Anti-Craving Medications for Alcoholism and Drug Addiction

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Disclosure

- I have no relevant financial relationships to disclose concerning any topic in this presentation.

Objectives: Pharmacists

- Identify anti-craving drugs used in alcoholism and drug addiction

- Compare and contrast anti-craving drugs used in alcoholism and drug addiction

- Review key evidence-based research supporting use of anti-craving medications

- Recommend an anti-craving medication, given a patient case study

Objectives: Pharmacist Technicians

- Identify key anti-craving drugs used in alcoholism and drug addiction

- Categorize key anti-craving drugs used in either alcoholism or drug addiction

- Recognize regulations for dispensing specific anti-craving drugs
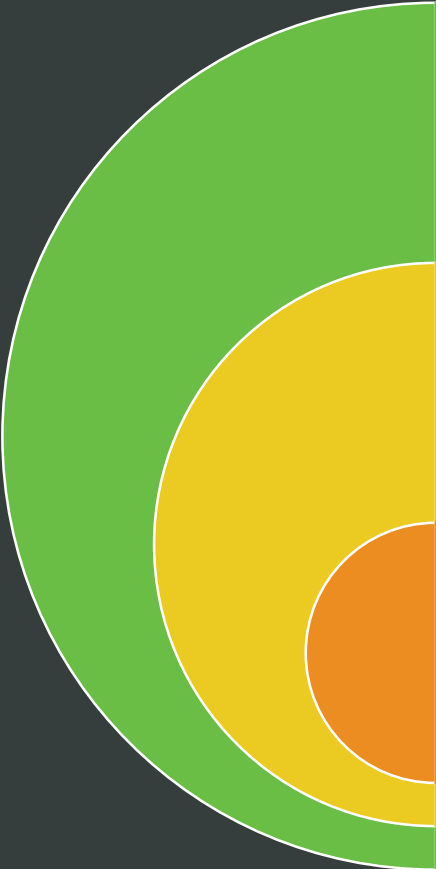
Presentation Overview

Overview of Addiction

Review Medications

Analyze Literature

Understand Clinical Application

Background: Why these dependencies?

- 24.6 million Americans used illicit drugs in 2013
  - 2/3 of those used ALCOHOL

- Top 3 drugs causing addiction

  - Cocaine

  - Opioids

  - Marijuana (controversial)

Treatment of Addiction

- Goals
  - Re-establishes normal brain function
  - Prevent lapse and diminish craving

- Behavioral Treatments
  - Outpatient behavioral treatment
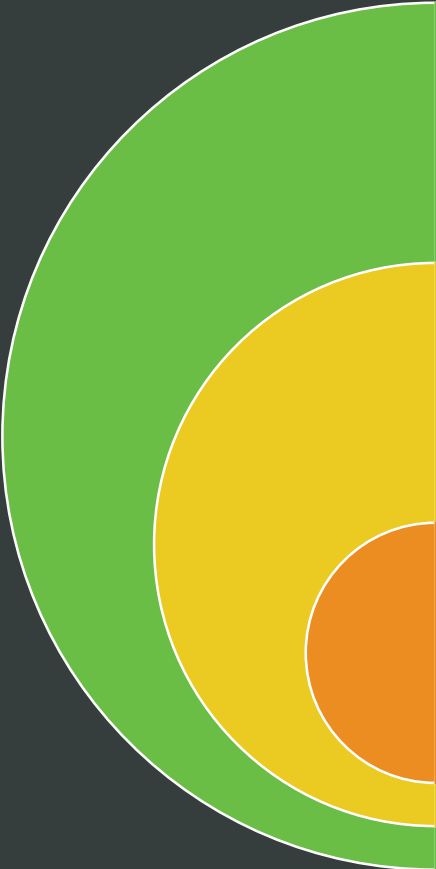 - Residential treatment

- Medications

Established Medications

Alcohol Dependence	• Acamprosate • Naltrexone • Disulfiram
Cocaine Dependence	• Still under investigation
Opiate Dependence	• Buprenorphine/Naloxone • Methadone • Naltrexone

"Novel" Medications

Alcohol Dependence	• Topiramate • Gabapentin • Baclofen	
Cocaine Dependence	• Disulfiram • Nepicastat	
Opiate Dependence	• New Formulations	

Literature Analysis

Alcohol Dependency Medications

| |
|---|
| Disulfiram |
| Naltrexone |
| Acamprosate |
| Gabapentin |
| Baclofen |
| Topiramate |
| Nalmefene |
| Ondansetron |
| Varenicline |

Gabapentin

- Been used in alleviation of somatic symptoms of drug and alcohol withdrawal

- Protective effects on CNS hyperexcitability associated with alcohol withdrawal

- Alcohol Dependence
  - Found to have statistically significant positive effects on heavy drinking

Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial

- **Objective:** To determine if gabapentin increases rate of sustained abstinence and no heavy drinking and decreases alcohol-related insomnia, dysphoria and craving in a dose dependent manner.

- **Design:** 12 week double blind, placebo-controlled, single-site, outpatient facility, n=150 participants

- **Interventions:** Oral gabapentin (placebo vs. 900 mg vs. 1800 mg/day)

- **Main Outcome and Measures:**
  - Rate of complete abstinence and no heavy drinking (coprimary)
  - Change in mood, sleep and craving (secondary)

