MAT TRAINING

PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

Pharmacotherapy for Alcohol Use Disorder

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Larissa Mooney Disclosures

- Dr. Larissa Mooney has no financial relationships to disclose.

The contents of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose this information.

Target Audience

- The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.

Educational Objectives

- At the conclusion of this activity participants should be able to:
  - Summarize mechanisms of action for three approved medications for alcohol use disorder treatment
  - Describe common adverse effects of approved medications for alcohol use disorder
  - Report dosing regimens for alcohol use disorder medications

Outline

- Establishing alcohol use disorder (AUD) diagnosis
- Rationale for use of pharmacotherapy for alcohol use disorder
- Dosing, mechanism of action, and adverse effects for FDA approved medications for AUD
  - Disulfiram
  - Acamprosate
  - Naltrexone
- Evidence-based but off-label medication options for AUD: gabapentin and topiramate
- Case vignette: AUD pharmacotherapy options

AUD Meds are Underutilized

- Alcohol use disorder (AUD) is one of only 3 substance use disorders with FDA approved medications (tobacco, opioids, alcohol)
- Also have some efficacious non-approved pharmacotherapy options
- 17 million US adults have an AUD
- Yet very little use of AUD medications
- Fewer than 1 in 10 individuals treated for AUD receive medications (NSDUH 2013)

NIAAA 2014, NIH Publication No. 14-7974)

Context for Use of Pharmacotherapy

- Addiction is a chronic, relapsing brain disease characterized by compulsive use despite harmful consequences
- Medications may be used as a tool within a *comprehensive* treatment plan:
  - Medications (Bio)
  - Behavioral interventions (Psycho)
  - Social support, lifestyle changes (Social)

I'll only have one glass!

NIAAA Drinking Guidelines: "At-Risk" Cutoffs for AUD

- **Men**: No more than **4** drinks on any day and **14** drinks per week
- **Women**: No more than **3** drinks on any day and **7** drinks per week
- **Men and Women >65**: No more than **3** drinks on any day and **7** drinks per week

NIAAA, 2014

At-Risk, Binge, and Heavy Episodic Drinking

- "**At-risk"/heavy drinking**: use above NIAAA cutoffs (per prior slide)
  - 1 in 4 who exceed these limits has an AUD; remainder are at greater risk of development of AUD, injuries, and other health problems
- **Binge drinking** (NIAAA definition): 4 or more drinks in 2 hrs for women, 5 or more drinks in 2 hrs for men
  - Levels bring blood alcohol concentration (BAC) to 0.08 g/dL
- **Heavy Episodic drinking**: 4 or more drinks at least once in the past 2 weeks for women, 5 or more for men

Establishing AUD Diagnosis: DSM-5

- Use in larger amounts/longer periods than intended
- Persistent desire or unsuccessful attempts to cut down
- Excess time spent obtaining or recovering from use
- Craving or strong desire to use
- Failure to fulfill major role obligations
- Important social or recreational activities given up
- Recurrent use in physically hazardous situations
- Continued use despite knowledge of medical or psychological consequence(s)
- Continued use despite recurrent social or interpersonal problems
- Tolerance
- Withdrawal

Mild: 2-3 Criteria; **Moderate**: 4-5 criteria; **Severe**: 6 or more

Four Main Neurotransmitters Relevant to Alcohol Effects

endogenous opioids
Reduces pain and causes euphoria

glutamate
excitatory neurotransmitter…
speeds you up

dopamine
makes you happy

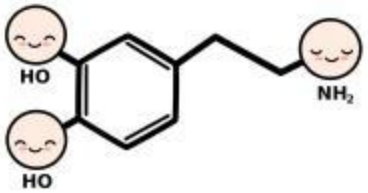
GABA
inhibitory neurotransmitter…
slows you down

Alcohol Neuronal Activity

1. Alcohol is consumed.

2. Endogenous opioids are released into the pleasure centers of the brain.

3. In response to this increased endogenous opioid activity, dopamine is released.



4. Dopamine makes the drinker feel good. This reinforces the behavior and increases the likelihood that it will recur.

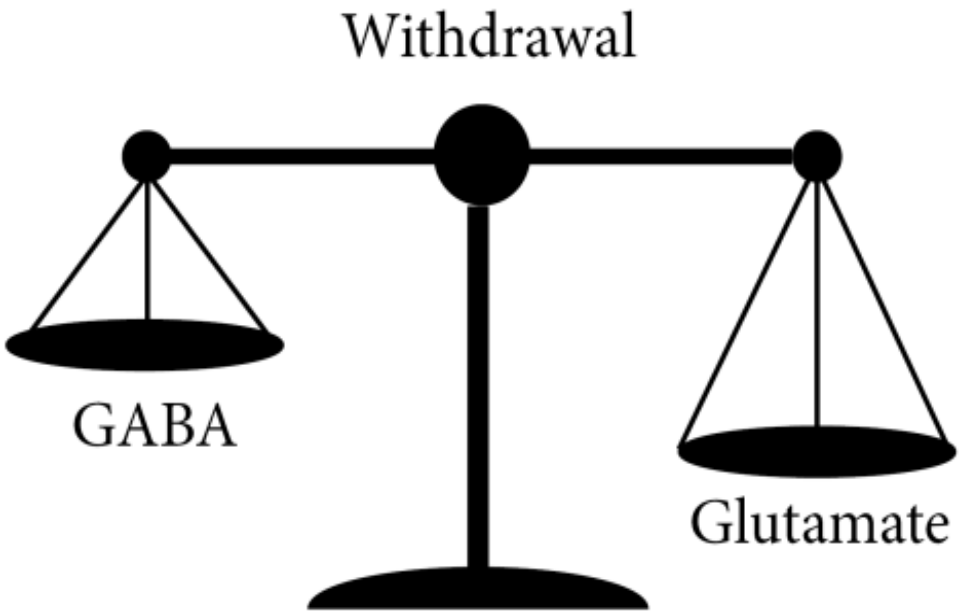
At the same time…

GABA is increased, slowing the brain down

Over time, the brain reacts to the over-abundance of GABA, by creating more receptors for glutamate—increasing the effect of glutamate and restoring balance

