Alcohol Use Disorder Medication Supported Recovery

Substance Use Disorder in Hospital Care ECHO

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Disclosures

- Presenter: Raymundo Garcia-Dwyer has nothing to disclose

Learning Objectives

- At the conclusion of this session, participants will be able to:
  - Summarize the epidemiology of alcohol use disorder
  - Describe the inpatient management of alcohol use disorder
  - Identify medications for alcohol use disorder, their mechanisms of action, and their evidence base

Context

- Excessive alcohol use is the third leading cause of preventable death in the US (~88,000 deaths annually)
- NIH estimates that AUD affects 9% of adult men and 5% of adult women in the US
- Less than one-third of patients with AUD receive treatment, and only a small percentage (<10%) receive medications to assist in reducing alcohol consumption

Abuse, Alcohol, and Alcoholism Consensus. Am Fam Physician 93.6 (2016): 457-465.
Jonas, Daniel E., et al. *JAMA* 311.18 (2014): 1889-1900.

Management of AUD: Beyond Withdrawal

- Medically managed withdrawal "detoxification" is not treatment
- The hospitalized setting is a reachable moment to offer treatment and recovery resources:
  - Brief intervention
  - Treatment
    - Psychosocial counseling
    - **Pharmacotherapy**
  - AA, Smart Recovery
  - Peer support services
  - Manage comorbidity (medical and psychiatric)

Friedmann PD, Saitz R, Samet JH. JAMA 1998;279(15):1227-31
Adapted from slide by Richard Saitz MD, MPH, FACP, DFASAM. The Immersion Training in Addiction Medicine Programs from Boston University School of Medicine

Patient Selection for Medication Supported Recovery

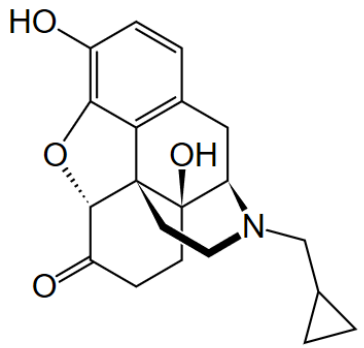
- All individuals with moderate to severe alcohol use disorder who are:
  - Currently drinking
  - Undergoing medically managed withdrawal or recently completed withdrawal management
  - Experiencing cravings or at risk for return to drinking
  - Prefer medication along with or instead of a psychosocial intervention

Adapted from slide by Richard Saitz MD, MPH, FACP, DFASAM. The Immersion Training in Addiction Medicine Programs from Boston University School of Medicine

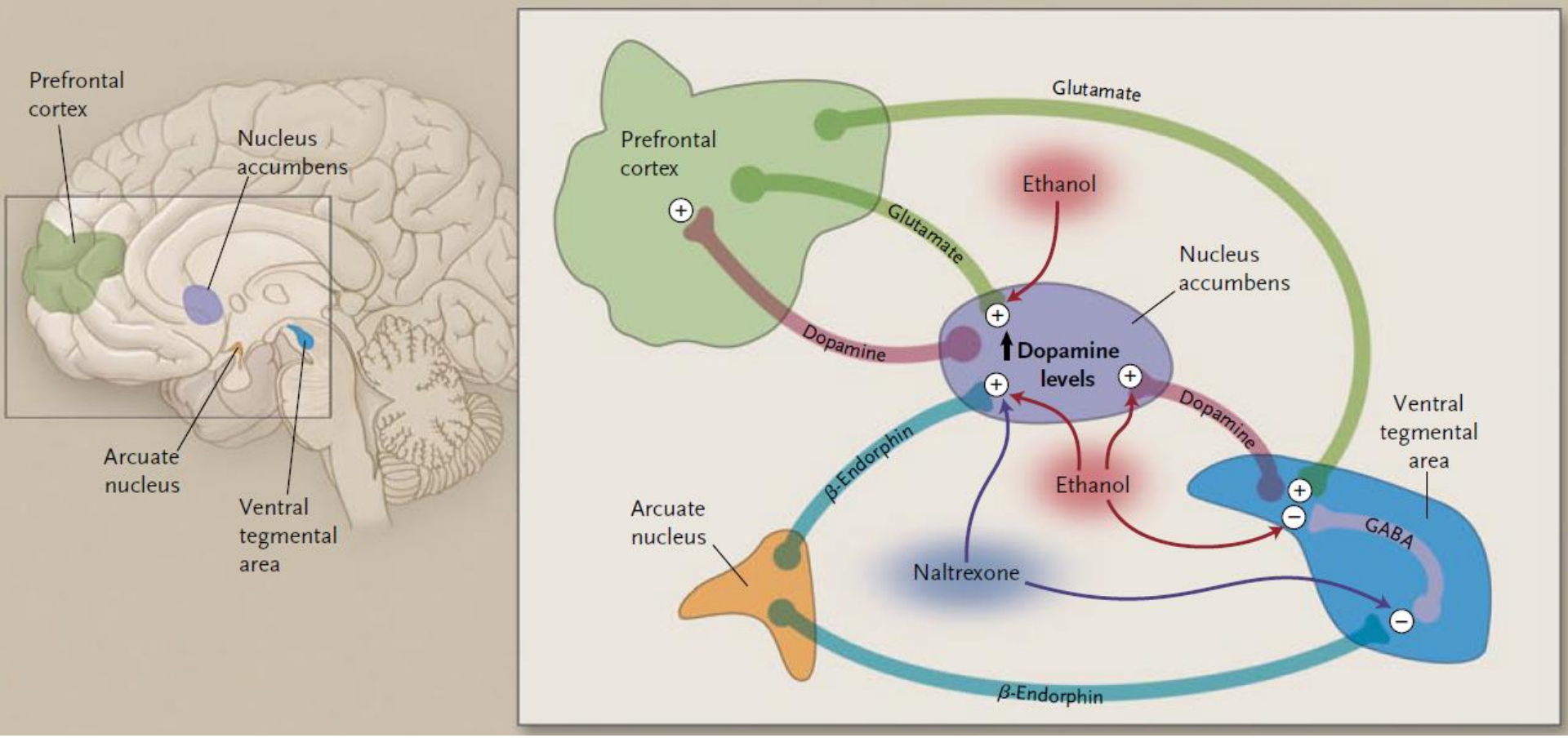
Medications Used for Alcohol Use Disorder

