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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

MEDICATION MANAGEMENT & AUD: 1ST, 2ND, & 3RD LINE OPTIONS

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UW Psychiatry & Behavioral Sciences

project ECHO

SPEAKER DISCLOSURES

- ✓ Any conflicts of interest?

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OBJECTIVES

Review evidence-based pharmacotherapy options for AUD

Discuss clinical considerations when choosing MAT

Highlight the underutilization of MAT and encourage its use

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AUD IS A CHRONIC RELAPSING BRAIN DISORDER CHARACTERIZED BY AN IMPAIRED ABILITY TO STOP OR CONTROL ALCOHOL USE DESPITE ADVERSE SOCIAL, OCCUPATIONAL, OR HEALTH CONSEQUENCES.

DIAGNOSTIC CRITERIA (DSM-5): IN THE PAST YEAR, HAVE YOU...

- Had times when you ended up drinking more, or longer than you intended?
- More than once wanted to cut down or stop drinking, or tried to, but couldn't?
- Spent a lot of time drinking? Or being sick or getting over the aftereffects?
- Experienced craving — a strong need, or urge, to drink?
- Found that drinking — or being sick from drinking — often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
- Continued to drink even though it was causing trouble with your family or friends?
- Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?
- More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
- Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?
- Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
- Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, irritability, anxiety, depression, restlessness, nausea, or sweating? Or sensed things that were not there?

Meeting two of the 11 criteria during the same 12-month period receives a diagnosis of AUD.
Mild: The presence of 2 to 3 symptoms
Moderate: The presence of 4 to 5 symptoms
Severe: The presence of 6 or more symptoms

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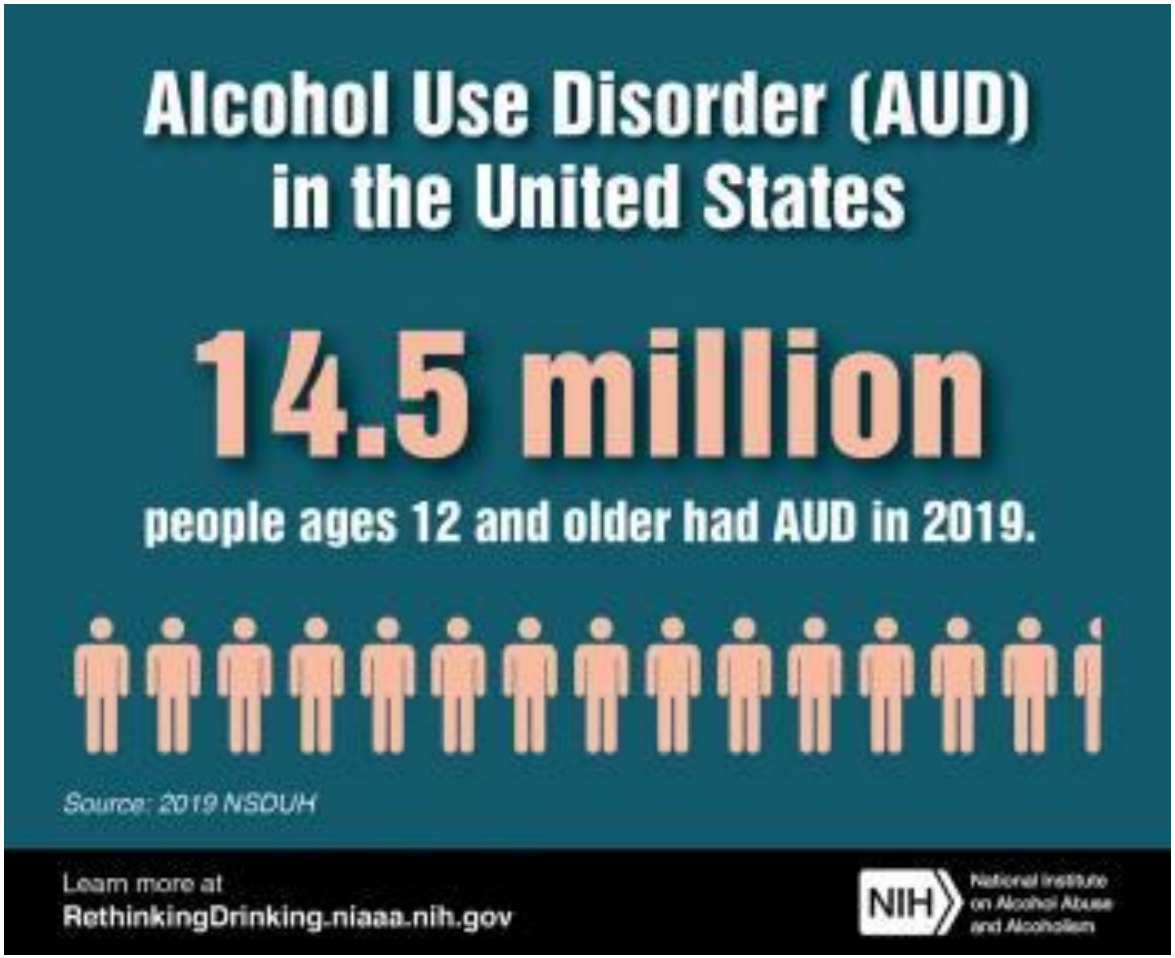
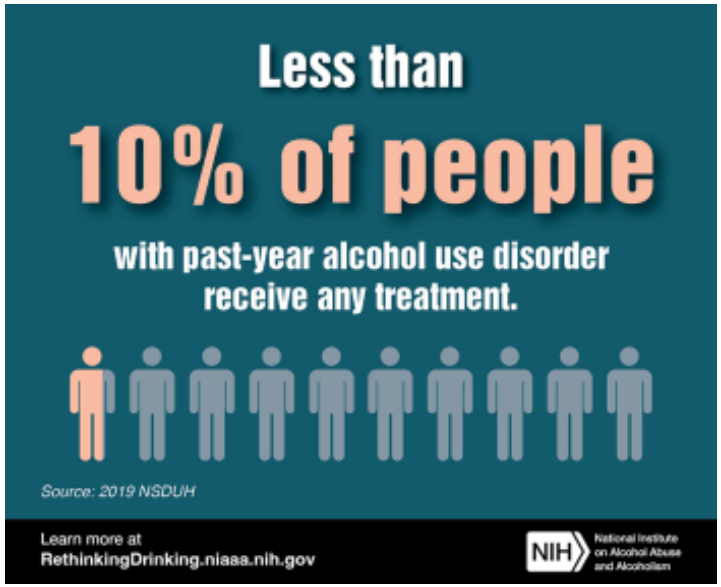
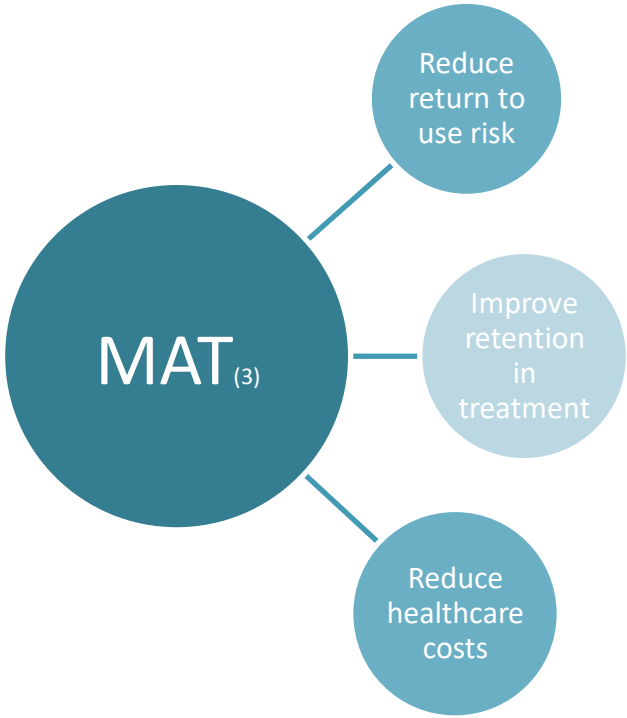


UNDERUTILIZATION OF PHARMACOTHERAPY FOR AUD





- Disulfiram - approved in 1949
- In 2020, less than 6% of individuals who received care for AUD were treated with an FDA - approved medication (1)
- 2015 - 2019: over 140,000 deaths, attributable to excessive alcohol use, annually. Each year, there was a total of 3.6 million years of potential life lost due to these deaths (2).

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How?

Several neurotransmitter systems can influence the reinforcing effects of alcohol(4,5).

Dysregulation of motivation circuits:

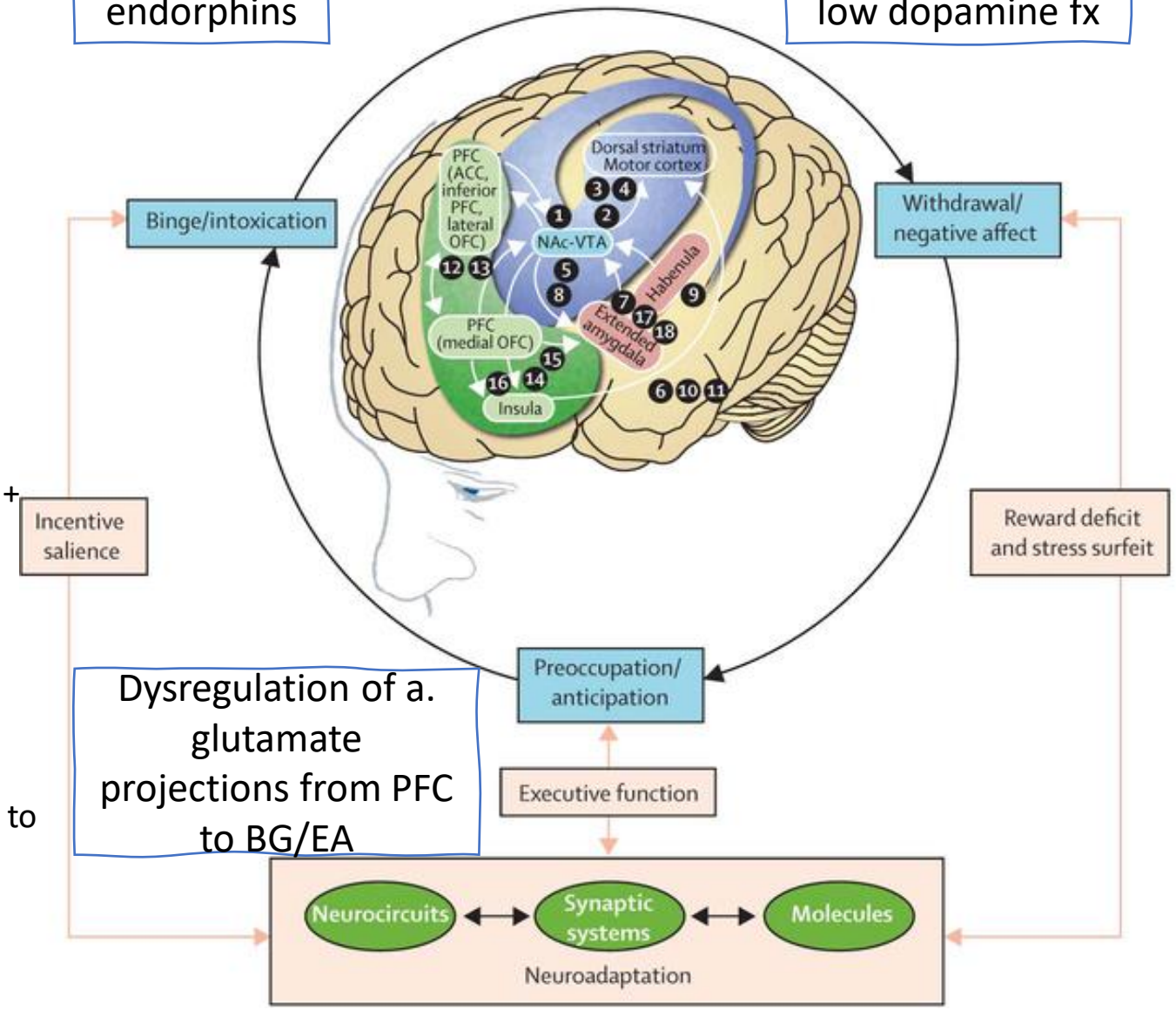
- Exaggerated incentive salience/habit formation + reward deficit/stress surplus + compromised executive function.

Medications for AUD:

- Restore the upregulation of impulse and reward circuitry and down regulation of cognitive control, which lead to compulsive use despite negative consequences. (6).

GABA, Dopamine, endorphins

Glutamate Stress NTs (CRF), low dopamine fx



Dysregulation of a. glutamate projections from PFC to BG/EA

Lancet Psychiatry. 2016 Aug;3(8):760-773. doi: 10.1016/S2215-0366(16)00104-8.

FDA – APPROVED MEDICATIONS

Medication	Year Approved	Description
Disulfiram	1949	Aversive medication; after ingestion, alcohol consumption leads to a variety of aversive symptoms. Approved dosage is 250 - 500 mg/d.
Naltrexone	1994	Orally bioavailable opioid antagonist that decreases the reinforcing effects of alcohol. Most robust effects clinically are to reduce risk of heavy drinking. Approved dosage is 50 mg/d.
Acamprosate	2004	GABA receptor agonist and NMDA receptor modulator. Most robust effects clinically are to maintain abstinence. Approved dosage is 666 mg three times daily.
Long-acting naltrexone	2006	Injectable formulation that produces detectable plasma concentrations for 30 d. May help to improve adherence compared to oral formulation. Approved dosage is 380 mg/mo.

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NALTREXONE

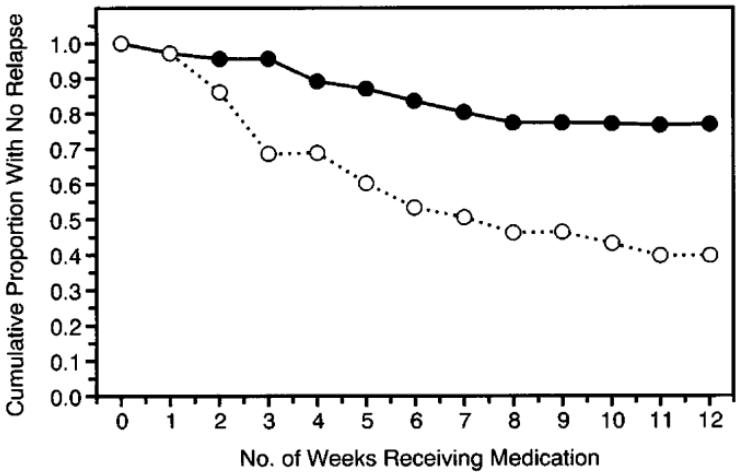

Fig 2.—*Relapse rates (as defined in the text) for the naltrexone hydrochloride- (closed circles) and placebo-treated (open circles) groups across the 12 weeks of the study.*

Naltrexone—Volpicelli et al

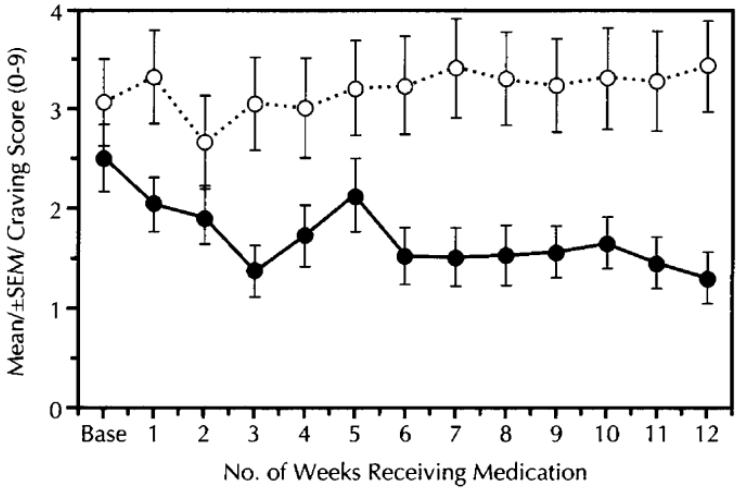

Fig 1.—*Mean (±SEM) craving scores for the naltrexone hydrochloride-(closed circles) and placebo-treated (open circles) groups across the 12 weeks of the study.*