Gabapentin Treatment for Alcohol Dependence–Coprimary Outcomes: Figure 1

Gabapentin Effects on Rates of No Heavy Drinking and Complete Abstinence During the 12-Week Study in the Intention-to-Treat Population
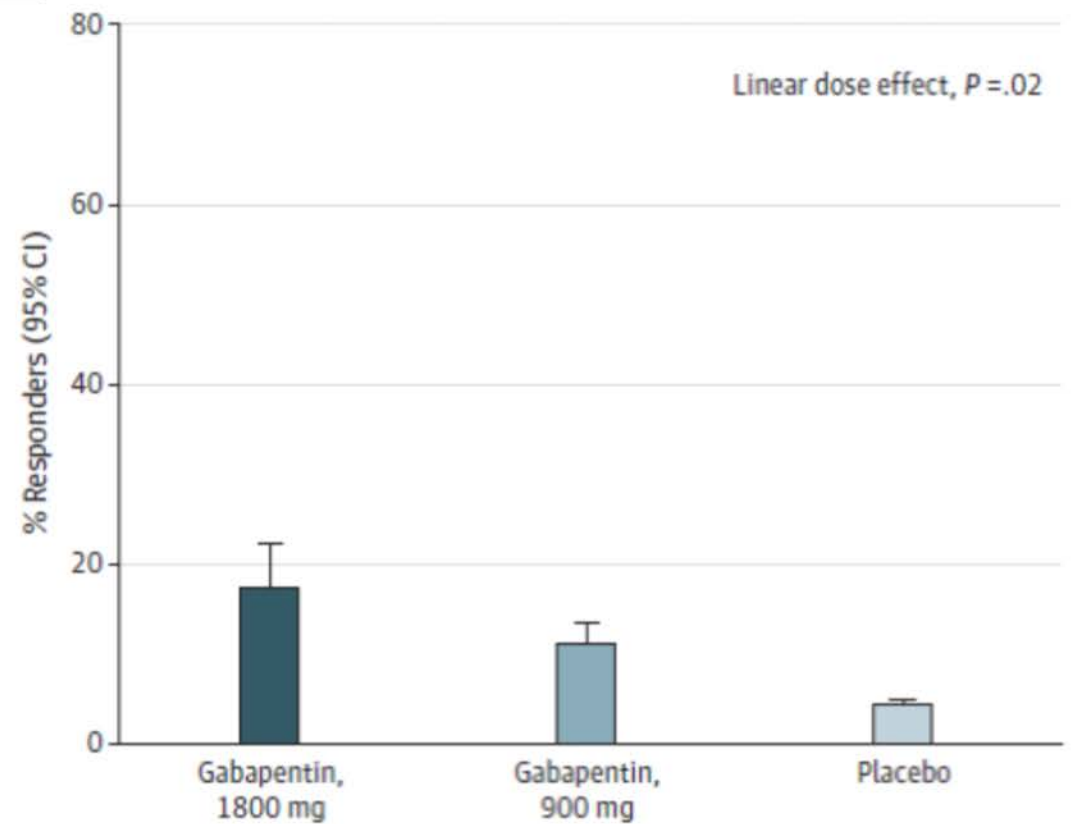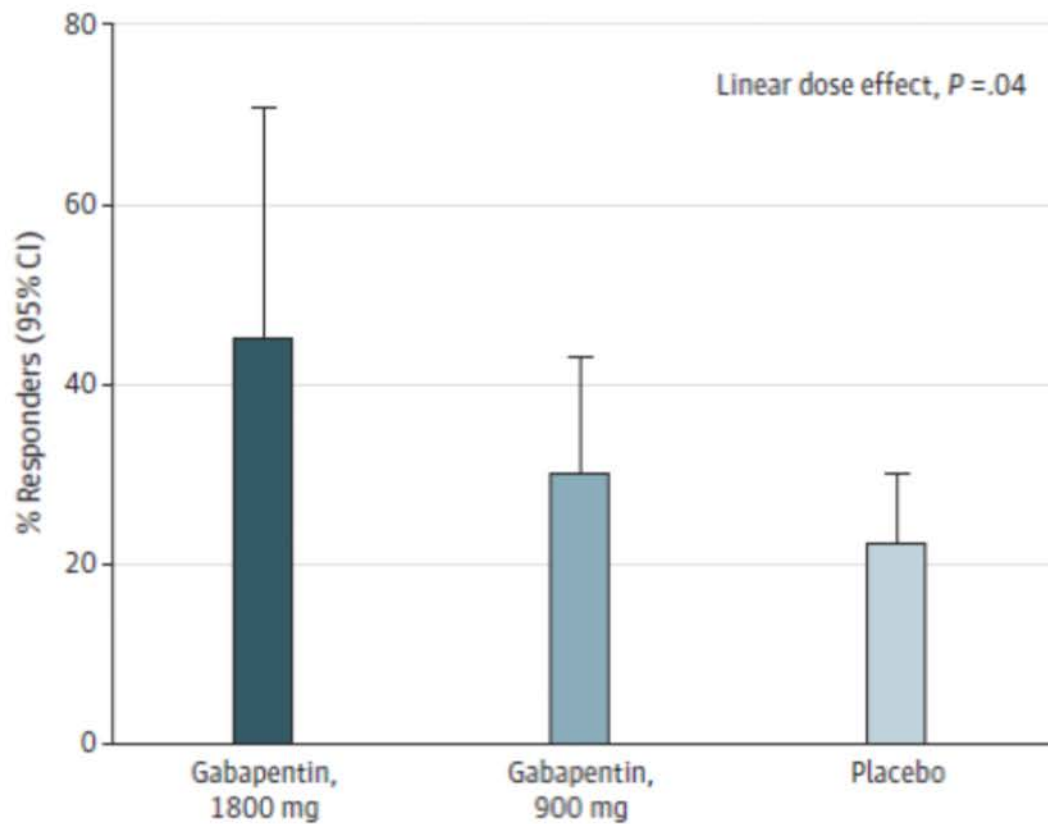
Gabapentin Treatment for Alcohol Dependence – Coprimary Outcomes: Figure 2