- FDA Approved
  - Naltrexone (1st line)
  - Acamprosate
  - Disulfiram
- Non-FDA Approved
  - Topiramate
  - Gabapentin
  - Baclofen
  - Ondansetron
  - SSRIs

Naltrexone



- Opioid antagonist
- Labeled
  - Opioid dependence: 50 mg/d PO (1984), 380 mg/4wk IM (2010)
  - AUD: 50 mg/d PO (1994), 380 mg/4wk IM (2006)
- Off-label
  - Cholestatic pruritis



Mechanism of Action

Blocks opioid receptors --> Reduces dopamine release at the Nu Accumbens

Anton, Raymond F. *New England Journal of Medicine* 359.7 (2008): 715-721.

Jonas et al (2014): Pharmacotherapy for Adults with AUD, Naltrexone

- Systematic Review and Meta-Analysis
- 53 studies on naltrexone (n= 9140), 44 RCTs
- Evaluated medication for at least 12 wks
- Oral naltrexone was associated with improvement in consumption outcomes:
  - Reduced return to any drinking, RD -0.05, NNT 20 (95% CI 11 to 500)
  - Reduced return to heavy drinking, RD -0.09, NNT 12 (95% CI 8 to 26)
  - Reduced % drinking days, WMD -5.4
  - Reduced % heavy drinking days, WMD -4.1
  - Minimally reduced drinks/ drinking day, WMD -0.49
- Moderate strength of evidence for all outcomes expect for drinks/drinking day

Jonas, Daniel E., et al. *JAMA* 311.18 (2014): 1889-1900.

Starting Oral Naltrexone

- 50 mg daily
- Consider starting if
  - Currently drinking, admitted for withdrawal management
  - LFTs < 5x upper limit normal and no liver failure
  - Urine drug screen negative for opioids
  - At least 3 days and probably more like a week since last opioid
- Monitor LFTs periodically and stop if LFT elevation develops > 5x ULN
- Common side effects include nausea, vomiting, headache, and dizziness