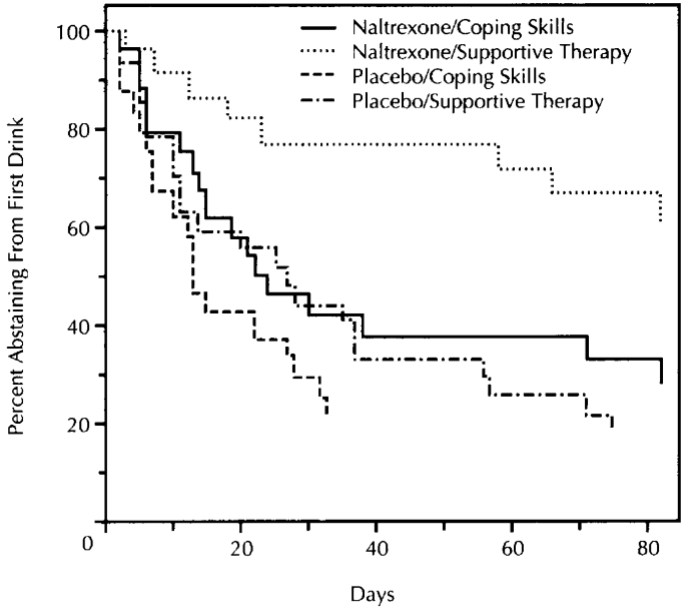

Fig 1.—*Rates of continuous abstinence according to treatment groups (n=97).*

Naltrexone—O'Malley et al

NALTREXONE

2022 meta-analysis included 54 RCTs – Naltrexone > Placebo in reducing heavy drinking days and improving abstinence (9)

2014 meta-analysis of 44 RCTs found NNT = 12 to prevent return to heavy drinking and NNT = 20 to prevent return to any drinking (10)

2010 Cochrane review of 50 RCTs – Naltrexone reduced risk of: Heavy drinking, drinking days, heavy drinking days, consumed amount of alcohol, and the alcohol consumption biomarker, gamma-glutamyl transferase. Naltrexone was not found to effectively prevent return to any drinking (11)

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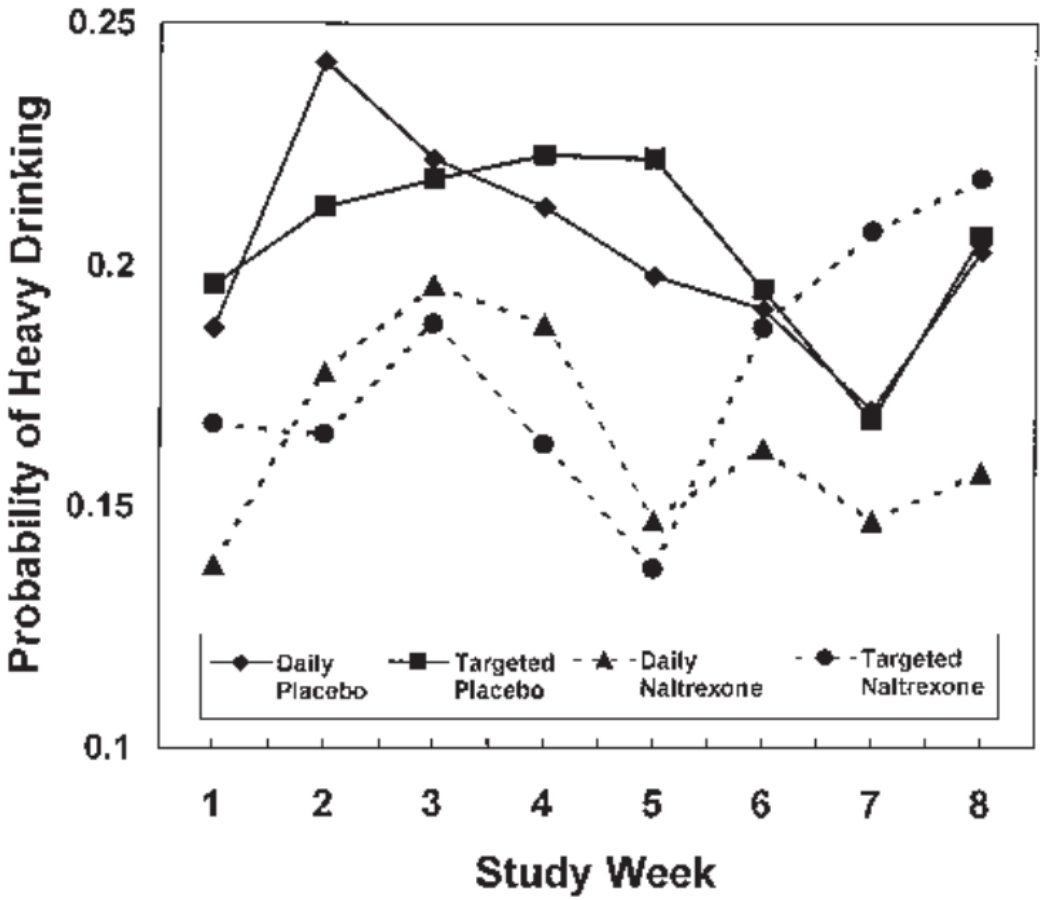
NALTREXONE (TARGETED)



8 week study in patients with unhealthy drinking. Naltrexone 50mg vs Placebo

Targeted: for use in situations identified by the patients as being high risk for heavy drinking (with the number of tablets available for use by patients in the targeted conditions decreasing over the course of the trial). (12)

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NALTREXONE – EXTENDED RELEASE (XTR)

6 months study, n=600 with AUD. Compared 190mg vs 380 mg vs placebo, all with low intensity psychosocial intervention. Abstinence was not required. Compared with placebo, 380 mg reduced the event rate of heavy drinking by 25%. The reduction due to 190 mg was not statistically significant (17%). Their data also showed that patients who were abstinent by choice for at least a week before treatmentm had the most robust effects.(13)

So, FDA approved monthly 380 mg and stated in the package insert that the medication should be used only in individuals who are abstinent at treatment initiation.

In meta-analysis of 7 RCTs (n=1500). XTR - naltrexone (vs placebo) was found to significantly reduce drinking and heavy drinking days per month. Larger reductions in HDD were seen in treatment duration > 3 months and in trials not requiring pre-treatment abstinence. (14)

Abstinence should not be a requirement for initiating treatment with XTR-naltrexone

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CLINICAL CONSIDERATIONS

Contraindications: Acute hepatic impairment, decompensated cirrhosis

Caution: in chronic hepatic impairment. Avoid if LFTs> 3-5 x upper limit of normal range.

Monitoring: Baseline LFTs (would not withhold if no clinical signs of decompensation). Ongoing monitoring (?) - Naltrexone consistently showin in studies of AUD to decrease liver enzyme concentrations.

Adverse events: GI, dizziness/headache/fatigue, injection site.

Predictors of response? Patients who have a family history of AUD, early age of drinking onset ("biological vulnerability"), or who have comorbid use of other substances than alcohol, may have a better clinical response to naltrexone (15).

Long-acting naltrexone should be considered when adherence to medication is challenging.

Patient education. "Can I drink on naltrexone?" Yes. May alter experience of intoxication but risk of tx +drinking < risk of no tx + drinking

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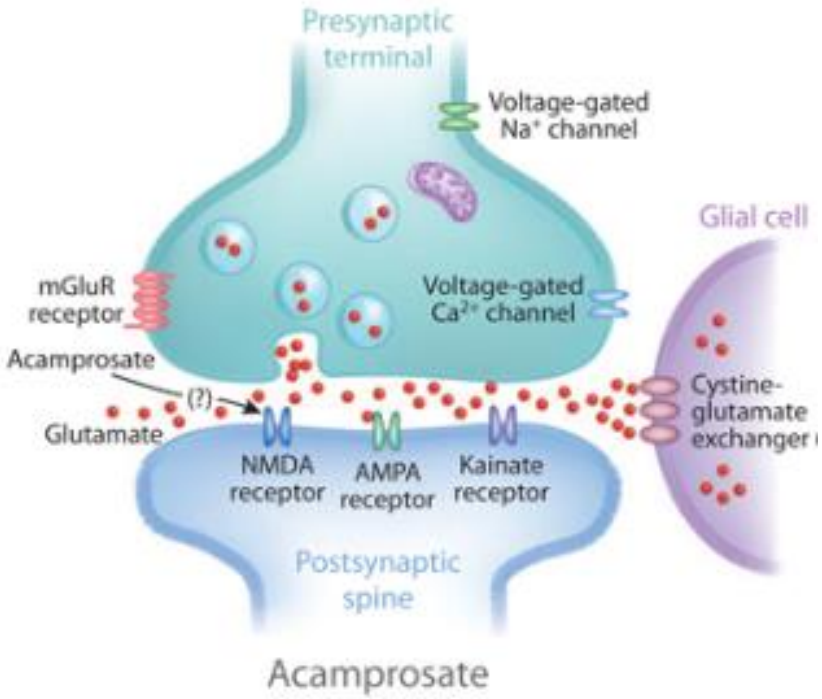
ACAMPROSATE



- An amino acid derivative
- MOA: officially uncertain. Likely: increases GABA neurotransmission, has complex effects on excitatory amino acid (ie, glutamate) neurotransmission, and modulates the activity of NMDA receptors -> restores balance between excitatory and inhibitory neurotransmission that is altered by chronic alcohol consumption which is likely how it exerts its therapeutic effect in AUD(16)

ACAMPROSATE

1985 study in France first showed that Acamprosate was twice as effective as placebo in reducing the rate at which AUD patients returned to drinking (17).

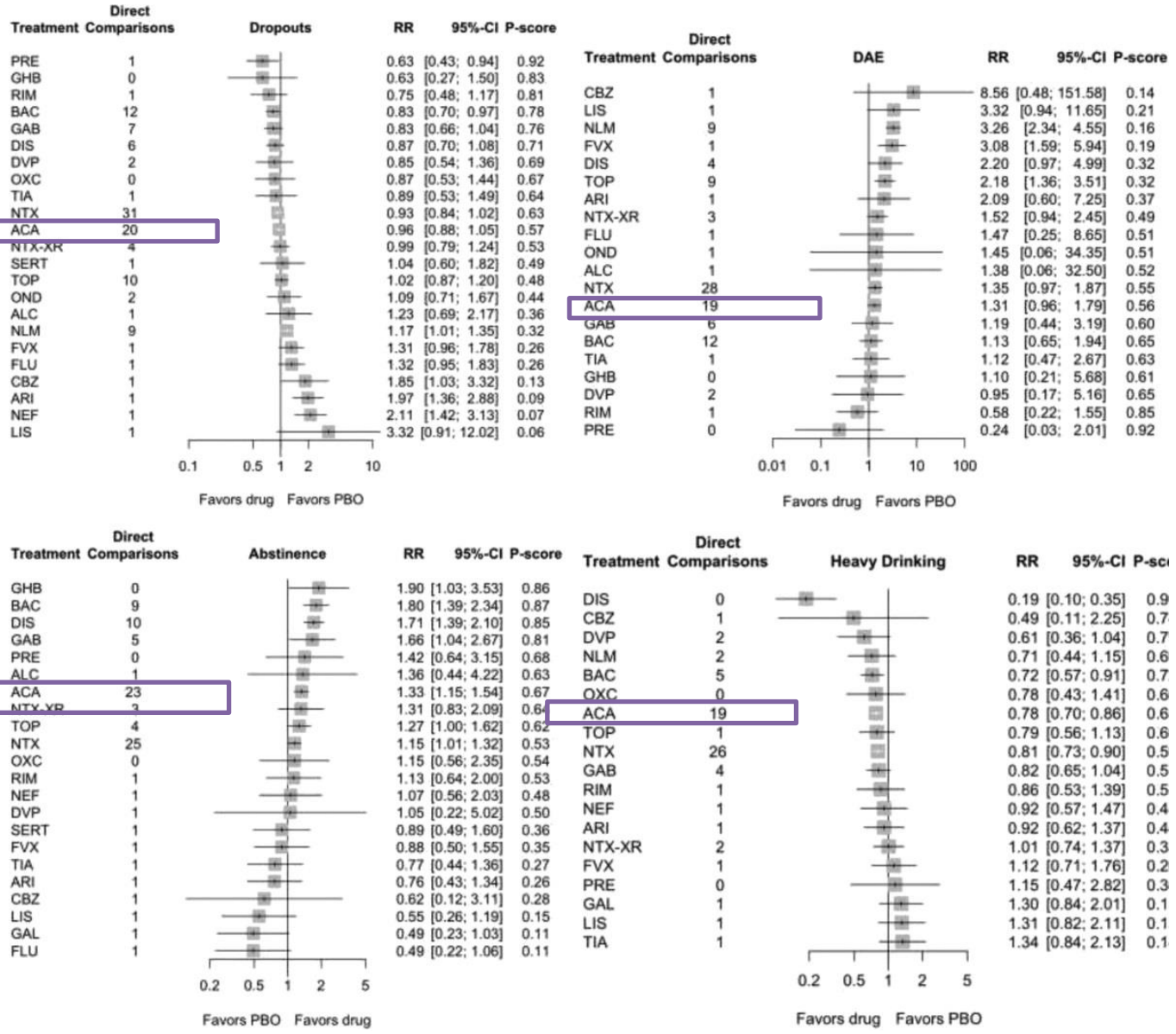
FDA approved it based on 3 European studies (n=998) (18)

European studies (>4000 pt) support its benefit in the prevention of return to drinking and in the reduction of drinking in those who return to use.

Two US, multicenter trials (including the COMBINE study) , failed to show a difference from placebo. (19,20)

? Differences in study design (European studies required a lengthier period of abstinence) and samples studied (European subjects were heavier drinkers)

ACAMPROSATE



35 RCTs
ACA = improved abstinence and heavy drinking.

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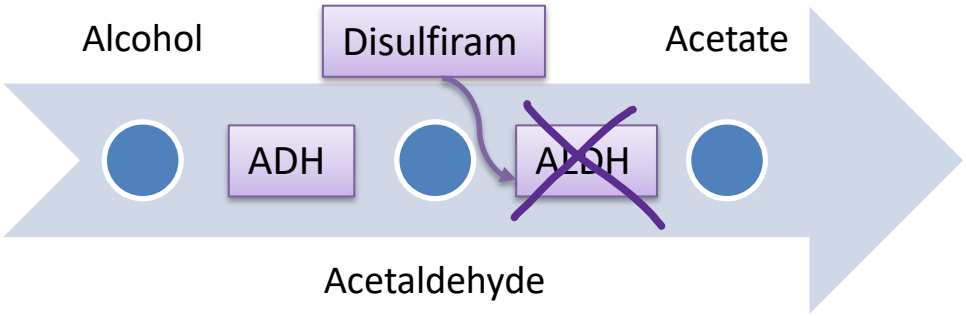
ACAMPROSATE

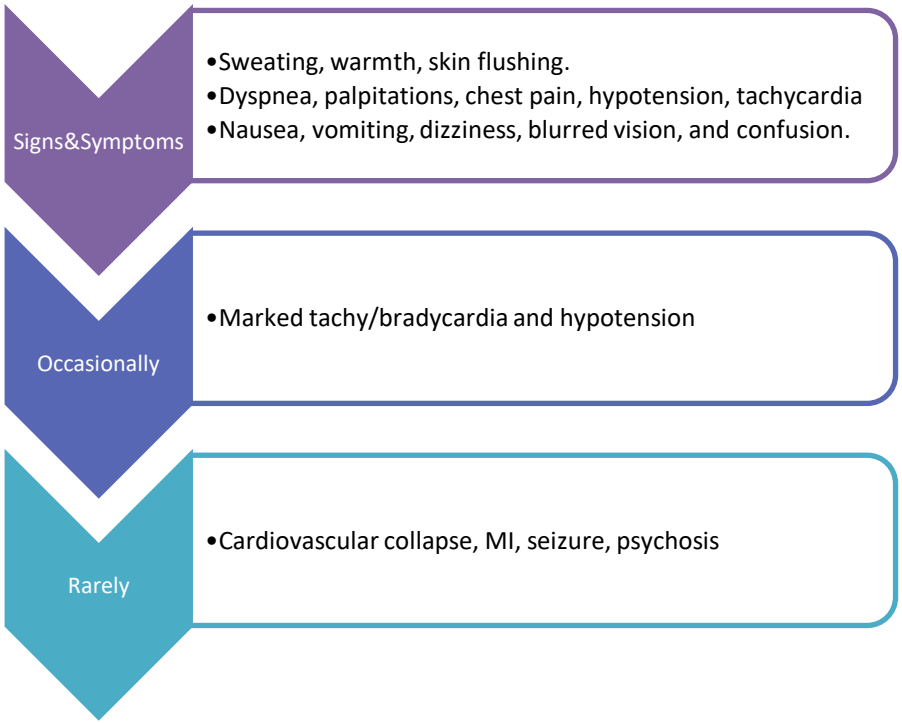
Difference of proportion of patients drinking on average five or more drinks per day

Period	Placebo, %	Acamp, %	Adj Diff	Sample size
D30	53%	41%	–13 (–19, –8)	983
D90	48%	36%	–11 (–19, –8)	927
D180	51%	32%	–14 (–22, –6)	651
D360	51%	33%	–11 (–23, 0)	244

- Meta-analysis of 15 studies (n=3309)
- Acamprosate > Placebo : reducing quantity(29%), frequency(27%), uncontrolled drinking (13%)
- Effects increased with treatment duration (from 3 to 6 and then to 12 months) (22).

