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Alcohol: Assessment & Maintenance Medications

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Disclosures

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

Agenda

- Assessments
- Maintenance Medications
  - FDA-approved
  - Non FDA-approved

Substance use disorder: DSM-5 criteria

Impaired control

1. Consuming a larger amounts or over a longer period than was intended.
2. Persistent desire or unsuccessful efforts to cut down or control
3. A great deal of time is spent in activities necessary to obtain or use the substance, or recover from its effects.
4. Craving, or a strong desire or urge to use.

Social impairment

5. Failure to fulfill role obligations at work, school, or home.
6. Social or interpersonal problems
7. Important social, occupational, or recreational activities are given up or reduced

Risky use

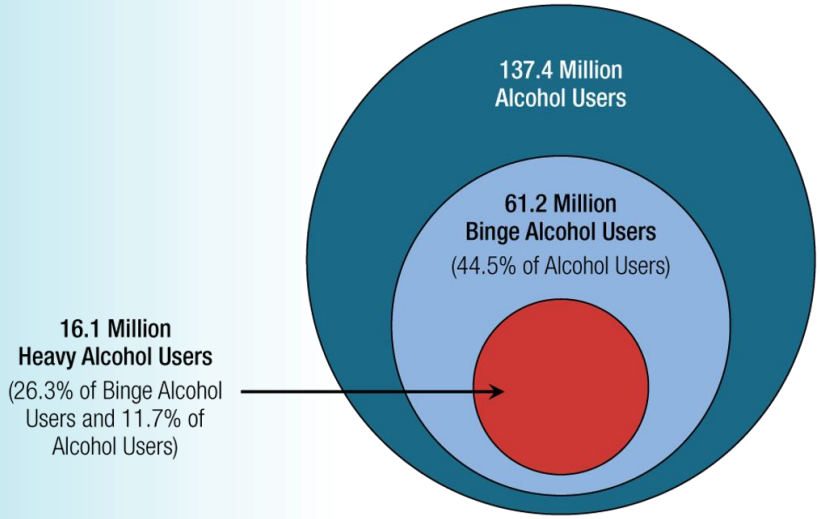
8. Use in situations in which it is physically hazardous.
9. Continued use despite ongoing physical or psychological problem