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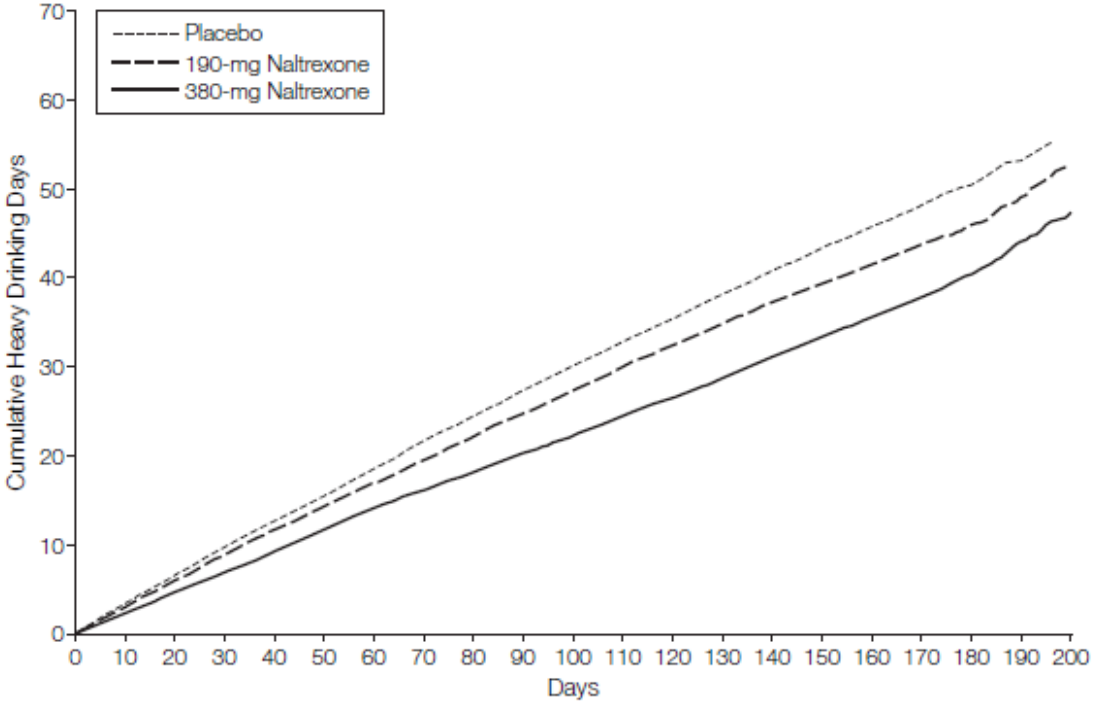
Extended Release Injectable Naltrexone

- Bypasses first-pass liver metabolism, lower dose required and therefore expected to show less hepatotoxicity than oral form
- Improved adherence (Bryson, 2011)
- Associated with % reduction in heavy drinking days (Garbutt et al, 2005; Jonas et al, 2014)

Adapted from slide by Richard Saitz MD, MPH, FACP, DFASAM. The Immersion Training in Addiction Medicine Programs from Boston University School of Medicine

Garbutt et al (2005): Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence

Figure 2. Primary Efficacy Analysis: Mean Heavy Drinking Event Rate



Treatment Dose	1	2	3	4	5	6
No. of Patients						
Placebo	209	194	169	160	142	134
Naltrexone						
190 mg	210	187	169	156	144	137
380 mg	205	186	161	147	139	130

Intention-to-treat analysis shows the cumulative mean event rate of heavy drinking during the study by treatment group. The participant retention rates are shown at 4-week intervals through 24 weeks, which was the intended duration of the treatment.

Garbutt, James C., et al. "Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial." Jama 293.13 (2005): 1617-1625.

Starting IM Naltrexone

- 380 mg monthly
- Consider starting if
  - Opioid free for 7-10 days (10-14 days off buprenorphine, methadone); consider oral challenge
  - Comorbid OUD (not on methadone or buprenorphine)
  - Trouble with adherence to daily dosing
  - No anticipated surgery or severe pain
  - Can be done in the hospital if it is available and coordinated with inpatient pharmacy

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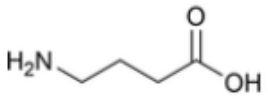
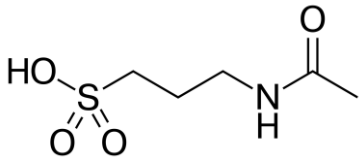
Acamprosate



GABA



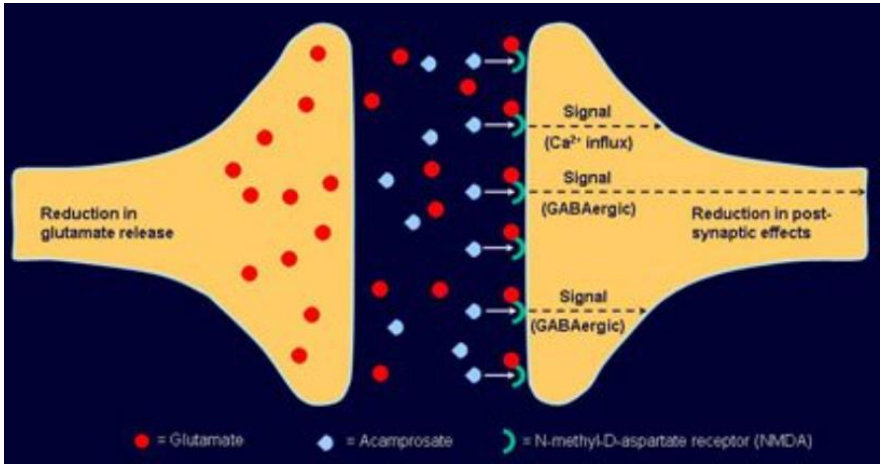
Acamprosate

- GABA analogue
- FDA approved for AUD in 2004: 666 mg TID

Mechanism of Action

Blocks calcium ion channels presynaptically --> reduces glutamate release

Inhibits glutamate NMDA receptors and modulates GABA postsynaptically --> reduces glutamate's effects



Jeffery Wilkins. Neurobiology and Pharmacotherapy for Alcohol Dependence.

