Pharmacotherapy of Substance Use Disorders

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Reports no relationships with ineligible companies.

Today's Talk

- Selective topics, not comprehensive overview
- Focus on the key medications to treat substance use disorders

What is the Overall Role of Pharmacotherapy in the Treatment of Substance Use Disorders?

- Pharmacotherapy supports the treatment of alcohol (perhaps cannabis, methamphetamine) use disorder
- Pharmacotherapy drives the treatment of opioid use disorder

Alcohol Use Disorder

What Should be the Goal of Alcohol Use Disorder Treatment?

- Abstinence?
- Reduction in drinking?
- If so, by how much?
- Different medications for different goals?

Drinking Reduction: Considerations

“Drinking” vs. “Heavy Drinking”

Heavy Drinking Day

≥5 standard drinks in a day (M)

≥4 drinks in a day (F)

One Standard Drink

- 12 ounces of regular beer (5% alcohol)
- 5 ounces of wine (12% alcohol)
- 1.5 ounces of distilled spirits (40% alcohol)

World Health Organization Mortality Risk Levels for Men

Risk Level	No. of drinks per day
Low	0-2.9
Medium	3-4.3
High	4.4-7.1
Very high	7.2 or more

World Health Organization Mortality Risk Levels for Women

Risk Level	No. of drinks per day
Low	0-1.4
Medium	1.5-2.8
High	2.9-4.3
Very high	4.4 or more

Effect of Reduction in WHO Risk Levels

Reductions of 1-2 risk levels associated with

- Improved LFTs, mental health, overall functioning
- Lower BP
- Fewer negative consequences of drinking

Recent Shift in FDA and European Medicines Agency (EMA) Regulations for Alcohol Medications

- An alcohol medication can be approved by FDA if it eliminates heavy drinking days, not just if it produces total abstinence
- An alcohol medication can be approved by the EMA if it reduces WHO risk level by 2 levels
- Helps to determine whether a reduction in drinking is meaningful

Why is Controlling Drinking so Difficult?

- Alcohol priming effect
- Disinhibition
- Availability

FDA-Approved Medications for Alcohol Use Disorder

- Disulfiram
- Naltrexone (oral and XR-injection)
- Acamprosate

Disulfiram

- Inhibits aldehyde dehydrogenase, an enzyme in the metabolism of alcohol
- Acetaldehyde poisoning if alcohol ingested
- Reaction occurs 10-15 min. after drinking
- Reaction can be severe, occasionally fatal; severity related to dose, pt characteristics
- Vigilance, not paranoia
- Only for people seeking abstinence

Disulfiram: Dosing

- Can prescribe 125-500 mg/day
- Since disulfiram works via the FEAR of its effects, low doses can be as effective as higher doses to start

Disulfiram: Side Effects

Most common:

- Garlicky or metallic taste, mild elevation of LFTs

Most serious:

- Hepatic: Idiosyncratic severe hepatitis

Disulfiram: Advantages

- Built-in impulse control because of prolonged elimination time (up to 2 weeks)
- May indirectly reduce desire to drink
- May be used prn later
- Importance of adherence strategies

Disulfiram: Disadvantages

- Side effects, including the 2 side effects of greatest concern
  1) Liver toxicity
  2) Risk of unintentional or intentional alcohol reaction

Naltrexone for Alcohol Use Disorder

- Mechanism of action: May reduce alcohol-induced craving (priming response)
- Does not reduce likelihood of any drinking, but reduces likelihood of heavy drinking; helps contain a slip (lapse) rather than leading to relapse
- Typical dose: 50 mg/d, but can start at 25 mg/d to reduce side effects (esp. nausea)
- Also comes in extended-release (4-week) IM form, which is also used to treat opioid use disorder

Naltrexone Side Effects

- Nausea 10%
- Headaches 7%
- Dizziness 4%
- Fatigue 4%
- Insomnia 3%
- Anxiety/nervousness 2%
- Sleepiness 2%

Croop RS et al. Arch Gen Psychiatry. 1997(Dec);54(12):1130-1135; Open label trial of 570 treated patients

Naltrexone for Alcohol Use Disorder: Precautions

- Cannot be used if concomitant or recent use of opioids or if patient requires opioids
- Liver function test elevation, especially with higher doses
- Use with caution if history of suicide attempts

Extended-Release Injectable Naltrexone for Alcohol Use Disorder

- Reduces heavy drinking days
- Pivotal trial showed beneficial effect in men, not in women
- Appears to achieve beneficial effect in 2-3 days after initial injection (Ciraulo et al., 2008)

Naltrexone: Advantages

- Won't make you sick if you drink
- May reduce desire to drink
- Can be used successfully in patients not committed to abstinence
- May be particularly helpful for combined alcohol and opioid dependence

