MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Pharmacology for Alcohol & Opioid Use Disorders

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Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Agenda

- Talking to patients about SUD and medications
- Virtual care
- Pharmacology for opioids
- Pharmacology for alcohol

Avoid language with implicit stigma

Stigma: “an attribute, behavior, or condition that is socially discrediting”

- “Addict” or “Person with a substance use disorder”
- Are tox screens “positive” or “dirty”?
  - (Is an elevated high A1c “dirty”?)

Why discuss this?

- Stigma can push people away from treatment.

Substance use disorders are a biological disease

Brain disease vs Bad choices: FALSE dichotomy

Why discuss this?

- Shame is incredibly common and complicates recovery.
- Medicalizing can normalize their experience.
- Can improve willingness to consider medications.

Substance use disorders are chronic

Think DM, hypertension or epilepsy (not infections)

Why discuss this?

- People fantasize about 'cure.'
- It will always require some management. Sometimes a lot of attention, at others little.

Taking medications does not mean ‘substituting one drug for another’

Can you live life according to your own values?

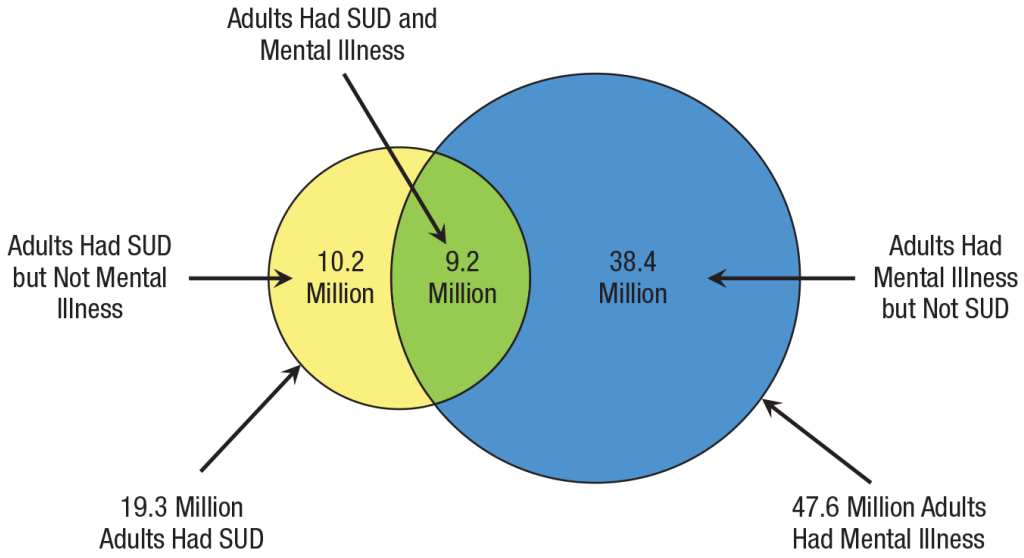
- sustainable with the substance?
- sustainable with medication?

Why discuss this?

- Stigma against medications
- Explore meaning of “addiction”

Diagnose and treat psychiatric comorbidities

- Self-medication hypothesis
- Should you treat SUD first or treat mental health issues first? Treat concurrently.



Substance Abuse and Mental Health Services Administration, 2019

Agenda

- Talking to patients about SUD and medications
- Virtual care
- Pharmacology for opioids
- Pharmacology for alcohol

Outpatient care in the age of COVID-19

- Increased need
  - CDC: 13% having started or increasing substance use to cope with COVID-related stresses
- Adoption of video-based or telephone-based virtual care
- Relaxation of toxicology screens

Czeisler, 2020

Outpatient care in the age of COVID-19

Benefits

- Decreased no-show rates
- Can increase access
- COVID-19 fear can promote change

Challenges

- Lack of privacy
- Lack of internet / phone access
- Increased need for services
- Worsening of comorbidities
- Clinician isolation
- Insurance coverage for virtual care long-term?