Gabapentin Effects on Number of Drinks per Week and Number of Heavy Drinking Days per Week During the 12-Week Study in the Intention-to-Treat Population
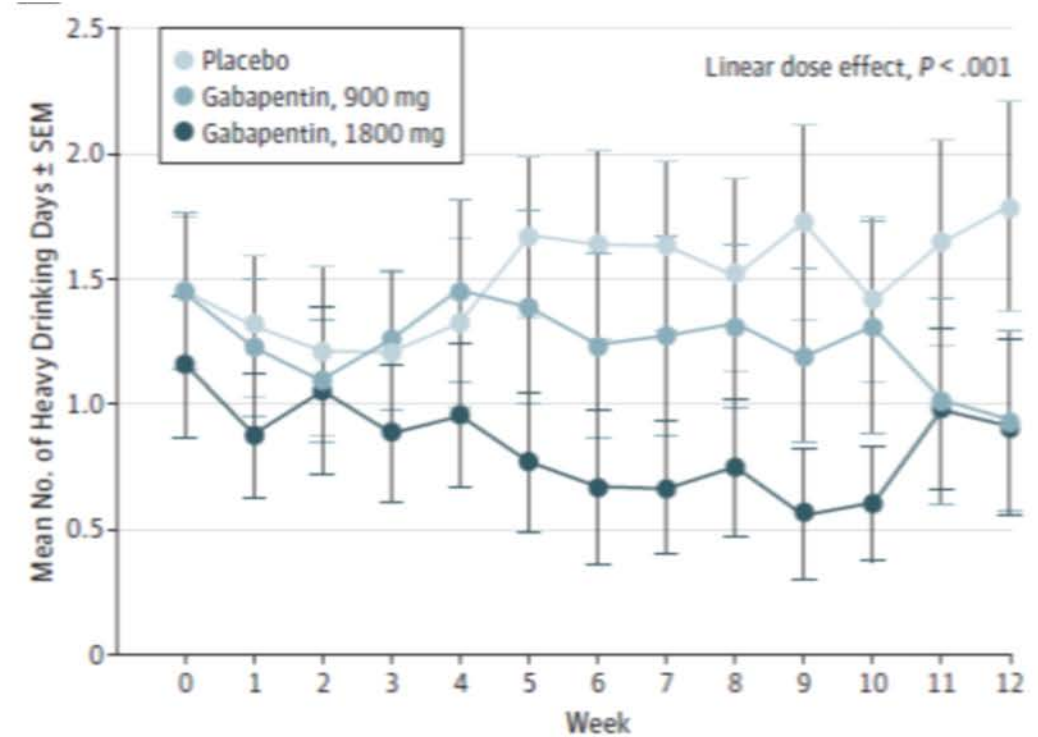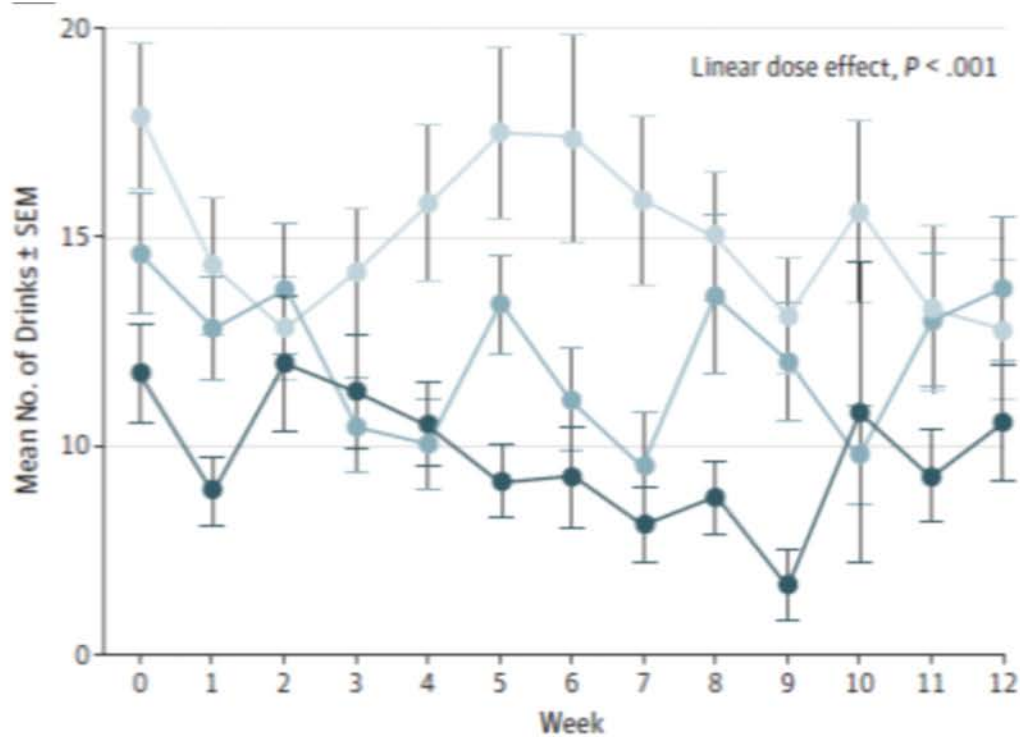
A, Number of drinks per week; B, number of heavy drinking days per week. Error bars indicate SEM (N = 150).

Mason J et al. *JAMA Intern Med*. 2014;174(1):70-77

Gabapentin Treatment for Alcohol Dependence – Secondary Outcome on Craving: Figure 3

- Data based on Alcohol Craving Questionnaire

- Data showed significant linear dose effects on craving

- Data also showed significant linear dose effects on sleep and mood (not pictured)