Naltrexone: Disadvantages

- Relatively small effect size
- Some negative trials
- Promotes reduction in heavy drinking, not necessarily complete abstinence for those who should abstain
- Problem for those who need opioids on an emergency basis
- May work only in subgroup of patients
  - Smokers
  - Reward drinkers, not relief drinkers
  - Strong family history

Acamprosate

- Mechanism of action: interacts with glutamate & GABA neurotransmitter systems
- May reduce protracted withdrawal symptoms
- Targets abstinence, not heavy drinking

Practical Considerations with Acamprosate Treatment

- Usual dose: two 333-mg tablets 3 x daily
- Excreted in kidney, not metabolized in liver, so can be given in face of severe liver disease, unlike naltrexone or disulfiram

Acamprosate Side Effects

- Diarrhea (17% acamprosate vs. 10% placebo)
- Nausea
- Depression
- Anxiety
- Bloating
- Rash

Acamprosate: Advantages

- Won't make you sick if you drink
- May reduce desire to drink
- Helpful for those with liver disease
- Increases likelihood of abstinence

Acamprosate: Disadvantages

- Relatively small effect size
- Many negative trials
- May be best for people who have attained short-term sobriety and are struggling
- Requires 3x a day dosing

Topiramate (not FDA-indicated)

- 371 pts at multiple sites received topiramate 50-300 mg/d (tapered upward) or placebo x 14 wks, then 2-week taper
- Patients were drinking heavily at study entry
- Topiramate pts had better drinking outcomes, beginning at 100 mg/d
- Fewer heavy drinking days
- Greater likelihood of abstinence

Johnson et al., 2007 – multi-site study

Topiramate

Kranzler et al., 2014

- 138 pts received topiramate up to 200 mg/d or placebo x 12 wks
- Patients were drinking heavily at study entry
- Topiramate pts had fewer heavy drinking days, more abstinent days
- Heavy drinking day reductions only occurred among those with a mutation in a gene related to glutamate activity

Baclofen (not FDA-indicated)

- GABA-B receptor agonist
- Used to treat spasticity, e.g., in multiple sclerosis
- Dr. Olivier Amiesen's 2009 book, "The End of My Addiction" sparked interest in very high-dose baclofen
- Studies with low-dose baclofen (e.g., 30 mg/d) have had mixed results
- Two French multi-site trials of high-dose baclofen (up to 150 mg/d): no benefit, many side effects

Van den Brink et al., 2013.

Gabapentin (not FDA-indicated)

- 150 Ss assigned to placebo or 900 or 1800 mg of gabapentin x 12 weeks
- Abstinence rate: 4%, 11%, and 17%, respectively
- Rate of no heavy drinking: 23%, 30%, and 45%, respectively
- Similar findings for mood and craving
- However, areas of gabapentin misuse around the U.S.

Mason et al., 2014.

Ketamine, Psilocybin (not FDA-indicated)

- Several studies have been conducted
- Different methodologies: patient population, dose, type of psychotherapy
- Promising results for reduction in heavy drinking days, but varying results
- Key exclusion criteria, esp. in psilocybin research
- Specialized psychotherapy typically involved

Choosing an Alcohol Use Disorder Medication

- Easy decisions
  - Liver function
  - Other medications, e.g., opioids
- More complicated issues
  - Goal of treatment, patient wishes
  - Who is a candidate for disulfiram?
  - Current status, i.e., abstinence duration
  - Likelihood of adherence
    - Acamprosate tid dosing
    - Disulfiram restrictions
    - Daily po naltrexone vs. monthly injectable

Medications for Opioid Use Disorder (MOUD)

Methadone, Naltrexone, Buprenorphine

Methadone

- Full opioid agonist, oral tablet and liquid
- Used for detoxification and for maintenance at opioid treatment programs only (not office-based)
- FDA-indicated for pain (office)
- Dosing varies from 40 mg – 120 mg or higher
- Most effective for severe OUD and chronic relapsing, those who fail alternate treatments

Naltrexone for Opioid Use Disorder

- Opioid antagonist, no opioid effects
- Oral form, 50 mg/d, has poor adherence
- IM extended-release: lasts ~4 weeks
- Russian pivotal study showed 36% abstinence, vs. 23% for placebo
- US study in criminal justice pts showed better outcomes than community treatment (agonist recommended)

Buprenorphine

- Partial agonist; does not fully activate opioid receptors.
- Ceiling effect on opioid activity, including respiratory depression.
- Lower retention than methadone but may have better results on opioid use (studies vary)
- Naloxone added to SL form to discourage injection
- Most widely used medication for OUD
- Used sublingually or via SC monthly injection

Buprenorphine

Tkacz et al., 2011

- Adherence is a key to retention and success
- Patients taking buprenorphine on <80% of days were 10x more likely to relapse than those who took buprenorphine at least 80% of the time

How effective is buprenorphine?