Agenda

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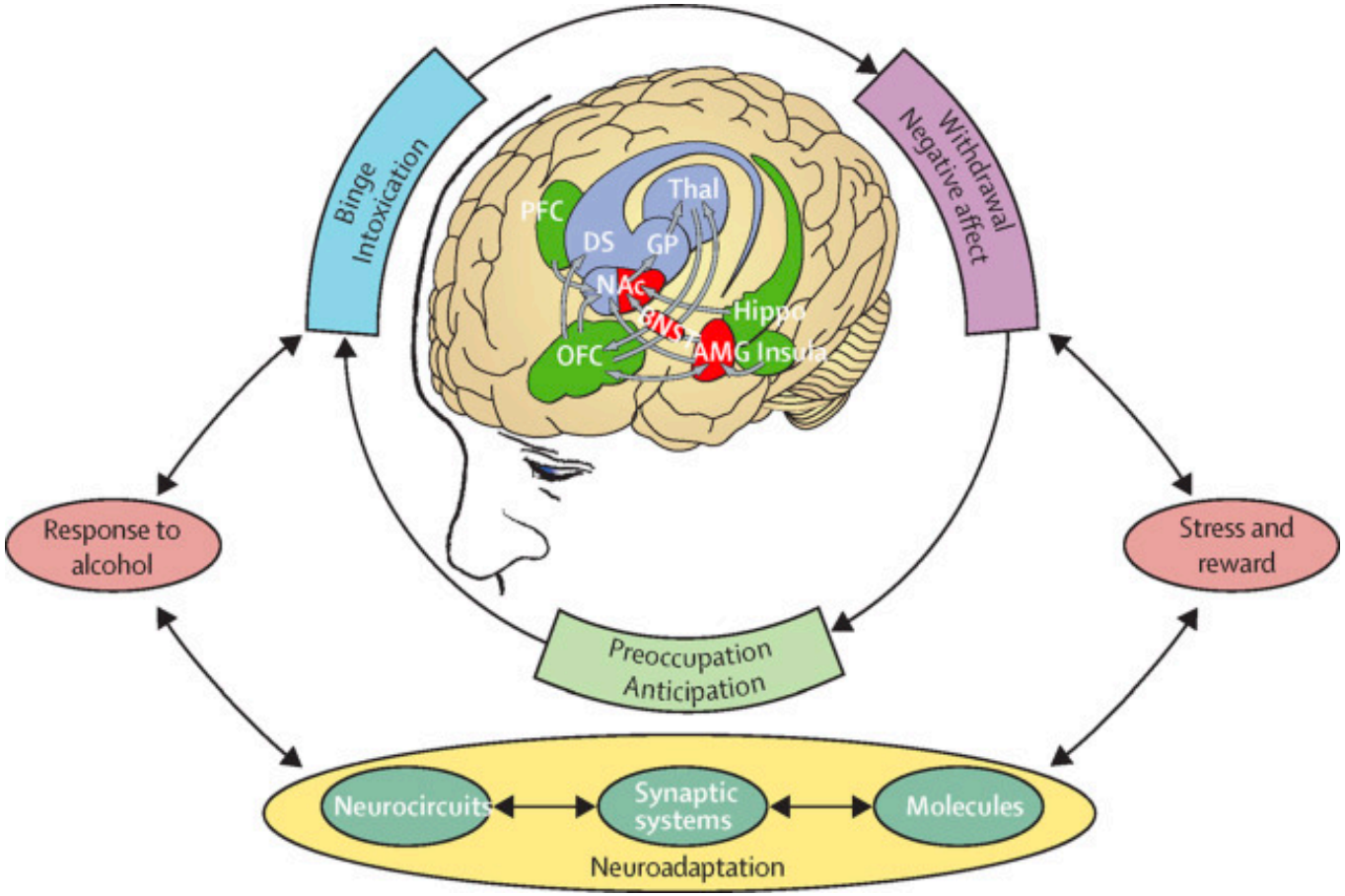
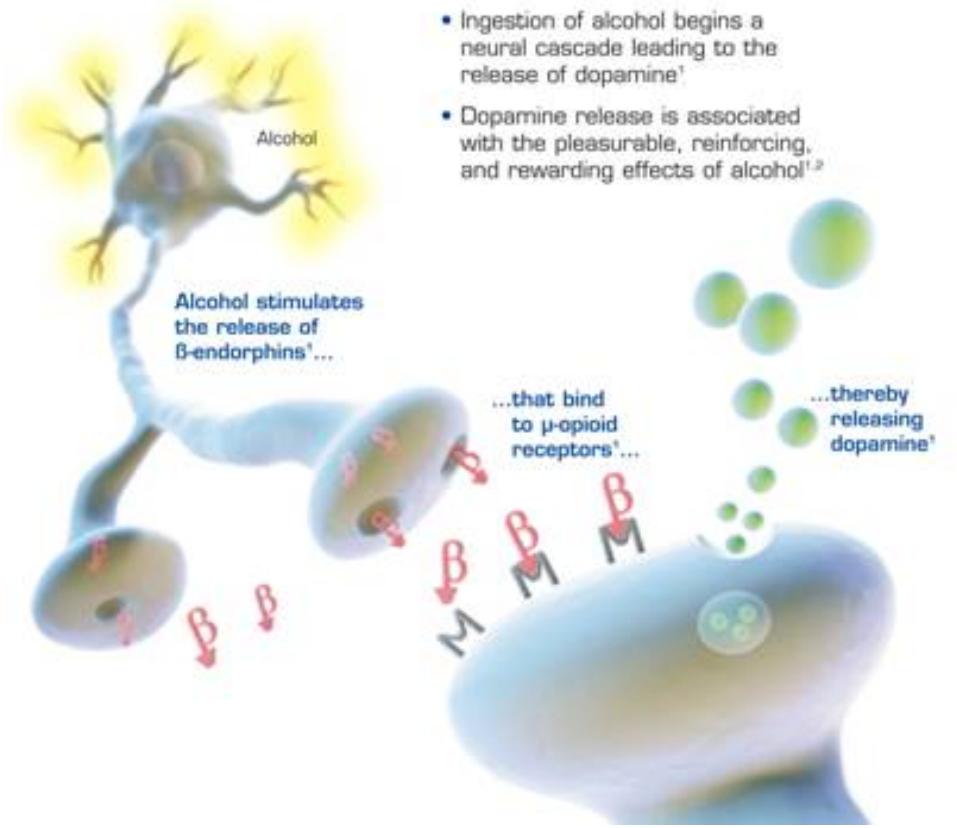
- Virtual care
- Pharmacology for opioids
- Pharmacology for alcohol



