trials					
Paille et al. [38]	ACA 1332 mg/day (188)	18[b] (27* at 6 months)[b]	198	55[c]	135[d]
(12 months)	ACA 1998 mg/day (173)	19[b] (32* at 6 months)[b]	223***	62***[c]	153**[d]
	PL (177)	11[b] (19 at 6 months)[b]	173	48[c]	102[d]
Sass et al. [39]	ACA (136)	45**[b]	225***[b]	62***	131[b]
(≈11 months)	PL (136)	25[b]	162[b]	45	45[b]
Whitworth et al. [40]	ACA (224)	18**[b]	139*	39*	
(12 months)	PL (224)	7[b]	104	29	

Study participants underwent detoxification (or were abstinent for a brief but sustained period) prior to randomization to study treatment, which was used as an adjunct to psychosocial interventions

ACA acamprosate, *NSTE* no significant treatment effect, *PL* placebo, *pts* patients

* $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$ vs. PL

[a] ACA dosage was based on bodyweight (1332 mg/day if <60 kg; 1998 mg/day if ≥60 kg), aside from the studies by Berger et al., Chick et al., Gual and Lehert, Higuchi et al., and Tempesta et al. (1998 mg/day for all ACA pts), Mason et al., Paille et al., and Pelc et al. (randomization to different ACA regimens was irrespective of bodyweight); some studies also allowed for dosage reductions if distressing adverse gastrointestinal effects occurred

[b] Primary or co-primary efficacy endpoint

[c] Calculated value [mean cumulative abstinence duration (days)/study treatment period (days) × 100 %]

[d] Mean value

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Acamprosate

- PREDICT Study (Mann et al., 2012) – similar methods to COMBINE study, found
  - 49.3% did not have a heavy-drinking day during the 90 days they were taking medication
  - No difference in adherence to medications between groups (73.5 to 76.7% adherent)
  - No significant difference in time to first day of heavy drinking between groups

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Disulfiram

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Disulfiram

- Approved in 1949
- Deters patient from drinking because patient knows he/she will have aversive reaction if drinks
- Patient is not meant to have the reaction

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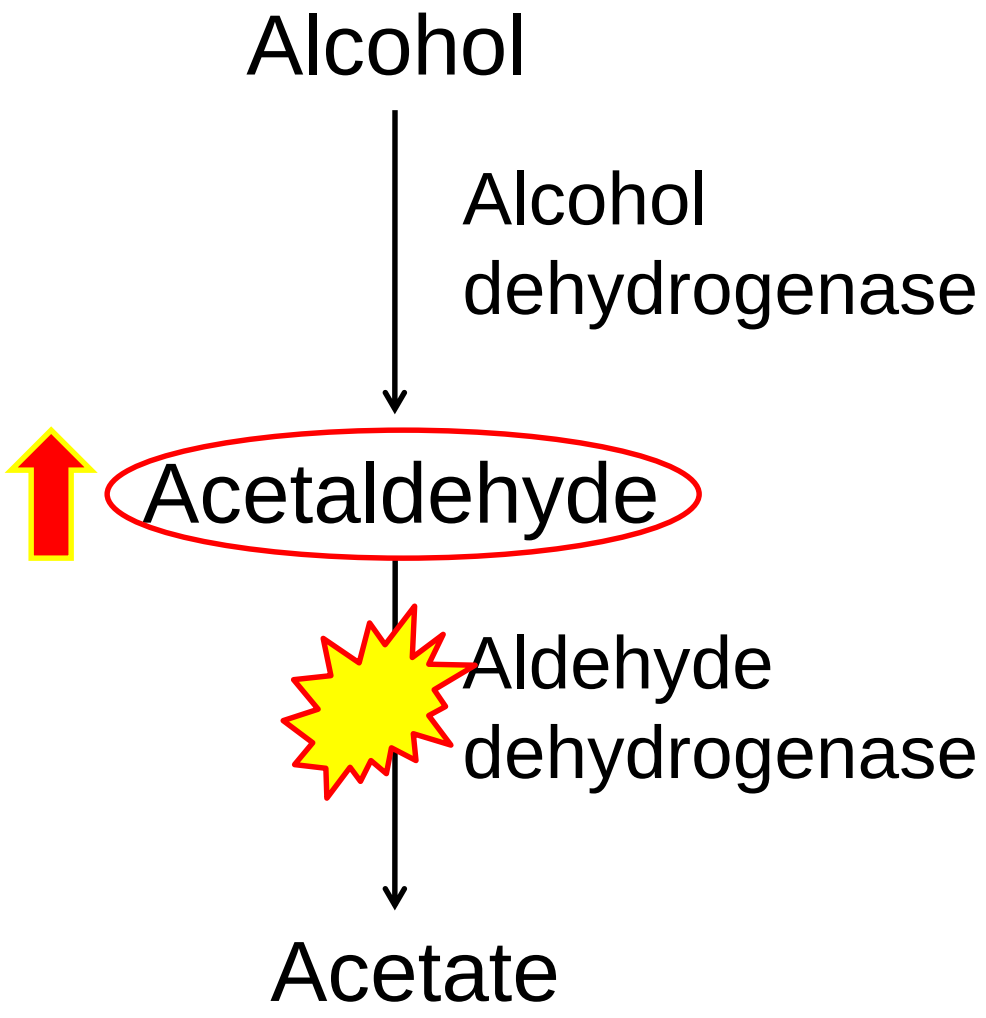
Disulfiram Mechanism of Action