DISULFIRAM





- Elevated blood acetaldehyde concentration result in the disulfiram–ethanol reaction (DER).
- Most DERs are self-limited ~ 30 minutes.
- Disulfiram dose and amount of alcohol ingested affect the intensity of the DER.
- Some patients: complete absence of a DER. Others: Severe reaction even with a small amount of alcohol (23).
- Severe reactions occur usually with high doses of disulfiram (>500 mg/d) + >2 oz of alcohol(24,25).

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DISULFIRAM

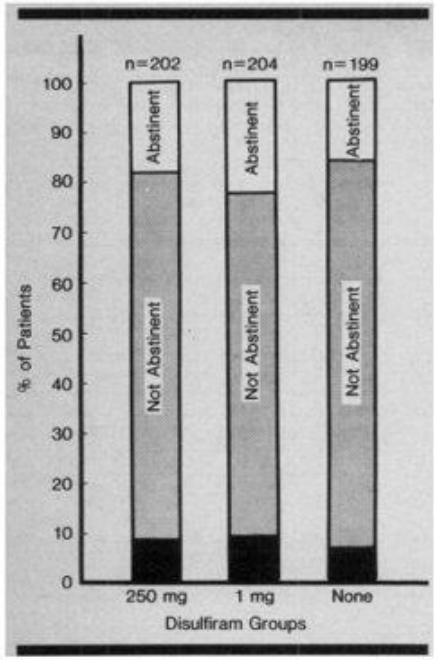
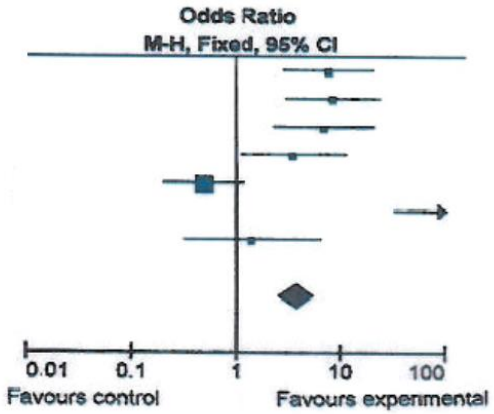


Fig 1.—Abstinence rates. Clear portion of each bar gives percentage of patients totally abstinent for one year in each treatment group; dotted portion indicates percentage of patients not abstinent; and lined portion gives percentage of patients for whom there were insufficient data to evaluate abstinence.

- VA 1986 RCT
- Greater adherence = greater complete abstinence. (20% adherent, of these 43% were abstinent vs 8% of non-adherent)
- In patients who resumed drinking, 250 mg group reported significantly fewer drinking days than other two groups.
- Disulfiram = reducing the frequency of drinking in pt who continue to drink(26)



Systematic review of 11 RCTs, (n=1,527): supervised administration of disulfiram improved short-term abstinence, prolonged days until relapse, and reduced the number of drinking days (27).

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DISULFIRAM

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DISULFIRAM

Binds irreversibly to aldehyde dehydrogenase -> need to synthesize new enzyme to avoid DER. This can take at least 2 weeks from last administration.

Monitor for: Optic neuritis, peripheral neuropathy, and hepatotoxicity (rare). Discontinue medication if they occur(28).

LFTs: monthly in first 3 months of treatment, then check every 3 months.

Inhibits dopamine beta-hydroxylase (increases dopamine concentrations) -> monitor patients with hx of psychosis.

Adverse effects <-> dosage except for risk of hepatic injury. So dose is limited to 250-500 mg/d.

OFF-LABEL MEDICATIONS FOR AUD

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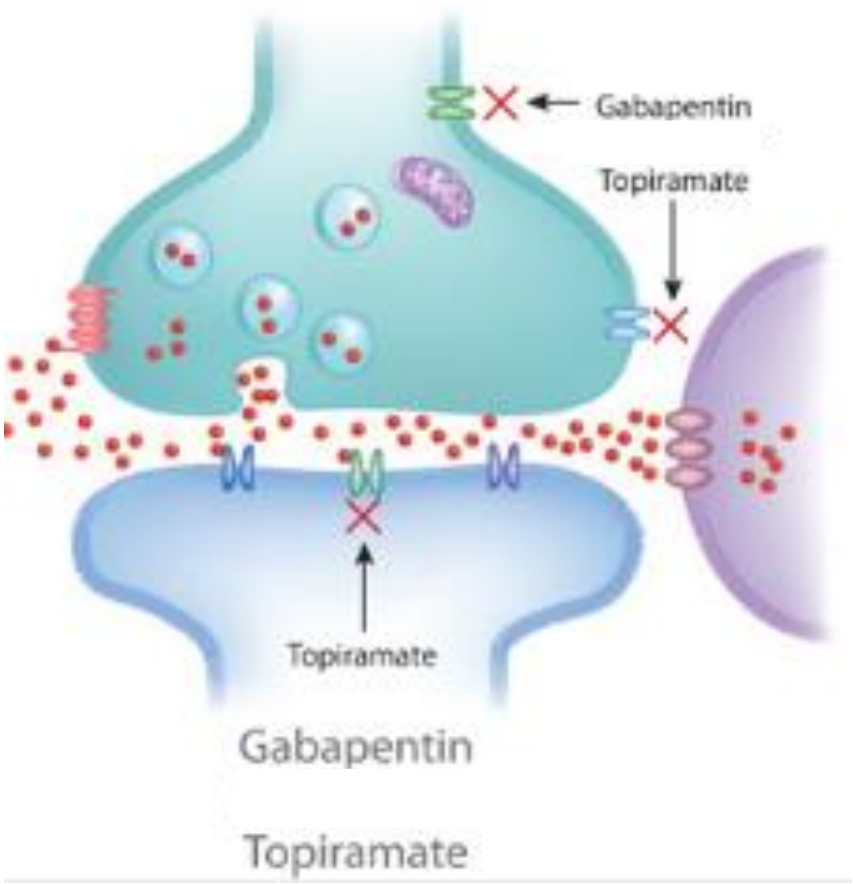
GABAERGIC AGENTS



- Enhance GABA effects (agonism)
- Modulate glutamate effect (antagonism)
- Normalize the imbalance in these neurotransmitter systems associated with chronic heavy drinking.
- Medications in this group include Topiramate, Gabapentin, Pregabalin, and Baclofen

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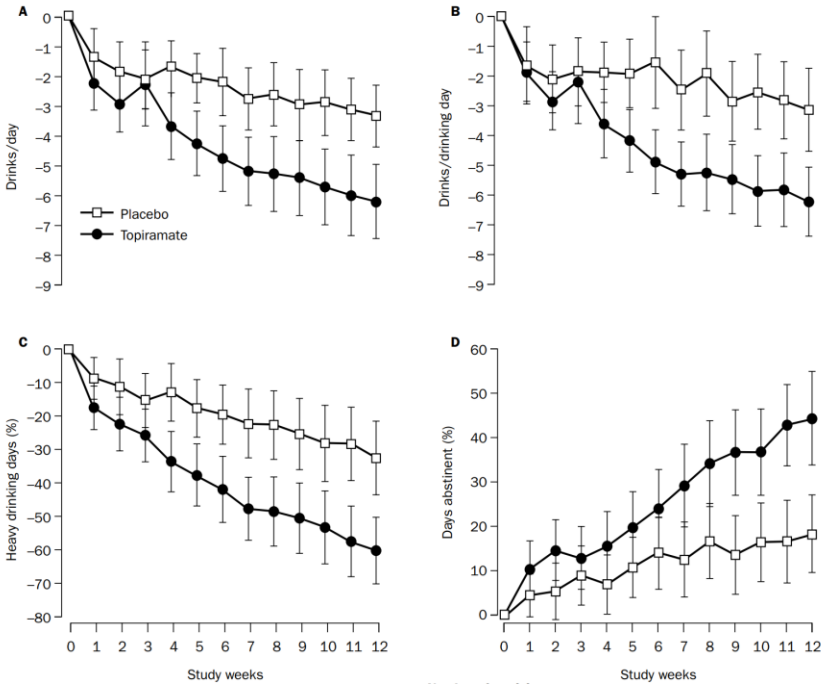
TOPIRAMATE



- 12-week study
- Effect started at 200mg
- Lower GGT levels in topiramate group

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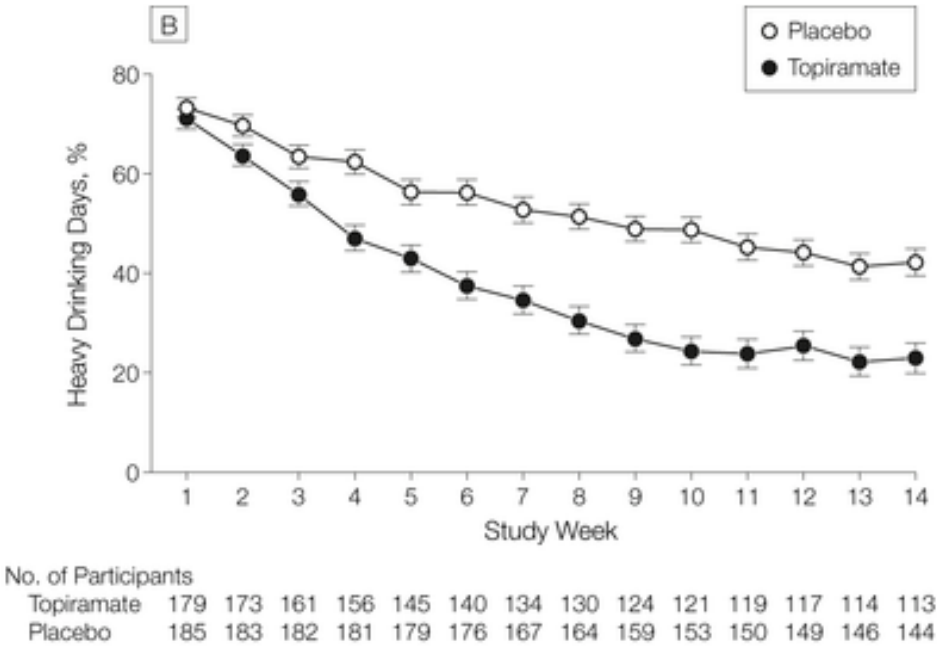
TOPIRAMATE



- Similar outcomes (Less HDD and improved abstinence)
- Not as well tolerated as the initial trial (single site)
- ? more rapid dose titration (to a maximum of 300 mg, but over 6 weeks).
- paresthesia (50.8% vs 10.6%), taste perversion (23.0% vs 4.8%), anorexia (19.7% vs 6.9%), and difficulty with concentration (14.8% vs 3.2%). (30)

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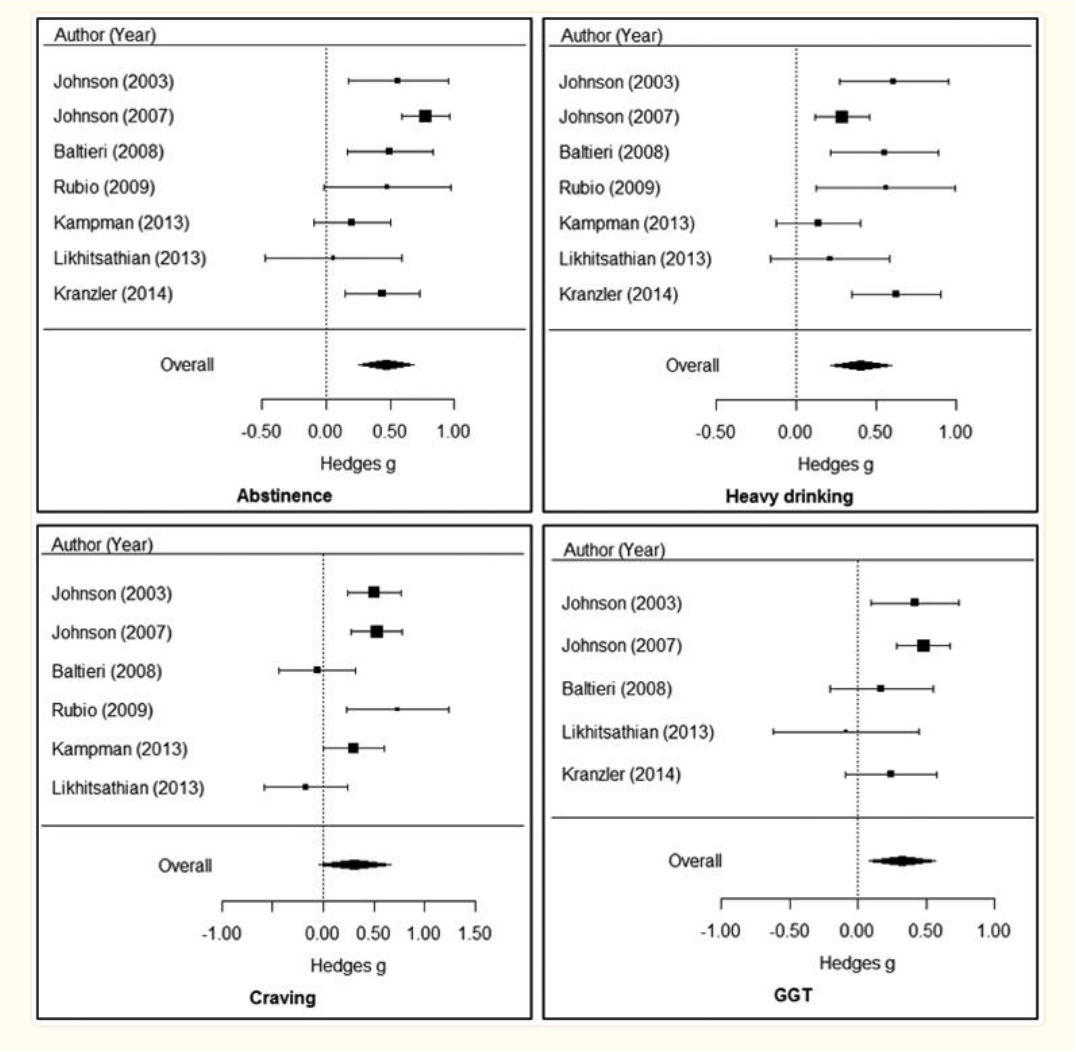
TOPIRAMATE



meta-analysis of 7 RCTs (n=1125)