Koob & Volkow, 2016

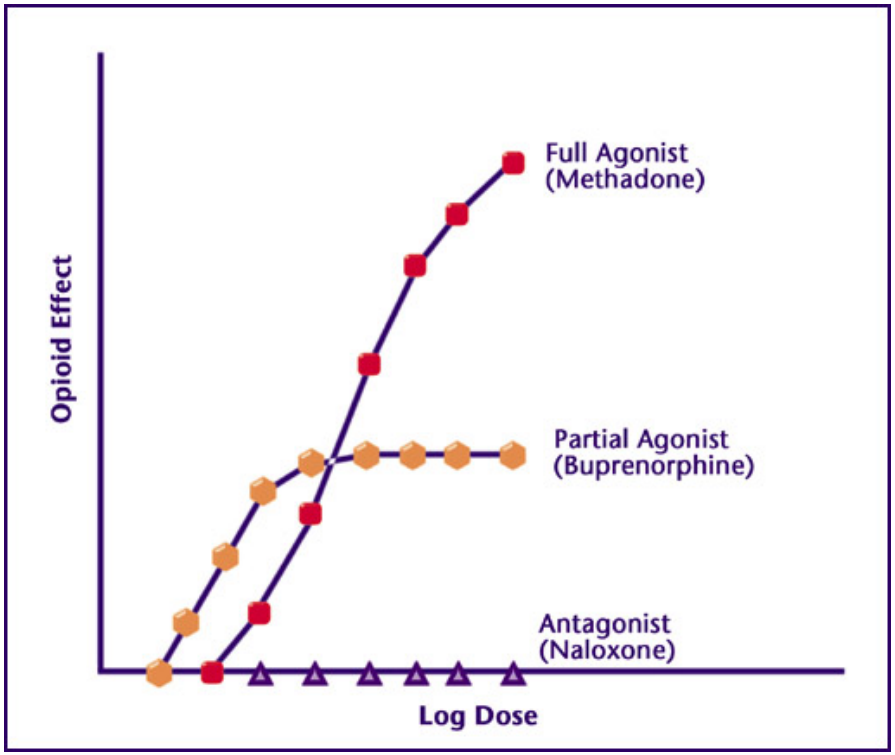
A closer view of reward circuitry

- GABA-ergic receptors upstream of dopamine neurons
- Release of endogenous opioids onto μ-opioid receptors cause dopamine release



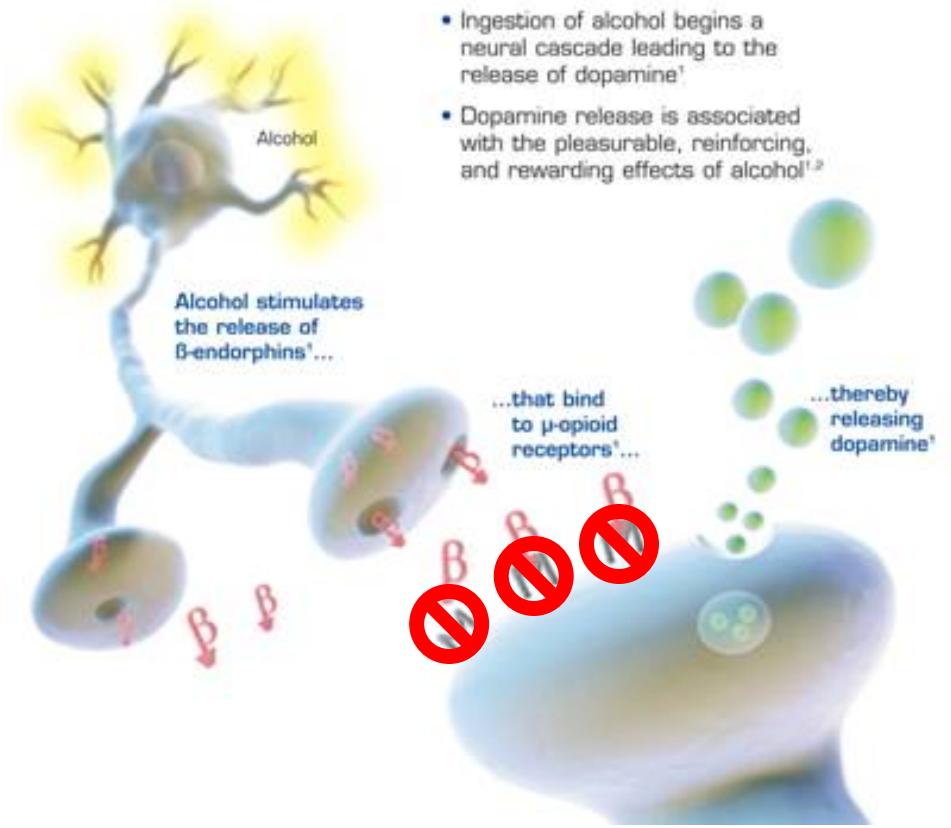
FDA Approved Options

- Naltrexone
- Buprenorphine
- Methadone



Naltrexone: mechanism

- Opioid receptor blocker interferes with dopamine release



Naltrexone: efficacy (opioids)

- Oral naltrexone not effective for abstinence or retention
  - Driven by non-adherence
  - Forcing adherence improved outcomes
- XR-naltrexone increased abstinence, decrease cravings, improved retention
  - Most patients discontinue within 6 months
  - Challenge to induce patients on naltrexone, perhaps aided by naltrexone-aided detox.

