Welcome to Virtual Colorado MAT Forum

- ***As you join you will be muted***
- ***Please unmute yourself by clicking on the microphone icon for asking questions and participation in discussions.***
- ***You may also put your questions and comments in the Chat box.***
- ***We encourage active participation!***

Monthly Webinars

- ***Virtual CO MAT Learning Forum***

  1st Thursday 12:30pm-1:30pm

- ***Induction Basics: Tips from the Trenches****

  2nd Tuesday 7:30am-8:30am

  **same topic each month*

- ***Denver Health Addiction Learning Collaborative***

  3rd Wednesday 12:15pm-1:15pm

Denver Health Addiction Journal Club

Scheduled dates for 2020

- *Every fourth Tuesday January-October*
- *November 10th*
- *December 8th*

Time; noon to 1 pm

To join; email ITMATTTRs2@UCDENVER.EDU

- See our website for previous presentations & resources as well as upcoming topics
  - https://www.practiceinnovationco.org/itmatttrs2/mat-forum/

Webinars

See our website for previous presentations & resources as well as upcoming topics

https://www.practiceinnovationco.org/opioids/mat-forum/

MAT Learning Forum August 6, 2020

Medication Assisted Treatment for Alcohol Use Disorder

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Objectives

- 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

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)

NIAAA Drinking Guidelines: "At-Risk" Drinking

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

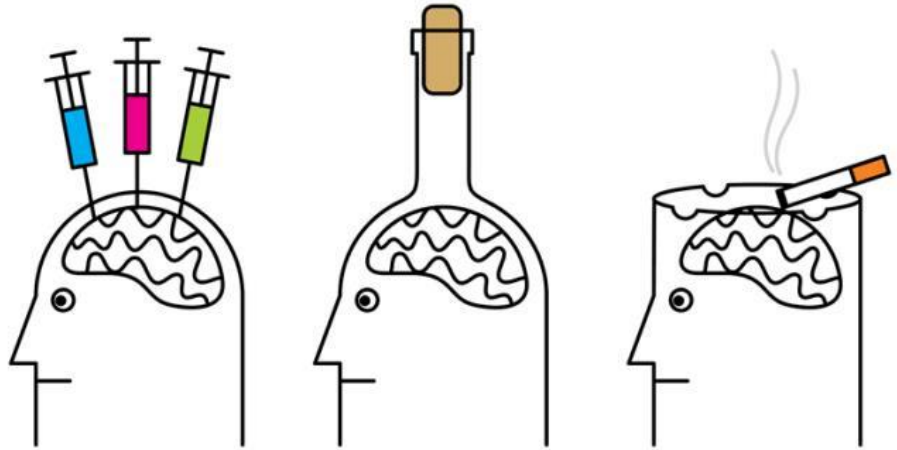
NIAAA, 2014

Substance Use Disorder

- The criteria on the following three slides must be present at any point during the prior year

DSM-5 Criteria – Loss of Control

- Taking larger amounts for longer than intended
- Wanting to cut down or quit but unable to
- Increasing time getting, using, and recovering from drug
- Craving



DSM-5 Criteria: Use Despite Consequences

- Failure to carry out obligations at work, school or home
- Continued use despite social and/or interpersonal problems
- Stopping or reducing other important activities
- Recurrent use in hazardous situations
- Use despite medical or psychological consequences

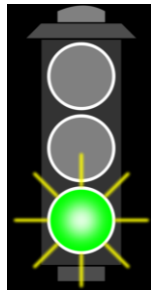
DSM-5 Criteria: Physical Dependence

- Tolerance
- Withdrawal

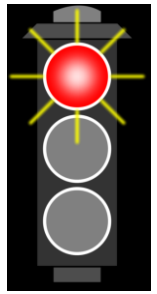
Four Main Neurotransmitters Relevant to Alcohol Effects

endogenous opioids
Reduces pain and causes euphoria

dopamine
makes you happy



glutamate
excitatory neurotransmitter…
speeds you up



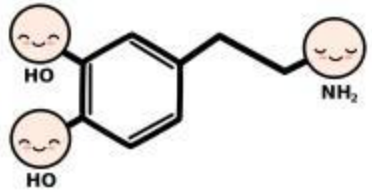
GABA
inhibitory neurotransmitter…
slows you down

Alcohol Neuronal Activity

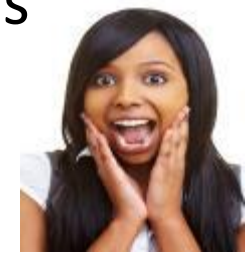
1. Alcohol is consumed.