Jonas et al (2014): Pharmacotherapy for Adults with AUD, Acamprosate

- Systematic Review and Meta-Analysis
- 27 studies on acamprosate (n= 7519), 22 RCTs
- Evaluated medication for at least 12 wks
- Acamprosate was associated with improvement in consumption outcomes:
  - Reduced return to any drinking, RD -0.09, NNT 12 (CI 8 to 26)
  - Reduced % drinking days, WMD -8.8
- Acamprosate was not associated with reduction in return to heavy drinking or drinks/ drinking day
- Data suggests more positive results seen for maintenance of abstinence rather than reduction of drinking by non-abstinent patients.

Jonas, Daniel E., et al. *JAMA* 311.18 (2014): 1889-1900.

Starting Acamprosate

- 666 mg TID
- Consider starting if
  - Severe liver disease without renal impairment
  - Highly motivated
  - Recently completed medically managed withdrawal (in the admitted patient, ideally before discharge)
  - Comorbid OUD (on methadone or buprenorphine)
  - Already on multiple medications BID-TID
- Requires renal impairment dose adjustment
  - Reduce to 333 mg TID for CrCl 30-50
  - Contraindicated in CrCl<30
  - Monitor sCr/ CrCl periodically and stop if CrCl<30
- Most common side effect is diarrhea

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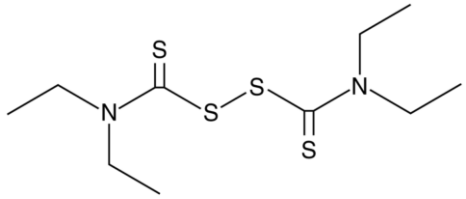
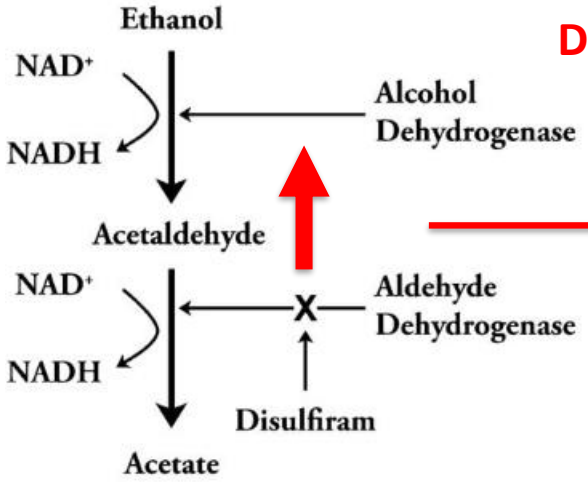
Disulfiram



- FDA approved for alcohol dependence in 1949: 250 mg/d

Mechanism of Action

Irreversible inhibitor of aldehyde dehydrogenase



Disulfiram-Ethanol Reaction (DER)

Flushing
Headache
Palpitations
Dizziness
Nausea
Hypotension

Courtesy of Morris D Faiman. Neurobiological Explanation for the Effectiveness of Disulfiram in Substance Use Disorders. University of Kansas.

Skinner et al (2014): Disulfiram Efficacy in the Treatment of Alcohol Dependence

- Meta-analysis
- 22 RCTs (n= 2414), included blind and open-label studies with and without supervision
- Objectives
  - Assess efficacy and safety of disulfiram in supporting abstinence
  - Compare the outcomes blind vs open-label studies
    - Hypothesized that blinded studies would show no difference as the threat of the disulfiram-ethanol reaction (DER) would be evenly spread across all groups

Skinner, Marilyn D., et al. "Disulfiram efficacy in the treatment of alcohol dependence: a meta-analysis." PloS one 9.2 (2014): e87366.

Skinner et al (2014): Results

- Disulfiram was associated with improvement in abstinence outcomes to a medium size effect (g= 0.70, 95% CI 0.46 to 0.93) only for open-labeled studies
- RCTs with blind designs showed no efficacy (g= 0.1, 95% CI -0.29 to 0.32)
- In the open-label trials sub-analysis, disulfiram was significantly superior to controls to a large size effect (g= 0.82, 95% CI 0.59 to 1.05) only when medication adherence was supervised; this effect disappeared when disulfiram treatment was not supervised.
- More adverse events with disulfiram vs controls (adverse rate ratio 1.4, 95% CI 1.01-1.94), but no differences in studies reporting deaths and serious adverse events requiring hospitalization

Skinner, Marilyn D., et al. "Disulfiram efficacy in the treatment of alcohol dependence: a meta-analysis." PloS one 9.2 (2014): e87366.

