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

(SAMHSA. *Results from the 2012 National Survey on Drug Use and Health:* *://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/Index.aspx*. Accessed July 15, 2014.

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

Anton et al . 2014 Pharmacologic treatment of alcoholism. Ch 30 in *Handbook of Clinical Neurology*. 125 (3rd Ed) Alcohol and the Nervous System, Sullivan EV & Pfefferbaum A Eds.

- 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 →acetate→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 $\leq$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

Gabapentin, 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 → cut dose in half
  - Topiramate
  - Acamprosate
  - Gabapentin
  - Baclofen
- These are hepatically metabolized
  - Naltrexone
  - Disulfiram

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Questions?

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