Neuronal Activity During Withdrawal

If alcohol is abruptly discontinued = Withdrawal



Symptoms/Risks: tremulousness, anxiety, elevated vital signs, seizures, delirium tremens (potentially fatal)

Case Vignette: Primary Care Setting

- 52 y.o. male with long history of heavy drinking, reports daily consumption of 2 bottles wine
- Denies other substance use and endorses symptoms of depression and insomnia
- Meets criteria for alcohol use disorder (AUD), moderate severity, and endorses cravings for alcohol
- Liver function enzymes are elevated 2 Xs upper limit of normal; macrocytosis is only other lab abnormality
- Denies symptoms of alcohol withdrawal or history of complicated withdrawal
- Has never received treatment for AUD or psychiatric disorder
- Has a history of chronic lower back pain for which he takes low-dose oxycodone 1-2 X/s month during flare-ups

Question 1

Which medication would you consider for treatment of alcohol use disorder in this patient?

1. Acamprosate
2. Disufiram
3. Naltrexone
4. (PO or IM)Gabapentin
5. Topiramate

Treatment of Alcohol Withdrawal Symptoms

1st step in evaluation process: would patient benefit from medically managed withdrawal (i.e. “detox”)?

Medications for Symptomatic Treatment

- Benzodiazepines
  - Symptom-triggered vs. standing taper
- Supportive meds

Thiamine, folate, and multivitamin

Alcohol Withdrawal Symptoms

- Minor withdrawal (within 36 hrs)
  - Tremor, diaphoresis, anxiety, insomnia, nausea/vomit
- Seizures (within 1-2 d after reducing/stopping EtOH)
  - Usually singular, generalized tonic clonic
  - Treat with benzos
- Hallucinosis (within 1-2 d after reducing/stopping EtOH)
  - Normal mental status, vitals
  - Usually visual (but may be auditory, tactile)
- Delirium Tremens (DTs) (1-4 d after withdrawal onset)
  - Disorientation, agitation, hallucinations
  - Autonomic instability, 5% mortality risk

CIWA Scale

Category	Range of scores	Scoring examples
Agitation	0 – 7	0=normal activity; 4=moderately fidgety and restless; 7=constantly thrashes about
Anxiety	0 – 7	0=no anxiety, at ease; 4=moderately anxious or guarded; 7=acute panic states
Auditory disturbances	0 – 7	0=not present; 4=moderately severe hallucinations; 7=continuous hallucinations
Clouding of sensorium	0 – 4	0=oriented and can do serial additions; 2=disoriented for date by no more than two calendar days; 4=disoriented for place and/or person
Headache	0 – 7	0=not present; 4=moderately severe; 7=extremely severe
Nausea or vomiting	0 – 7	0=no nausea and no vomiting; 4=intermittent nausea with dry heaves; 7=constant nausea; frequent dry heaves and vomiting
Paroxysmal sweats	0 – 7	0=no sweat visible; 4=beads of sweat obvious on forehead; 7=drenching sweats
Tactile disturbances	0 – 7	0=none; 4=moderately severe hallucinations; 7=continuous hallucinations
Tremor	0 – 7	0=no tremor; 4=moderate, with patient's arms extended; 7=severe, even without extended arms
Visual disturbances	0 – 7	0=none; 4=moderately severe hallucinations; 7=continuous hallucinations