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

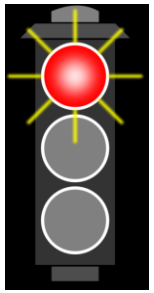
3. In response to this increased endogenous opioid activity, dopamine is released.



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

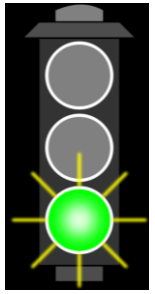


At the same time…



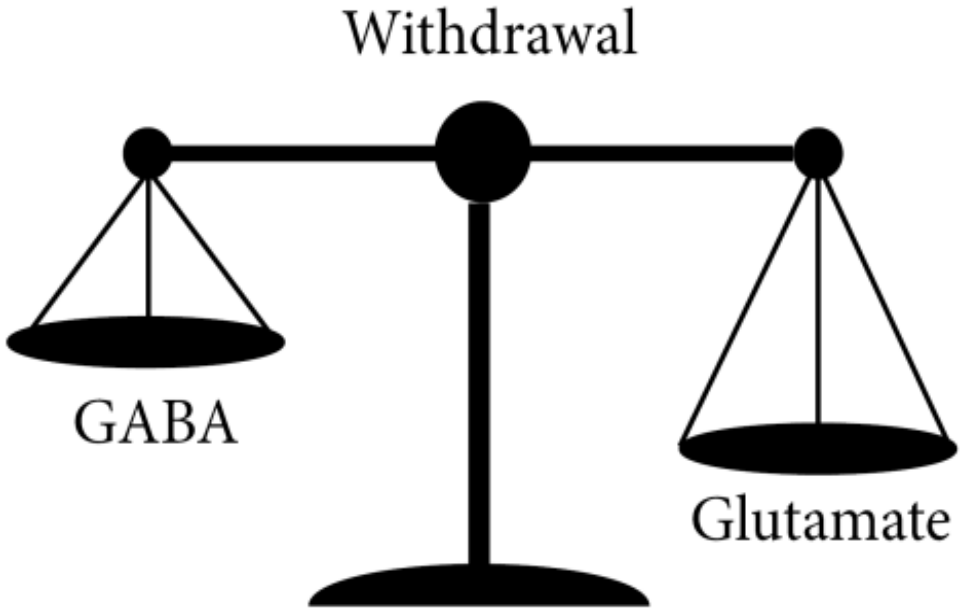
GABA is increased, slowing the brain down

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)

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

Drugs Used to Treat Alcohol Withdrawal

- Benzodiazepines (most common)
  - Chlordiazepoxide (*Librium*) – 25-50mg
  - Diazepam (*Valium*) – 10mg
  - Lorazepam (*Ativan*) – 2mg
  - Oxazepam – 15-30mg

Can also be given in fixed-dose schedules for w/d management.

- Anti-convulsants
  - Carbamazepine (*Tegretol*) – 600-800mg
  - Gabapentin (*Neurontin*) – 300-600mg TID
  - Oxcarbazepine (*Trileptal*) – 450-900mg
  - Valproic Acid (*Depakene*) – 1000-1200mg
- Beta-blockers
  - Atenolol (*Tenormin*) – dose dependent on HR
- Alpha-adrenergic agonist
  - Clonidine (*Catapres*) - 0.2mg

https://www.aafp.org/afp/2013/1101/p589.html#sec-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 (Antabuse)

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.
- **Mechanism:** Disfulfiram discourages drinking by making the patient physically ill when alcohol is consumed.