Mason J et al. *JAMA Intern Med*. 2014;174(1):70-77
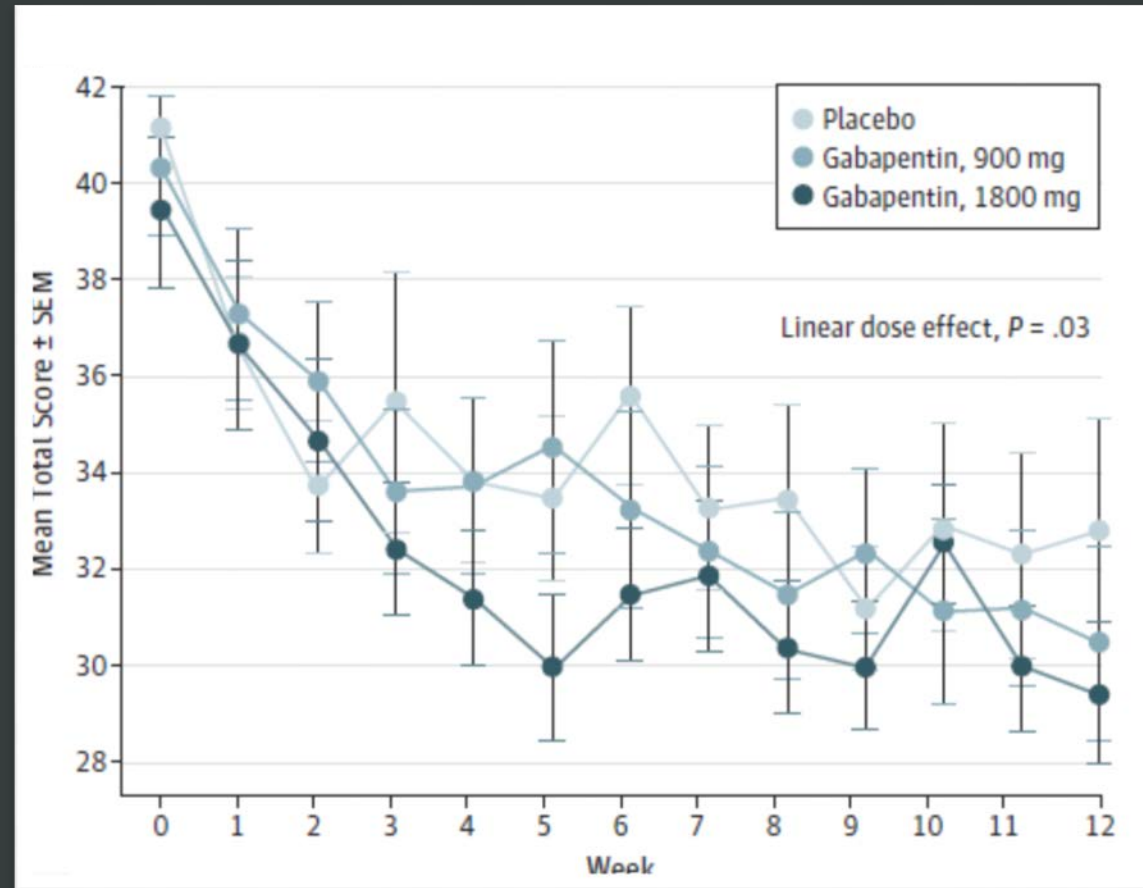
Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial

- **Limitations**
  - Single site study
  - Dropout rate was significant

- **Strengths**
  - Could be used for co-occurring dependencies
  - Gabapentin is not appreciably metabolized in the liver

- **Concluding Thoughts**
  - Gabapentin 1800 mg effectively treated alcohol dependence and relapse associated symptoms.
  - Favorable safety profile
  - Sustained post treatment effect on drinking outcomes was found in those who responded well to gabapentin in the study

Baclofen

- FDA approved for spasticity associated with neurologic conditions

- May benefit in alcohol dependency
  - Activation of $GABA_B$ receptors in mesolimbic system may result in local inhibition of surrounding dopamine neurons
  - Result in decrease of alcohol-stimulated dopamine release
  - Decreasing positive reinforcement from alcohol consumption

Brennan J et al. *Clinical Pharmacology: Advances and Applications* 2013:5 99-107

Baclofen: A Review

- **Objective:** To assess the benefit of baclofen for alcohol dependence

- **Design**: Review of 6 randomized controlled trials (n=287) from inpatient and outpatient sites

- **Intervention:** Baclofen (30-60 mg) vs. placebo

- **Main Outcome and Measures**
  - % maintain abstinence
  - % heavy drinking
  - Time to relapse
  - Drinks per day

Description of randomized controlled trials assessing Baclofen in alcohol dependency (modified according to Brennan et al. 2013 [i]).