Pharmacologic criteria

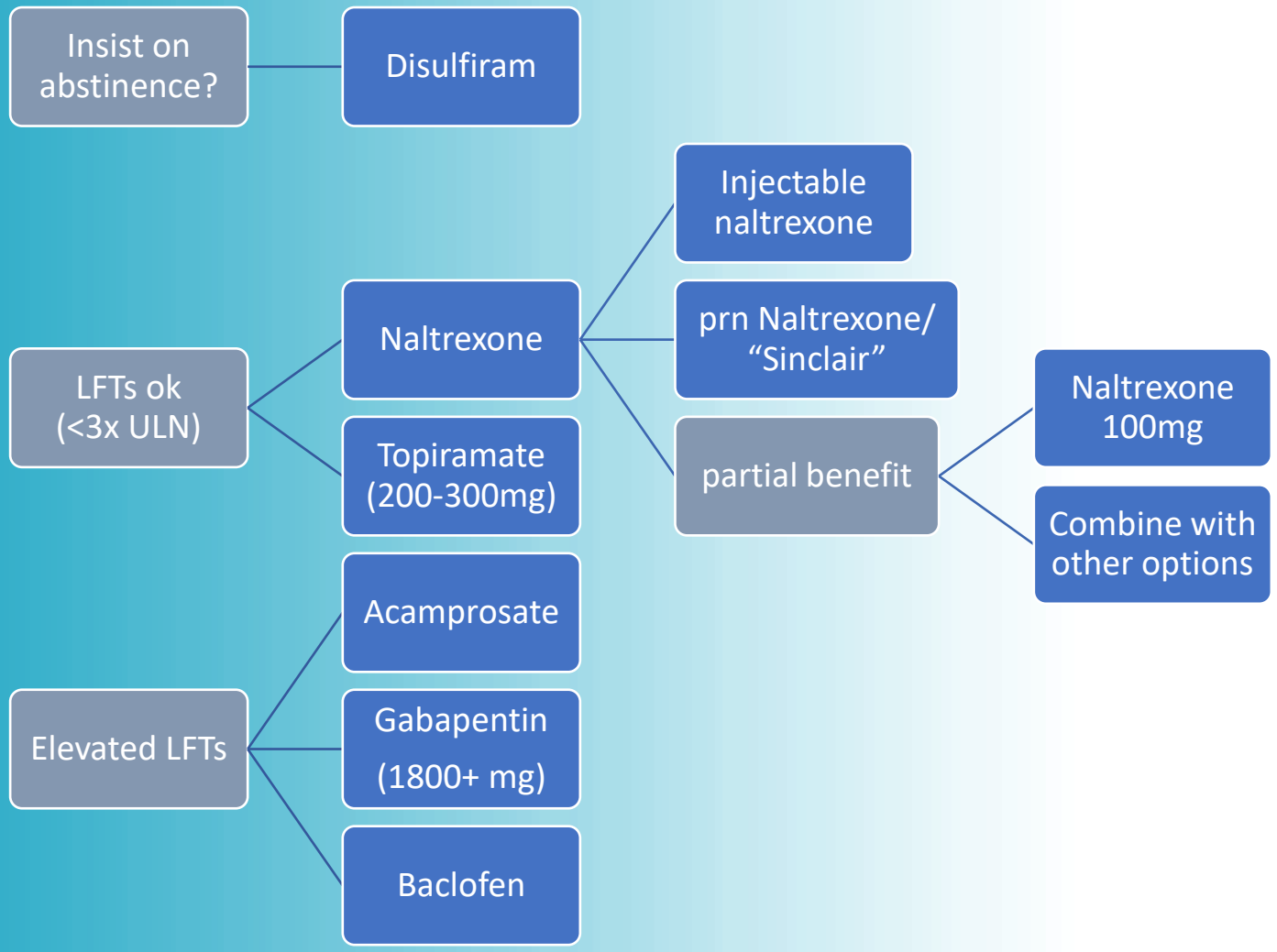
10. Tolerance
11. Withdrawal

Definitions re: Alcohol Quantity

- Binge Drinking
  - Males: 5+ drinks
  - Females: 4+ drinks
  - One occasion in last 30 days
- Heavy Drinking
  - Same amounts as Binge drinking
  - 5+ occasions in last 30 days
- Low-risk drinking
  - Males: <5 / day; <15 / week
  - Females: <4 / day; <8 / week



A Personal Recommendation tree

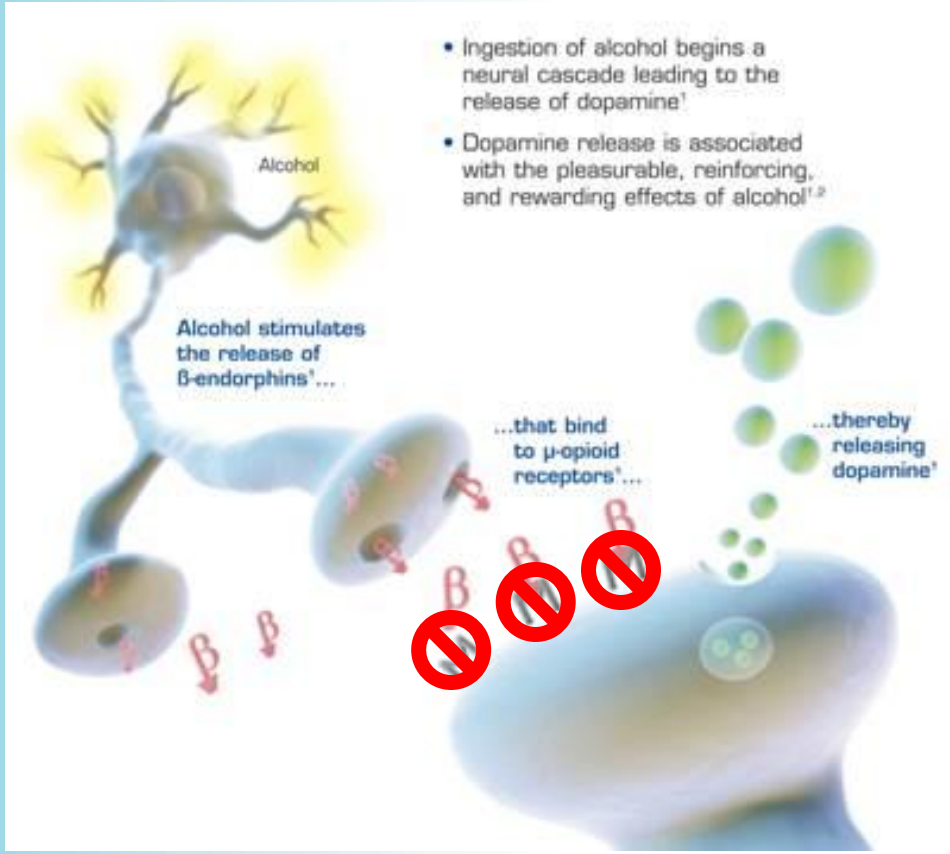


FDA Approved Options

- 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

Leighty and Ansara, 2019; Jonas et al., 2014

Naltrexone (for alcohol)

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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

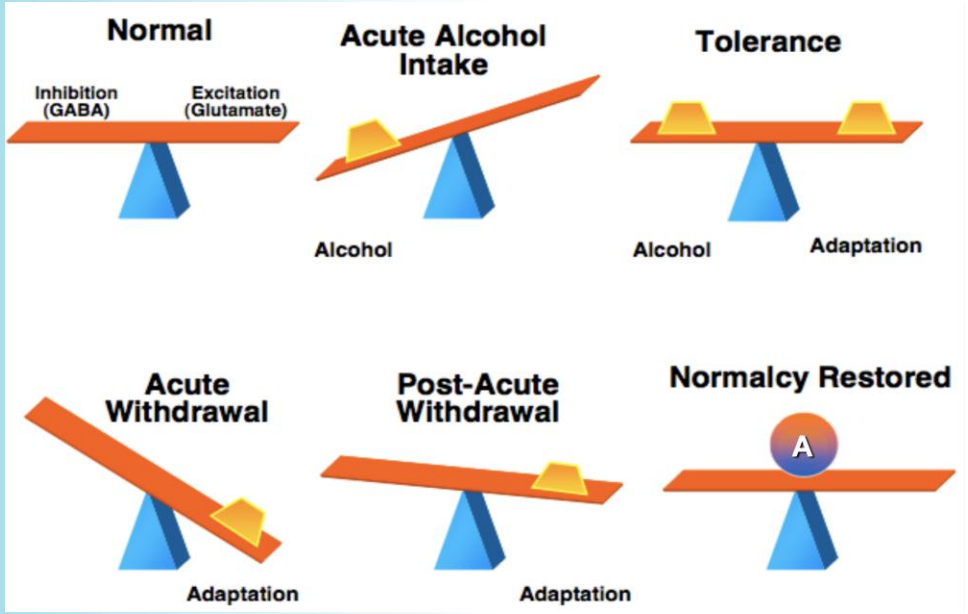
Pearls

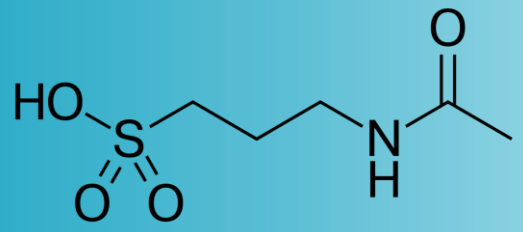
- Can drink on naltrexone
- Less evidence for prn use, or "The Sinclair Method"
- Stop 48-72 hours before surgery