Additional Disulfiram Information

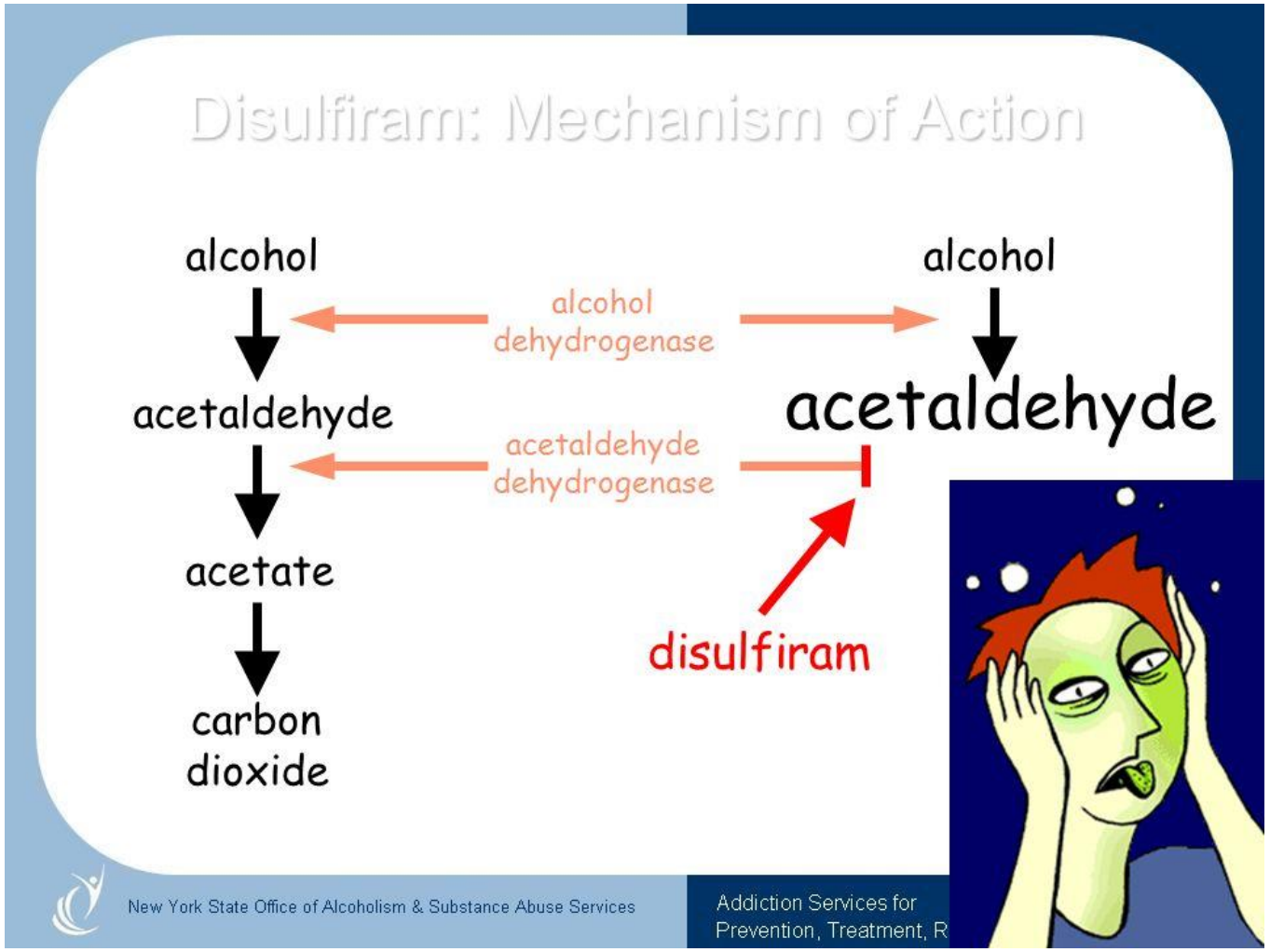
- **Third-Party Payer Acceptance:** covered by most major insurance carriers, Medicare, Medicaid, and the VA.
- **Dosing:** 250-500 mg po daily
- **Abstinence Requirements:** must be taken at least 12 hours after last alcohol use
- **Adverse Effects:** metallic taste, hepatotoxicity, optic neuritis,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