Minozzi et al., 2011; Jarvis et al., 2018; Krupitsky et al., 2011

Naltrexone

Dosing

- First dose 7-10d after short-acting opioids (up to 14d after buprenorphine/methadone)
- 25mg for first 6 days (with food to mitigate side effects). Then increase to 50mg
- 380mg qMonth injectable

Side effects

- Nausea / ↓ appetite
- Headaches
- Elevated LFTs (rare)
  - Baseline and within first month

Contraindications

- Opioid dependent
- LFTs >3x normal

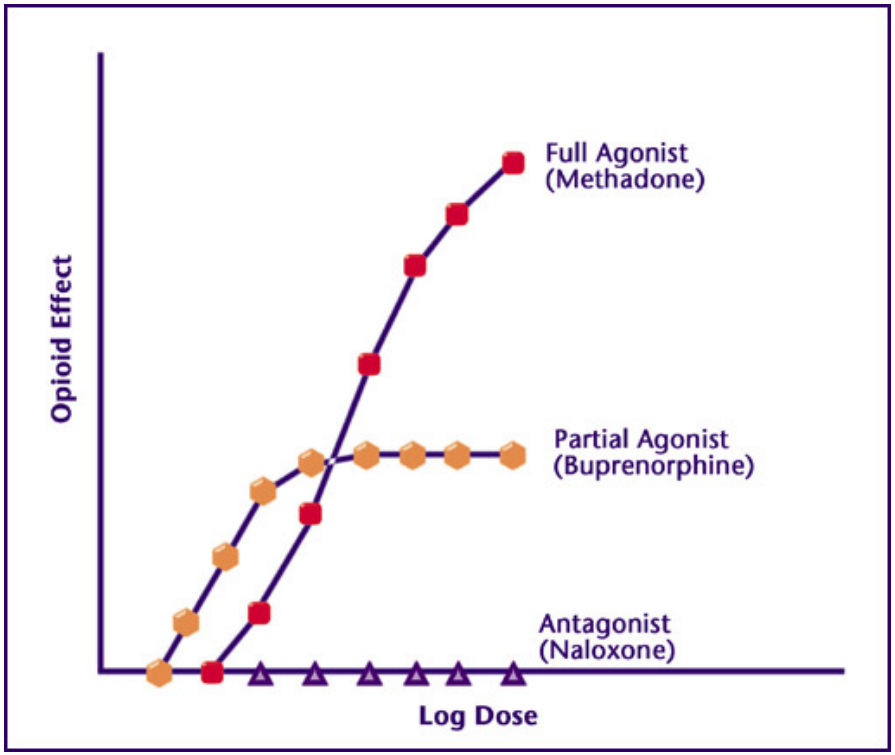
Pearls

- There exist naltrexone-assisted detox protocols to allow XR-naltrexone at day 7.
- Need to plan ahead for surgery

Sullivan et al., 2017

Buprenorphine mechanism

- Partial agonist at μ-opioid receptor
- Very small K_d (tight binding to μ-OR)
- Antagonist at κ-opioid receptor (antidepressant effect?)



Buprenorphine - effectiveness

- All doses retain in treatment better than placebo
- Doses >= 16mg per day suppress illicit use
- Reduces all-cause mortality (4.3 vs 9.5 deaths/1000 person-years in vs out tx)

Mattick, Breen, Kimber, & Davoli, 2014;
Sordo et al., 2017

Buprenorphine

- Office-based dosing
- Formulations
  - Sublingual: bup/nal (tab), Suboxone (film), Subutex (tab), Zubsolv (tab)
  - Intramuscular (q30 days): Sublocade
  - Subdermal (q6 months): Probuphine
  - Transdermal: Bunavail

- Naloxone prevents injection (little absorption)
  - Buprenophine only (Subutex) if pregnant

Buprenorphine

Dosing

- 2-32mg daily
- Can split doses
  - Analgesic benefits 6-8 hours
- Doses 16+mg daily shown to decrease positive tox screens.