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=12)
- 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

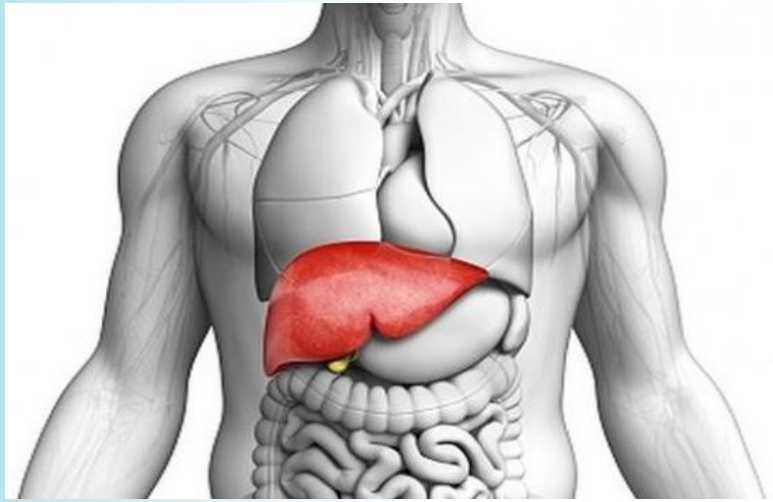
Contraindications
- CrCL <30
- Hypercalcemia
  - (TC≥10.3; IC ≥5.4)

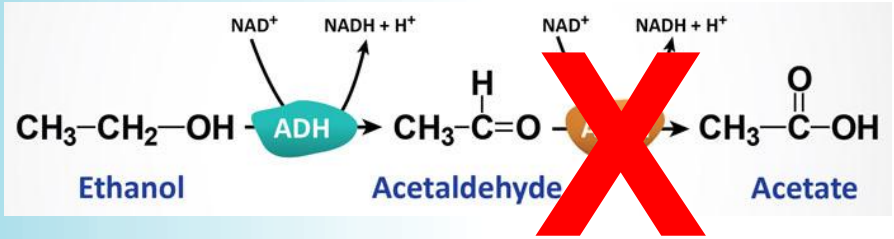
Pearls
- Safe for liver
- Particularly helpful for negative-emotional state craving (e.g., drinking when sad)
- Can improve alcohol-alterations to sleep architecture
- Best if started while abstinent

Luc et al., 2006

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

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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, at 1, 2 and 3 months, then q3mo

Contraindications

- Severe disease / coronary myocardialocclusion
- Confusion
- LFTs > 3x normal

Pearls

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

O'Farrell, Allen, & Litten, 1995

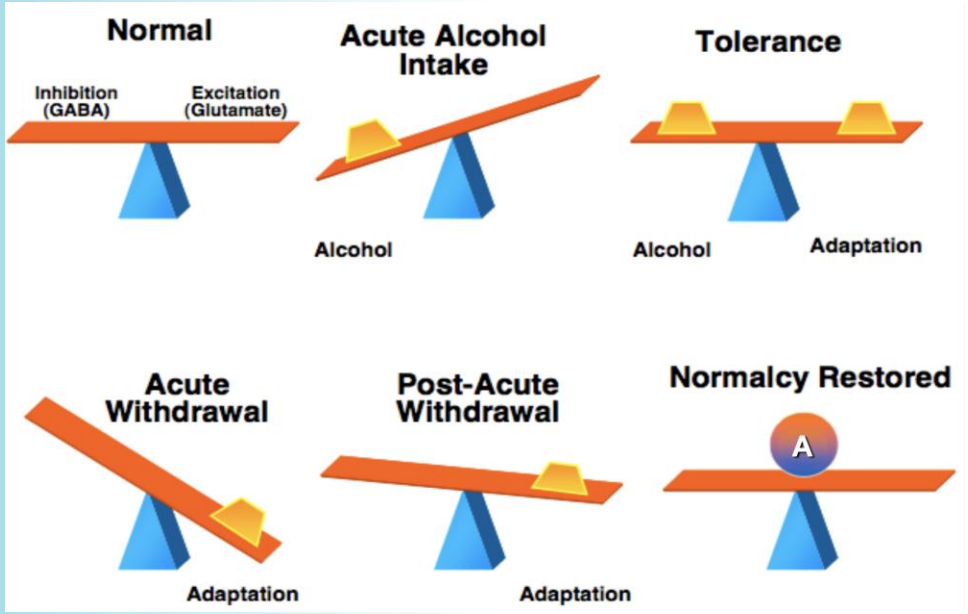
Non-FDA Approved Options

- Topiramate
- Gabapentin
- Baclofen

- Valproate
- Ondansetron
- Carbamazepine
- Oxcarbazepine
- Memantine
- Kudzu Root

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

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Dosing
- 200-300mg divided bid