Disulfiram Mechanism of Action

- irreversibly blocks aldehyde dehydrogenase

- acetaldehyde accumulates in blood at **5 to 10 times higher amounts** than normal EtOH metabolism

- Acetaldehyde→dysphoria (flushing, nausea, headache)



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/100 mL, but mild reactions can occur in sensitive patients with levels as low as 5-10mg/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:** 333 mg tablets – 2 tabs PO TID
- **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

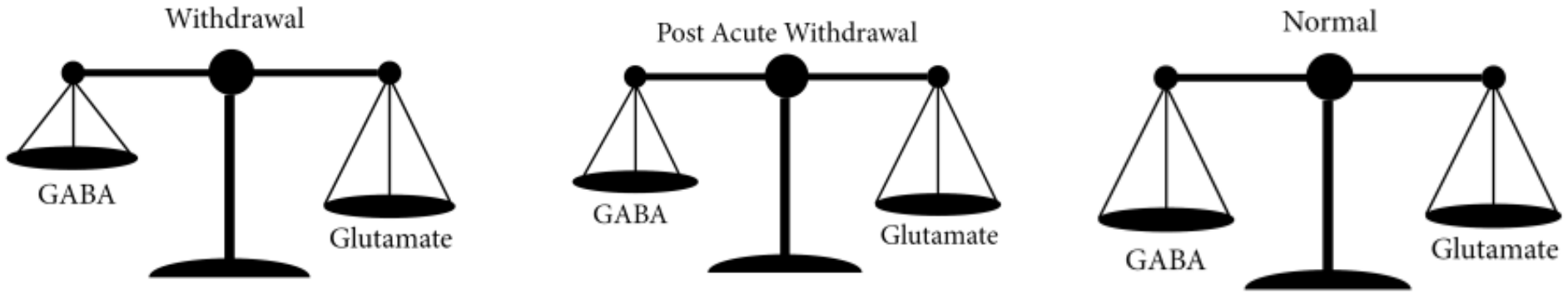
While the exact mechanism of action is not known, acamprosate is thought to be:

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

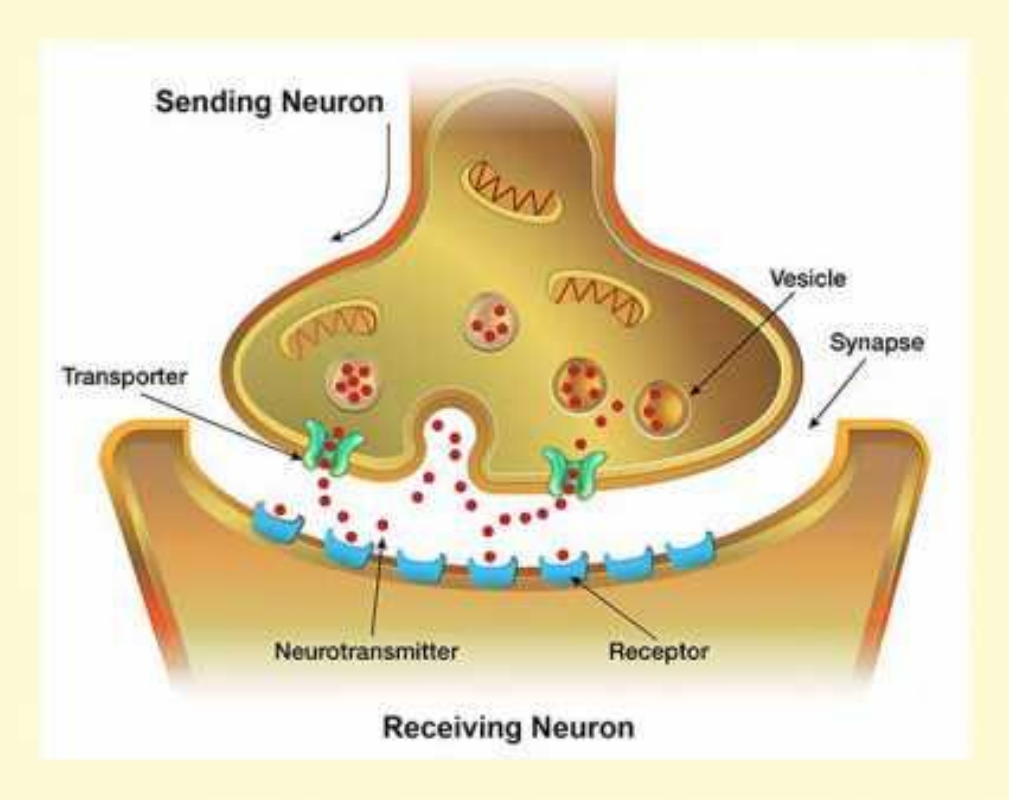
How Does Acamprosate Work?



