Pharmacotherapy of Alcohol Use Disorders

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Objectives

• Following this presentation, participants should be able to:
  – Name the 4 FDA-approved and 2 other efficacious medications for AUD
  – Identify adverse effect and adherence characteristics for AUD medications
  – Name which AUD medications can be used with which specific AUD patient populations
Case #1

• 54 y/o male with hx of DM Type 2, A1c = 7.4, HTN refractory to medications
• Increasing alcohol consumption after separation from wife
• Binge drinks 8-10 standard drinks weekend days
• AST 75, ALT 38, CBC normal, INR not elevated
• CC: “I need to get this under control, I’m not ready to stop drinking yet though
• Works as under the table in day labor
• What other questions would you have?
• What medication to choose?
Case #2

- 36 y/o female – works 2 jobs to support family
- Works in restaurant industry and retail
- CC: “I need to stop, I’m ready to quit, it’s affecting my marriage, my husband just got sober and wants me to as well”
- Drinking bottle of wine 4/7 nights/week
- Has 2 minor children at home – abuse screen negative
- Husband is with her at appointment
- Labs – nl LFT, EKG normal, CBC normal
- What other questions do you have?
- Which medication?
Case #3

- 65 y/o male / Drinks all day, every day
- Homeless, multiple ED visits for intoxication
- Limited support (no family, no sober friends)
- CC: Chronic LBP
- Medical Issues: DM, HTN, HCV-, HIV-
- Labs: AST 120/ALT 90, CBC shows low platelets, INR 1.7, UDS + for cannabis, cocaine, - for others
- PEX: Rosacea, hard shrunken liver, no e/o ascites, +SLR right side
- What additional questions do you have?
- Which medication to choose?
Underutilization of AUD Pharmacotherapy

• Alcohol is one of only 3 substances (others are tobacco and opioids) with FDA-approved efficacious medications available

• Reasons unclear, multiple, may include perception of ineffectiveness

• only 8% of adults in the US with AUD are treated with medications

AUD Pharmacotherapy: Some Key Issues

• AUD patients are heterogeneous
  – Alcoholism probably better described as the Alcoholisms

• Different AUD medications present different
  – adverse effect profiles
  – risk/benefit ratios
  – adherence challenges
  – costs
Alcohol’s Neuropharmacologic Effects


- **Elevates DA** in the NAcc ➔ salient attention, reinforcement, brain reward

- **Opioid** (Beta-endorphin) release ➔ DA release in NAcc

- **GABAergic effects** during intoxication; downregulation after chronic use

- **Glutamate** upregulation with chronic use, increase during withdrawal

- **Other neurochemical effects** include
  - nicotinic cholinergic receptors
  - 5-HT
  - NA
  - Cannabinoid
  - Nociceptin-orphanin/ORL
Efficacious AUD Pharmacotherapies

- **FDA-approved**
  - Disulfiram (Antabuse)
  - Acamprosate (Campral)
  - Naltrexone
    - Oral
    - Extended-release intramuscular (Vivitrol)

- **Non-FDA-approved**
  - Topiramate (Topamax, others)
  - Gabapentin (?)
  - Baclofen (?)
  - Some others:
    - Nalmefene
    - Ondansetron (?)
    - Varenicline (?)
    - Pregabalin
    - Zonisamide
Some Patient Groups with Clinical Relevance

- Abstinent vs nonabstinent
- On opioids vs not on opioids
- Liver disease vs no liver disease
- Renal impairment vs not

Goal
  - abstinence vs use reduction ("controlled use")

Logistical:
  - Access to financial means or to providers with specialized training
Possible Predictors

• Gender
• Craving
• Family history
• Sweet-liking
• Typology: early vs late onset
• Abstinence vs still using at tx onset
• Adherence capacity

• Genetic variation involving alleles for genes coding for opioid, glutamate, and other receptors
Disulfiram, 1

• Oldest: FDA approved in 1949

• Mechanism of action of disulfiram (Antabuse)
  – Irreversible inhibitor of acetaldehyde dehydrogenase
  – Prevents conversion of acetaldehyde $\rightarrow$ acetate $\rightarrow$ CO2+H2O
  – Inhibition can last for days – occasionally up to 14 days
  – Disulfiram-alcohol reaction: headache, flushing, nausea, vomiting, chest pain, vertigo, sweating, weakness, hypotension