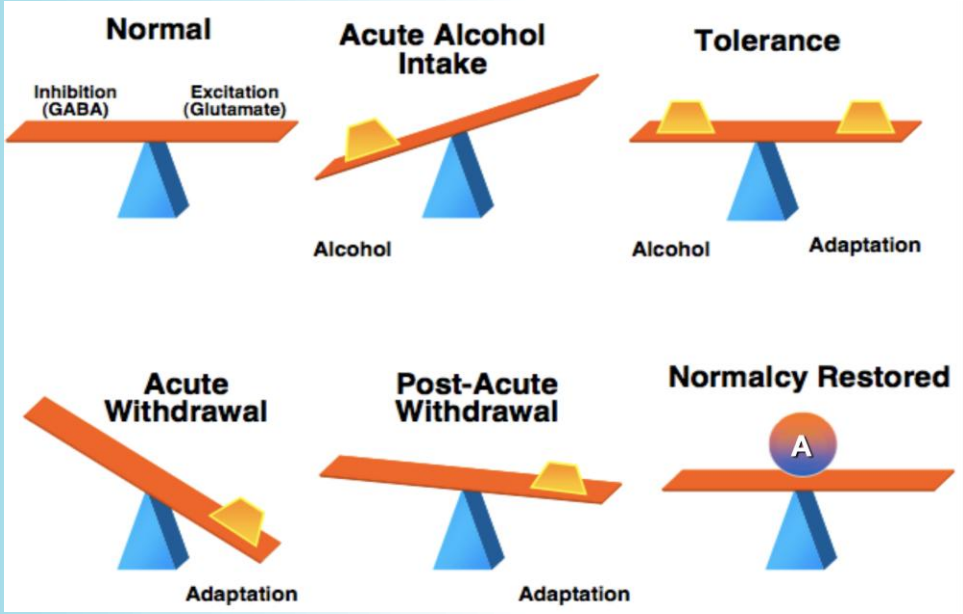
Side effects
- Cognitive dulling
- Appetite suppression
- Kidney stones

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

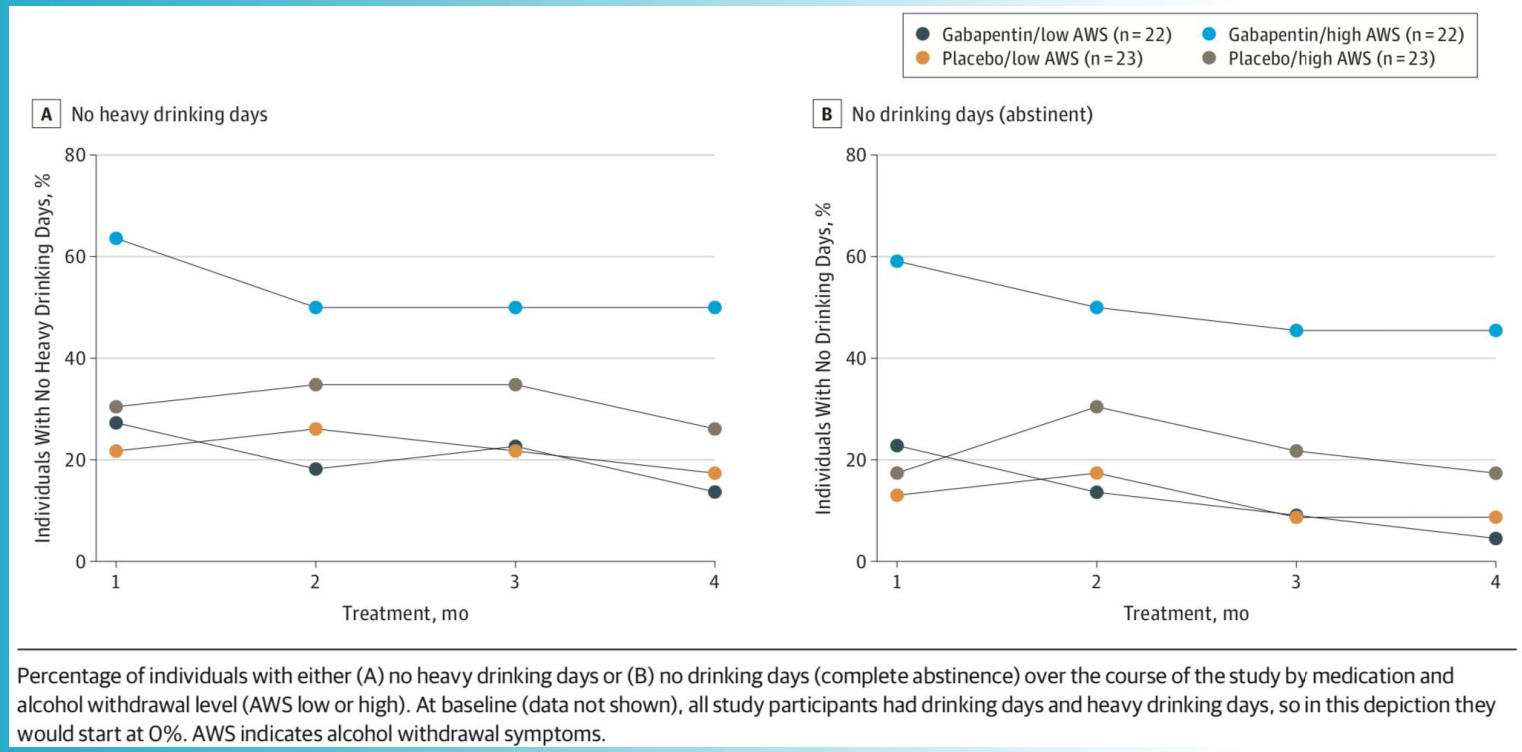
- Decreased number of drinks
- Delayed return to heavy drinking

- Gabapentin enacarbil – no impact on heavy drinking days, abstinence, drinks per week, etc.
- Separate RCT suggests effects for subset with high withdrawal scores

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

Gabapentin: efficacy

- Separate RCT suggests effects for subset with high withdrawal scores



Percentage of individuals with either (A) no heavy drinking days or (B) no drinking days (complete abstinence) over the course of the study by medication and alcohol withdrawal level (AWS low or high). At baseline (data not shown), all study participants had drinking days and heavy drinking days, so in this depiction they would start at 0%. AWS indicates alcohol withdrawal symptoms.