- Even after acute withdrawal, the glutamate system continues to be overactive.
- 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 glutamate receptors



= Glutamate

Research on Acamprosate for AUD

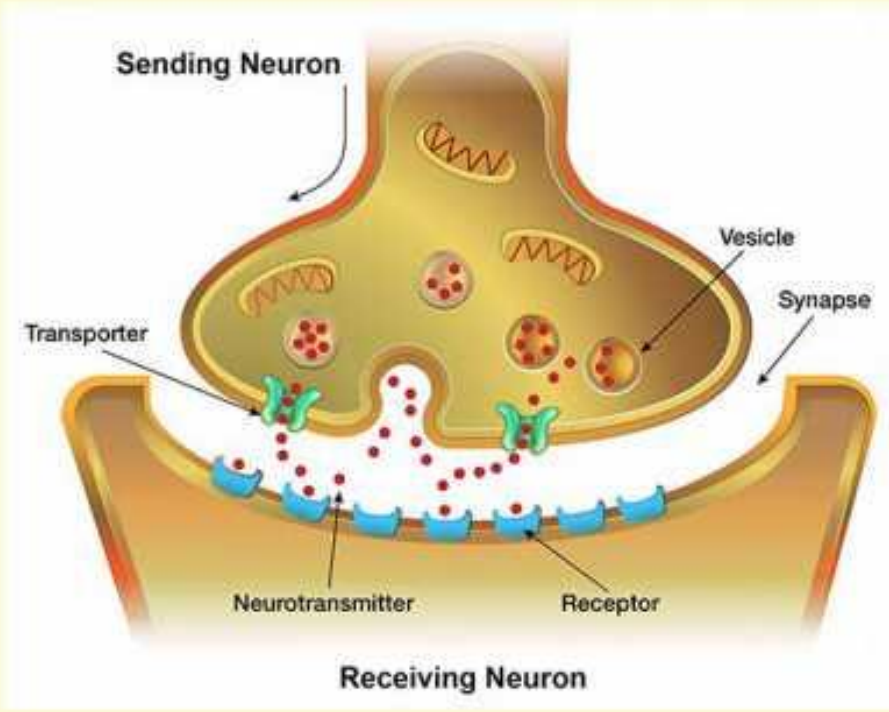
- In studies leading to FDA approval, participants treated with acamprosate were able to **maintain complete abstinence** more frequently and had **prolonged time to first drink** than those treated with placebo.
- Participants treated with acamprosate had a greater reduction in the number of drinking 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.
- Subsequent dopamine release is diminished after alcohol consumption, reducing the pleasurable effects.
- ALSO prevents the effects of self-administered opioids.



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, 3-4 times upper limit

Additional Information

- **Third-Party Payer Acceptance:** covered by most major insurance carriers, Medicare, Medicaid, and the VA.

- **Abstinence requirements:** Abstinence from alcohol is not required must be taken at least 7-10 days after last consumption of opioids;.