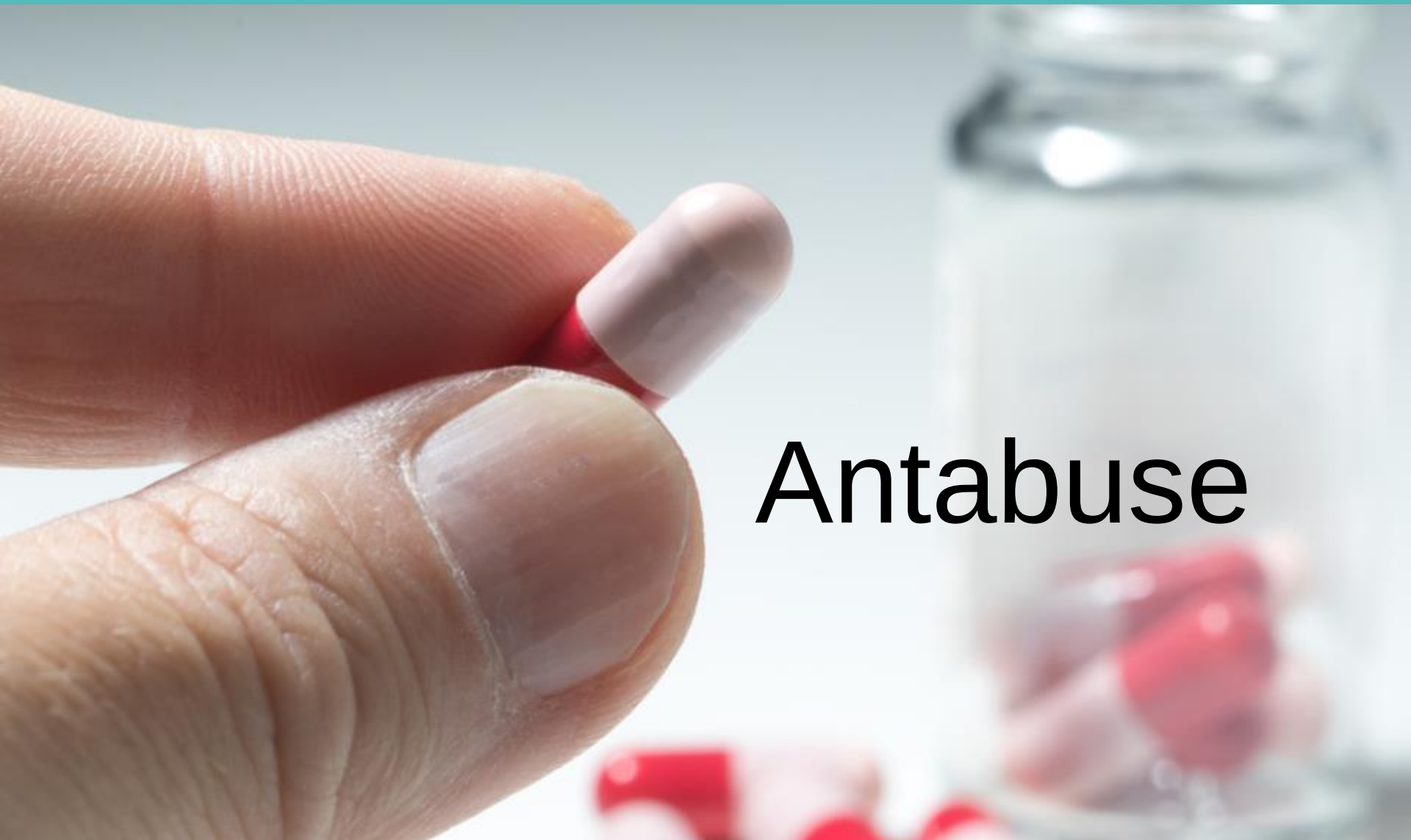
Sources: 1. Kosten, T. R., & O'Connor, P. G. (2003). Management of alcohol and drug withdrawal. *N Engl J Med, 348*(18), 1786. **2.** Saitz, R. (1998). Introduction to alcohol withdrawal. *Alcohol Health Res World, 22*(1), 5.

Alcohol Use Disorder (AUD) Pharmacotherapy

Medications for AUD have different mechanisms of action:

- Discourage drinking by creating unpleasant association with alcohol
  - *Aversive effect (i.e. "punishment")*
- Block or reduce euphoria from alcohol
  - *Reduce positive reinforcement*
- Reduce post-acute withdrawal
  - *Negative reinforcement*

Disulfiram



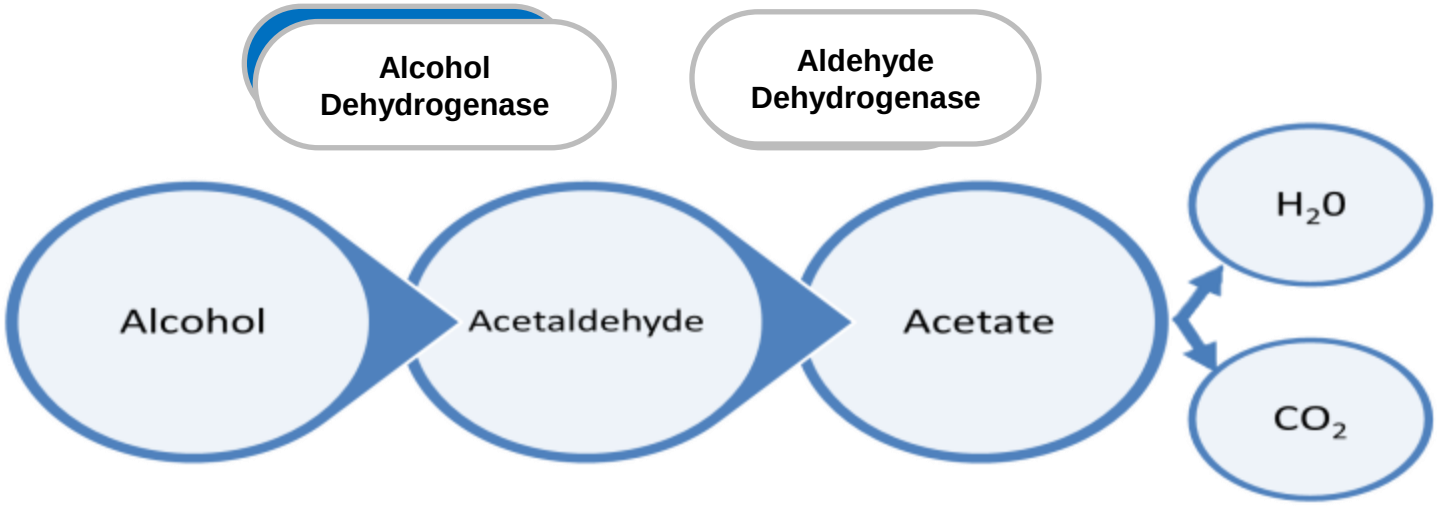
Disulfiram

- Marketed as Antabuse®
- FDA Approved in 1951
- Indication: An aid in the management of selected AUD patients who could benefit from “enforced sobriety” so that supportive and psychotherapeutic treatment may be applied to best advantage.
- Disfulfiram discourages drinking by making the patient physically ill when alcohol is consumed.