Anton et al., 2020

Gabapentin

Dosing

- 600mg tid
- Higher better?

Side effects

- Sedation

Contraindications

- Renal disease

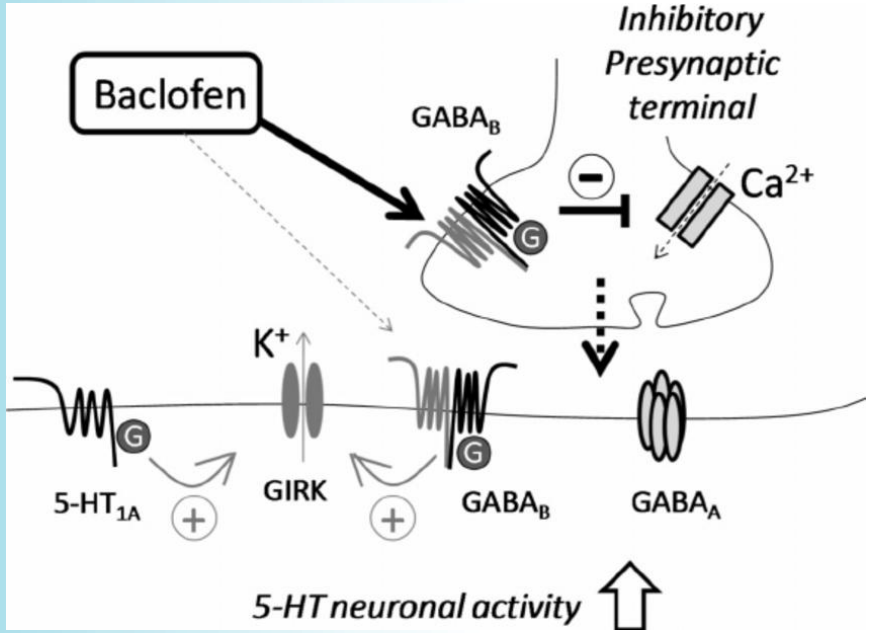
Pearls

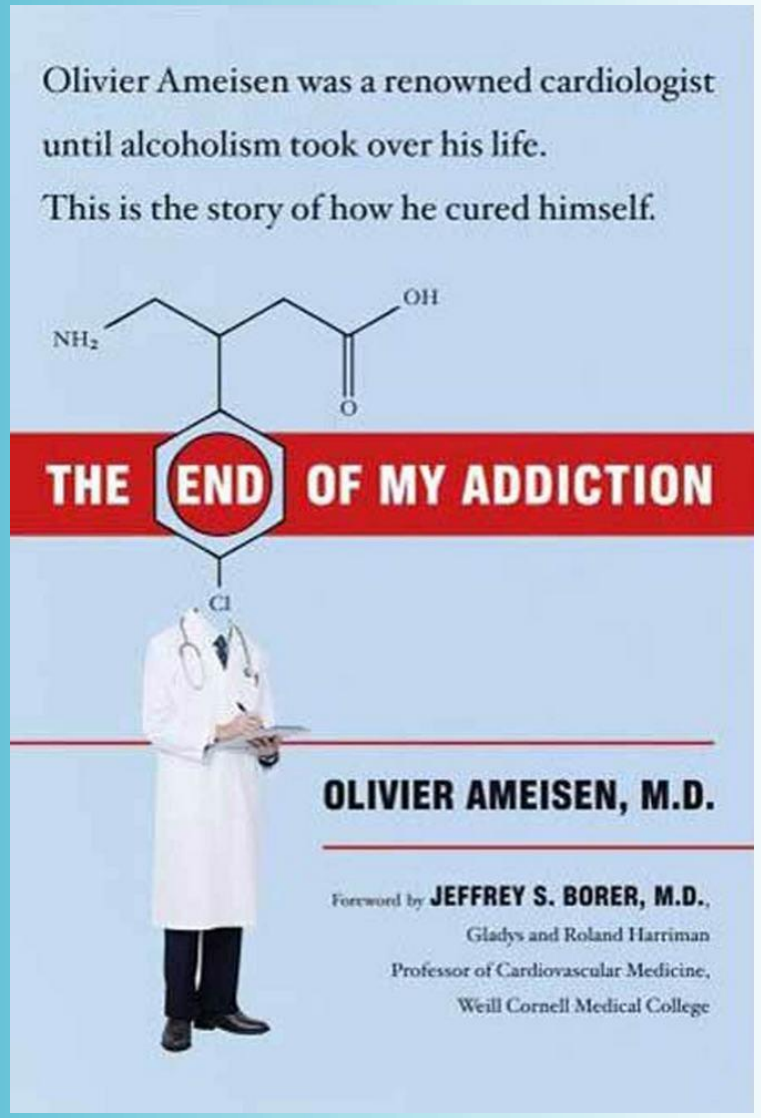
- Start 300mg nightly, rapidly increase to 300mg tid. Then increase to 600mg tid.
- Can be helpful with comorbid anxiety and/or neuralgia
- Don’t sweat misuse if no OUD