Starting Disulfiram

- 250 mg daily
- Consider starting if
  - Abstinence from alcohol at least 12 hours and/or breath or blood alcohol level is zero
  - Highly motivated
  - Directly observed dosing or supportive family environment that can facilitate adherence
  - Patient requesting it
  - No severe CAD or advanced liver disease
  - Informed consent (severity of reaction, 2 week tail effect)
- Obtain baseline LFTs, monitor periodically, stop if LFT elevation develops
- Contraindications: Severe CAD, advanced liver disease, psychosis, pregnant or nursing women
- Adverse effects: drowsiness is most common; all others are uncommon, including hepatotoxicity (1:25,000), dermatitis, acne, neuropathy, optic neuritis; cardiovascular collapse/ death is rare
- Many medication interactions: chlordiazepoxide, diazepam, warfarin, TCAs, metronidazole, phenytoin, theophylline, isoniazid, rifampin

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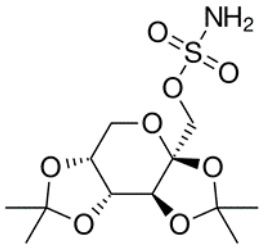
Topiramate



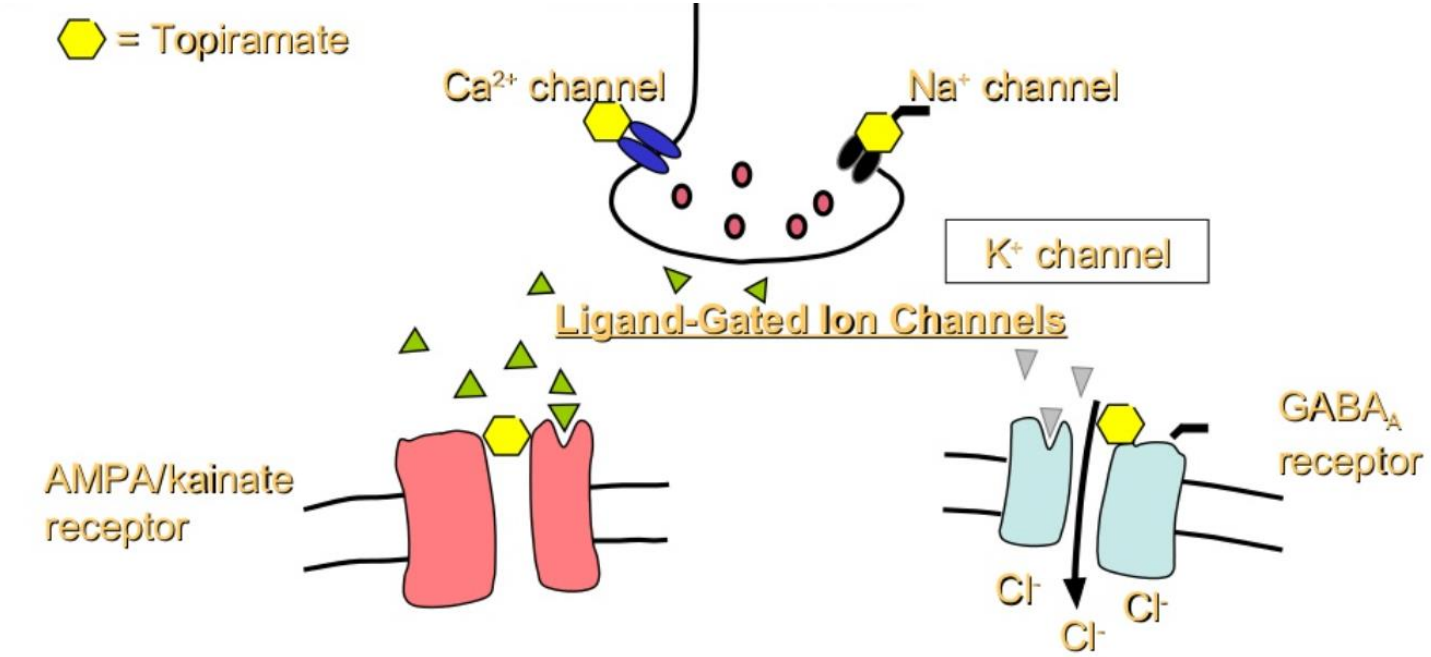
- Anticonvulsant
- Labeled
  - Seizures (1996): 25-400 mg/d
  - Migraine prevention (2004): 25-200 mg/d
  - Weight loss (in combination with phentermine, 2012)
- Off-label
  - Antipsychotic-induced weight gain
  - AUD
  - Binge-eating disorder
  - Bipolar affective disorder
  - Borderline personality disorder
  - Cluster headache prevention
  - Essential tremor

Mechanism of Action

Blocks voltage-gated sodium and calcium channels
--> reduces presynaptic glutamate release

Blocks activity of AMPA/kinase glutamate receptors and
--> inhibits glutamate function

Activates chloride channels via postsynaptic $GABA_A$ receptors
--> facilitates GABAergic neurotransmission