Additional Disulfiram Information

- **Third-Party Payer Acceptance:** covered by most major insurance carriers, Medicare, Medicaid, and the VA.
- **Dosing:** 250-500 mg by mouth per day
- **Abstinence Requirements:** must be taken at least 12 hours after last alcohol use
- **Adverse Effects:** metallic taste, hepatotoxicity, optic neuritis, peripheral neuropathy

Disulfiram Mechanism of Action



Disulfiram works by irreversibly blocking the enzyme aldehyde dehydrogenase. This causes acetaldehyde to accumulate in the blood at **5 to 10 times higher amounts** than what would normally occur with alcohol alone.

Disulfiram-Alcohol Reaction

Since acetaldehyde is toxic, a buildup of it produces a highly unpleasant series of symptoms

- throbbing in head/neck
- brief loss of consciousness
- throbbing headache
- lowered blood pressure
- difficulty breathing
- marked uneasiness
- copious vomiting
- nausea
- flushing
- sweating
- thirst
- weakness
- chest pain
- dizziness
- palpitation
- hyperventilation
- rapid heartbeat
- blurred vision
- confusion
- respiratory depression
- cardiovascular collapse
- myocardial infarction
- congestive heart failure
- unconsciousness
- convulsions
- death

Disulfiram-Alcohol Reaction

- Symptoms usually begin 10-30 min after alcohol consumed.
- As long as there is alcohol in the blood, the disulfiram-alcohol reaction will continue.
- Symptoms are usually fully developed when the patient's blood alcohol concentration is 50 mg per 100 mL, but mild reactions can occur in sensitive patients with levels as low as five to ten mg per 100 mL.
- Further, the disulfiram-alcohol reaction can be triggered when alcohol is consumed one or even two weeks after the last dose of disulfiram was taken.

Disulfiram Contraindications

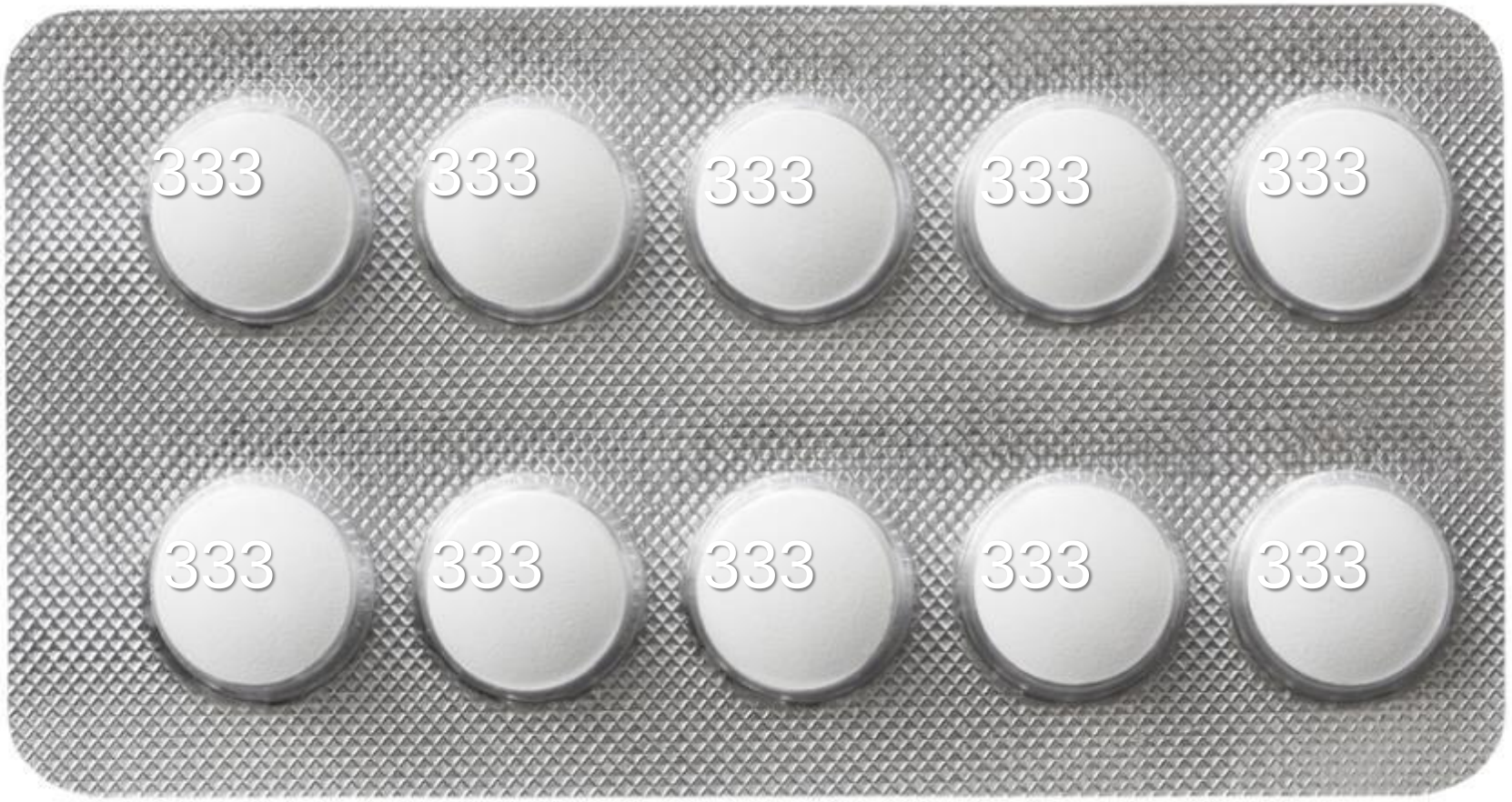
- The disulfiram-alcohol reaction usually lasts for 30 to 60 minutes, but can continue for several hours depending on the amount of alcohol consumed.
- Should never be administered to a patient when he or she has consumed alcohol recently or is currently intoxicated from alcohol.
- Should never be administered to a patient that has consumed alcohol-containing preparations such as cough syrup, tonics, etc.