Mason et al., 2014; Wilens, Zulauf, Ryland, Carrellas, & Catalina-Wellington, 2015

Baclofen: mechanism

- GABA-B agonist
- Mechanisms not well understood




Olivier Ameisen was a renowned cardiologist
until alcoholism took over his life.
This is the story of how he cured himself.
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THE END OF MY ADDICTION
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OLIVIER AMEISEN, M.D.
Foreword by JEFFREY S. BORER, M.D.,
Gladys and Roland Harriman
Professor of Cardiovascular Medicine,
Weill Cornell Medical College

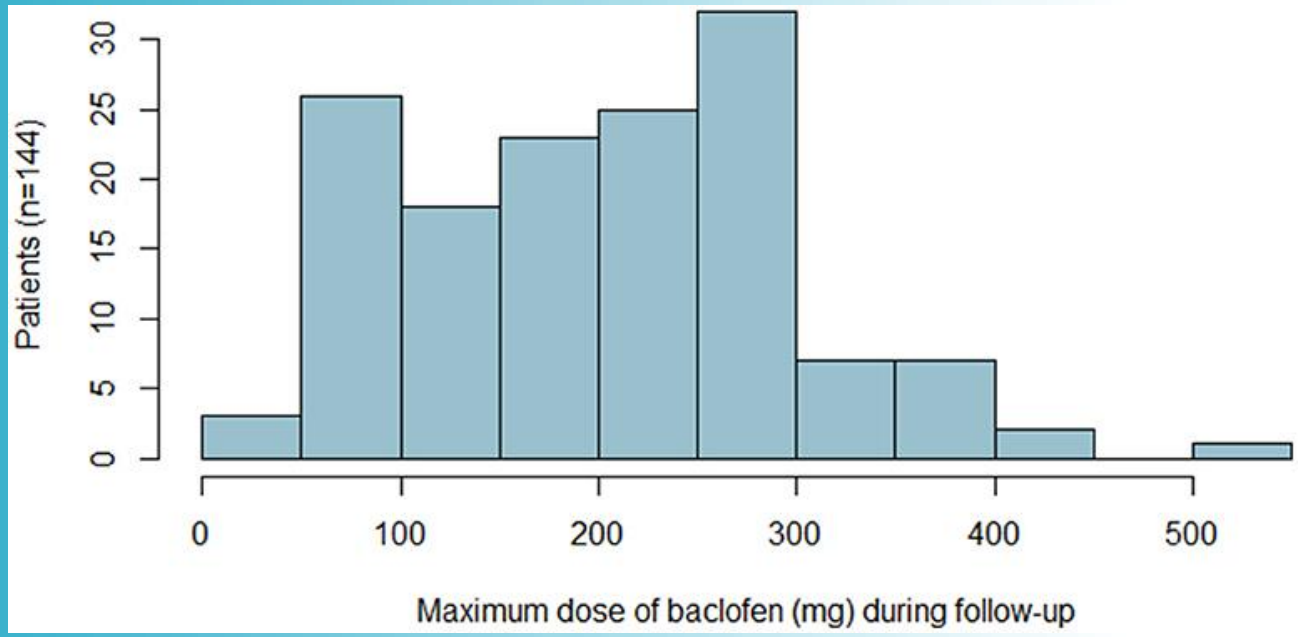
Baclofen: efficacy

- Meta-analyses: 12+ RCTs with varying doses of baclofen.

Bschor, Henssler, Müller, & Baethge, 2018; Chaignot et al., 2018

Baclofen: max dose range

- 1 group's max dose in a N=144 case review



Pinot, Rigal, Granger, Sidorkiewicz, & Jaury, 2018

Baclofen: efficacy

- Meta-analyses: 12+ RCTs with varying doses of baclofen.
- Increase abstinence? OR 2.67 [1.03-6.93]
  - Driven by a few small trials; larger trials negative
  - Other meta-analyses slightly bigger didn't replicate
- Dose dependent harm:

Dose	Mortality Hazard Ratio [95%CI]
<30mg	1.00 [0.74-1.36]
30-75mg	1.41 [1.09-1.84]
75-180mg	1.50 [1.06-2.14]
>180mg	2.27 [1.27-4.07]

Bschor, Henssler, Müller, & Baethge, 2018; Chaignot et al., 2018

Baclofen

<u>Dosing</u>

- 5 mg bid or tid
- Increase by 5 or 10mg per day, every 2-4 days as tolerate.
- Target decrease in drinking, and side effects

<u>Contraindications</u>

- Renal disease

<u>Side effects</u>

- Sedation
- Asthenia
- Dizziness
- Vertigo
- Insomnia
- Concentration

<u>Pearls</u>

- Consideration for severe liver disease.
- Supposed to help people become disinterested in EtOH.

Andrade, 2020

GLP-1 Receptor Agonists: Promising, But Early Days

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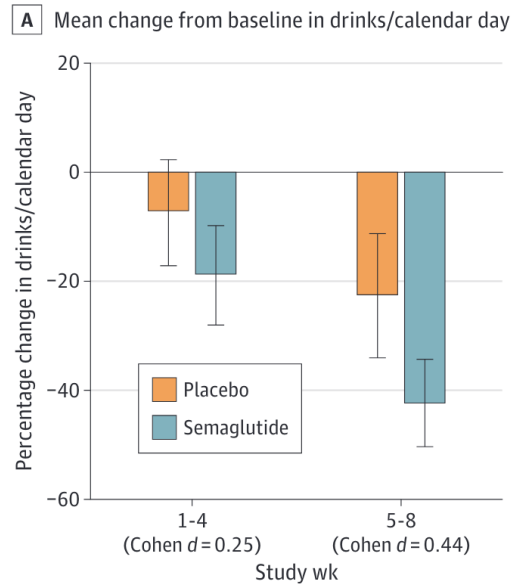
- GLP-1 receptors in VTA, NAcc → modulate mesolimbic dopamine