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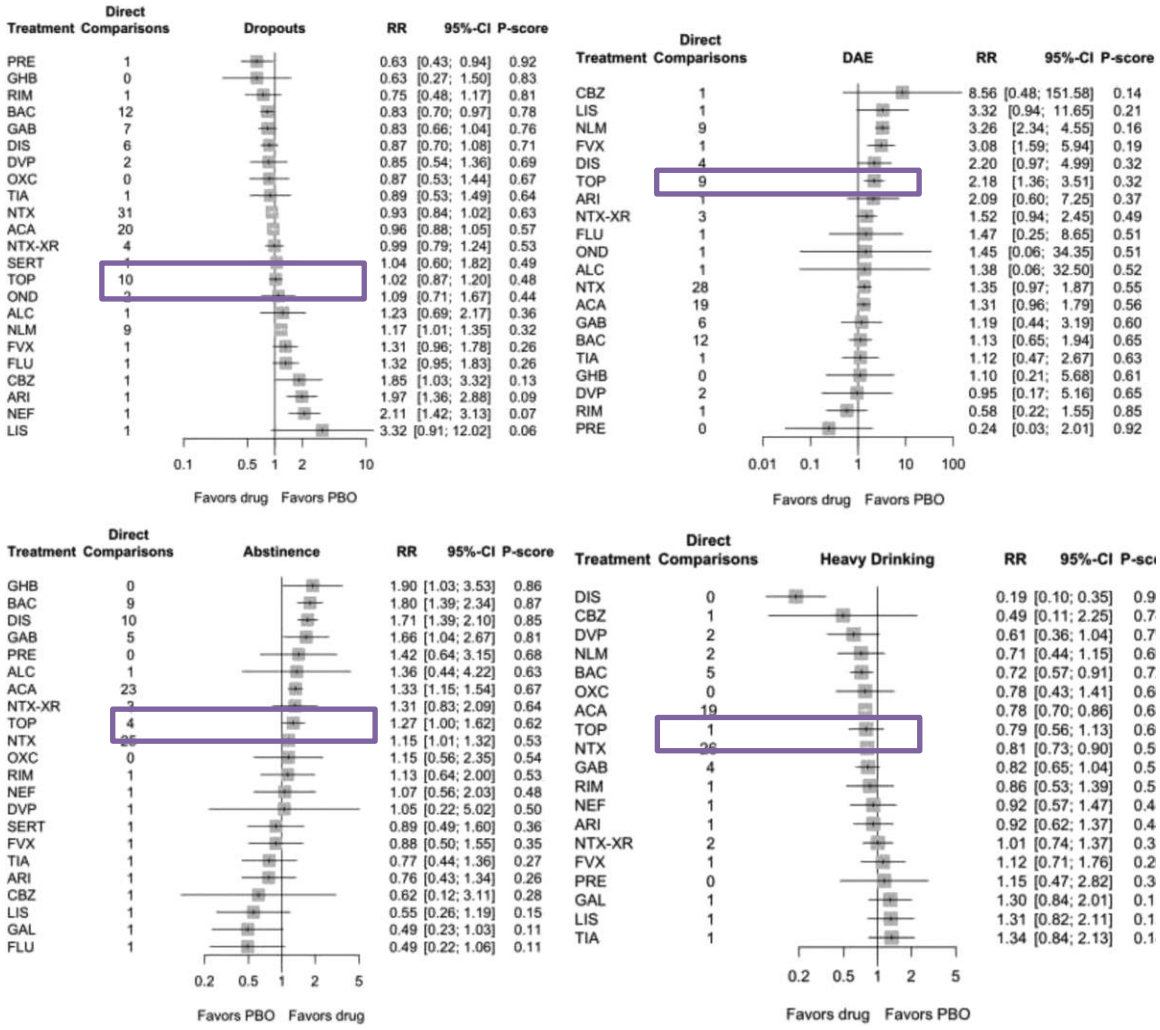
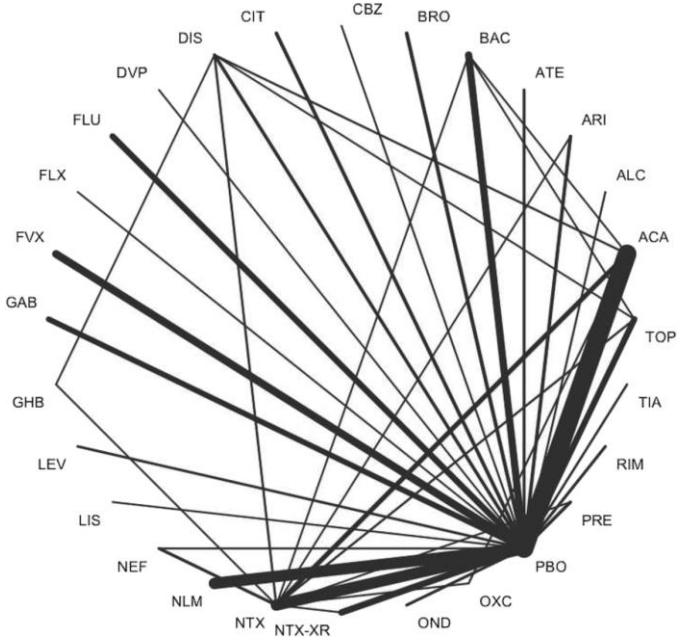
TOPIRAMATE





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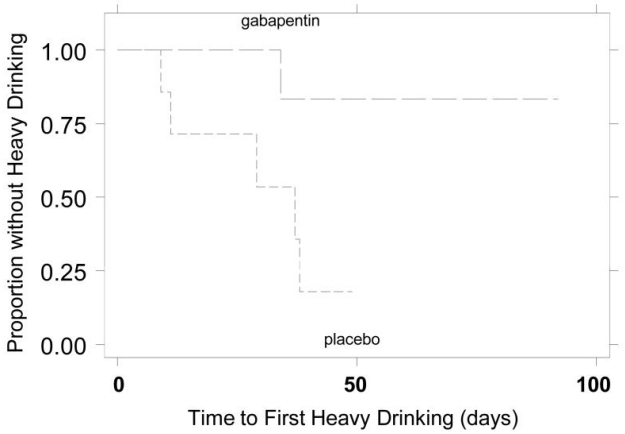
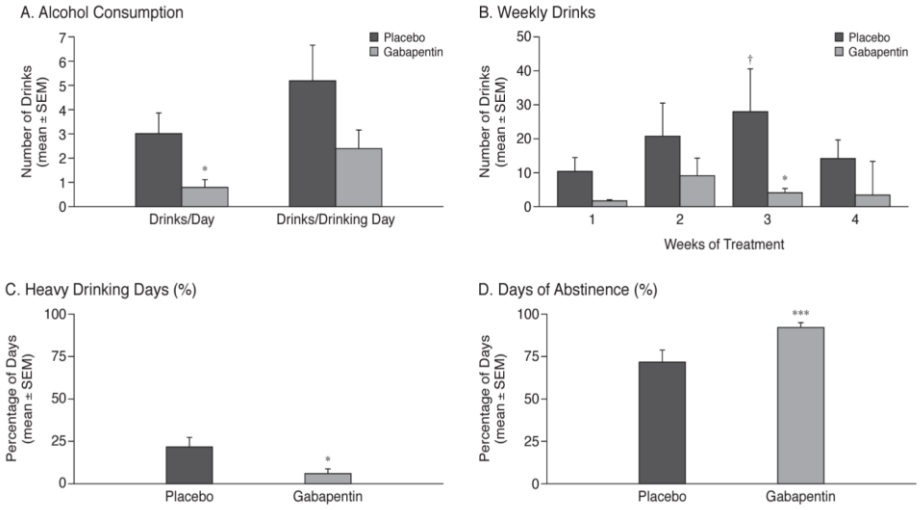
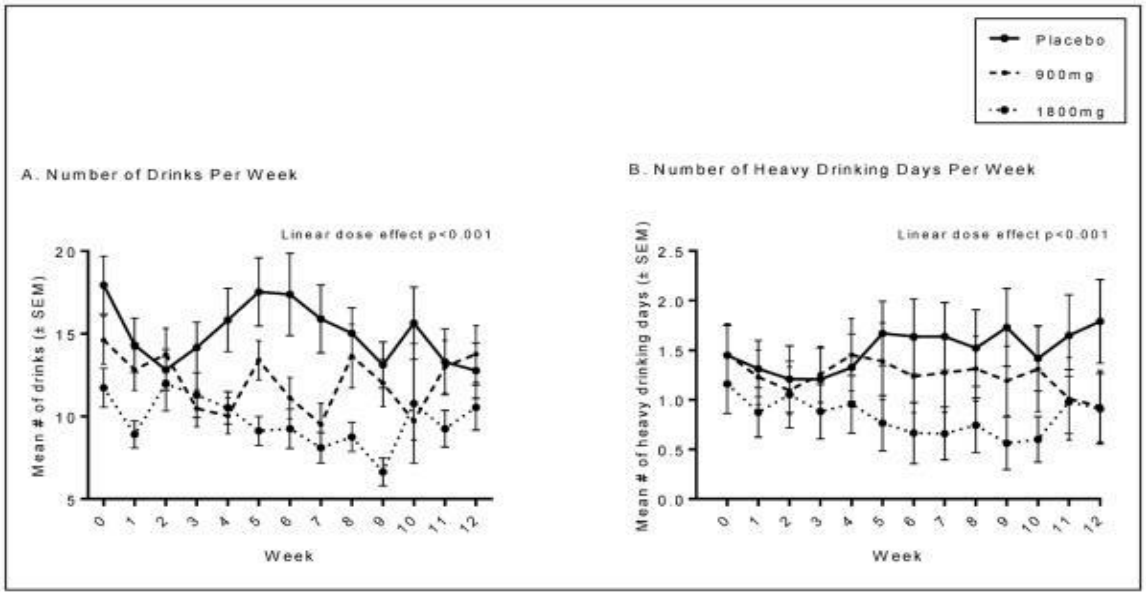
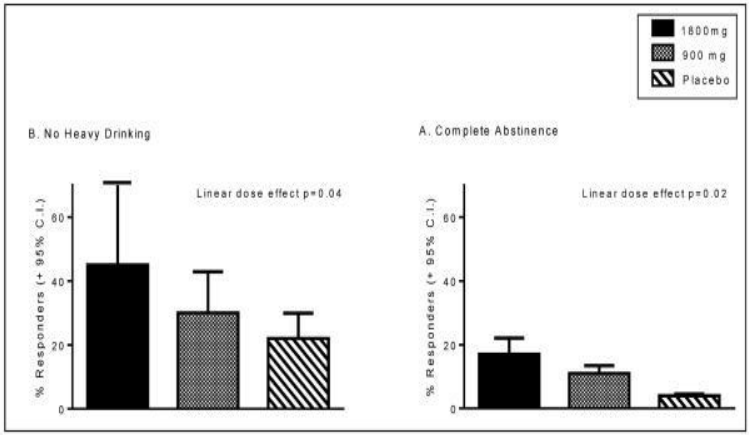
GABAPENTIN





3 RCTs (n=231): gabapentin reduced heavy drinking and withdrawal sx, increased abstinence, and improved sleep (32,33). A dose-related effect was found (1800 mg group -abstinence: NNT = 8; no heavy drinking: NNT 5) (34)





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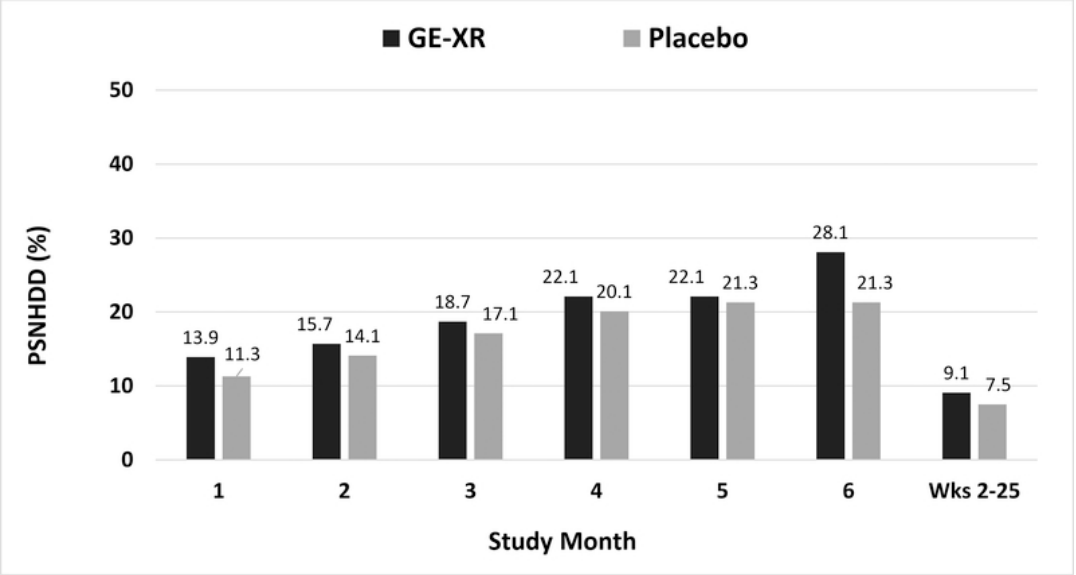
GABAPENTIN

- RCT of (n=346) with AUD
- extended-release formulation, gabapentin, enacarbil.
- No significant difference vs placebo in any outcome (percent of no heavy drinking days, subjects abstinent, days abstinent, heavy drinking days, drinks per week, drinks per drinking day, alcohol craving, alcohol-related consequences, sleep problems, smoking, and depression/anxiety sx (35).



Notes: missing data were not imputed. All p's>0.05. Wks = Weeks. Weeks 2-25 were the maintenance period.

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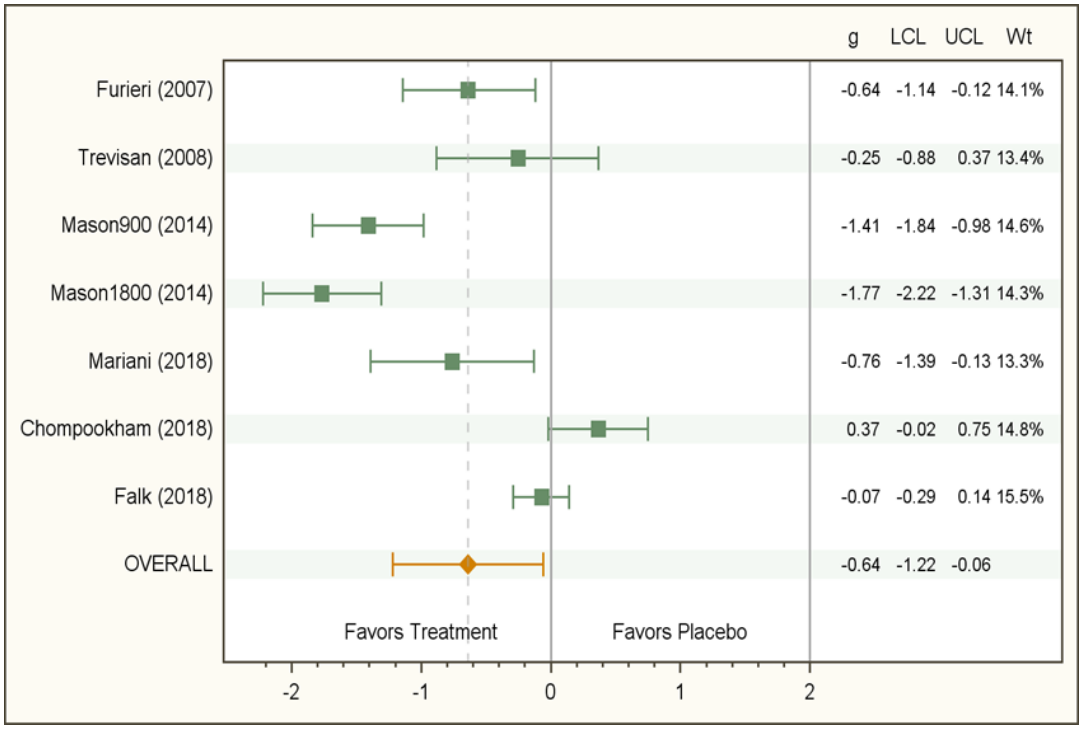
GABAPENTIN

- A meta-analysis of 7 RCTs
- Outcomes: complete abstinence, relapse to heavy drinking, percent days abstinent, percent heavy drinking days, drinks per day, and gamma-glutamyl transferase (GGT) concentration.
- Only reduction of HDD % was significant
- The rest trended favorably for gabapentin (36)