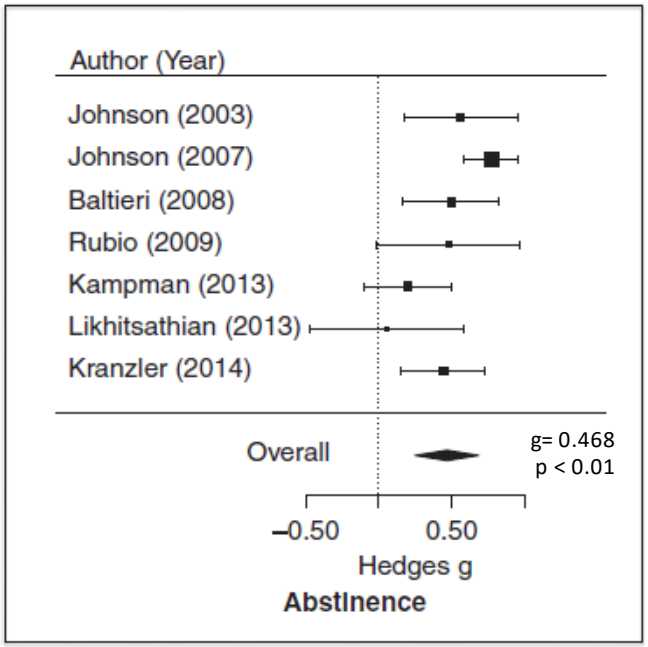


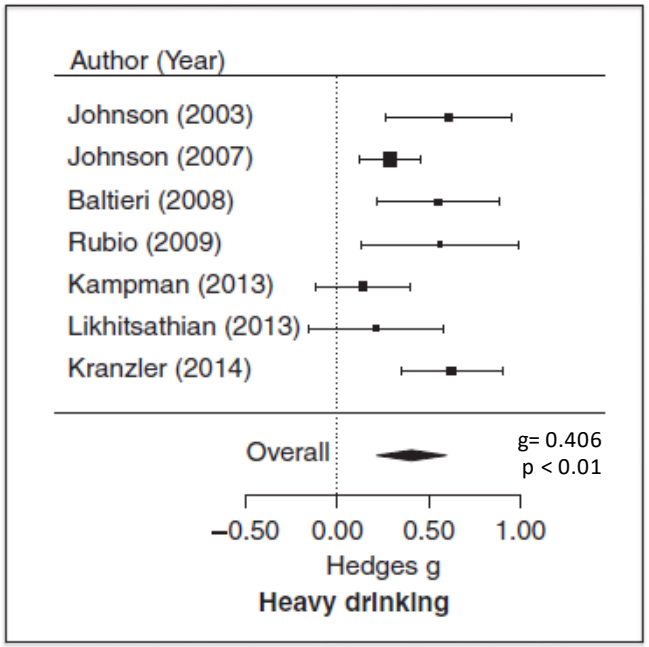
Shank RP et al. Epilepsia. 2000;41 (suppl 1).
Figure courtesy of Lubna Mohammad via slideshare.net

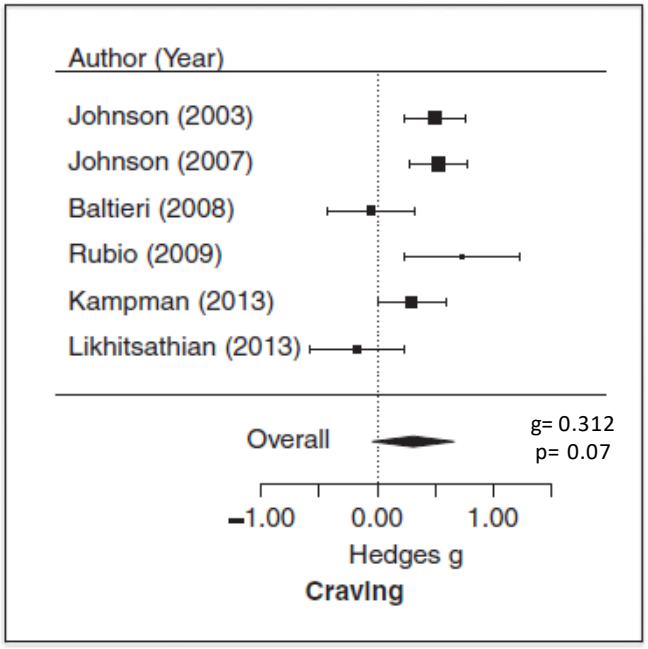
Blodgett et al (2014): Topiramate's Effects for Individuals with AUD