Disulfiram-Alcohol Reaction

- Symptoms start 10-30 mins after drinking alcohol
- Reaction dependent on dose of alcohol and medication
- Reaction may occur for up to 14 days after stopping medication due to irreversible enzyme inhibition

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Disulfiram-Alcohol Reaction

Typical

- Flushing
- Sweating
- Nausea, vomiting
- Dehydration
- Increased heart rate

Severe

- Trouble breathing
- Irregular heart beat
- Myocardial infarction
- Heart failure
- Seizures
- Unconsciousness
- Death

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Disulfiram (Antabuse)

- Metabolized by the liver
- Check liver functions prior to starting and periodically through treatment
- Adverse effects include rash, acne, drowsiness, headache, impotence, metallic aftertaste, neuropathy, hepatitis, liver failure, psychosis
- May be helpful in promoting abstinence for highly motivated patients who are monitored to make sure they take their medication.
- A reasonable choice when abstinence is the desired and necessary goal.
- Standard clinical dose: 250 mg/d (dose needs vary)
- Contraindicated in: psychosis, significant liver disease, esophageal varices, pregnancy, impulsivity

(Barth et al., 2010)

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Disulfiram

- May increase motivation not to drink
- Jorgensen et al., 2011 – review of literature
  - Increases periods of abstinence (6 of 11 studies)
  - People taking disulfiram had more days until relapse and fewer drinking days (6 of 9 studies)
- Good medication for people whose goal is abstinence, such as those who attend AA
- Concerned significant others may be called upon to observe dosing

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Naltrexone

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Naltrexone

- Approved in 1994 for alcohol use disorder
- Mu-opioid antagonist
- When people drink, endorphins released and bind to mu-receptor, resulting in dopamine release in VTA to NAc pathway
- Naltrexone blocks endorphin binding thereby reducing pleasure from drinking

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Naltrexone

- Some people may respond better to naltrexone than others
  - Family history of alcoholism
  - Cravings for alcohol

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Naltrexone

- Naltrexone tablets are typically dosed
  - 50 mg daily, but can give up to 100 mg
- It is metabolized by the liver, $T_{½}$ = 4-13 hrs
- Check liver function prior to starting and periodically during treatment
- Adverse effects include: nausea, vomiting, diarrhea, constipation, headache, dizziness, fatigue, muscle cramps, rash, diaphoresis, delayed ejaculation, precipitated opioid withdrawal, hepatitis, liver failure

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Naltrexone

- Cochrane review (Rosner et al., 2010) found naltrexone decreases the chance of relapse for 36% compared to placebo (NNT = 7)

- Reduces the frequency and intensity of drinking, preventing lapse from becoming relapse (Rosner et al., 2008)

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COMBINE Study (Anton et al., 2006)

- 1383 patients with alcohol dependence randomly assigned to 1 of 9 groups after baseline assessment and achieving 4 days of abstinence from alcohol
- Naltrexone 100 mg daily (typical dose 50 mg)
- Acamprosate 3000 mg daily (typical dose 1998 mg)
- Outcomes: % days abstinent, time to 1st heavy drinking episode
- Naltrexone was more effective than placebo and benefits were maintained 1 year later
- Acamprosate was not more effective than placebo

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Meta-Analysis of Naltrexone vs. Acamprosate

Table 2 Main effects and comparisons of naltrexone and acamprosate for the 61 studies with either naltrexone or acamprosate compared with placebo (excluding the 3 studies which included both medications).