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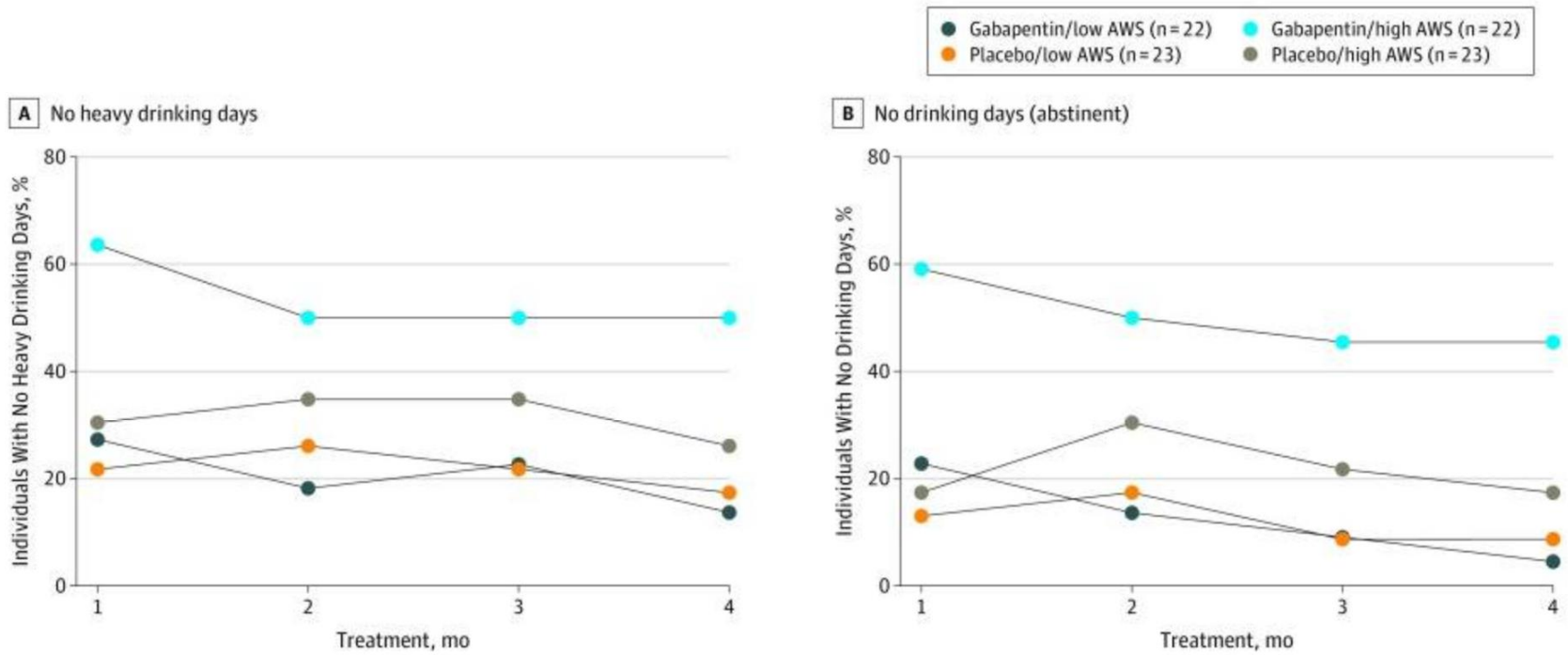
GABAPENTIN



- RCT (n=96)
- G 1200mg/day
- HDD (NNT =5.4)
- Abstinence (NNT = 6.2)
- W/ high alcohol wd: HDD NNT =3.1, abstinence NNT = 2.7
- W/ low alcohol wd: no difference from placebo(37)

PREGABALIN

- Similar to gabapentin in terms of structure and action at voltage-gated calcium channels. Different in terms of pharmacokinetics/dynamics - more binding affinity at its target, more potency, more bioavailability and better absorption (38).
- A 3-month double-blind RCT (n=100)- pregabalin 150mg vs placebo. Pregabalin = better treatment retention, less total alcohol consumption, less heavy drinking days, and more abstinent days. Pregabalin did not affect cravings, depression, anxiety, or GGT activity (39).

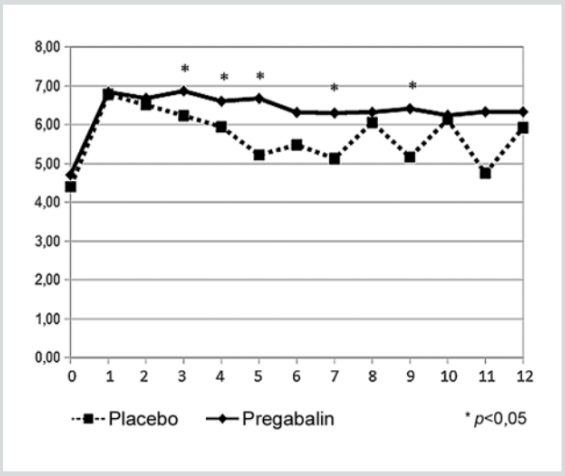


Fig. 4. **The number of days of sobriety.**
General linear model with repeated measures; independent variables are group and time.

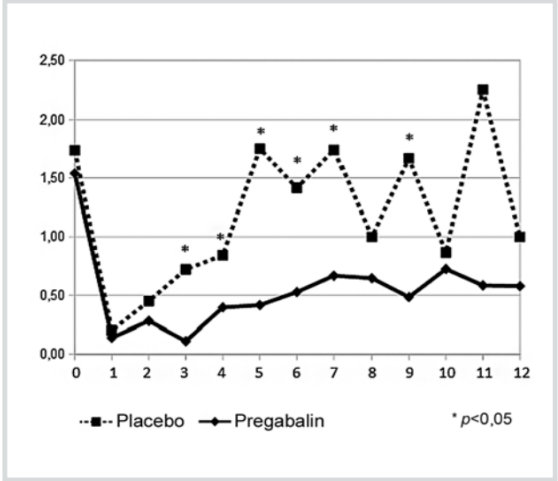


Fig. 3. **The number of heavy drinking days.**

- An open label, 8-week, study (n=18) showed similar outcomes but dose was to 600 mg/d and 80% of participants reported adverse events with 11% dropping out (40).

Difference (Last Week of Study Participation – Baseline)

% Days abstinent	% Heavy drinking days	Mean weekly amount of standard drinks	Mean drinks per drinking day
36.1% (35.0%)	−48.7% (35.1%)	−39.6 (26.0)	−5.01 (3.82)

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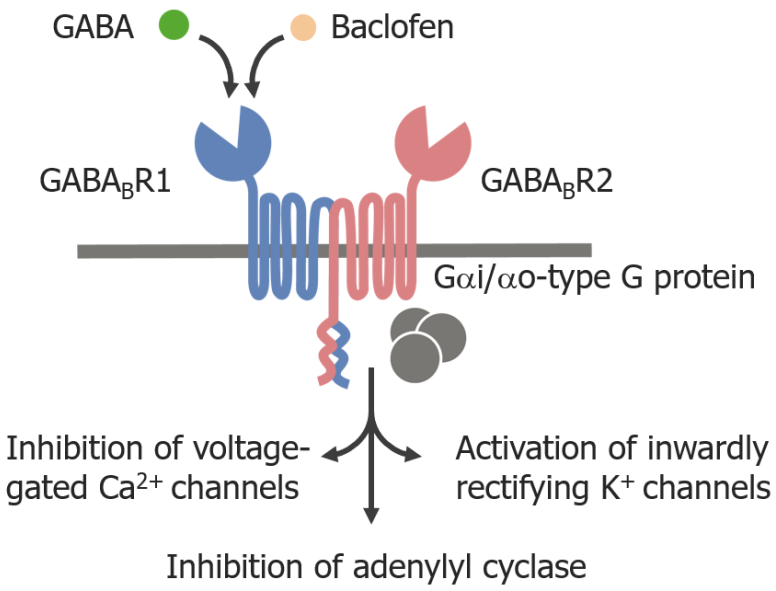
BACLOFEN

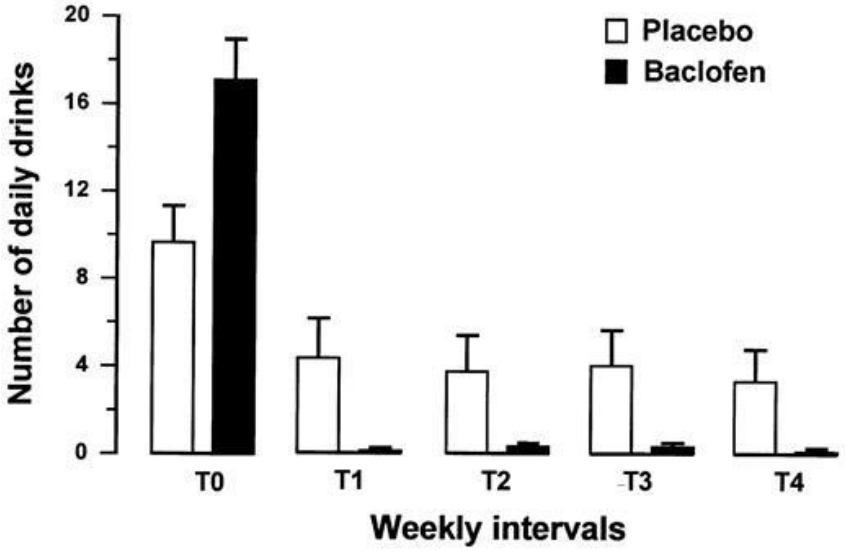
- Baclofen is a gamma-aminobutyric acid (GABA) analog that activates the GABA-B receptor subtype
- Reduces the release of excitatory neurotransmitters in the pre-synaptic neurons and stimulates inhibitory neuronal signals in the post-synaptic neurons

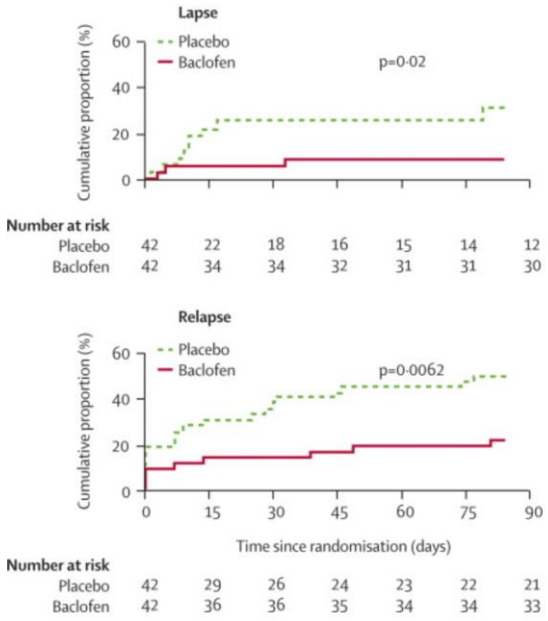


The $GABA_B$ receptor complex

BACLOFEN

- Recently abstinent. Baclofen up to 30mg/day vs placebo.
- Baclofen was well tolerated
- Baclofen-treated group was more likely to remain abstinent over the 1-month treatment period(41).





- Same investigators looked at n=84 pt with AUD and liver cirrhosis
- Baclofen > placebo - abstinence (71% vs. 29%),
- Well tolerated, (less dropout rate than placebo 14% vs. 31%) (42).

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BACLOFEN

Flexible dosing double-blind RCT (n=56). Higher total abstinence (68.2% vs. 5/21, 23.8%) and abstinence duration (mean 67.8 vs. 51.8 days) among baclofen group (mean dose = 180 mg /day) (43)

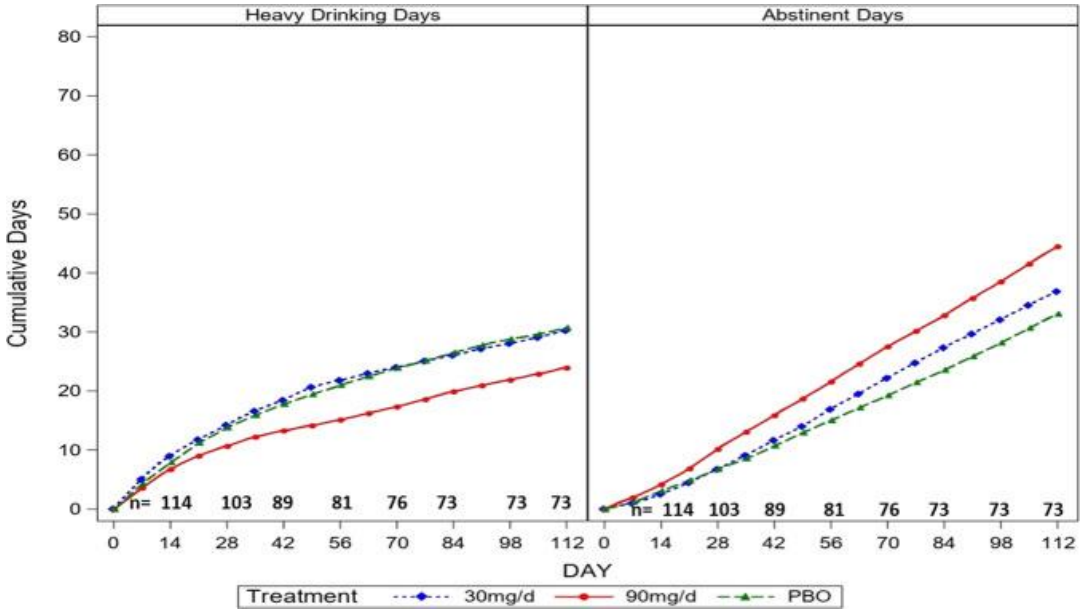
Larger double blind RCT (n=151): high dose baclofen (mean = 93.6 mg /day) VS 30 mg/d VS placebo.No differences between groups in any measure of alcohol use + frequent adverse events in the high-dose group (44).

VA double blind RC (n=180) found no effect of baclofen 30 mg/d compared to placebo on any alcohol use outcomes (45)

Cochrane review - 12 RCTs: no significant difference between baclofen and placebo with regards to AUD treatment outcomes (46).

BACLOFEN

- Moderators of benefit?
- RCT o (n=120). Baclofen 30mg vs 90mg vs placebo
- Baclofen reduced heavy drinking days (-13.6 days) and increased abstinent days (+12.9 days) over the 16-week trial period
- 90mg was more effective.
- Moderating effect of sex: men benefitting from and tolerating 90mg. Women benefited only from 30mg and did not tolerate 90mg (47).



Baclofen is safe in patients with alcohol-related liver disease (48).

Higher doses of baclofen may improve AUD treatment outcomes in such patients.

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ALPHA ADRENERGIC ANTAGONISTS

Prazosin: selective for alpha 1-adrenoceptor blocker . Half-life 2-3 hours. Duration of action: 6 - 10 hours -> need 2-3 times a day dosing.

Doxazosin: Half-life 16-30 hours. Can be taken once daily.

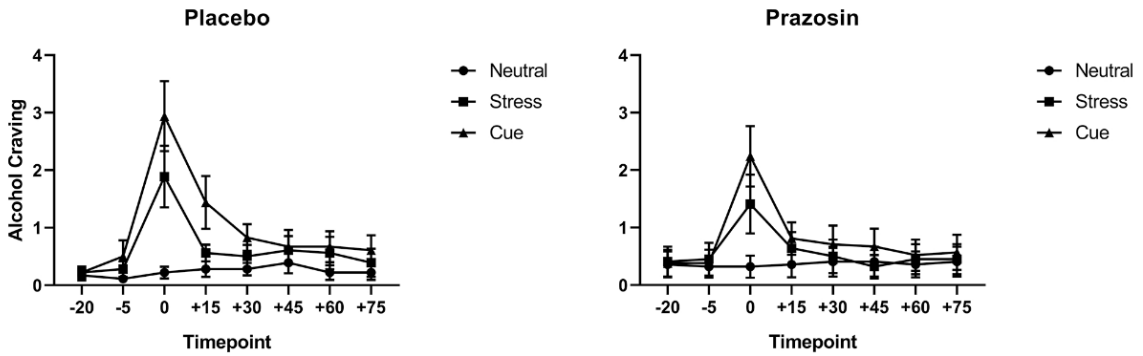
In contrast to prazosin, doxazosin has an improved absorption profile, which likely minimizes the risk for hypotension. (49)

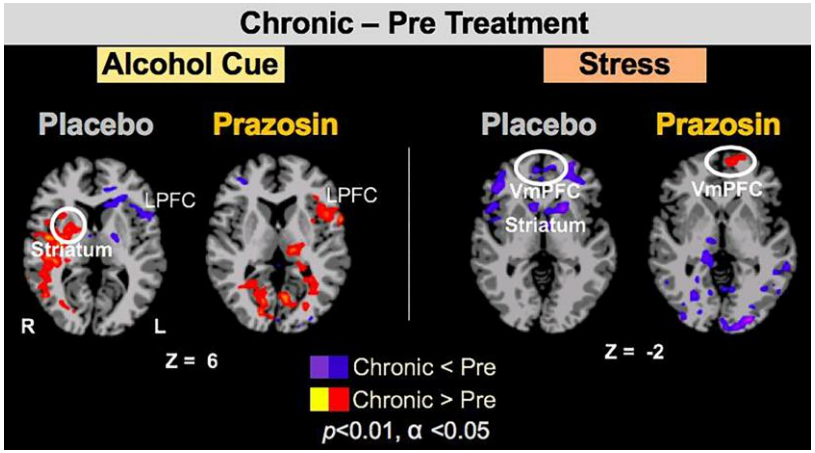
? Normalization of autonomic stress response improve alcohol drinking outcomes.