Mattick, Breen, Kimber, & Davoli, 2014

Buprenorphine - Induction

- **Withdrawal:** sx from ↓ opioid availability
- **Precipitated withdrawal:** intense sx from ↓ opioid activity after adding opioid antagonist or partial agonist
- **Bupe induction:** prevent precipitated withdrawal by not starting buprenorphine until opioid activity is low (although patient in some withdrawal)

Buprenorphine - Injectable

RBP-6000 (Sublocade): q30d at 300mg or 100mg

- 300mg/2mo + 100mg / 4 months beat placebo and equivalent to 300mg / 6mo.
- Often requires some amount of supplemental sublingual bup/nal for first few weeks

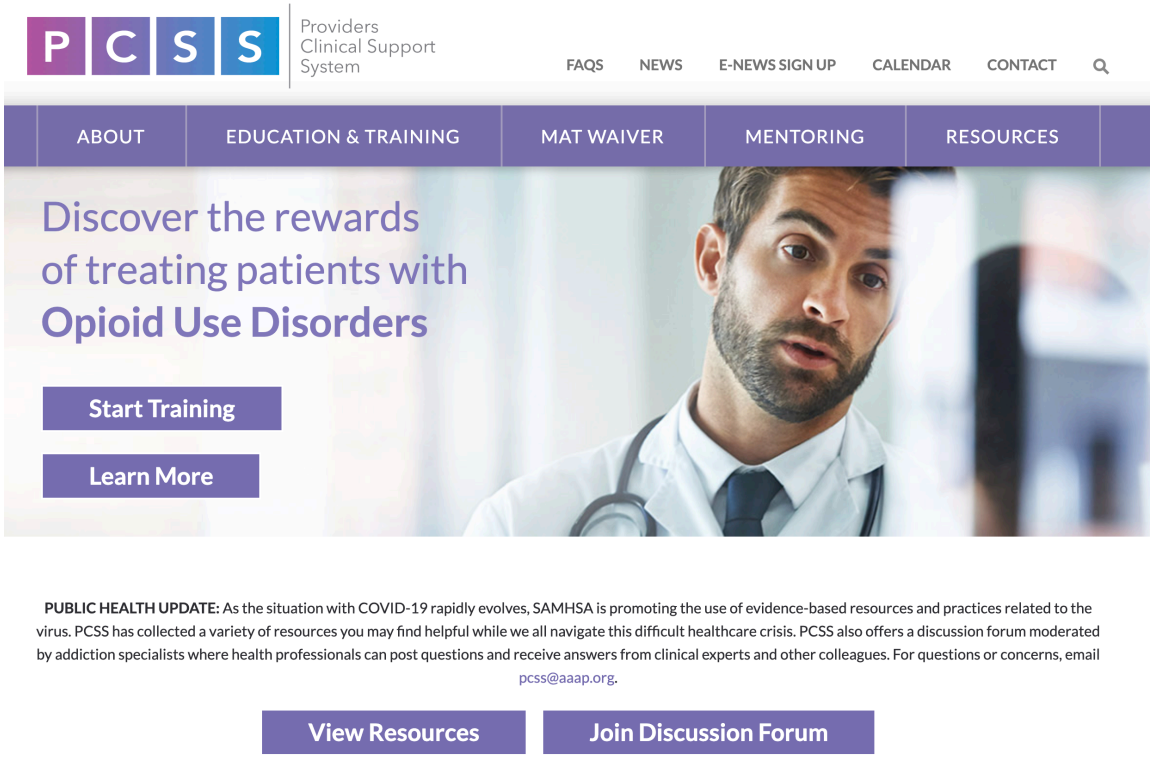
CAM2038 (Brixadi): weekly or monthly; flexible dosing

- Non-inferior response rates to sublingual bup/nal
- Tentative approval by FDA (as of Aug 2020)

Haight et al., 2019; Lofwall et al., 2018

Buprenorphine – Get started

Learn more at https://PCSSnow.org



- Free training re: SUD care
- Online X-waiver training
- Online mentoring
- Free CME

Methadone

Pharmacology

- Variable half-life 24-36 hrs
- Analgesic benefit for 8-12 hrs
- Liver metabolism
  - Induces own metabolism

Methadone

Dosing

- Only at licensed Opioid Treatment Programs (OTPs)
- Can earn “take home” doses
- Typical dose range: 60-120mg once daily
- Liver metabolism
  - Induces own metabolism

Methadone

Contraindications

- Respiratory compromise
  - Severe COPD, severe OSA
- QTc > 500ms
- Paralytic ileus
- Prescribed benzodiazepines (relative)

Methadone

Whom to refer?

- Need structure of daily dosing
- Chronic pain
  - but recall limited duration of analgesic effect; eventual split dosing?

How to choose MOUD treatment

Injectable Naltrexone vs Buprenorphine/Naloxone

- US: 570 in opioid detox randomized to XR-NTX or Bup/Nal with 24 week f/u
  - Better induction with Bup/Nal (94%) vs XR-NTX (72%)
  - If successfully inducted, similar rates of relapse, positive urines tox screens, adverse events
- Norway: 159 outpatients randomized to XR-NTX or Bup/Nal with 12 week f/u
  - XR-NTX non-inferior to bup re: retention and superior re: illicit opioid use

Ongoing trials to compare XR-Bup with sublingual Bup/Nal and XR-NTX.