Research about Disulfiram

- Best efficacy in motivated patients with supervised dosing
- Some effect on short-term abstinence, reduction in drinking days, time to relapse relative to placebo
- In randomized, double blind trials, participants treated with disulfiram did not maintain complete abstinence more frequently than those treated with placebo, but greater reduction in number of drinking days has been demonstrated (*problems with design*)

Skinner et al., 2014. PLoS ONE

Acamprosate



Acamprosate

- Marketed as Campral®
- FDA Approved in 2004
- Dosing: two 333 mg tablets PO three times a day
- Indication: For the maintenance of abstinence from alcohol in patients with alcohol use disorder who are abstinent at treatment initiation by reducing post-acute withdrawal symptoms.
- Side effects: diarrhea, GI upset
- Renal clearance; thus dose adjustment required in renal impairment

Acamprosate Mechanism of Action

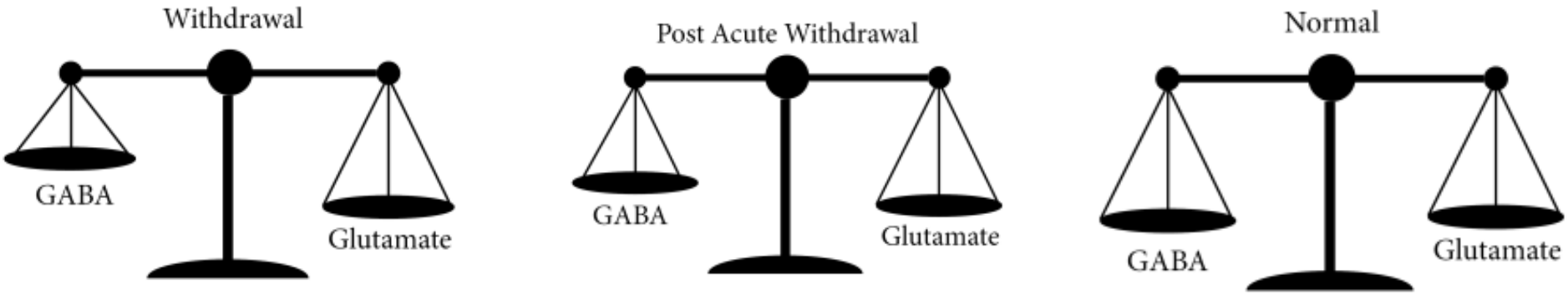
While the exact mechanism of action is not known, acamprosate is thought to be:

a glutamate receptor modulator

The brain responds to repetitive consumption of alcohol by increasing glutamate receptors, thereby counteracting alcohol's depressive (GABAergic) effects.

Scott et al., 2005

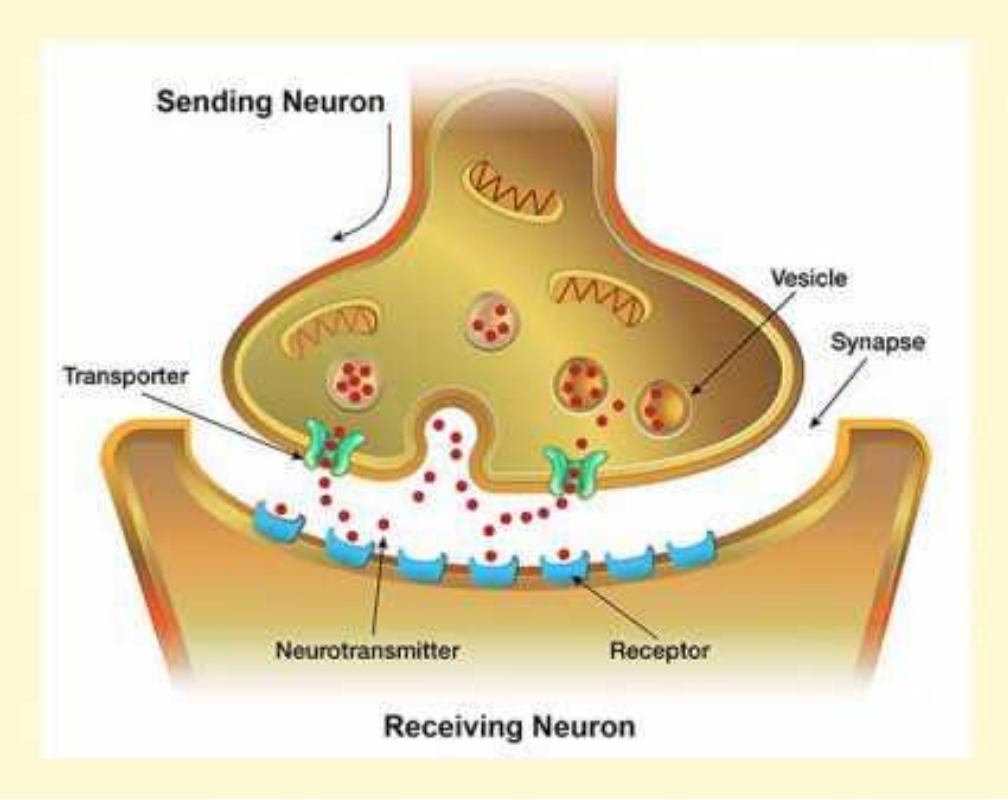
How Does Acamprosate Work?