Source	Addolorato et al. 2007 [ii]	Garbutt et al. 2010 [iii]	Addolorato et al. 2002 [iv]	Morley et al. 2014 [v]	Addolorato et al. 2011 [vi]
setting	single inpatient site	outpatients recruited from community	single inpatient site	single outpatient site	single inpatient site
number of subjects	84	80	39	42	42
age	49.0 (range 43.0–61.0)	47.5 ± 7.6	45.8 ± 10.6	placebo: 46.0 (39.5–52.5) baclofen 30 mg: 48 (47.9 (42.2–53.5)) baclofen 60 mg: 46.6 (39.8–53.5)	placebo: 43.1 (23–59) baclofen 30 mg: 45.6 (32–60) baclofen 60 mg: 43.1 (30–57)
male gender	76 %	55 %	n.a.	placebo: 64 % baclofen 30 mg: 50 % baclofen 60 mg: 21 %	placebo: 78 % baclofen 30 mg: 86 % baclofen 60 mg: 64 %
daily drinks	n.a.	7.3 ± 3.7 (baclofen group)	14.2 ± 7.9 (all subjects)	placebo: 14.3 (8.1–20.5) baclofen 30 mg: 15.6 (8.2–16.9) baclofen 60 mg: 15.1 (8.5–21.8)	placebo: 12.0 (9.1–14.9) baclofen 30 mg: 13.9 (10.4–17.5) baclofen 60 mg: 9.7 (7.3–12.0)
duration of use (y)	22.0 (range 17.0–27.0)	23.5 ± 9.9	12.6 ± 4.8	n.a.	n.a.
comorbidities	cirrhosis (Child-Pugh A, B, or C)	no medical/psychiatric	no medical/psychiatric	no medical/no clinical relevant psychiatric (anxiety disorder according to Mini International Neuropsychiatric interview n = 17)	no medical/psychiatric
intervention	baclofen 3 × 10 mg for 12 weeks	baclofen 3 × 10 mg for 12 weeks	baclofen 3 × 10 mg for 4 weeks	baclofen 3 × 10 mg vs. 3 × 20 mg for 12 weeks	baclofen 3 × 10 mg vs. 3 × 20 mg for 12 weeks
primary outcome	percentage of patients maintaining abstinence: 71 % vs. 29 % (P = 0.0001) cumulative abstinent days: 62.8 ± 5.4 vs. 30.8 ± 5.5 (P = 0.001)	percentage of heavy drinking days: 19.3 % vs. 24.7 % (P = 0.73) percentage of abstinent days: 51.7 % vs. 51.6 % (P = 0.61)	percentage of patients maintaining abstinence: 70 % vs. 21.2 % (P, 0.005) cumulative abstinent days: 19.6 ± 2.6 vs. 6.3 ± 2.4 (P, 0.005)	time to lapse (days): placebo 3.1 (1.9–4.4) vs. baclofen 30 mg 13.1 (2.8–23.5) vs. Baclofen 60 mg 17.6 (3.5–31.8) (Chi, treatment vs. placebo p = 0.18, n.s.) time to relapse (days): placebo 7.1 (2.4–11.8) vs. baclofen 30 mg 23.8 (9.6–38.0) vs. baclofen 60 mg 19.2 (4.9–34.5) (Chi, treatment vs. placebo p = 0.08, n.s) Drinks per drinking day Placebo 2.8 (0.0–5.6) vs. baclofen 30 mg 5.9 (2.8–8.9) vs. baclofen 60 mg 5.6 (3.2–8.1) (mixed model, p = 0.68, n.s.) heavy drinking days per week: placebo 1.4 (0.3–3.0) vs. Baclofen 30 mg 2.1 (0.3–3.9) vs. baclofen 1.9 (0.4–3.3) (mixed model, p = 0.91 n.s.)	drinks per day placebo 0.55 (0.4–0.7) vs. baclofen 30 mg: 0.3 (0.21–0.4)(p < 0.0001) vs. baclofen 60 mg: 0.14 (0.09–0.19) (p < 0.0001)

Baclofen

- Conflicting evidence

- Safe to use in patients with alcohol dependence including those with moderate to severe liver cirrhosis

- Randomized studies were less promising than the findings in case reports

- Baclofen doses may attribute to different responses
  - Majority of the RCTs used ¼ of the dose Ameisen used on himself

- Future studies
  - 3 major studies are currently being conducted in France and Germany

Brennan J et al. *Clinical Pharmacology: Advances and Applications* 2013:5 99-107

Topiramate

- FDA approved for epilepsy, migraine prophylaxis

- May benefit in alcohol dependency
  - Decreasing positive reinforcement from alcohol consumption by reducing craving through antagonizing the glutamate receptors and inhibiting dopamine release.

- Earlier meta-analysis found support for topiramate; however, analysis was limited due to small sample of studies (k=3)

Topiramate: Meta-Analysis

- **Objective:** Review and highlight outcomes for the use of topiramate in Alcohol Use Disorders (AUDs)

- **Design**: Systemic review seven randomized controlled trials (n=1,125 participants)

- **Main Outcomes and Measures:**

  - Compared topiramate vs. placebo

    - Abstinence

    - Heavy drinking

    - Craving

    - Y-glutamyltranspeptidase (GGT)

Blodgett J et al. *Alcohol Clin Exp Res.* 2014; 38: 1481-1488

Topiramate-Meta-Analysis: Table 2

Characteristics of Randomized, Placebo-Controlled Trials Included in the Meta-Analysis

First author (year)	Medication groups (desired daily dosage)	N randomized	N completers[a]	Months of planned treatment	Required initial abstinence?	Psychotherapy provided
Johnson (2003)	Topiramate (300 mg)	78	55	3	No	Weekly sessions of manual-guided brief behavioral enhancement therapy
	Placebo	80	48			
Johnson (2007)	Topiramate (300 mg)	183	112	4	No	Weekly sessions of manual-guided Brief Behavioral Compliance Enhancement Treatment (BBCET)
	Placebo	188	144			
Baltieri (2008)	Topiramate (300 mg)	52	33	3	Yes	Weekly sessions of standardized relapse prevention counseling
	Naltrexone (50 mg)	49	29			
	Placebo	54	23			
Rubio (2009)	Topiramate (250 mg)	n/a[b]	31	3	Yes	Weekly sessions of supportive group therapy
	Placebo	n/a[b]	32			
Kampman (2013)	Topiramate (300 mg)	83	54	3	Yes	Weekly sessions of manual-guided CBT (adapted from MATCH manual)
	Placebo	87	46			
Likhitsathian (2013)	Topiramate (100 to 300 mg)	53	28	3	Yes	3 to 5 Sessions of motivational enhancement therapy[c]
	Placebo	53	25			
Kranzler (2014)	Topiramate (200 mg)	67	55	3	No	9 Sessions of manual-guided medical management
	Placebo	71	62			

[a]Number of participants who continued to take their assigned pills throughout the planned medication period.
[b]Of 76 randomized overall, group sample size not specified.
[c]Participants were recruited from inpatient detoxification and residential treatment programs (mean length of stay: 25 days). Topiramate or placebo was initiated a mean of 3.7 days prior to discharge.