Lee et al., 2017
Tanum et al., 2017

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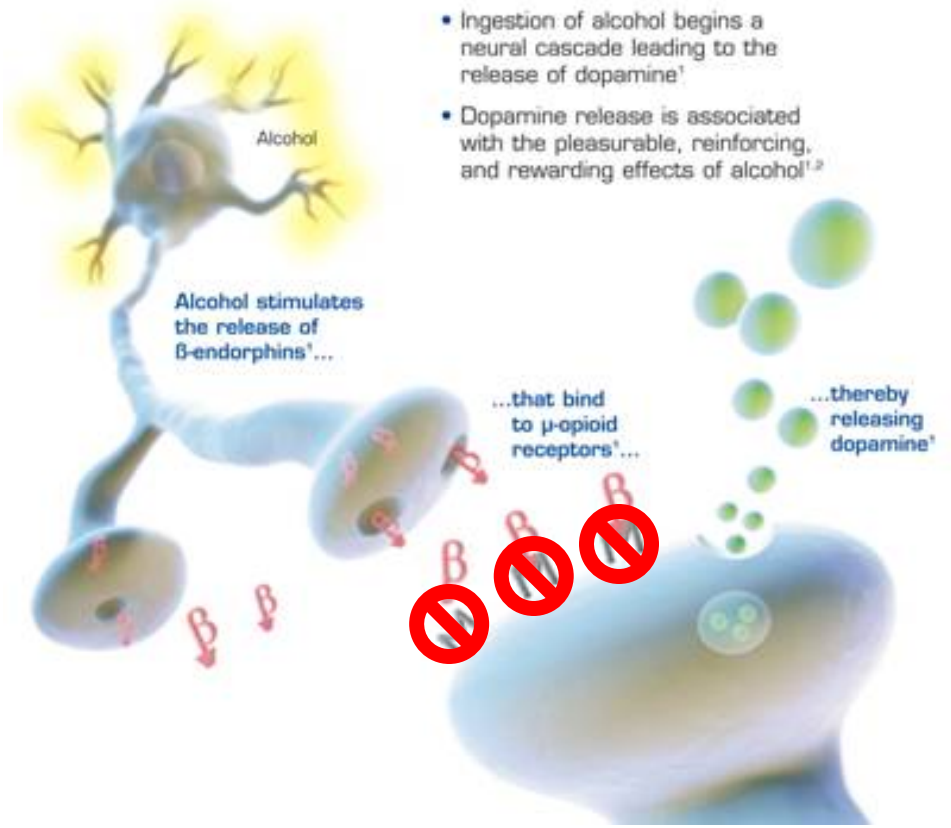
- Pharmacology for alcohol

FDA Approved Options

- Naltrexone
- Acamprosate
- Disulfiram

Naltrexone: mechanism

- Opioid receptor blocker interferes with dopamine release from alcohol



Naltrexone: efficacy (alcohol)

Oral naltrexone

- Reduced heavy drinking (NNT=12)
- Decrease daily drinking (NNT=25)
- Abstinence (NNT=20)
- Decrease cravings

Extended-release (IM) naltrexone

- Similar as naltrexone
- Ongoing clinical trial vs oral naltrexone

Rösner et al., 2010; Jonas et al., 2014

Naltrexone (for alcohol)

Dosing

- 50mg daily
- 25mg for first 6 days, with food to mitigate side effects
- 380mg qMonth injectable

Side effects

- Nausea / ↓ appetite
- Headaches
- Elevated LFTs (rare)
  - Baseline and within first month

Contraindications

- Opioid dependent
- LFTs >3x normal

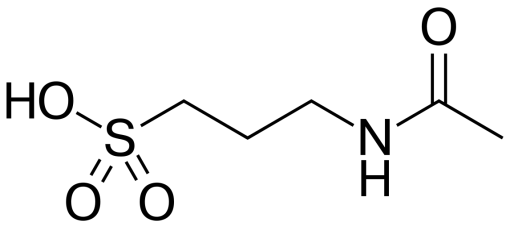
Pearls

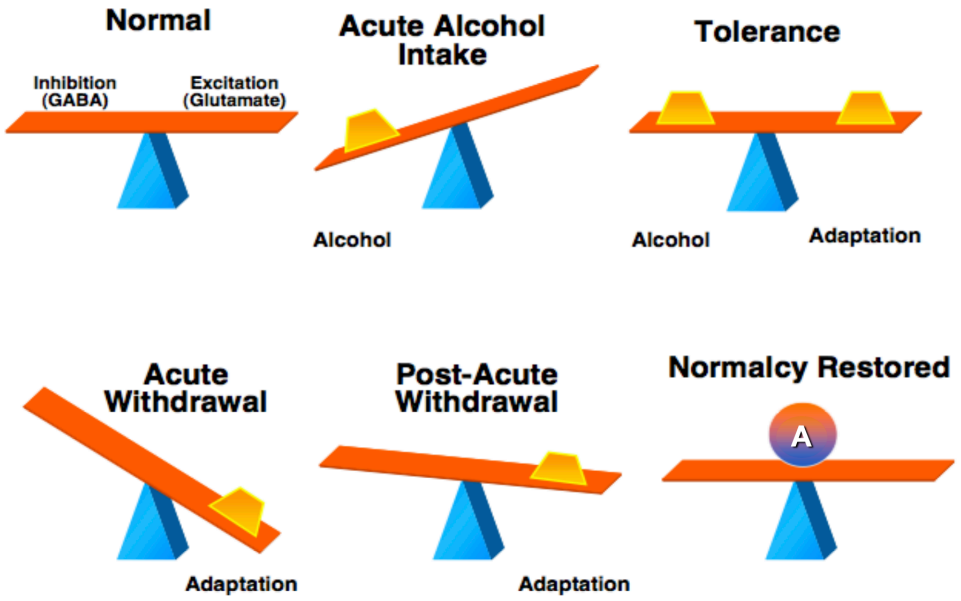
- Can drink on naltrexone
- Less evidence for prn use, or ”The Sinclair Method”
- Stop 48-72 hours before surgery