- Even after acute withdrawal, the glutamate system continues to be overactive as it readjusts by down regulating the glutamate receptors.
- During this time, individuals may continue to feel anxiety, irritability and insomnia that can lead to relapse.

Acamprosate and Glutamate

- Acamprosate is thought to reduce amount of glutamate released, and
- Reduce the activity of the glutamate receptors



Research on Acamprosate for AUD

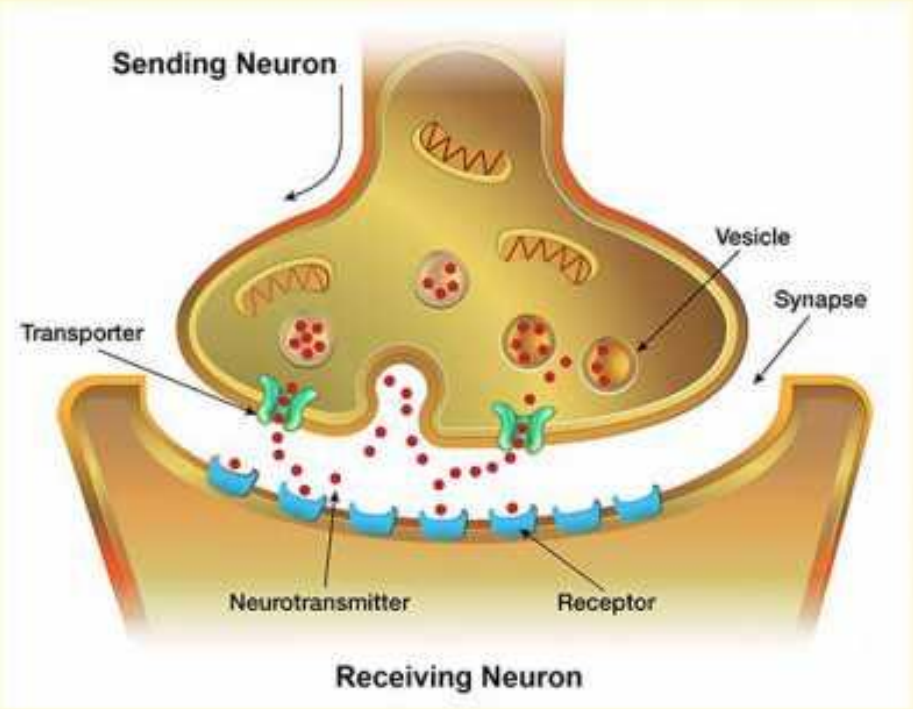
- In studies leading to FDA approval, participants treated with acamprosate were able to **maintain complete abstinence** more frequently and had **prolonged time to first drink** than those treated with placebo.
- Participants treated with acamprosate had a greater reduction in the number of drinking days during the entire study than those treated with placebo.
- In all three studies, participants treated with acamprosate were able to **regain complete abstinence** after one relapse more frequently than those treated with placebo.

Pelc et al., 1997; Sass et al., 1996; Paille et al., 1995

Naltrexone

Naltrexone Mechanism of Action

- Naltrexone is an opioid receptor antagonist and blocks opioid receptors.
- This prevents the effects of self-administered opioids.
- Subsequent dopamine release is also diminished after alcohol consumption, reducing the pleasurable effects.



Oral Naltrexone

- Marketed as ReVia® and Depade®
- **Indication:** used in the treatment of alcohol use disorder or opioid use disorder; for blockade of effects of exogenous administered opioids and/or decreasing pleasurable effects experienced by consuming alcohol.
- Administering naltrexone will cause opioid withdrawal symptoms in patients who are physically dependent on opioids.
- **Dosing:** one 50mg tablet per day (may start with 25 mg/day to minimize nausea)
- **Side Effects:** nausea, vomiting, elevated liver function enzymes (rare at standard dosing)
- Contraindication: Child-Pugh Class C