Topiramate-Meta-Analysis Figure: 4

- **Overall Results**: Small to moderate effects of topiramate

- Largest effect was found on abstinence (g=0.468, p<0.01)

- Followed by heavy drinking (g=0.406, p<0.01) and GGT (g=0.324, p=0.02)

- Effects on cravings did not reach significance

Blodgett J et al. *Alcohol Clin Exp Res.* 2014; 38: 1481-1488
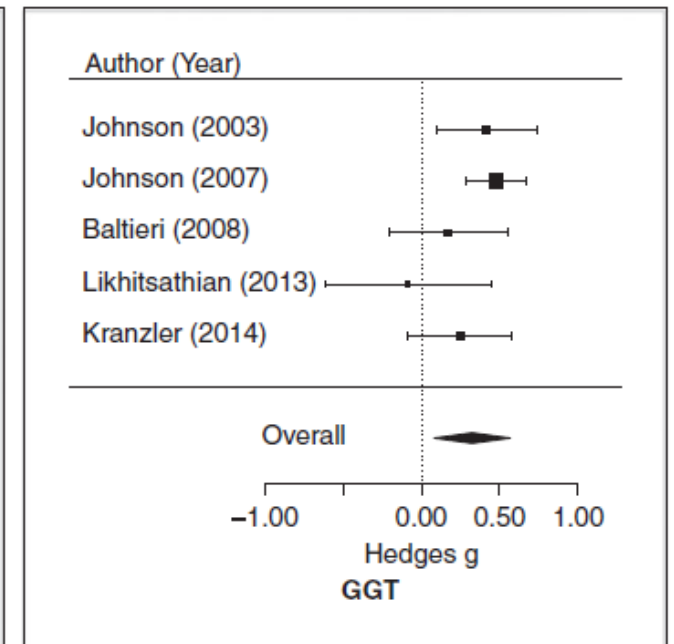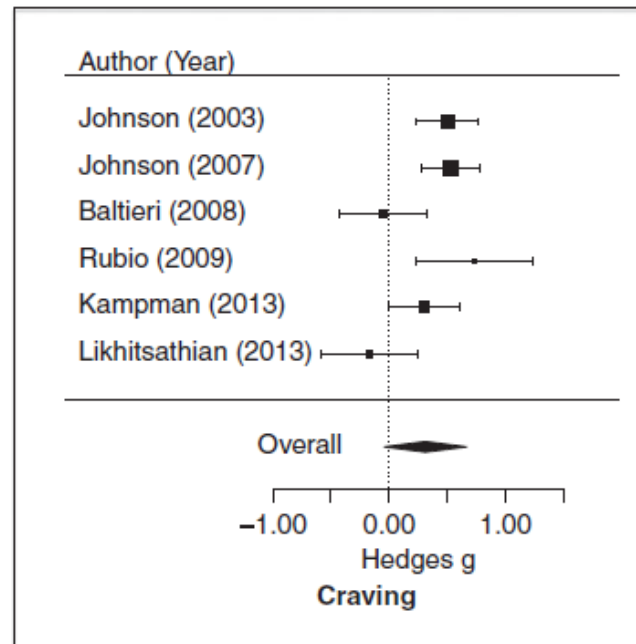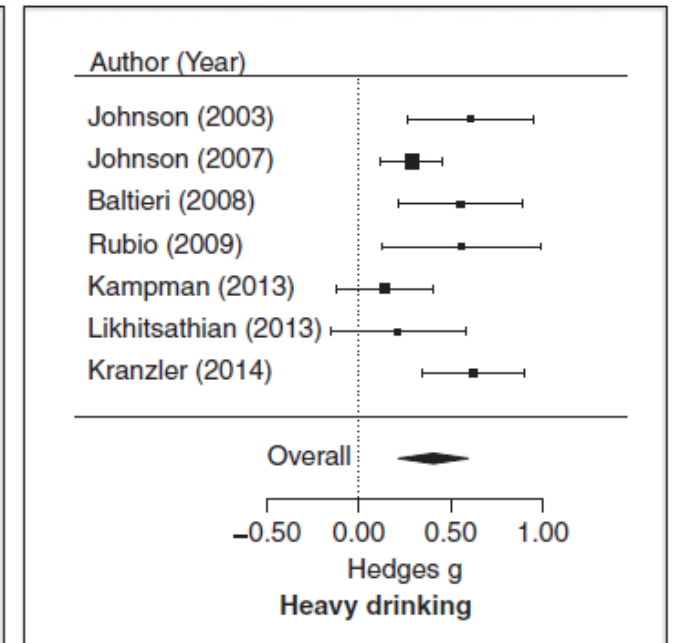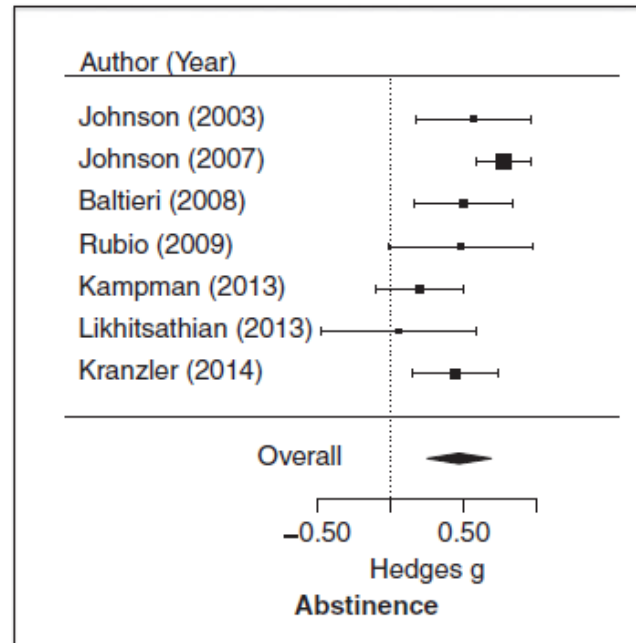
Topiramate: Meta-Analysis

- **Limitations:**
  - Small number of studies
  - Target doses were higher than the most recent study (Paparrigopoulos et al.)