Sinclair, 2001

Acamprosate: mechanism

- Mechanism unclear
- Restores “balance” of excitatory to inhibitory tone
  - mGluR5 antagonist (thereby inhibitory modulator of NMDA-Rs)





Littleton, 2007

Acamprosate: efficacy

Acamprosate

- Maintained abstinence (NNT=8)
- No effect on return to heavy drinking
- Decrease cravings

Jonas et al., 2014

Acamprosate

Dosing
- 666mg tid (333mg pills)
- 333mg tid initially

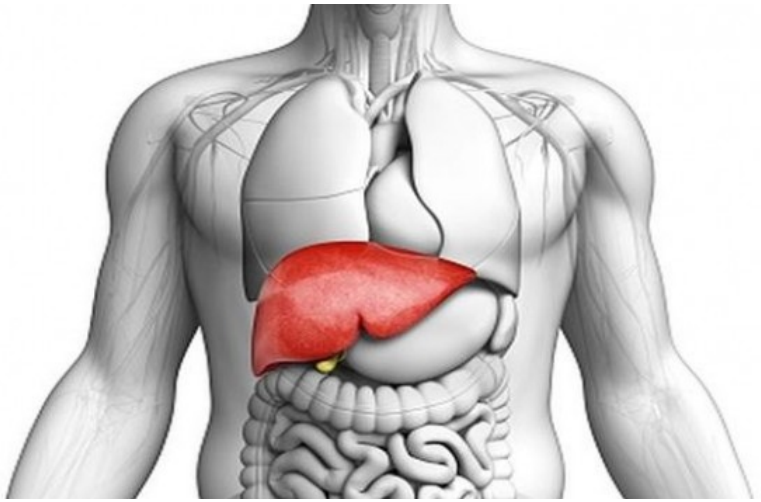
Side effects
- Flatulence/diarrhea
- Nausea
- Itching

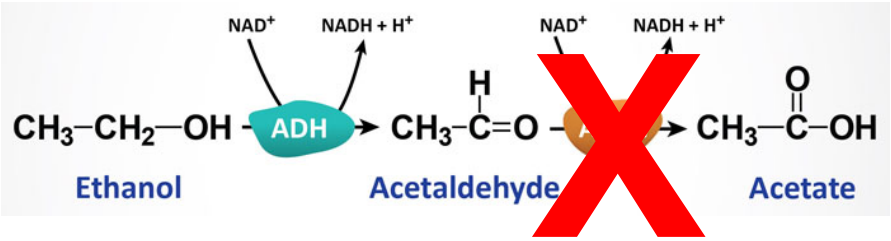
Contraindications
- CrCL <30
- Hypercalcemia
- (TC≥10.3; IC ≥5.4

Pearls
- Particularly helpful for negative-emotional state craving (e.g., drinking when sad)
- Can improve alcohol-alterations to sleep architecture
- Best if started while abstinent

Disulfiram – mechanism of action

- Inhibiting acetaldehyde dehydrogenase
- Build up acetaldehyde:
  - Decrease BP
  - Increase HR
  - Sweating
  - Flushing
  - Headaches
  - Vomiting
- Psychological med





Disulfiram - efficacy

- Significantly improved:
  - abstinence
  - Percentage of abstinence days
  - Time to first drink
- Benefits seen only in open-label trials

Skinner, Lahmek, Pham, & Aubin, 2014

Disulfiram

Dosing

- 250-500mg daily
  (or ↓ dose or ↓ freq)
- First dose 12+ hrs after last drink
- Disulfiram reaction up to 14d after last dose

Side effects

- Drowsiness (8-10%)
- Garlic/metallic taste
- Fulminant hepatic failure
  - Check LFTs: baseline, 2 weeks, 2 months

Contraindications

- Severe myocardial disease / coronary occlusion
- Confusion
- LFTs > 3x normal

Pearls

- MUST education on reaction
  - No sauces, perfume, hand santiizer, etc
- More effective when ingestion is monitored
  - Timothy O'Farrell trust conversations
- Useful to prevent impulsive drinking