		Main effect of each medication compared with placebo				*Subgroup test of heterogeneity: naltrexone versus acamprosate*	
Outcome	*Medication*	*g*	*CI*	*P*	*k studies*	*Q*	*P*
Abstinence aggregate	Naltrexone	0.116	0.049–0.183	0.001	36	13.22	<0.001
	Acamprosate	0.359	0.246–0.472	<0.001	15		
Heavy drinking aggregate	Naltrexone	0.189	0.123–0.255	<0.001	39	1.98	0.159
	Acamprosate	0.072	−0.078–0.221	0.346	5		
Craving	Naltrexone	0.144	0.045–0.244	0.005	26	3.17	0.075
	Acamprosate	0.034	−0.036–0.104	0.347	9		
Heavy drinking and craving aggregate	Naltrexone	0.180	0.118–0.243	<0.001	42	8.40	0.004
	Acamprosate	0.041	−0.029–0.112	0.246	9		

Maisel et al., 2012

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Table 2 Efficacy of acamprosate in randomized, active comparator-controlled (or combined therapy) trials in adults with alcohol dependence

Study (treatment period) [acronym]	Regimen (no. of pts)[a]	Mean cumulative abstinence duration (days)	Percentage of alcohol-free days	Relapse to ≥1 episode of heavy drinking (% of pts)[b]	Mean time to first episode of heavy drinking (days)	Mean time to first drink (days)
Anton et al. [42]	ACA (152)		75.6[c]	71.1[c]		
(16 weeks)	NAL (154)		80.0[†c]	67.5[c]		
[COMBINE]	ACA + NAL (148)		80.5[c]	64.9[c]		
	PL (153)		73.8[‡c]	75.2[c]		
	ACA + CBI (151)		78.2[c]	68.2[c]		
	NAL + CBI (155)		75.9[†c]	66.5[c]		
	ACA + NAL + CBI (154)		77.6[c]	73.9[c]		
	PL + CBI (154)		79.8[†‡c]	71.2[c]		
	CBI (155)		66.6[c]	79.0[c]		
Besson et al. [43][d]	ACA ± DIS (55)	137*[c]	40*[c]			
(360 days)	PL ± DIS (55)	75[c]	21[c]			
De Sousa et al. [44]	ACA (50)			54		
(8 months)	DIS (50)			12[§§§]		
Kiefer et al. [45]	ACA (40)			VNS*[c]		
(12 weeks)	NAL (40)			VNS*[c]		
	ACA + NAL (40)			VNS**[§c]		
	PL (40)			VNS		
Laaksonen et al. [46]	ACA (81)				17.6[c]	11.4[c]
(12 weeks)	NAL (81)				22.0[c]	16.2[c]
	DIS (81)				46.6[§§§c]	30.4[§§c]
Mann et al. [47]	ACA (172)			51.7[c]		
(12 weeks)	NAL (169)			50.9[c]		
[PREDICT]	PL (85)			48.2[c]		
Morley et al. [48]	ACA (55)	66[c]	74[c]		33.6[c]	24.1[c]
(12 weeks)	NAL (53)	58[c]	64[c]		39.2[c]	24.3[c]
	PL (61)	57[c]	63[c]		33.4[c]	24.6[c]

Study participants abstinent for ≥4 days prior to randomization to study treatment

ACA acamprosate, *CBI* combined behavioural intervention, *DIS* disulfiram, *NAL* naltrexone, *PL* placebo, *pts* patients, *VNS* value not specified

* $p \leq 0.05$, ** $p < 0.01$ vs. PL; † $p = 0.009$ for NAL × CBI interaction; ‡ $p < 0.001$ vs. CBI; § $p < 0.01$, §§ $p < 0.001$, §§§ $p \leq 0.0001$ vs. ACA (and NAL in Laaksonen et al.)

[a] ACA dosage was based on bodyweight (1332 mg/day if <60 kg; 1998 mg/day if ≥60 kg) except in the COMBINE study (which used ACA 3 g/day), Kiefer et al., Mann et al. and Morley et al. (which used 1998 mg/day). NAL dosages were 100 mg/day in COMBINE and 50 mg/day in Kiefer et al., Laaksonen et al., Mann et al. and Morley et al.; DIS dosage was either not specified or determined by the physician. In COMBINE, the no. of pts shown is for the percentage of alcohol-free days analysis; aside from the CBI arm, all other groups in the COMBINE study also received medical management, which focused on enhancing medication adherence and abstinence

[b] Derived from analysis of time to first episode of heavy drinking (a co-primary endpoint) in the COMBINE study; heavy drinking defined as ≥4 drinks/day for women and ≥5 drinks/day for men in applicable studies (although relapse could also include ≥5 drinking days/week in Kiefer et al. and was specified as ≥6 drinks/day for men in Morley et al.)