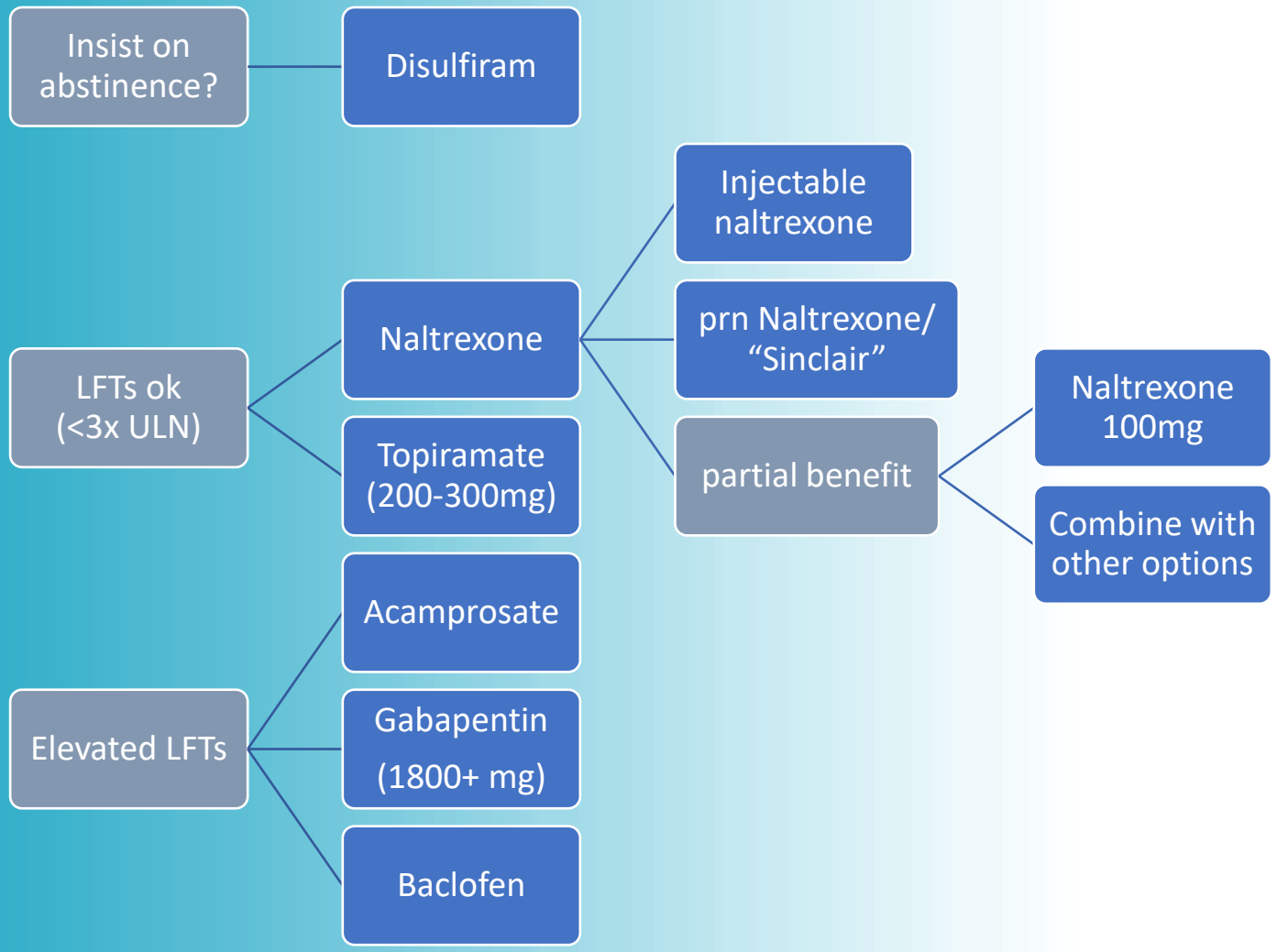
- Many anecdotes, retrospective data
- First clinical trial:
  - Low-dose semaglutide may ↓ heavy drinking in non-treatment-seekers
  - Small sample, short follow-up, possible confounders