Additional Information

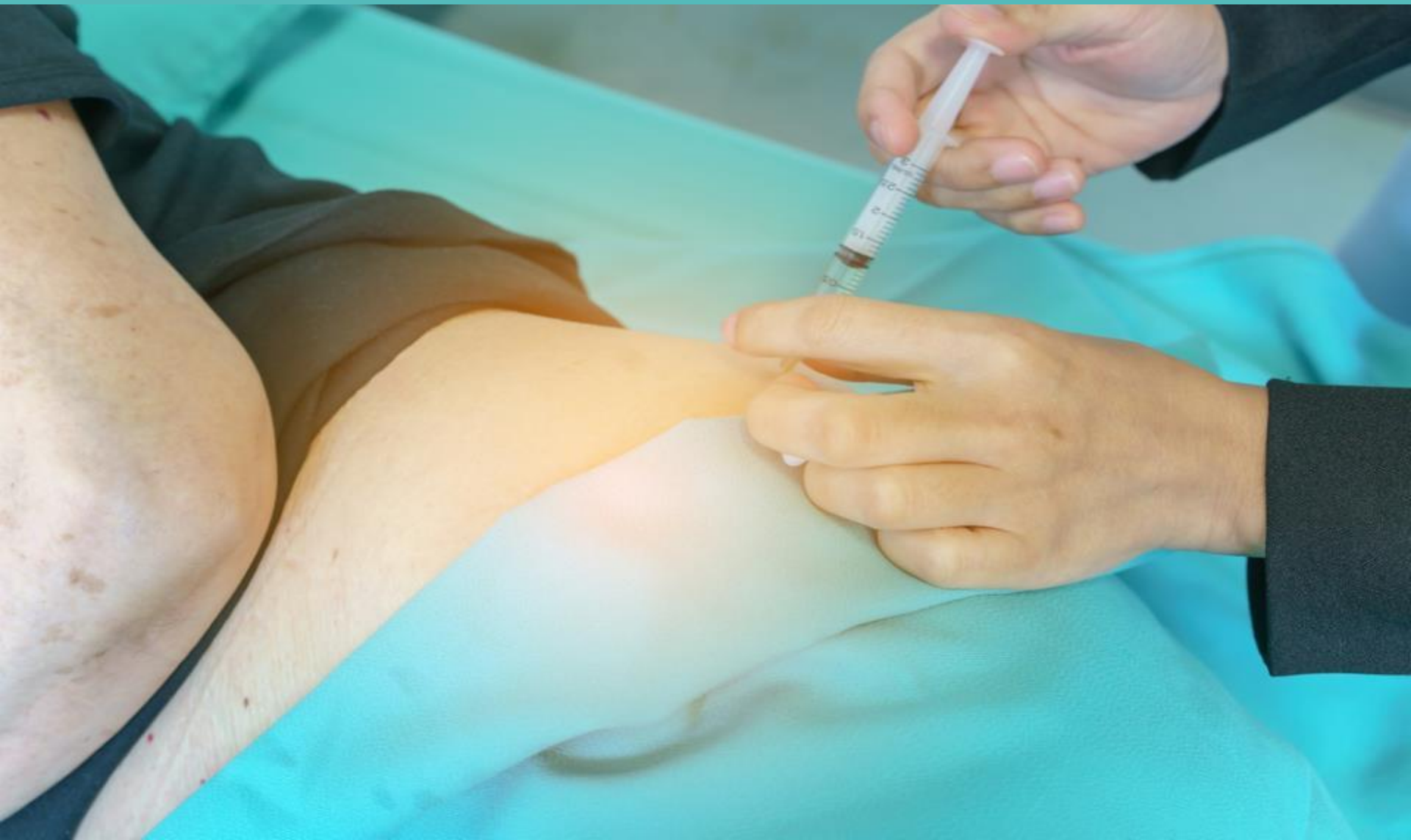
- **Third-Party Payer Acceptance:** covered by most major insurance carriers, Medicare, Medicaid, and the VA.
- **Abstinence requirements:** must be taken at least 7-10 days after last consumption of opioids; abstinence from alcohol is not required.

Research on Naltrexone for AUD

- In some studies, participants treated with naltrexone were not able to maintain complete abstinence more frequently than those treated with placebo.
- More consistently, participants treated with naltrexone had a **greater reduction in relapse** during the study than those treated with placebo and had reduced cravings.
- Participants treated with naltrexone had **fewer heavy drinking days** than those treated with placebo

Volpicelli et al., 1992; Pettinati et al., 2006

Extended-Release Injectable Naltrexone



Extended-Release Naltrexone

- Marketed as Vivitrol®
- **Dosing:** 380mg injection in deep gluteal muscle every 4 weeks; alternate sides each month.
- Blocks opioid receptors for **one entire month** compared to approximately 28 doses of oral naltrexone.
- **Adverse effects:** injection site reactions, nausea/vomiting, precipitated opioid withdrawal, depression, elevated LFTs
- ***Note:*** *Large doses of opioids may be required to override the blockade in a medically monitored setting*.

Research on Extended-Release Naltrexone for AUD

- Participants treated with extended-release naltrexone had a greater reduction in the number of heavy drinking days than those receiving placebo.
- Effects on heavy drinking were greatest in those who had **at least four days of abstinence from alcohol** prior to treatment initiation.
- In the subset abstinent for at least 4 days prior to treatment initiation, extended-release naltrexone also improved continuous abstinence rates.