[c] Primary or co-primary efficacy endpoint

[d] Study participants were stratified by voluntary use of DIS (about half of pts in both groups were taking DIS)

[e] Calculated value

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Naltrexone-XR

- Approved in 2006
- Administered 380 mg IM once monthly to improve adherence
- Study showed people taking naltrexone-XR had significantly fewer heavy drinking days compared to those receiving placebo (Garbutt et al., 2005)
- This medication may have less nausea than the tablets
- Costly but insurance and some state Medicaid plans cover

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Naltrexone-XR

- Prior to starting check liver function and urine tox to ensure no opioid use
- Check labs periodically throughout treatment
- Possible adverse effects: nausea, vomiting, injection site reactions (e.g., induration, pruritus, nodules, and swelling), muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite

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Naltrexone-XR - administration

- PCSSnow.org
- https://vimeo.com/101010120/940e72505d

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Naltrexone-XR versus placebo (O'Malley et al., 2007)

	NTX-XR 380 mg	Placebo	P
Time to first drink	41 days	12 days	0.02
Continuous abstinence at end of study	32%	11%	0.02
Time to first heavy drinking event	>180 days	20 days	0.04
Median number of any drinking days/mo	0.7 days	7.2 days	0.005
Median number of heavy drinking days/mo	0.2 days	2.9 days	0.007

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Case Presentation - Katie

- A 27 year old female presents to clinic for a physical, pap, pelvic, and bloodwork.
- No hx of STDs. Not sexually active. No contraception used. LMP 1/18/14. G0P0.
- Hx of HPV, 2012, biopsy x2 (2012, 2013). Last pap and pelvic 2013. Interested in restarting Lexapro for anxiety. Lexapro 20mg for 8 months in 2012, feels "like it helped a lot".
- Currently sees a therapist every 2 weeks. Depression PHQ-9: 11.

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Case Presentation - Katie

- 2 months later came to get help for her EtOH problem.
- She has been missing work. she started drinking at age 18. she has tried AA before. she had stopped drinking for about 2months in past because of sad events happened in her life back then. She is seeing therapist
- she drinks at home and at bar. preferred drink is wine.
- has no H/o seizures or hallucinations.
- Admits to tremors the following day after her last drink.
- NO Family history of EtOH problem. brother had SUDin past.
- Taking her lexapro for anxiety.
- lately when she takes lexapro and drinks, she feels really dizzy.

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Case Presentation - Sherry

- 25 year old woman, 1st alcoholic drink when 18 years old
- Drinking increased to "keep up" with men she was dating
- 1st detox in 2016, said she was drinking two 40-oz Colts (9.4 standard drinks) or ½ fifth of vodka daily (8.5 standard drinks)
- Finished detox, said her goal was to drink socially, planned on drinking beer to control her use and consequences
- Attended IOP, was drinking within weeks of completing detox while in IOP
- Took naltrexone 50 mg sporadically after detox and in the past year

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Case Presentation - Katie

- Referred to treatment at Local IOP
- she has just finished with the program and loved it over there.
- She has been sober for 71 days now
- she reports cravings and anxiousness for which she takes
- Attends meetings 2-3/week. patient says she no sponser for AA but she is looking for one.
- She has a sponsor for sex/love addiction.
- She also sees a therapist every two weeks.

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Case Presentation - Katie

- Started on Vivitrol
- Doing much better
- Cravings decreased on follow-up

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Case Presentation - Sherry

- Returned for detox in 2018, was drinking six 25-oz 8% beers on a daily basis (19.8 standard drinks per day), occasionally drinking brandy in addition or instead of beers
- Serum ethanol 409 in the ED
- Medical history includes HTN, mild transaminitis (within 3 times the upper limit of normal)
- Meds: amlodipine

- Towards end of detox, she wants a medication to help with cravings for alcohol. Still has hope that in maybe in 3 months she can "drink socially." What medication would you recommend based on her history?

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Case Presentation - Samantha

- 60 year old woman, started drinking alcohol in her 20s
- Drinking on a daily basis since late 20s
- Has had several treatment episodes, longest period of abstinence 2 years while taking disulfiram
- Reports she has had disulfiram-alcohol reaction in the past due to drinking on this medication
- Most recently drinking 6 beers per day for 4 months
- Medical history: allergic rhinitis
- Medications: antihistamine as needed
- Labs within normal range
- Would like to restart disulfiram, what are some considerations you would take into account?

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Questions
Comments

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