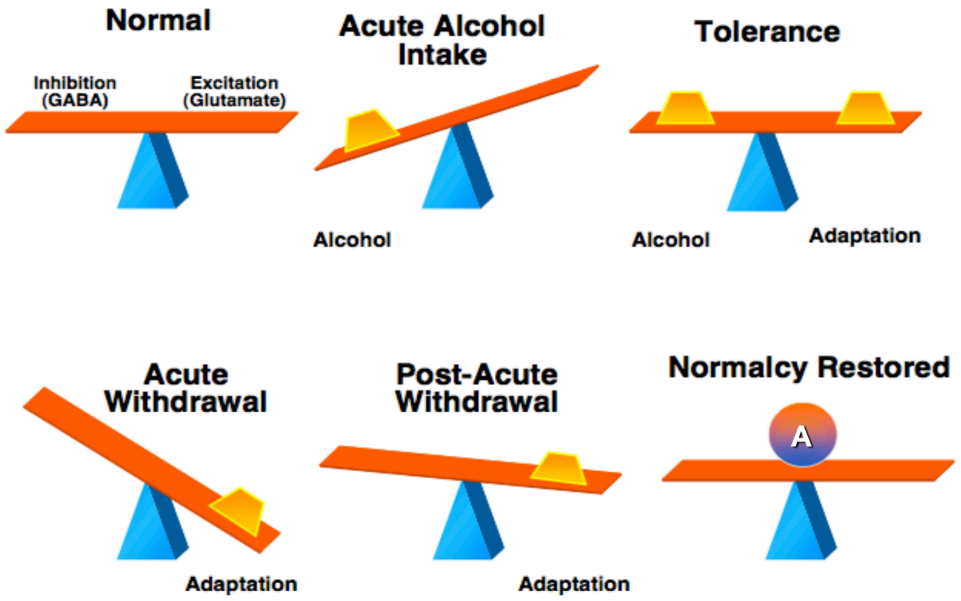
O'Farrell, Allen, & Litten, 1995

Non-FDA Approved Options

- Topiramate
- Gabapentin
- Baclofen
- Valproate
- Ondansetron

Topiramate: mechanism

- Mechanism unclear
- Facilitates $GABA_A$ activity and decreases AMPA and kainate glutamatergic receptors
- Normalizes VTA GABA activity



Topiramate - efficacy

- Decreases % heavy drinking days
- Decreases drinks per drinking day
- Fewer drinking days

- Non-inferior to naltrexone (non-significantly better)
  - Target dose of 300mg in one study; 200mg in another study

Baltieri, Daró, Ribeiro, & de Andrade, 2008; Flórez et al., 2011

Topiramate

Dosing

- 200-300mg divided bid

Side effects

- Cognitive dulling
- Appetite suppression
- Kidney stones

Contraindications

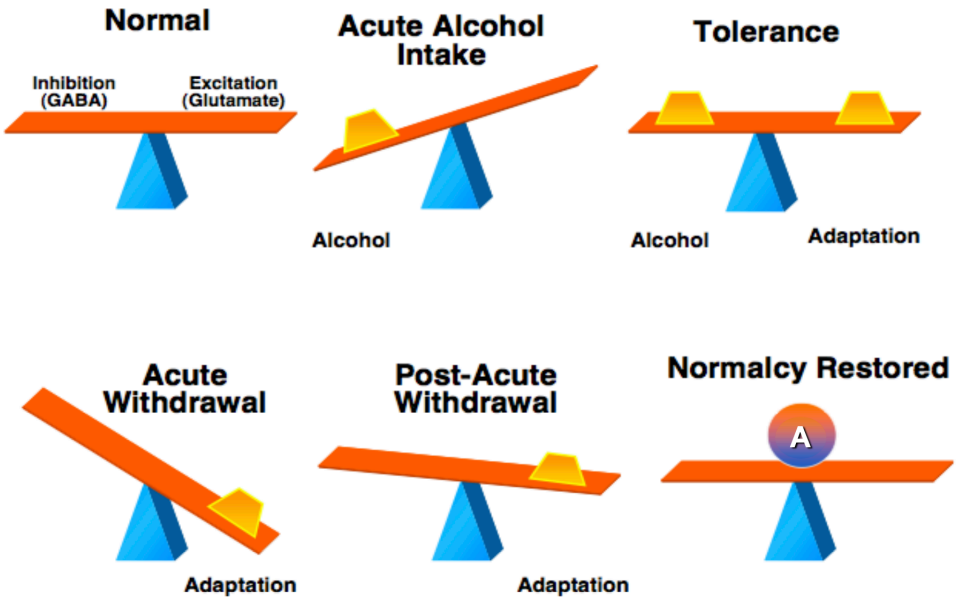
- Previous kidney stones

Pearls

- Increase dose by 25mg per week, until 100mg, then by 50mg per week to avoid cognitive dulling
- Particularly useful if patient desires migraine management and/or weight loss

Gabapentin - mechanism

- Inhibits Voltage-gated calcium channel
- Decrease glutamate release
- (No relation to GABA)



Gabapentin - efficacy

- Decreased number of drinks
- Abstinence (NNT=8)
- Delayed return to heavy drinking

- Gabapentin enacarbil – no impact on heavy drinking days, abstinence, drinks per week, etc.

Leung, Hall-Flavin, Nelson, Schmidt, & Schak, 2015;
Falk et al., 2019

Gabapentin

Dosing
- 600mg tid

Side effects
- Cognitive dulling
- Appetite suppression
- Kidney stones

Contraindications
- Previous kidney stones

Pearls
- Increase dose by 25mg per week, until 100mg, then by 50mg per week to avoid cognitive dulling
- Particularly useful if patient desires migraine management and/or weight loss

Mason et al., 2014

Take home points

- Your attitude and language around substance use disorders can make an important difference to patients.
- Virtual care is different, imperfect, and necessary in times of increasing use.
- Medications can be an effective tool towards improving outcomes for SUDs.
- Please get an X-waiver for buprenorphine prescribing. https://pcssnow.org

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