- Caution: May be lifelong treatment, long-term neuropsych effects unknown

Hendershot et al., 2025

A Personal Recommendation tree



References

- Anton, R. F., Latham, P., Voronin, K., Book, S., Hoffman, M., Prisciandaro, J., & Bristol, E. (2020). Efficacy of Gabapentin for the Treatment of Alcohol Use Disorder in Patients With Alcohol Withdrawal Symptoms: A Randomized Clinical Trial. *JAMA Internal Medicine*, *180*(5), 728. doi: 10.1001/jamainternmed.2020.0249
- Andrade, C. (2020). Individualized, High-Dose Baclofen for Reduction in Alcohol Intake in Persons With High Levels of Consumption. *The Journal of Clinical Psychiatry*, *81*(4), 0–0. doi: 10.4088/JCP.20f13606
- Baltieri, D. A., Daró, F. R., Ribeiro, P. L., & de Andrade, A. G. (2008). Comparing topiramate with naltrexone in the treatment of alcohol dependence. *Addiction*, *103*(12), 2035–2044. doi: 10.1111/j.1360-0443.2008.02355.x
- Bschor, T., Henssler, J., Müller, M., & Baethge, C. (2018). Baclofen for alcohol use disorder-a systematic meta-analysis. *Acta Psychiatrica Scandinavica*, *138*(3), 232–242. doi: 10.1111/acps.12905
- Chaignot, C., Zureik, M., Rey, G., Dray-Spira, R., Coste, J., & Weill, A. (2018). Risk of hospitalisation and death related to baclofen for alcohol use disorders: Comparison with nalmefene, acamprosate, and naltrexone in a cohort study of 165 334 patients between 2009 and 2015 in France. *Pharmacoepidemiology and Drug Safety*, *27*(11), 1239–1248. doi: https://doi.org/10.1002/pds.4635
- Falk, D. E., Ryan, M. L., Fertig, J. B., Devine, E. G., Cruz, R., Brown, E. S., … Litten, R. Z. (2019). Gabapentin Enacarbil Extended-Release for Alcohol Use Disorder: A Randomized, Double-Blind, Placebo-Controlled, Multisite Trial Assessing Efficacy and Safety. *Alcoholism: Clinical and Experimental Research*, *43*(1), 158–169. doi: 10.a1111/acer.13917
- Flórez, G., Saiz, P. A., García-Portilla, P., Álvarez, S., Nogueiras, L., & Bobes, J. (2011). Topiramate for the treatment of alcohol dependence: Comparison with naltrexone. *European Addiction Research*, *17*(1), 29–36. doi: 10.1159/0003204
- Hendershot, C. S., Bremmer, M. P., Paladino, M. B., Kostantinis, G., Gilmore, T. A., Sullivan, N. R., Tow, A. C., Dermody, S. S., Prince, M. A., Jordan, R., McKee, S. A., Fletcher, P. J., Claus, E. D., & Klein, K. R. (2025). Once-Weekly Semaglutide in Adults With Alcohol Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*. https://doi.org/10.1001/jamapsychiatry.2024.4789
- Jonas, D. E., Amick, H. R., Feltner, C., Bobashev, G., Thomas, K., Wines, R., … Garbutt, J. C. (2014). Pharmacotherapy for Adults With Alcohol Use Disorders in Outpatient Settings: A Systematic Review and Meta-analysis. *JAMA*, *311*(18), 1889. doi: 10.1001/jama.2014.3628
- Leighty, A. E., & Ansara, E. D. (2019). Treatment outcomes of long-acting injectable naltrexone versus oral naltrexone in alcohol use disorder in veterans. *Mental Health Clinician*, *9*(6), 392–396. doi: 10.9740/mhc.2019.11.392

References

- Leung, J. G., Hall-Flavin, D., Nelson, S., Schmidt, K. A., & Schak, K. M. (2015). The Role of Gabapentin in the Management of Alcohol Withdrawal and Dependence. *Annals of Pharmacotherapy*, *49*(8), 897–906. doi: 10.1177/1060028015585849
- Littleton, J. M. (2007). Acamprosate in Alcohol Dependence: Implications of a Unique Mechanism of Action. *Journal of Addiction Medicine*, *1*(3), 115–125. doi: 10.1097/ADM.0b013e318156c26f
- Luc S, Peter B, Thierry D, Isabelle G, Muriel M, Frédéric L, Rémy L (2006) Effects of Acamprosate on Sleep During Alcohol Withdrawal: A Double-Blind Placebo-Controlled Polysomnographic Study in Alcohol-Dependent Subjects. Alcoholism Clin & Exp Res 30:1492–1499.
- Lukas, S. E., Penetar, D., Su, Z., Geaghan, T., Maywalt, M., Tracy, M., … Lee, D. Y.-W. (2013). A Standardized Kudzu Extract (NPI-031) Reduces Alcohol Consumption in Non Treatment-Seeking Male Heavy Drinkers. *Psychopharmacology*, *226*(1), 65–73. doi: 10.1007/s00213-012-2884-9
- Mason, B. J., Quello, S., Goodell, V., Shadan, F., Kyle, M., & Begovic, A. (2014). Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial. *JAMA Internal Medicine*, *174*(1), 70–77. doi: 10.1001/jamainternmed.2013.11950
- O'Farrell, T. J., Allen, J. P., & Litten, R. Z. (1995). Disulfiram (antabuse) contracts in treatment of alcoholism. *NIDA Research Monograph*, *150*, 65–91.
- Pinot, J., Rigal, L., Granger, B., Sidorkiewicz, S., & Jaury, P. (2018). Tailored-Dose Baclofen in the Management of Alcoholism: A Retrospective Study of 144 Outpatients Followed for 3 Years in a French General Practice. *Frontiers in Psychiatry*, *9*. doi: 10.3389/fpsyt.2018.00486
- Rösner, S., Hackl-Herrwerth, A., Leucht, S., Vecchi, S., Srisurapanont, M., & Soyka, M. (2010). Opioid antagonists for alcohol dependence. *Cochrane Database of Systematic Reviews*, (12). doi: 10.1002/14651858.CD001867.pub3
- Sinclair, J. D. (2001). Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism. *Alcohol and Alcoholism*, *36*(1), 2–10. doi: 10.1093/alcalc/36.1.2
- Skinner, M. D., Lahmek, P., Pham, H., & Aubin, H.-J. (2014). Disulfiram Efficacy in the Treatment of Alcohol Dependence: A Meta-Analysis. *PLOS ONE*, *9*(2), e87366. doi: 10.1371/journal.pone.0087366
- Wilens, T., Zulauf, C., Ryland, D., Carrellas, N., & Catalina-Wellington, I. (2015). Prescription medication misuse among opioid dependent patients seeking inpatient detoxification. *The American Journal on Addictions*, *24*(2), 173–177. doi: 10.1111/ajad.12159