- **Strengths:**
  - Co-occurring conditions tested
  - Different types of settings (inpatient vs. residential treatment)

- **Concluding Thoughts:**
  - Topiramate is efficacious in AUDs
  - Significant benefits for abstinence and heavy drinking outcomes
  - Positive outcomes on GGT and alcohol cravings

Blodgett J et al. *Alcohol Clin Exp Res*. 2014; 38: 1481-1488
Paparrigopoulos T et al. BMC Psychiatry. 2011; 11:41-48

Topiramate: Other Studies

- Batki et al.
  - Preliminary results indicate that topiramate is effective in reducing alcohol consumption, cravings and PTSD symptom severity in the veteran population

- Cochrane review by Pani et al.
  - Topiramate had fewer drinks/drinking days, fewer heaving drinking days, more abstinent days
  - Failed to show superiority in reducing cravings

Batki S et al. *Alcohol Clin Exp Res.* 2014; 38:2169-2177
Pani P et al. Cochrane Database Syst Rev 2014; 2: CD008544

Cocaine Dependency Medications

| |
|---|
| Topiramate |
| Disulfiram |
| Nepicastat |
| Vigabatrin |
| Buspirone |
| Modafinil |
| Buprenorphine |
| Cocaine Vaccine |
| Butyrylcholinesterase |

Topiramate: Cocaine Dependency

- **Objective: To** determine the efficacy of topiramate vs. placebo as a treatment for cocaine dependency

- **Design**: Double blind, randomized placebo controlled, 12 week trial of 142 cocaine-dependent individuals

- **Intervention:** Topiramate (n=71) vs. placebo (n=71) in escalating doses from 50 mg/day to the target maintenance dose of 300 mg/day in weeks 6-12, combined with weekly cognitive behavioral therapy (CBT).

- **Main Outcomes and Measures:**
  - Primary outcome: Weekly difference from baseline in the proportion of cocaine nonuse days
  - Secondary outcome: Urinary cocaine free weeks

Johnson B et al. *JAMA Psychiatry* 2013; 70(12):1338-1346

Topiramate- Cocaine Dependency: Figure 5

Weekly Mean Proportion of Cocaine Nonuse Days From Baseline Through Study Week 12
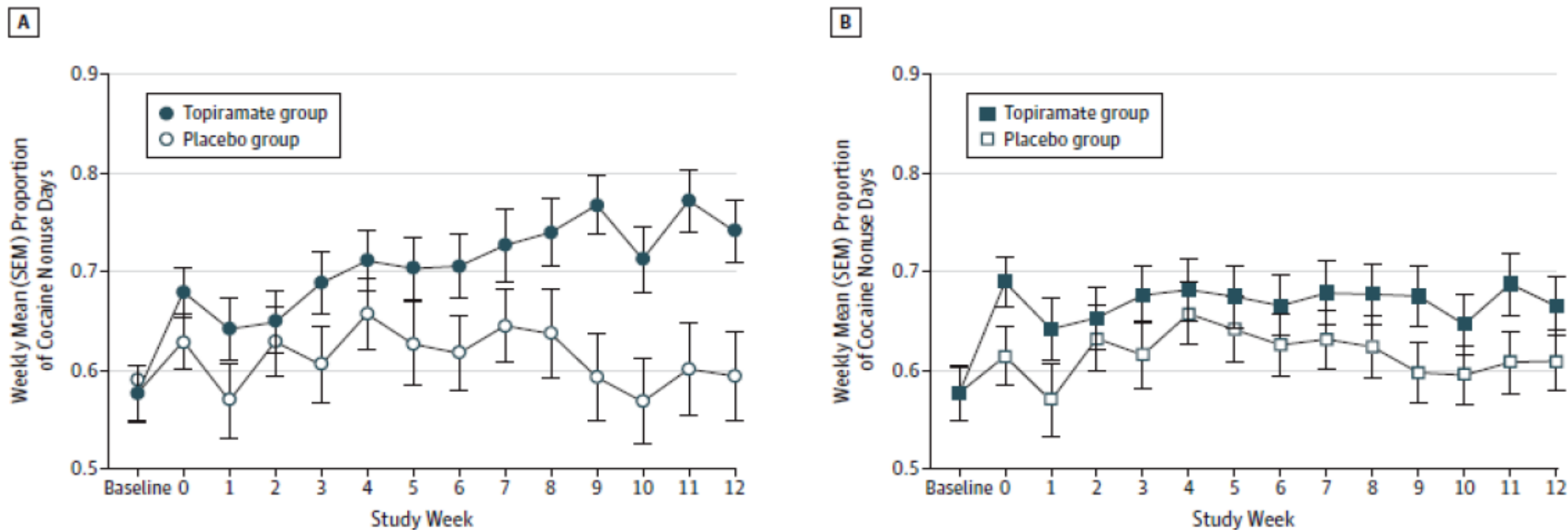
Each symbol represents the mean proportion of cocaine nonuse days for each study week, and the error bars indicate standard error (SEM). Weekly mean proportion of cocaine nonuse days was analyzed (A) without imputing missing data and (B) imputing missing data using baseline values. Mean (SEM) values for the weekly proportion of cocaine nonuse days at baseline (ie, mean cocaine use during the 2-week baseline period) for the 2 groups receiving topiramate and placebo were 0.5775 (0.0294) and 0.5665 (0.0302), respectively. Participants were allocated to treatment groups at the end of the 2-week baseline period. Study medication was provided at week 0 and, therefore, week 1 contains those individuals who had received 1 or more weeks of double-blind treatment.

Johnson B et al. *JAMA Psychiatry* 2013; 70(12):1338-1346

Disulfiram: Cocaine Dependency

- Aldehyde dehydrogenase inhibitor and dopamine-beta-hydroxylase (DβH) inhibitor

DβH

- Dopamine →→→Norepinephrine

- Dopamine > Norepinephrine

Disulfiram for the treatment of cocaine dependence in methadone-stabilized patients

- **Objective:** This study examined the dose-related efficacy of disulfiram for treating cocaine dependence in methadone-stabilized cocaine dependent participants.