PRAZOSIN

- Double – blind RCT (n= 40) - prazosin 16mg/day with placebo.
- Participants were exposed to cues related to stress, alcohol, and relaxation.
- Alcohol cravings, anxiety, heart rate, and ACTH levels were checked at baseline and after the cues.
- Prazosin reduced stress and cue-induced alcohol cravings and anxiety. It lowered basal cortisol and ACTH levels as well. This effect was only observed in those without a lifetime anxiety disorder (50).

Figure 1.





- Two-part study: 1) Patients with varying degrees of alcohol withdrawal, underwent functional MRI. 2) Randomized to a 12-week trial - prazosin versus placebo: ? effects on neural circuit stress response and subsequent heavy drinking outcomes.
- Patient with high AWS had a more dysregulated response to stress and alcohol cues in the mPFC and striatum, with a subsequent increase in heavy drinking days.
- Prazosin reversed this stress response(vs placebo) -> fewer drinking days during the 12-week treatment period (51).

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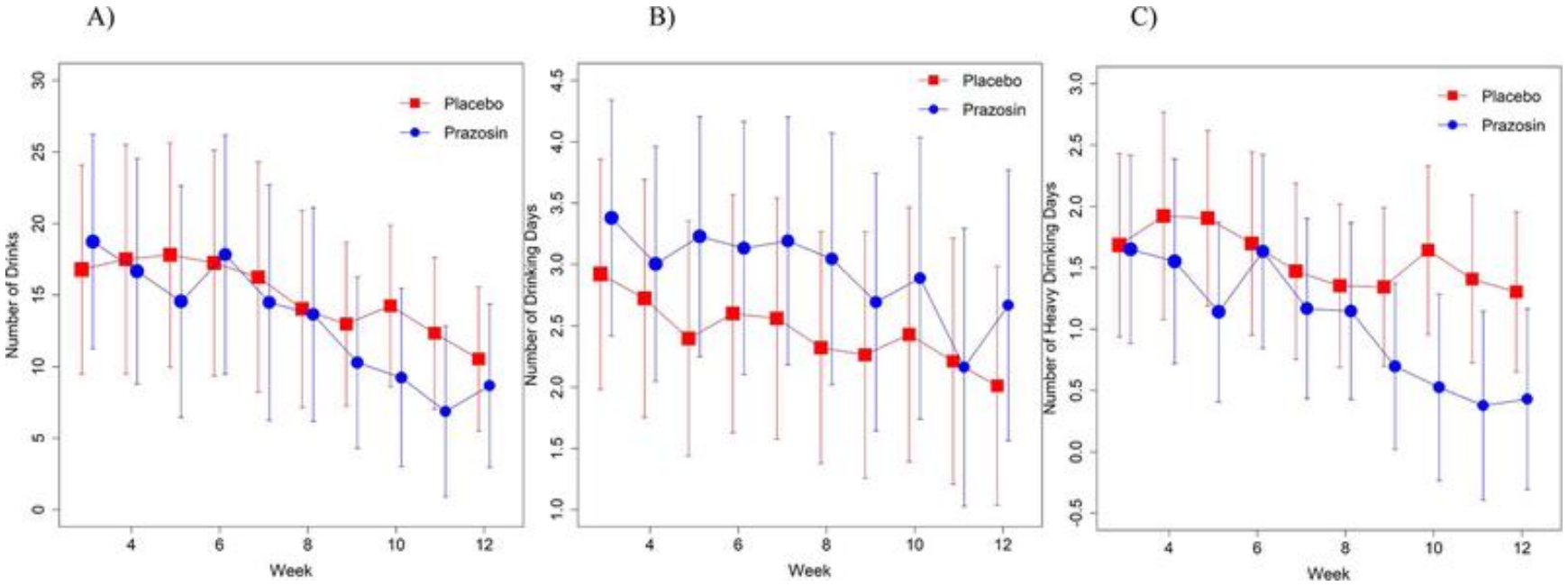
PRAZOSIN



- 12-week RCT (n=90) - Prazosin 16mg/day (divided in TID dosing) vs placebo
- Participants w/ PTSD were excluded to isolate prazosin's effect on AUD.
- (n= 80): able to complete the dose titration period. (52).

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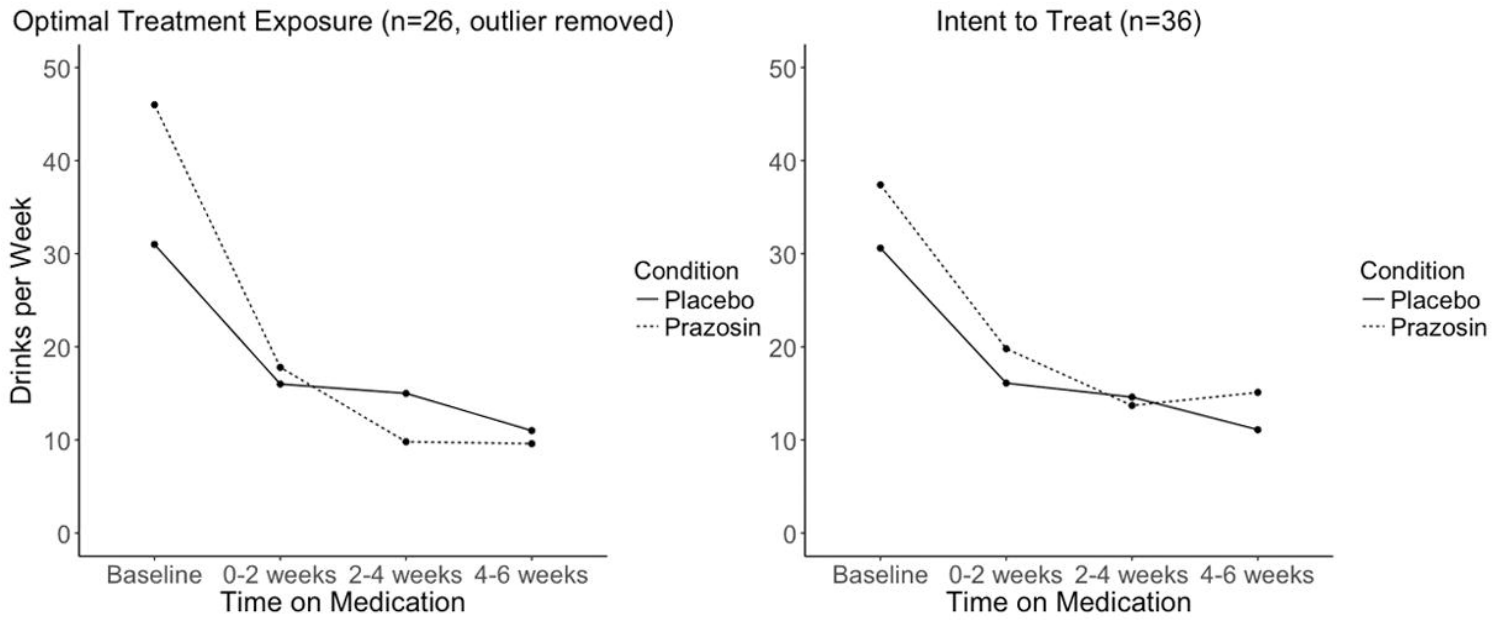
PRAZOSIN



- 6-week RCT (n=36) - prazosin (16mg over 2 weeks) vs placebo
- Excluded PTSD
- Prazosin = placebo in reduction of drinking.
- Poor adherence
- Post-hoc analyses: prazosin increased the rate of reduction in the number of drinks per week in pt able to adhere to it and in those with higher baseline diastolic blood pressure (53).

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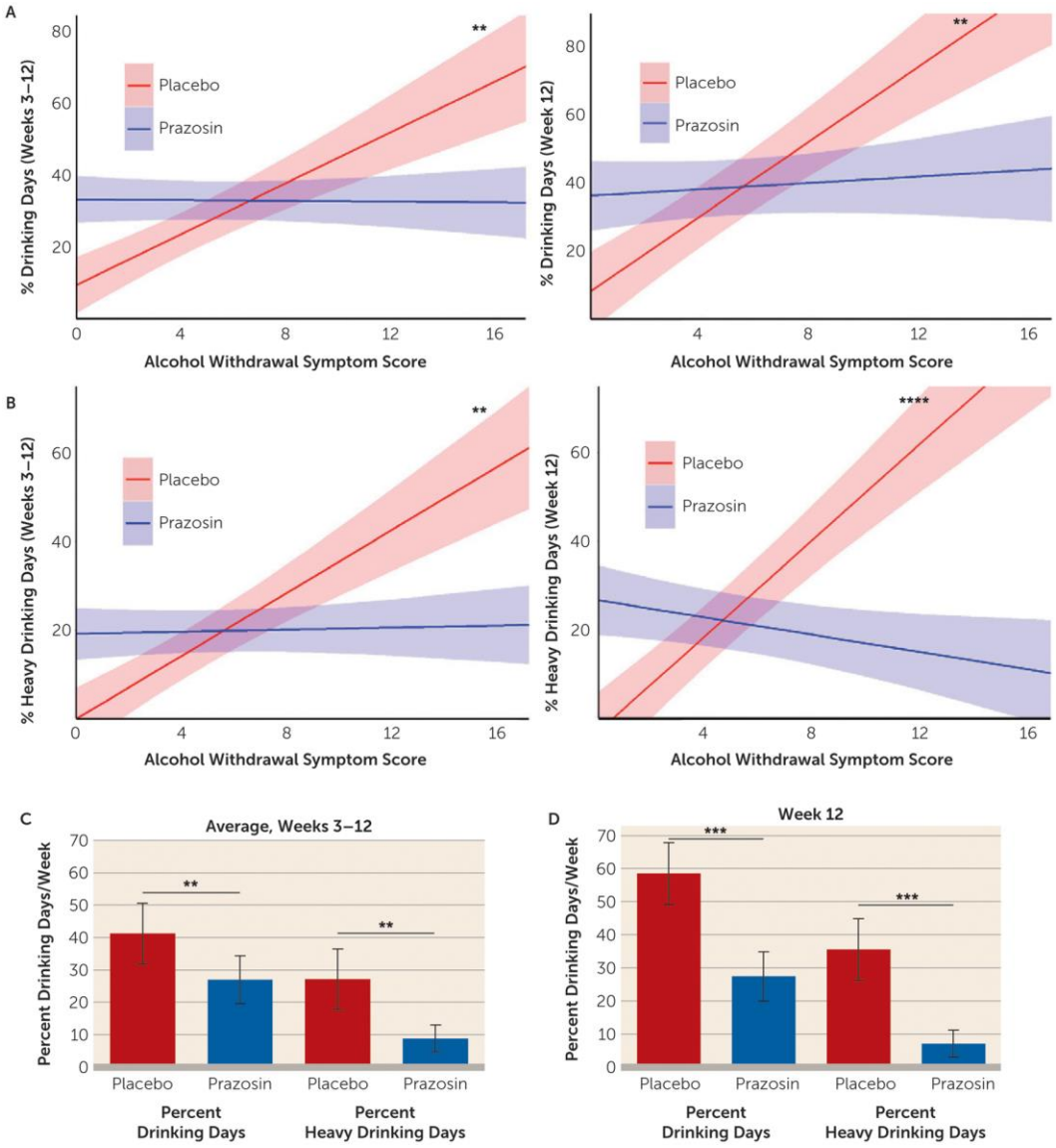
PRAZOSIN

- 12- week RCT (n=100) . Prazosin vs. Placebo
- In participants with high levels of alcohol withdrawal: prazosin = fewer drinking days and heavy drinking days than placebo
- This effect was not observed among the subset with low alcohol withdrawal. (54)

- Varying results? Tolerability ? More efficacious among individuals with high levels of alcohol withdrawal?



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DOXAZOSIN

- RCT (n=41)
- Doxazosin 16mg/day = placebo in effect on drinks per week and heavy drinking days per week.
- Doxazosin reduced drinking in participants with a high family history density(prevalence) of AUD (55).

Figure 2A

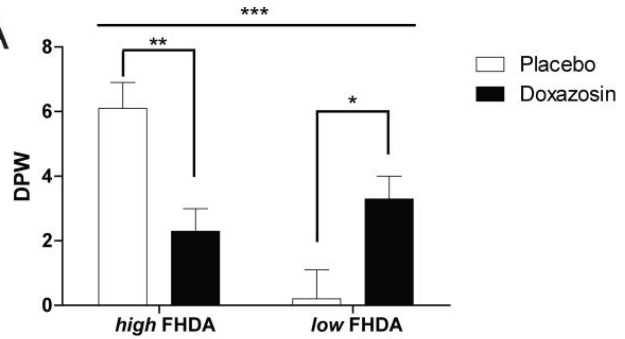
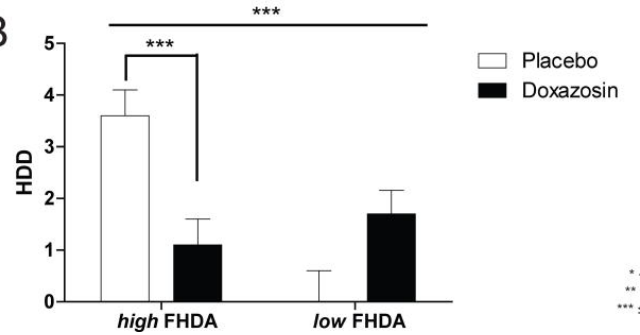
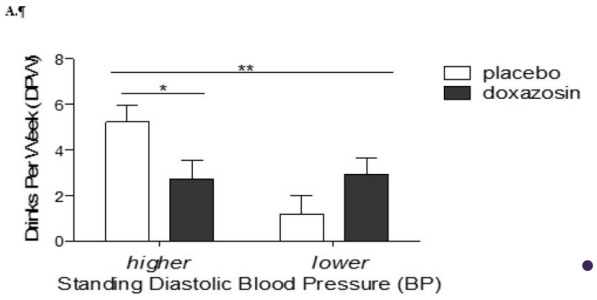
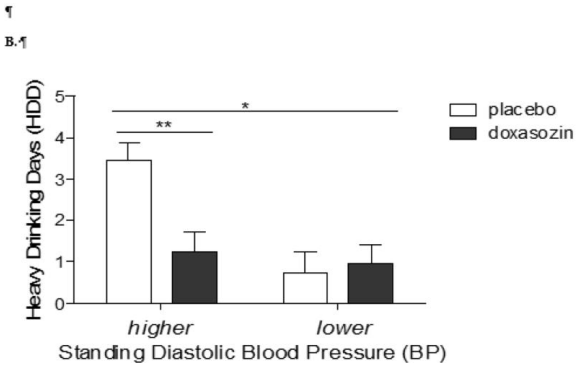


Figure 2B







- Further analyses from this study:
- Higher baseline DBP = significant effect of doxazosin in reducing heavy drinking days and drinks per week (56)

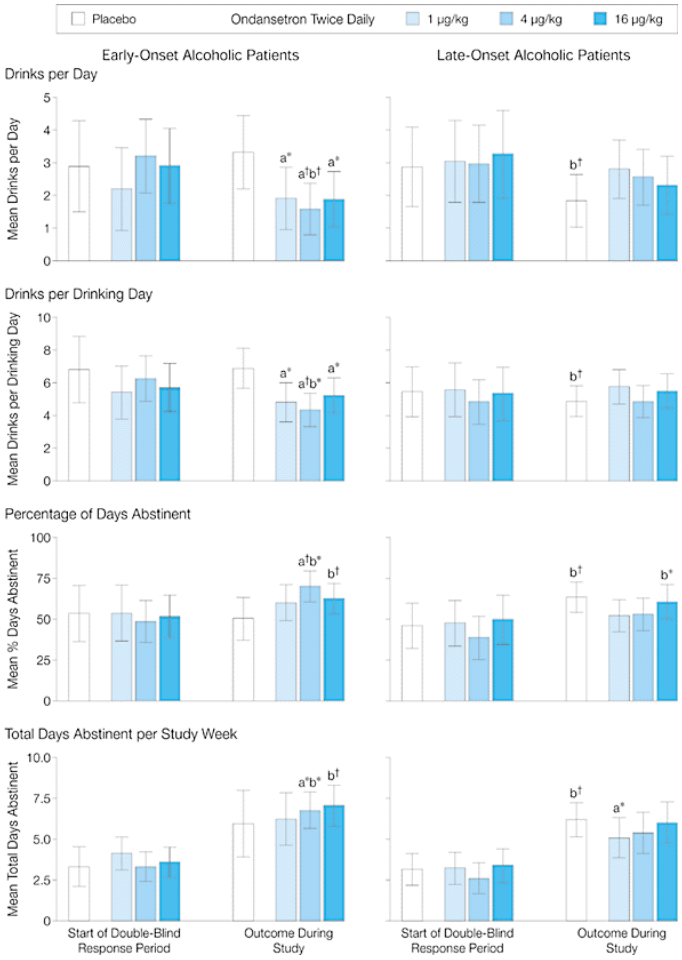
UW PACC

ONDANSETRON

- Ondansetron is a 5-HT receptor antagonist approved for the treatment of chemotherapy-induced and postoperative nausea.