Research on Naltrexone for AUD

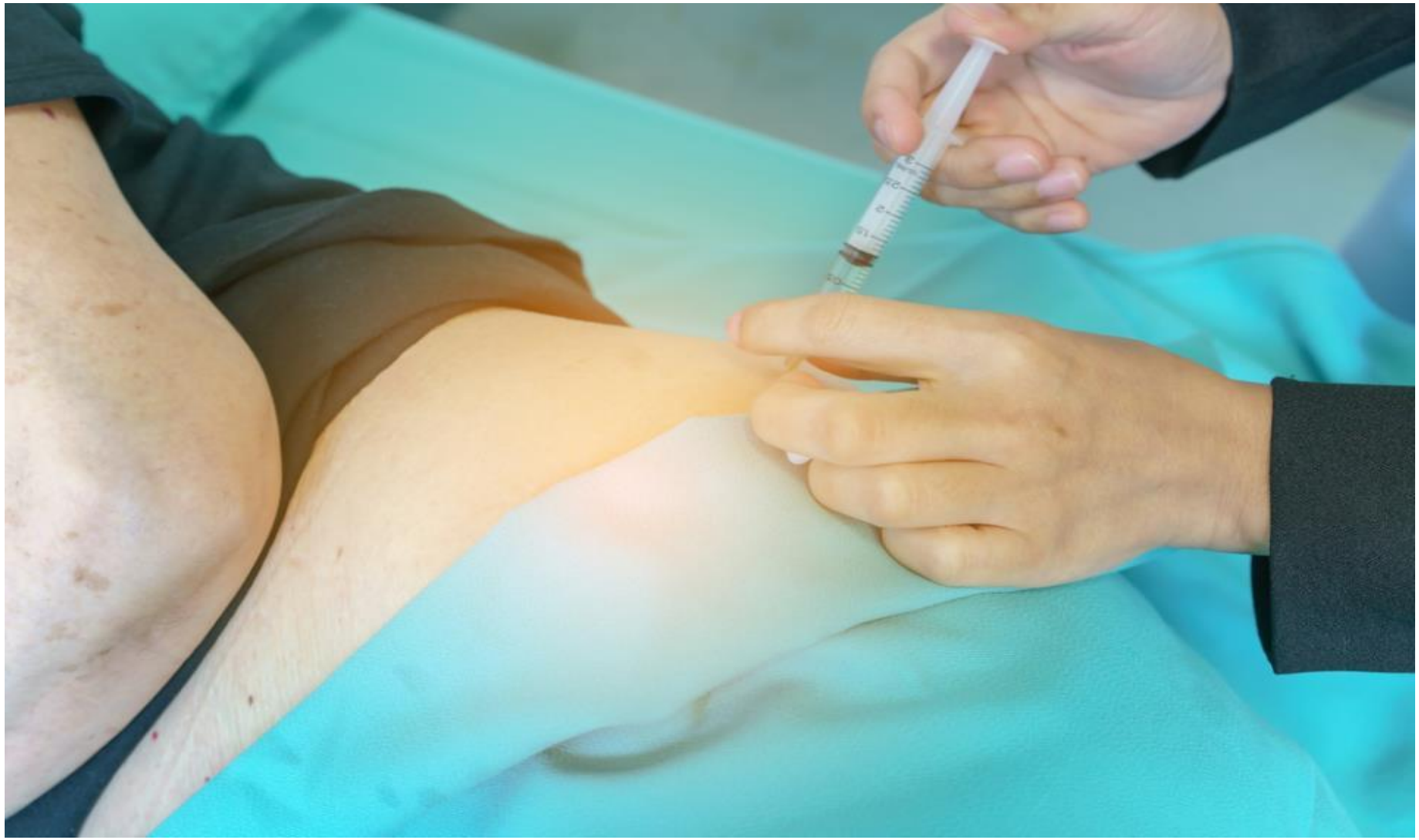
- In some studies, participants treated with naltrexone were not able to maintain complete abstinence more frequently than those treated with placebo.

- 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

Thank You!

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Practice Innovation Program

https://www.practiceinnovationco.org/alcohol/