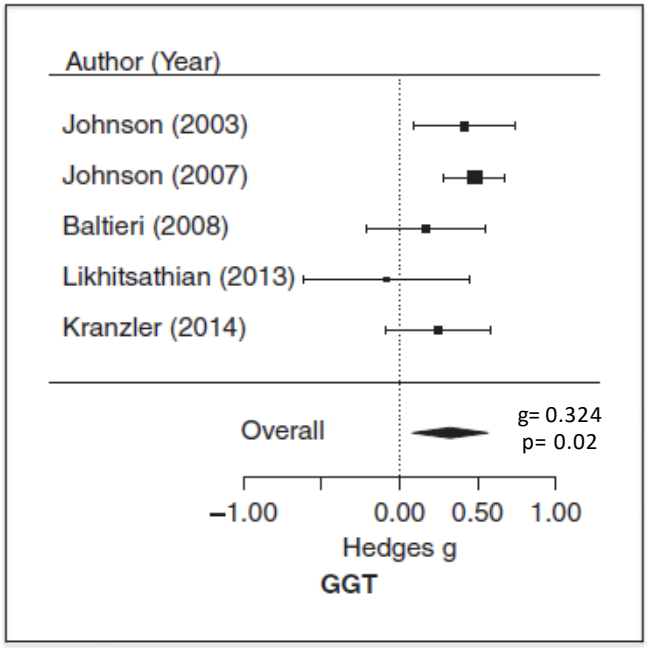
- Meta-analysis
- 7 RCTs on topiramate monotherapy for AUD (n= 1125)
- Target dose of 300 mg
- Overall effects favored topiramate to placebo:
  - Abstinence outcomes ($g = 0.468$, $p < 0.01$)
  - Heavy drinking ($g = 0.406$, $p < 0.01$)
  - GGT concentration ($g = 0.324$, $p = 0.02$)
  - Craving ($g = 0.312$, $p = 0.07$)
- Well tolerated; adverse effects more likely at higher doses and without gradual titration
- Adverse effects: paresthesia/ numbness, N/C, cognitive impairment, HA, dizziness

Blodgett, Janet C., et al. *Alcoholism: Clinical and Experimental Research* 38.6 (2014): 1481-1488.







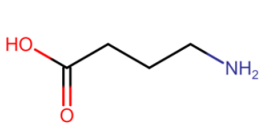


Blodgett, Janet C., et al. *Alcoholism: Clinical and Experimental Research* 38.6 (2014): 1481-1488.

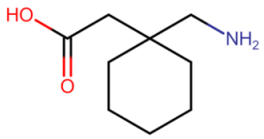
Take home points on topiramate

- Topiramate's effect sizes compare favorably to effect sizes in similar outcomes in a meta-analysis of naltrexone and acamprosate
- Significant and moderate benefit on increasing abstinence and reducing heavy drinking
- Small effect on GGT concentration and craving
- It is well tolerated, especially if dosed appropriately
- Rx: 25 mg daily, increase by 25 mg weekly and dose BID; target dose 200-300 mg/d
- Contraindication: glaucoma, renal impairment, advanced liver disease