• Evidence for efficacy
  – Blinded studies show no benefit over placebo (Jonas 2014; Skinner 2014)
  – Open-label studies show efficacy over control groups (Skinner 2014)
  – Most effective in supervised administration
Disulfiram, 2

- **Dose:**
  - 250 – 500 mg once per day

- **Adverse effects**
  - Drowsiness, headache, metallic/garlic taste, rash, very rarely psychosis
  - Occasional: transaminitis
  - Rare: fulminant hepatotoxicity

- **Contraindications:**
  - Alcohol use in past 24 hours
  - Severe cardiovascular disease
  - Pregnancy/nursing

- **Predictors of efficacy**
  - Commitment to abstinence, observed adherence

- **Clinical use**
  - LFTs before, every 3 months for 6 months, then every 6 months
  - Warn pts about “hidden” alcohol: food, mouthwash, etc.
Acamprosate, 1

- Mechanism of action of acamprosate (Campral)
  - Modulation of glutamatergic hyperactivity following cessation of alcohol use
  - Thought to reduce withdrawal-associated dysphoria
- Pharmacology
  - Short half life requires TID dose
- Dose: 2 tablets 3x/day (total 1998 mg/day)
- Evidence for efficacy
  - 3 European studies led to US FDA approval
  - Meta-analysis shows efficacy in reducing return to any drinking (NNT 12) (Jonas 2014 JAMA)
  - However, not a single US study has shown separation from placebo in ITT analyses (e.g. Project COMBINE failed to show efficacy)
Acamprosate, 2

• Adverse effects
  – Diarrhea, fatigue, insomnia

• Predictors of efficacy
  – Detoxification and abstinence prior to initiation
  – High motivation for abstinence
  – Adherence
  – Possibly: female gender, high anxiety, negative family hx, late age of onset (Franck & Jayaram-Lindsrom 2013)

• Contraindications
  – Pregnancy, renal failure

• Clinical use
  – Can be used in patients who are still drinking
  – Reduce dose in renal impairment (CrCl ≤30)
  – Difficult 3x/day regimen
Naltrexone, 1

- FDA-approved for AUD: oral in 1994, XR-NTX in 2006
- 2 forms: oral and injectable extended-release naltrexone (XR-NTX) (Vivitrol)
- Mechanism of action
  - Mu-opioid antagonist; reduces alcohol-mediated increase in beta endorphin and subsequent increase in DA in NAc
  - Reduces craving and reduces pleasurable effects of alcohol
  - May improve decision-making, reduce effect of alcohol cues, reduce impulsivity
- Pharmacology
  - Oral: once daily
  - Extended-release - given monthly
- Dose
  - Oral: 50 mg once per day
  - XR-NTX: monthly IM 380 mg
- Evidence for efficacy
  - Oral reduces return to any drinking and return to heavy drinking
  - Injectable reduces heavy drinking days (Jonas 2014)
Naltrexone, 2

• Adverse effects
  – GI upset: nausea, cramping; dizziness, nervousness, fatigue,
  – Occasional transaminitis
  – XR-NTX: injection site reactions; rare – abscess, necrosis

• Contraindications
  – Opioid treatment (within past 7-10 days)
  – Pregnancy
  – Acute hepatitis or liver failure

• Predictors of effectiveness
  – Positive family history
  – Having the G allele for the OPRM1 gene (A to G, or Asn40Asp substitution) responds better by greater NTX-mediated blunting of alcohol reward (Ray, Chin, Miotto 2010)
  – Early onset AUD (“Type B”)
  – High craving
  – “sweet-liking”
Naltrexone, 3

• Clinical use
  – NTX can be used in patients who are still drinking
  – Monitoring: LFTs before, q3 months for 6 months, then q6months
  – Pain control may require non-opioid approaches
    • NSAIDS, local, regional, conscious sedation
  – XR-NTX form greatly improves adherence
    • Intragluteal IM
Topiramate, 1