O'Malley et al., 2007

Gabapentin for AUD

- Off-label but emerging evidence for use in treatment of alcohol use disorder
- Proposed mechanism: reduction of post-acute withdrawal symptoms (anxiety, insomnia, etc.)
- Study results: Improved rates of complete abstinence and no heavy drinking, particularly at 1800 mg/day total dose (titrate from lower dose, e.g. 300 mg PO TID)
- Improved symptoms of insomnia, dysphoria, and craving
- Improved outcomes in 1st 6 weeks when added to naltrexone
- Adverse effects: dizziness, fatigue, GI sx's, headache, impaired coordination, abuse potential

Mason et al., 2014 and Anton et al., 2011

Topiramate for AUD

- Approved as anticonvulsant and for migraine prophylaxis
- Off-label for AUD, good evidence from clinical trials in reduction of heavy drinking days, drinking outcomes
- Mechanism of action: facilitates GABA neurotransmission, inhibits AMPA-kainate glutamate transmission
  - May reduce post-withdrawal dysphoria, cravings, impulsivity
- Studies have titrated dose slowly up to 300 mg/day
- Adverse effects: cognitive, paresthesias, dizziness, altered taste, weight loss; (rare: kidney stones, metabolic acidosis, narrow-angle glaucoma)

Johnson et al., 2007; 2008

Case Vignette Review and Discussion

- 52 y.o. man who meets criteria for alcohol use disorder
- Elevated liver function enzymes
- Occasionally uses opioids for back pain flares
- No prior treatment history

1. Is naltrexone contraindicated in this patient?
2. Under what circumstance would you consider disulfiram?
3. Under what circumstance would you consider combining medications?
4. What should you recommend in addition to medications?

Thank You!

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PCSS Mentor Program

- The PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.
- PCSS mentors are a national network of providers with expertise in **medication-assisted treatment and addictions**.
- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.
- No cost to providers.

For more information visit:

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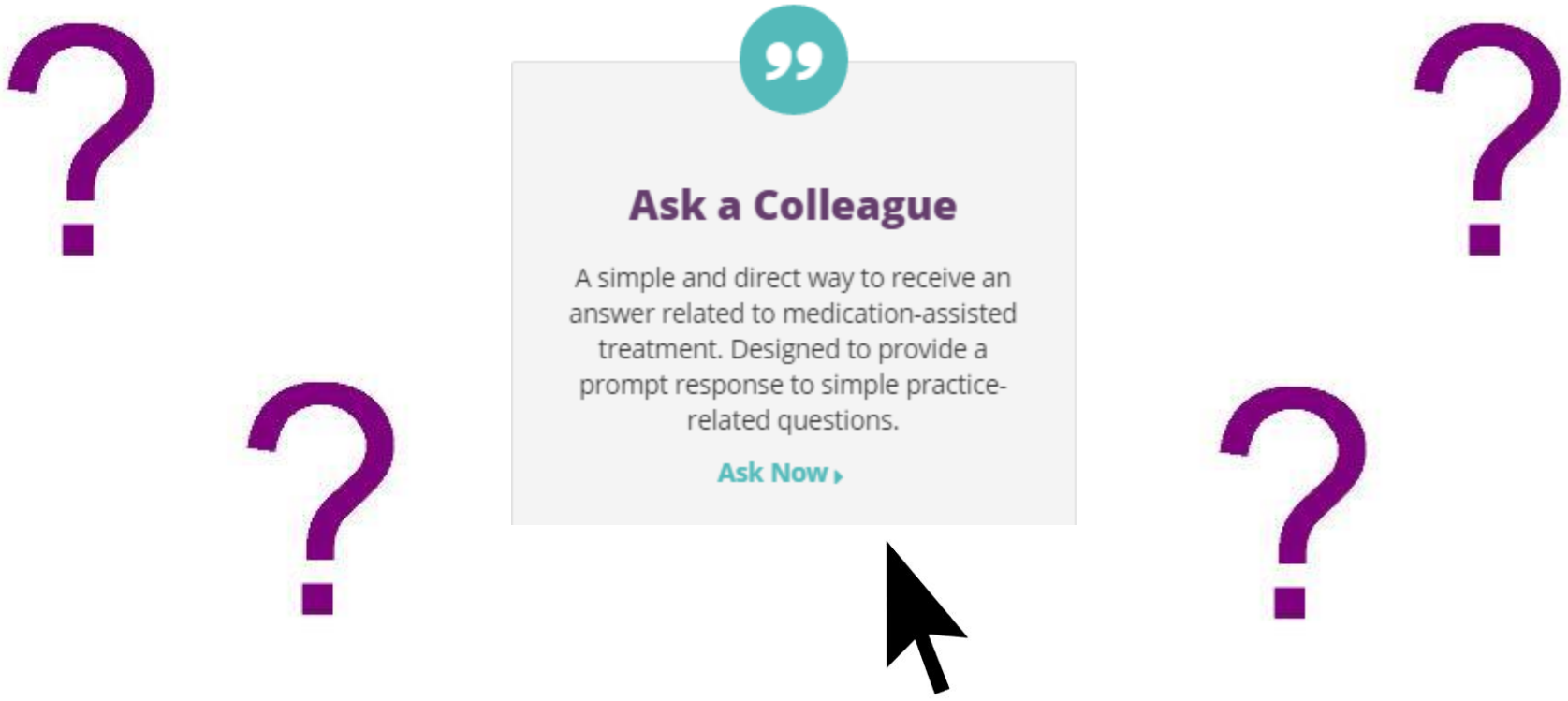
PCSS Discussion Forum

Have a clinical question?



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