Gabapentin



GABA



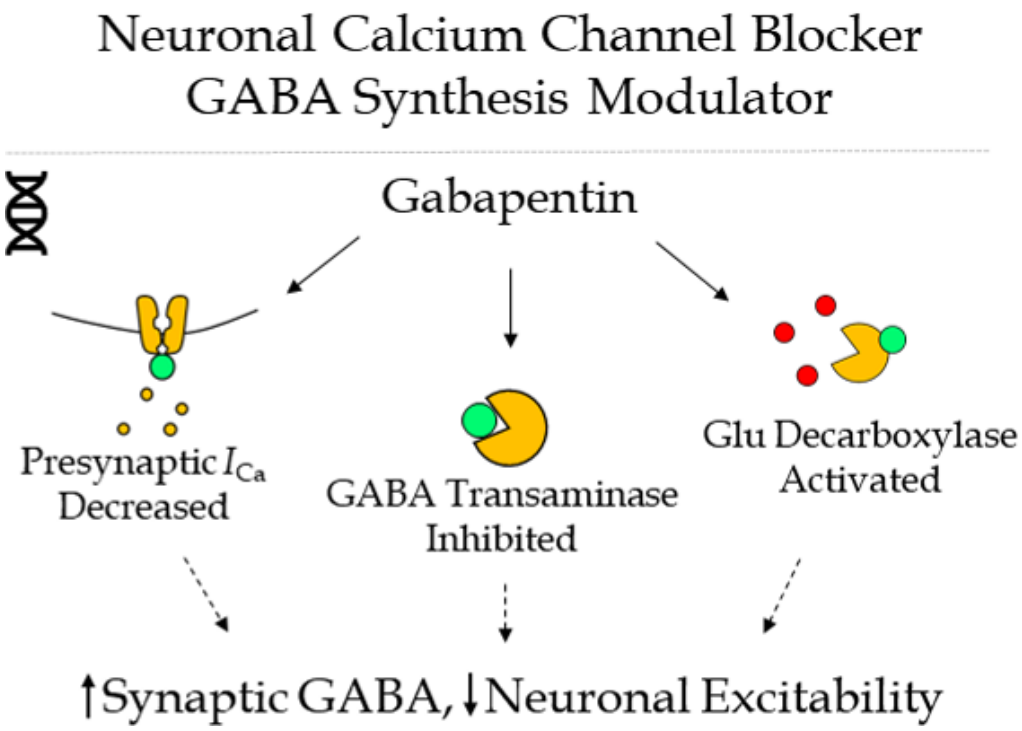
Gabapentin

- Anticonvulsant
- Labeled
  - Focal (partial) onset seizures (1993): 900-1800 mg/d
  - Postherpatic neuralgia (2002): 300-900 mg/d
  - Restless leg syndrome (2011): ER formulation 600 mg/d
- Off-label
  - AUD
  - AWS
  - Cough (refractory)
  - GAD
  - Fibromyalgia
  - Hiccups
  - Neuropathic pain other than postherpetic neuralgia
  - Postoperative pain
  - Pruritus
  - Vasomotor symptoms
- Dramatic increase in gabapentin prescribing: 25 to 64 million from 2012-2016
- Structurally related to GABA, but it has no direct effect on GABA binding

Goodman, Christopher W., and Allan S. Brett. "Gabapentin and pregabalin for pain—is increased prescribing a cause for concern?." *New England Journal of Medicine* 377.5 (2017): 411-414.

Mechanism of Action

Inhibits calcium channels containing the alpha-2-delta-1 subunit (highly concentrated in the brain-reward circuitry) and enhances voltage gated potassium channels



Courtesy of Pharmacology Review via Grepmed.com

Mason et al (2014): Gabapentin treatment for alcohol dependence

- Randomized, Double-Blind, Placebo-Controlled (n=150)
- Intervention: 12 weeks of gabapentin 900 mg or 1800 mg vs placebo (in parallel groups) + weekly visits with 20-minute manual-guided counseling
- Gabapentin resulted in higher sustained abstinence rates compared with placebo
  - 4.1% for placebo
  - 11.1% for gabapentin 900 mg
  - 17% for gabapentin 1800 mg; NNT = 8
- Gabapentin resulted in higher rates of no heavy drinking
  - 22.5% for placebo
  - 29.6% for gabapentin 900 mg
  - 44.7% for gabapentin 1800 mg; NNT 5
- Reduced number of heavy drinking days/ wk compared to placebo: -2 for the 1800 mg gabapentin group ($p < 0.001$)
- Reduced number of drinks consumed/ wk compared to placebo: -6.7 for the 1800 mg gabapentin group ($p < 0.001$)
- Improved mood, fewer cravings, and improved sleep.

Mason, Barbara J., et al. JAMA internal medicine 174.1 (2014): 70-77.

Kranzler et al (2019): Efficacy of gabapentin for treating AUD

- Meta-analysis
- 7 RCTs on gabapentin monotherapy for AUD (n= 751)
- Dosages in the studies ranged from 300 to 3600 mg daily.
- For all outcome measures the effect estimates favored gabapentin over placebo
  - Only for reduction in percentage of heavy drinking days was gabapentin statistically significant (p= 0.03) to a moderate size effect (Hedges g= 0.64)
  - Gabapentin did not significantly improve the five other outcomes

Kranzler, Henry R., et al. Addiction (2019).

Take home points on gabapentin

- Reduces percentage of heavy drinking days
- May have some benefit at reducing cravings and protracted abstinent symptoms
- Higher dose (~1800mg/d) may be more effective
  - Further studies needed to establish optimal gabapentin doses given wide range of dosages that been tested to date

Other medications

- Baclofen: meta-analysis in 2018 revealed no improvement in alcohol consumption outcomes (1)
- Ondansetron: study of full dose ondansetron provided insufficient evidence to support its use for AUD (2)
- SSRIs: antidepressants are likely to be effective in reducing alcohol use in people with AUD and coexisting depression (3)

(1) Minozzi, Silvia, Rosella Saulle, and Susanne Rösner *Cochrane Database of Systematic Reviews* 11 (2018).
(2) Corrêa Filho, João Maria, and Danilo Antonio Baltieri. *Addictive behaviors* 38.4 (2013): 2044-2051.
(3) Abuse, Alcohol, and Alcoholism Consensus. Am Fam Physician 93.6 (2016): 457-465.

Summary

- AUD is common and severely undertreated
- Treatment with medications show moderate effectiveness and should be considered for all patient's with moderate to severe AUD given minimal and passing side effects
- These medications can be used in the inpatient setting without subspecialty support
- Psychosocial counseling is also effective and when combined with medication can further improve alcohol use outcomes
- Check out the following resources (uploaded to ECHO website):
  - NIH's Pocket Guide for Alcohol Screening and Brief Intervention
  - AAFP's Medications for AUD