Prescription Opioid Addiction Treatment Study

- Largest study of tx of prescription opioid dependence (N=653 at 10 U.S. sites)
- Examined different lengths of bup-nx + different intensities of counseling
- 'Success':abstinence/near-abstinence from opioids
  - –7% success with 4-week taper
  - –49% success while stable on bup-nx x 12 weeks
  - –9% success after 2nd taper after 12-wk bup-nx

Sustained-Release Injectable Buprenorphine Efficacy

- Phase 3 study, N=504 patients with opioid use disorder
- Injectable monthly SC buprenorphine vs placebo injections × 6 months
  - – All received individual drug counseling
  - – "Successful outcome" defined as ≥ 80% opioid-free weeks (weeks 5-24)
- Success rate: 28% [buprenorphine] vs. 2% [placebo]

Sublingual Buprenorphine-Naloxone vs. Injectable Extended-Release Naltrexone

- U.S. multi-site trial: N=570, 8 sites, 24-week trial
- Recruited as inpatients, treated as outpatients
- Flexible randomization schedule
- 94% of buprenorphine-naloxone patients were inducted, 72% of extended-release naltrexone patients (*P*<.0001)
- Relapse rate among all those randomized: 65% (extended-release naltrexone) vs 57% (buprenorphine-naloxone)
- Among those inducted, relapse rates equal, slightly more opioid-negative urine tests among naltrexone patients
- Norwegian outpatient study: equivalent urine tests, fewer days of heroin use and less craving among naltrexone pts

Sublingual Buprenorphine-Naloxone vs. Extended-Release Naltrexone: Summary

- Both medications are equally effective once people start them
- In general, poorer long-term retention on XR-naltrexone
- Starting extended-release naltrexone is challenging because it requires detoxification and opioid abstinence first; 30% never received it in US study

Choosing a Medication for Opioid Use Disorder

- Buprenorphine: easy on, difficult off
- Naltrexone: difficult on, easy off
- Both easy-off and difficult-off are mixed blessings
- Challenge: getting off opioids and onto naltrexone
- Challenge: keeping pts on medication for OUD
- Methadone: built-in structure of the program, for better and for worse
- Agonist vs. antagonist:
  - –What does the patient/family want?
  - –Must be a collaborative process

Cannabis Use Disorder

Promising pharmacotherapies for Cannabis Use Disorder

- Gabapentin
- N-Acetylcysteine
  - NOTE: NO FDA-APPROVED MEDICATIONS FOR CANNABIS USE DISORDER

Gabapentin

- 12-week randomized, double-blind, placebo-controlled trial (N=50; 400 mg tid)
- Retention rate was 36% (18 completed trial)
- Gabapentin Ss had greater reduction of cannabis use, less withdrawal

N-acetylcysteine

- Available in supplement stores, a pro-drug of cysteine
- Modulates glutamate neurotransmission
- 1200 mg bid vs. placebo in 15-21 y.o. pts with CUD
- Twice-weekly contingency management (rewards for abstinence, med adherence)

Study results:

- NAC: 41% negative urine tests
- Placebo: 27% negative urine tests
- P<0.03

N-acetylcysteine

- Positive results in adolescents not found in large multi-site trial with adults
- However, in that trial, young adults appeared to do better with NAC than with placebo

Non-abstinent outcomes in cannabis use disorder

- Dronabinol, quetiapine, and dronabinol + lofexidine haven't shown advantage over placebo in producing abstinence
- However, in all 3 trials, active meds produced reduction from heavy (5-7 days/week) to moderate (2-4 days/wk) use

Methamphetamine Use Disorder

Promising pharmacotherapies for Methamphetamine Use Disorder

- Mirtazapine
- Bupropion + injectable naltrexone
  - NOTE: NO FDA-APPROVED MEDICATIONS FOR METHAMPHETAMINE USE DISORDER

Mirtazapine for Methamphetamine Use Disorder

- Two studies in primarily MSM populations showed benefit of mirtazapine 30 mg/d
- 44% vs. 63% positive urine tests in first trial (Colfax et al., 2011; N=60)
- 66% v. 78% positive urine tests in most recent trial (Coffin et al., 2020; N=120)

Bupropion + XR-Naltrexone for Methamphetamine Use Disorder

- Trivedi et al., 2021; N=403, multi-site
- Bupropion 450 mg/d + injectable XR-NTX 380 mg q 3 wks vs. placebo
- Active group had better 'success' rate (at least 3 of final 4 urines negative)
- 14% vs. 3% success rate

Thank you!