- **Design**: One hundred and sixty-one cocaine- and opioid-dependent volunteers were entered into a 14-week, double blind, randomized, placebo-controlled clinical trial at two sites.

- **Intervention:** Disulfiram (62.5 mg, 125 mg, 250 mg) vs. placebo

- **Main Outcome and Measures**
  - Positive urine drug screen for cocaine

Disulfiram for the treatment of cocaine dependence in methadone-stabilized patients: Table 3

The number of participants with urine samples that either tested all negative (neg) or had at least one positive (pos) test, respectively, for cocaine/cocaine metabolite within a given week.

Study week	Placebo		Disulfiram 62.5		Disulfiram 125		Disulfiram 250	
	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos
2	11	27	13	24	9	29	10	29
3	12	26	14	23	12	25	11	25
4	12	26	16	20	12	26	11	25
5	15	23	12	24	10	26	13	23
6	14	23	13	22	6	28	13	23
7	12	25	8	25	7	27	11	24
8	11	23	9	23	9	24	13	20
9	12	21	10	22	8	24	10	22
10	11	22	9	23	6	25	13	18
11	10	22	7	24	7	23	9	18
12	11	20	10	18	6	20	10	16
13	16	15	10	16	7	18	12	14
14	12	17	8	18	6	17	11	15

Disulfiram for the treatment of cocaine dependence in methadone-stabilized patients

- **Concluding Thoughts**
  - Groups receiving disulfiram 250 mg/ day had a significant decrease in cocaine-positive urines over time compared to lower doses

A Multi-Center Trial of Nepicastat for Cocaine Dependence

- **MOA:** Selective dopamine β hydroxylase inhibitor

- **Design**: Randomized, double-blind placebo-controlled trial in treatment-seeking cocaine-dependent subjects (n=179) using nepicastat

- **Intervention:** Nepicastat vs. placebo

- **Main Outcome and Measures**
  - Positive UDS for cocaine

- **Results:** When compared to placebo, nepicastat did not meet the primary efficacy endpoint of an increased proportion of subjects remaining abstinent from cocaine during the last two weeks of the treatment period.

Opioid Dependency

- Opioid agonist treatment
  - Methadone
  - Buprenorphine/Naloxone

- Opioid antagonist treatment
  - Naltrexone

- Psychosocial treatment

New Formulations
 -Bunavail™
 -Depot Buprenorphine
 -Buprenorphine Implant

New opioid antagonist
 -Samidorphan (ALKS33)

Opioid Dependency: Bunavail ™

- NDA approved on June, 6 2014

- Limited under the Drug Addiction Treatment Act (DATA)

- Maintenance treatment of opioid dependency

- Buccal film:
  - 2.1 mg Buprenorphine/ 0.3 mg Naloxone
  - 4.2 mg Buprenorphine/ 0.7 mg Naloxone
  - 6.3 mg Buprenorphine/ 1 mg Naloxone

- Small patch which adheres to the inside of the mouth with the drug being absorbed through the cheek
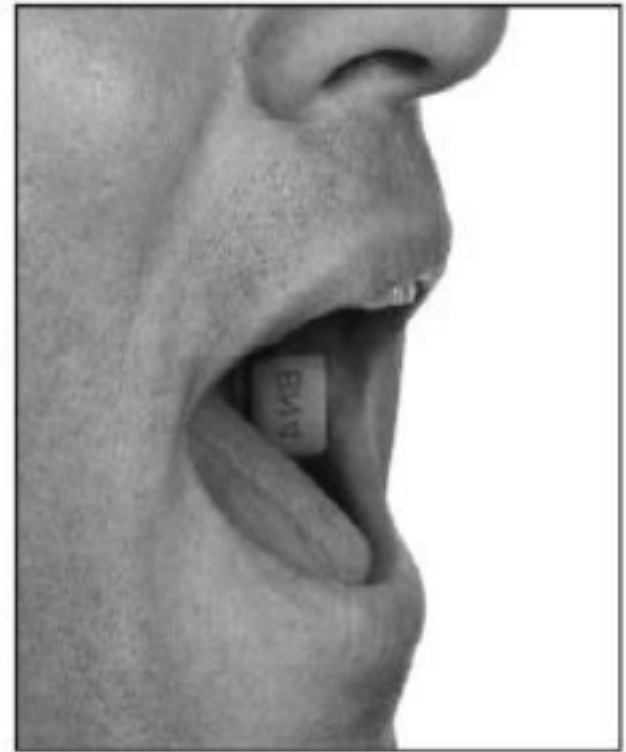
Samidorphan (ALKS33)

- Selective opioid antagonist u-opioid receptor

- Without affecting the delta-opioid or k-opioid R

- Similar to naltrexone but reduced side effects

- Indications

  - Opioid Dependency

  - Alcohol Dependency

  - Cocaine Dependency

  - Major Depressive Disorder

  - Binge Eating

Turncliff R et al. *Clinical Therapeutics* 2015; 37(2): 338-348

Clinical Application

Safety Considerations

- Well tolerated medications across the board in all dependencies

- Saw some benefit in lower doses

- Safe in using with dependent agents

- When looking at cost/accessibility/prescribing barriers
  - "Novel" medications look promising

Financial Burdens

- Addiction-$600 billion annually

- Treatment less expensive than its alternatives
  - Incarceration addicted $24,000 per person/year
  - Methadone maintenance treatment ~$4,700 per person/year

- For every $1.00 spent on treatment→$4.00-$7.00 ROI

Anti-Craving Medications Concluding Thoughts

- FDA approved medications for opioid and alcohol

- No medications approved for cocaine

- Long-term success of medications is low

- "Novel" medications being investigated

- Difficult to interpret statistics

- Ongoing investigation

Anti-Craving Medications for Alcoholism and Drug Addiction

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