- 12-week RCT (n=321).
- Ondansetron selectively reduced drinking among patients with early onset of AUD (i before age 25).
- Ondansetron > placebo in reducing the proportion of days abstinent and heavy drinking
- Late-onset patients: ondansetron = placebo in drinking behaviors. (57)

- 8-week, open-label study (n=40) of ondansetron, early-onset AUD patients had a significantly greater decrease in drinks per day, drinks per drinking day, and alcohol-related problems than did late-onset AUD patients(58).



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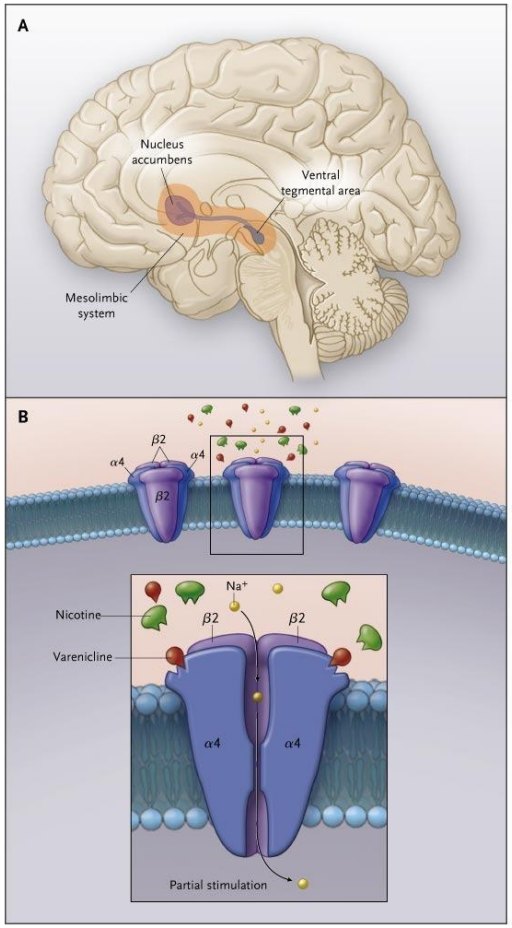
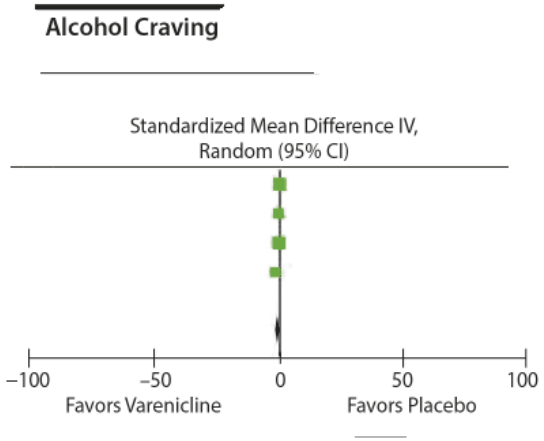
VARENICLINE



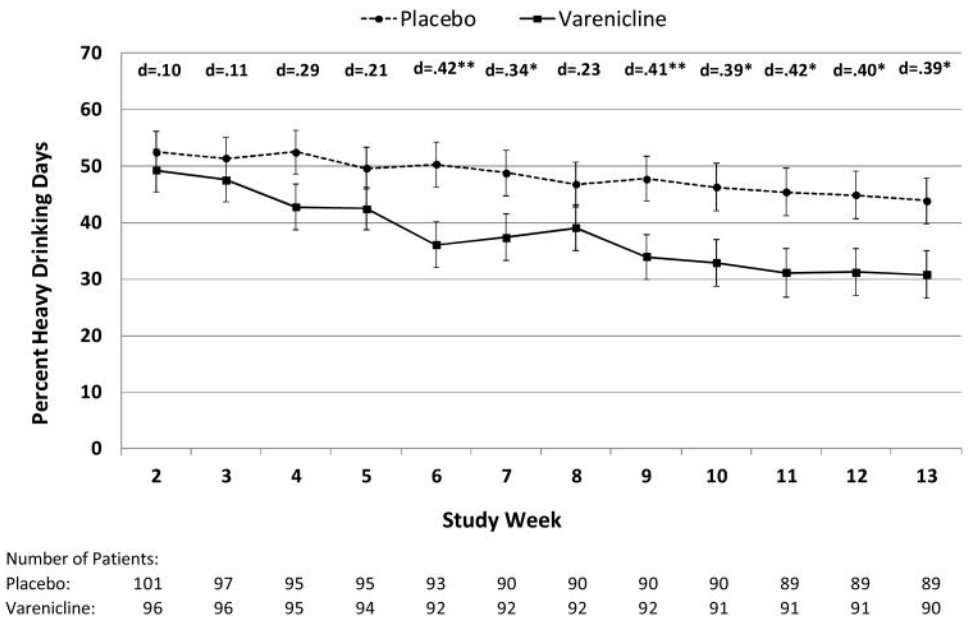
- Partial agonist of α4β2 nicotinic acetylcholine receptors
- Full agonist of α7 nicotinic acetylcholine receptors
- FDA approved for smoking cessation.
- Has central action in VTA -> may affect dopamine activity -> potential utility in AUD treatment.

VARENICLINE

- Meta-analysis of 10 studies (n=731)
- Statistically significant decrease in alcohol cravings for alcohol in Varenicline.
- It had no significant effect on other drinking outcomes (59).



- RCT of (n=200)
- Varenicline reduced both alcohol consumption and cravings (60)
- Potential moderators of response:
- More effective in patients with less severe AUD , of older age (>45), longer drinking time (>28 years), who preferred a goal of non-abstinence, and those who reduced their cigarette consumption due to treatment with varenicline (61).



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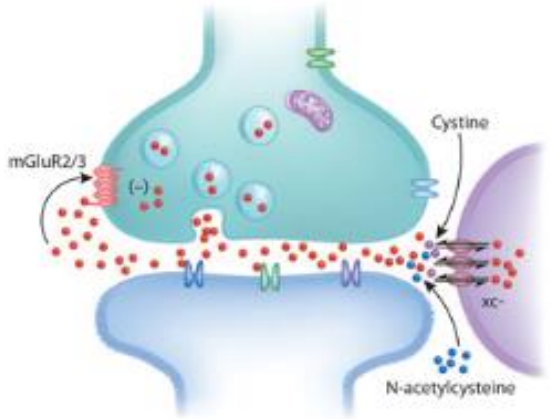
NAC

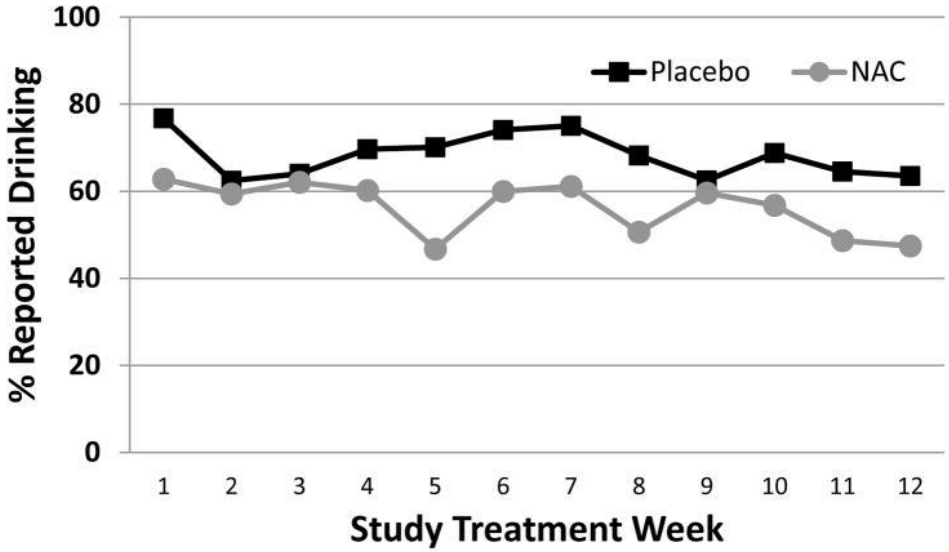
- NAC is a derivative of the amino acid L-cysteine.
- FDA approved for its hepatoprotective use in acetaminophen overdose and as a mucolytic.

- Its utility in treating substance use disorders maybe due to modulating glutamate transmission which is seen in craving and withdrawal states. (62).

- RCT with (N=302) participants randomized to treatment with NAC (600mg BID) or placebo for cannabis use disorder.
- NAC group had increased odds of abstinence, fewer drinks per week, and fewer drinking days per week.
- This was not correlated to changes in cannabis consumption (63).



N-acetylcysteine



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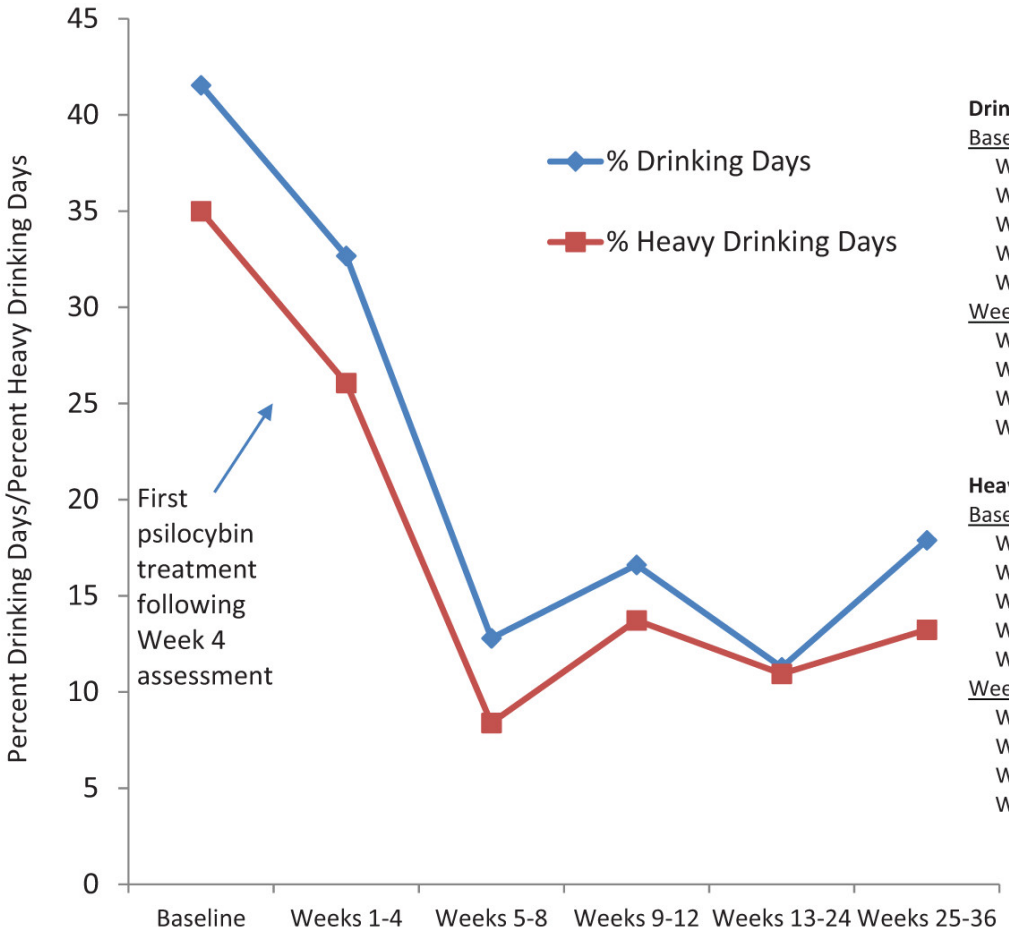
PSYCHEDELICS



Drinking Days

Baseline vs.		
Weeks 1-4	p = .164	d = 0.490
Weeks 5-8	p = .009	d = 1.194
Weeks 9-12	p = .015	d = 1.033
Weeks 13-24	p = .006	d = 1.332
Weeks 25-36	p = .007	d = 1.187
Weeks 1-4 vs.		
Weeks 5-8	p = .016	d = 1.109
Weeks 9-12	p = .033	d = 0.869
Weeks 13-24	p = .014	d = 1.163
Weeks 25-36	p =. 013	d = 1.036

Heavy Drinking Days

Baseline vs.		
Weeks 1-4	p = .158	d = 0.492
Weeks 5-8	p = .007	d = 1.249
Weeks 9-12	p = .019	d = 0.985
Weeks 13-24	p = .010	d = 1.161
Weeks 25-36	p = .004	d = 1.383
Weeks 1-4 vs.		
Weeks 5-8	p = .022	d = 1.046
Weeks 9-12	p = .059	d = 0.750
Weeks 13-24	p = .038	d = 0.876
Weeks 25-36	p = .018	d = 1.040

- Open label trial (n=10)
- Combined 2 doses of psilocybin with a 12-session psychosocial intervention
- Percent drinking days and heavy drinking days were significantly reduced, as compared to prior to treatment and sustained throughout the 36-week follow-up period.
- Reduced drinking consequences, cravings, self-efficacy, and mood with no notable adverse effects (64).

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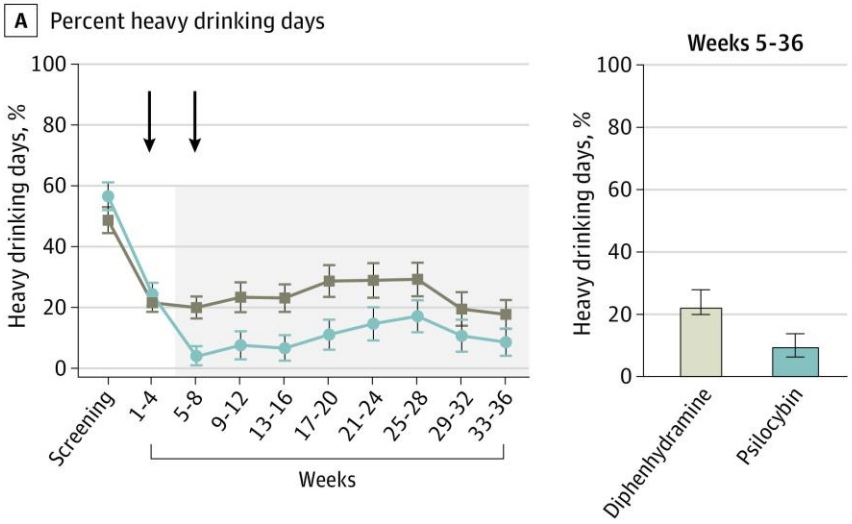
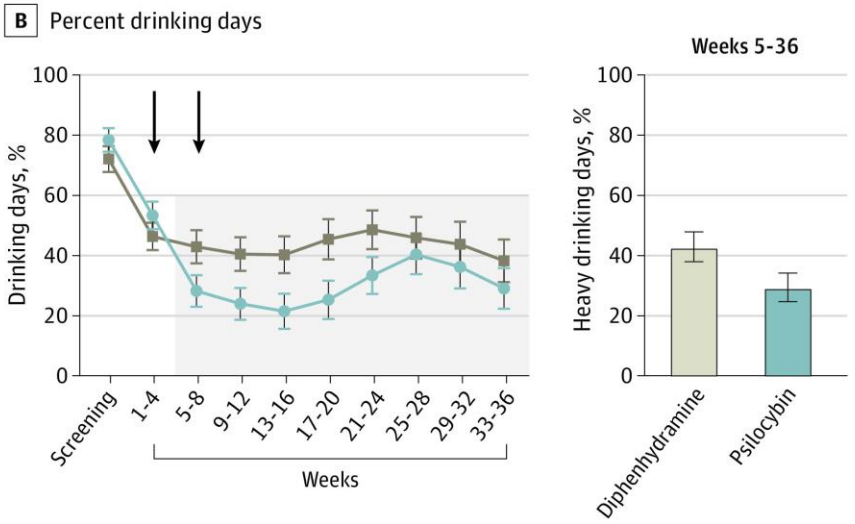
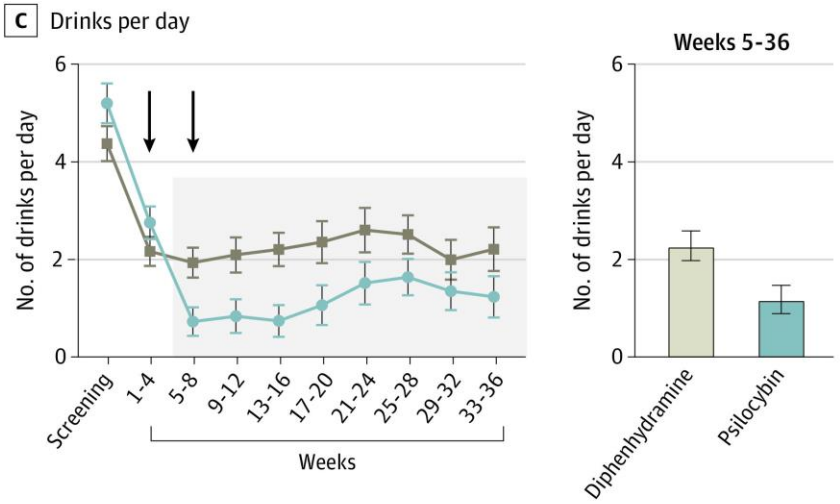
PSYCHEDELICS







- RCT (n=95)
- Diphenhydramine as control condition
- 12 psychotherapy sessions and two medication sessions at 4 and 8 weeks.
- Psilocybin treatment reduced percent of heavy drinking days and mean daily alcohol consumption over the 32 study weeks (65).