• Not FDA-approved for AUD, but approved as an anticonvulsant and migraine prophylaxis medication
• Mechanism of action of topiramate (Topamax and others)
  • Facilitates GABA neurotransmission; inhibits AMPA-kainate glutamate transmission
  • May reduce post-withdrawal dysphoria; reduces craving; may reduce impulsivity
• Pharmacology
  – BID dosing
• Dose
  – Precise dose needed is unknown; most studies have used dosing up to 300 mg/day, increase by 25-50 mg/day each week
  – Lower doses, eg. 100-200 mg/day may be effective – more research is needed.
  – BID dosing
• Adverse effects
  – Memory and concentration problems; dizziness; somnolence
  – Paresthesias, altered taste
  – Appetite/weight loss
  – Rare: kidney stones, metabolic acidosis, narrow-angle glaucoma
Topiramate, 3

• Evidence for efficacy: meta-analyses
  – Increased abstinence
  – Fewer drinking days and fewer drinks/drinking day

• Predictor of effectiveness
  – possible genetic predictor – alleles for GRIK1 gene

• Contraindications
  – Renal failure
  – History of kidney stones or narrow-angle glaucoma
  – pregnancy

• Clinical use
  – Can be used in patients who are still drinking
  – If CrCl <70 ml/min → cut dose by 50%
  – Check bicarbonate level if metabolic acidosis is suspected (hyperventilation, etc)
Gabapentin, 1

- Not FDA-approved for AUD, but approved as anticonvulsant; neuropathic pain med
- Mechanism of action of gabapentin (Neurontin and others)
  - Chemical: facilitates GABA transmission
  - Behavioral: reduces withdrawal-related anxiety, helps sleep,
- Pharmacology
  - Blocks alpha-2-delta subunit of calcium channel → modulates GABA neurotransmission
- Dose
  - 1800 mg/day in 3 divided doses
- Evidence for efficacy
  - Mason (2014) JAMA Int Med: increased abstinence, reduced craving
- Adverse effects
  - Sedation, dizziness, edema
Gabapentinin, 2

• Predictors of effectiveness
  – Not clear at this time

• Clinical use
  – Can be used in individuals still drinking
  – Can be used in patients with severe liver disease
  – Evidence exists for GBP aiding sleep in AUD patients
  – Care needs to be taken in cases of renal insufficiency; dose should be reduced
Baclofen, 1

- Not FDA-approved for AUD, but approved as a muscle relaxant for treating spasticity
- Mechanism of action
  - Chemical: facilitates GABA function
  - Behavioral: may reduce anxiety/dysphoria of post-withdrawal state
- Pharmacology
  - GABAb receptor agonist
- Dose
  - 10-20 mg TID
- Evidence for efficacy: mixed
  - Jonas 2014 meta-analysis failed to find efficacy, but several controlled trials support use; one large controlled trial failed to show benefit
- Adverse effects
  - Fatigue, sedation, dizziness, abdominal pain
Baclofen, 2

• Predictors of effectiveness
  – None established

• Clinical use
  – Can be used in patients who are still drinking
  – Renal clearance, so can be used in patients with severe liver disease
Other Possible AUD Pharmacotherapies

- Ondansetron
- Nalmefene
- Varenicline
Is There a First Line Medication for AUD?, 1

• It depends...
Is There a First Line Medication for AUD?, 2

- If abstinent:
  - Naltrexone oral or XR-NTX
  - Topiramate
  - Acamprosate
  - Disulfiram
Is There a First Line Medication for AUD?, 3

• If still drinking:
  – Can’t use disulfiram
  – Choices:
    • Naltrexone oral or XR-NTX
    • Acamprosate
    • Topiramate
Is There a First Line Medication for AUD?, 4

• If using opioids:
  – Can’t use Naltrexone oral or XR-NTX
  – Choices:
    • Acamprosate
    • Disulfiram
    • Topiramate
Is There a First Line Medication for AUD?, 5

• If **severe liver disease**:  
  – Disulfiram is risky  
  – Naltrexone oral or XR-NTX may cause transaminitis  
  – Choices:  
    • Acamprosate  
    • Topiramate  
    • Gabapentin  
    • Baclofen
Is There a First Line Medication for AUD?, 6

• If severe renal impairment:
  • These are renally cleared $\rightarrow$ cut dose in half
    – Topiramate
    – Acamprosate
    – Gabapentin
    – Baclofen
  • These are hepatically metabolized
    – Naltrexone
    – Disulfiram
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Questions?

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