PSYCHEDELICS

	Follow-up (months)	LSD (n/N)	Control (n/N)	Weight	Odds Ratio (95% CI)
First follow-up					
Smart *et al.*, 1966	6	[a]/10	[a]/20	7.2%	1.41 (0.36-5.60)
Hollister *et al.*, 1969	2	18/36	11/36	14.7%	2.27 (0.87-5.94)
Ludwig *et al.*, 1969	1	94/132	25/44	27.3%	1.88 (0.93-3.81)
Bowen *et al.*, 1970	12	9/22	7/22	8.9%	1.48 (0.43-5.10)
Pahnke *et al.*, 1970	6	34/73	13/44	21.6%	2.08 (0.94-4.60)
Tomsovic & Edwards, 1970	3	30/52	17/45	20.4%	2.25 (0.99-5.10)
Total		**325**	**211**	**100%**	**1.96 (1.36-2.84)**

Test for heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.65$, df = 5 ($P = 0.99$); $I^2 = 0\%$

Test for overall effect: $Z = 3.59$ ($P = 0.0003$)

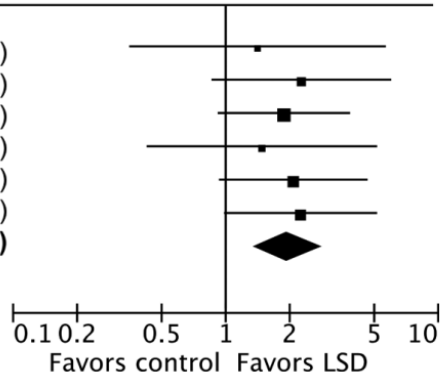


Figure 2. Improvement on alcohol misuse at the first available follow-up after LSD versus control treatments.

[a]Continuous outcome data.

A meta-analysis of 6 RCTs (n= 536)

Lysergic acid diethylamide's (LSD) use in AUD treatment

A single dose of LSD had a beneficial effect on alcohol misuse (NNT=6) until 6 months post treatment.

Increased total abstinence (NNT=7) after a single dose until 3 months post treatment (66).

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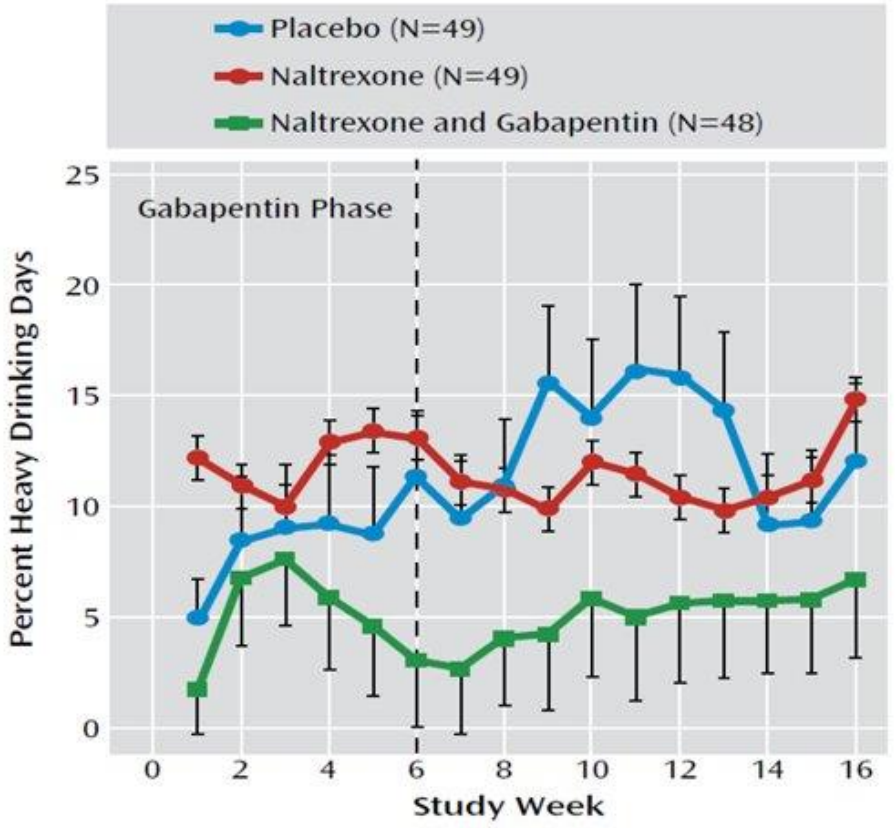
COMBINING TREATMENTS

- 16-week RCT (n=150)
- naltrexone 50 mg/d alone vs naltrexone 50 mg/d with gabapentin up to 1200 mg/d for the first 6 weeks vs double placebo
- All study patients received a combined behavioral intervention that combined CBT, motivation enhancement, and twelve-step facilitation techniques.
- Combination group = longer interval to heavy drinking, fewer heavy drinking days and fewer drinks per drinking day than did the naltrexone alone group and the placebo group.
- Effect was only during the first 6 weeks after cessation of drinking
- ? combination may work best in individuals who had previously experienced alcohol withdrawal. (67).



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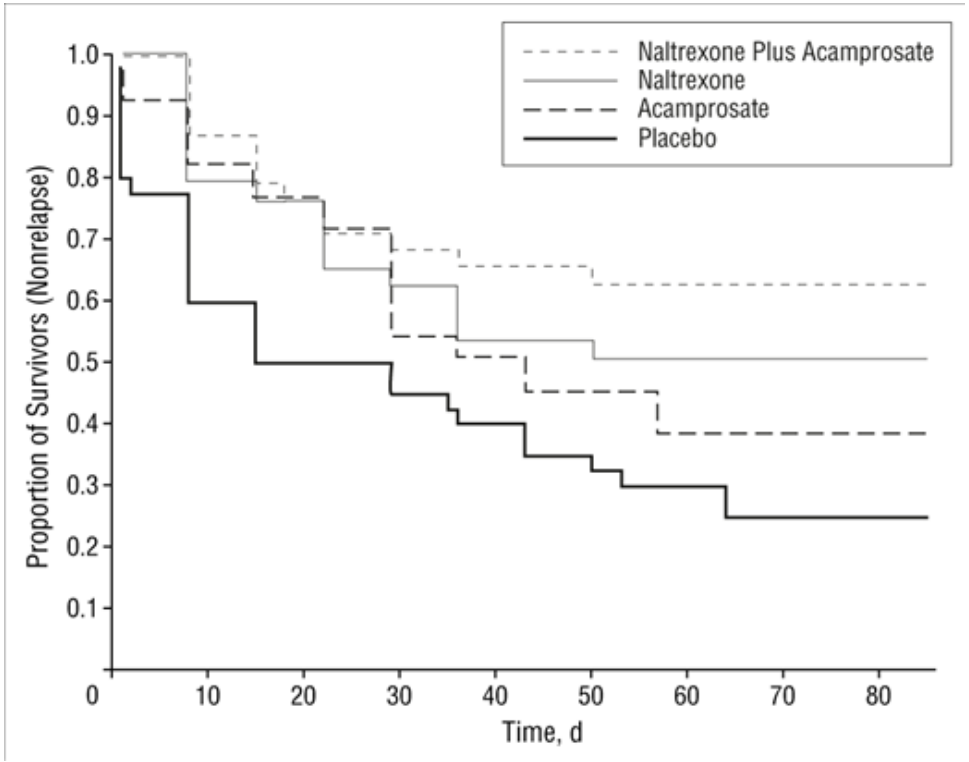
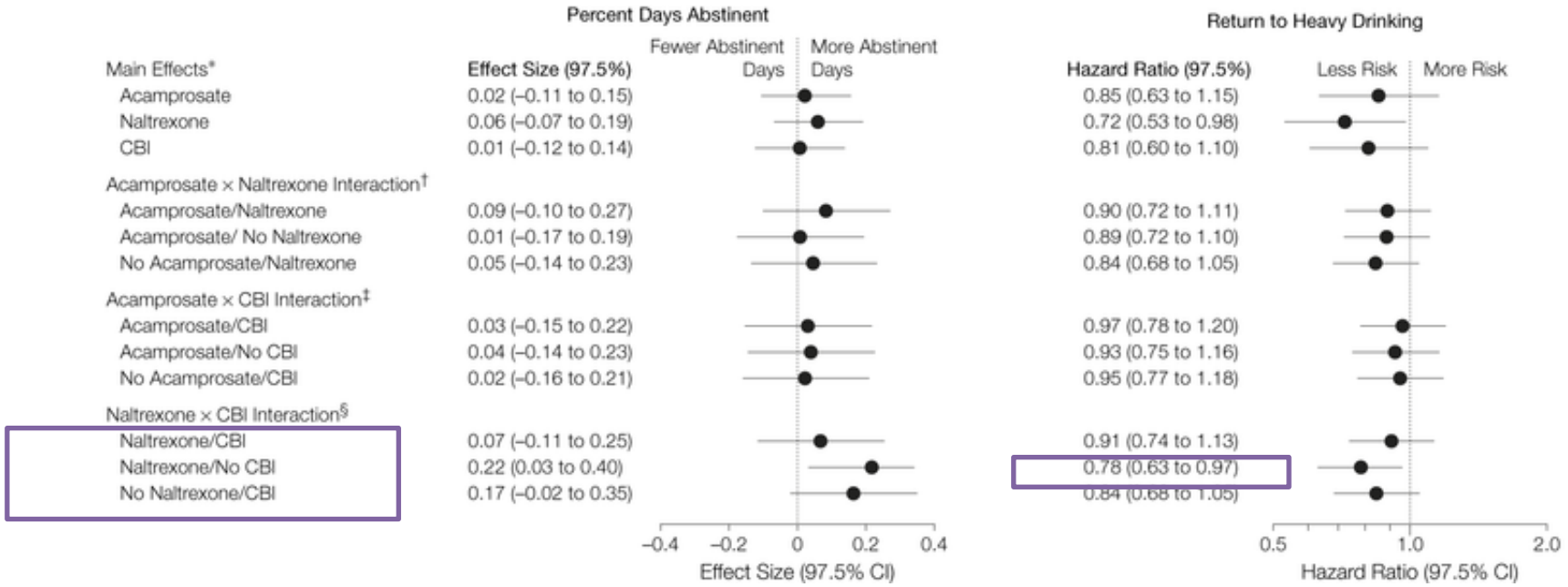
COMBINING TREATMENTS



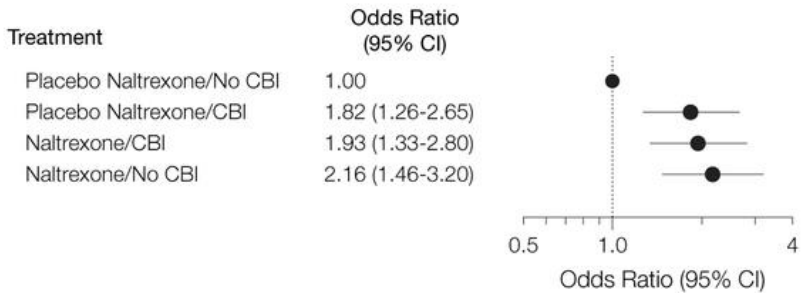
- 12-week trial (n= 160)
- All three active medication groups (naltrexone, acamprosate, and the two medications combined) were significantly more efficacious than was placebo (68).
- Combo > acamprosate & placebo but not naltrexone alone in terms of rate of return to use

COMBINING TREATMENTS



The COMBINE study

- 4-months RCT (n=1400) abstinent participants.
- 8 groups: MM+Medication (naltrexone/acamprosate/combo/placebo), or MM+Medication +CBI, OR just CBI
- Patients receiving medical management with naltrexone, CBI(intensive behavioral therapy), or both fared better on drinking outcomes, whereas acamprosate showed no evidence of efficacy, with or without CBI. No combination produced better efficacy than naltrexone or CBI alone in the presence of medical management.(69)



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CHOOSING MAT

Patient goal – Abstain? Moderate? Both goals are acceptable as many health outcomes improve significantly with the reduction of heavy drinking (70) & higher success when pt chooses goal(71)

Chronic hepatic impairment with LFTs < 5 times upper limit of normal -> Naltrexone still ok. Contraindicated in acute hepatitis/liver failure/concurrent opioid use

Acamprosate contraindicated in severe renal impairment

Adherence is a concern? Naltrexone IM > disulfiram (supervised) > Acamprosate

Partial response to one? Combine with another (e.g gabapentin)

Failed FDA approved: &high AW – gabapentin. AW/BP - prazosin. &FH – doxazosin. &comorbidities – topiramate. &liver disease – baclofen. &EOA – Ondansetron. &NUD – Varenicline. &CUD - NAC

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Beyond Pharmacotherapy : Medical Management

Frequent check ins – tracking progress

People, places, and things

Asking about self help group attendance or other recovery-oriented activities (lifestyle changes, employment, education)

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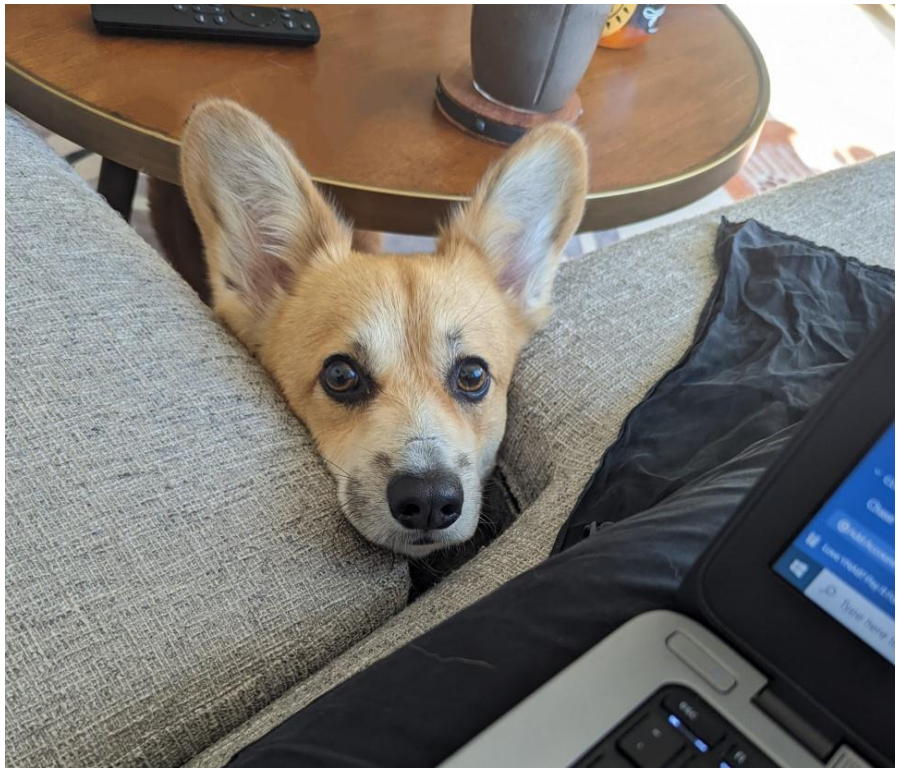

Thank you for listening!