RECOVER ALASKA

Reducing excessive alcohol use and harm in Alaska.

Medication Assisted Treatment for Alcohol Use Disorder: Current Status and Future Directions

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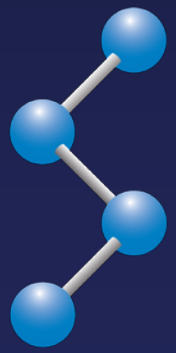

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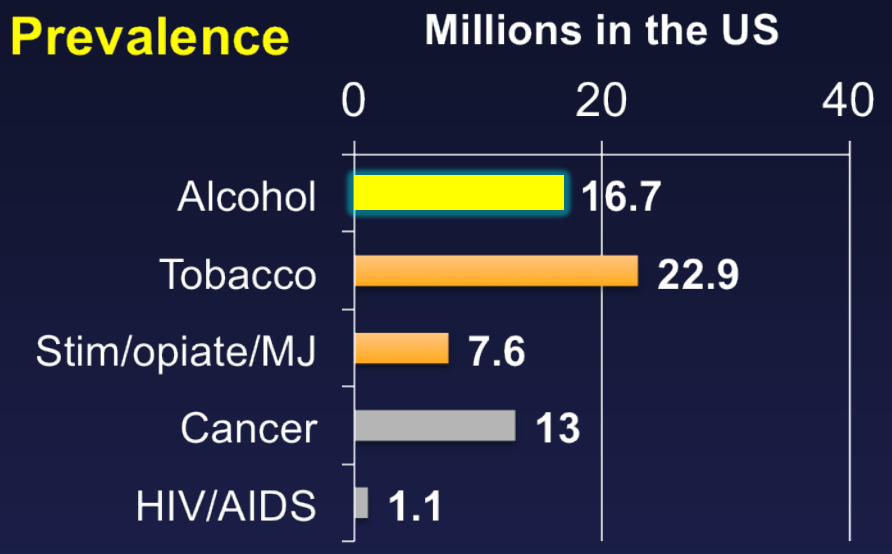
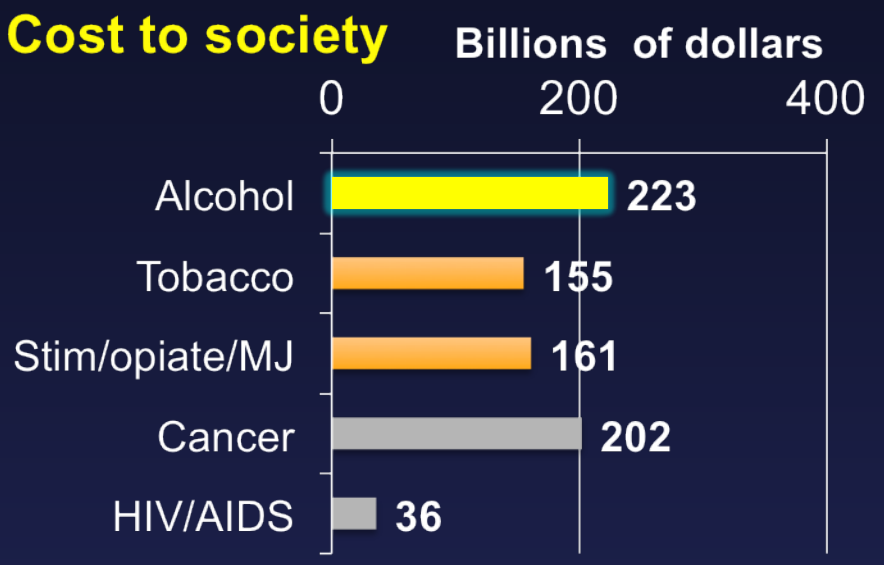
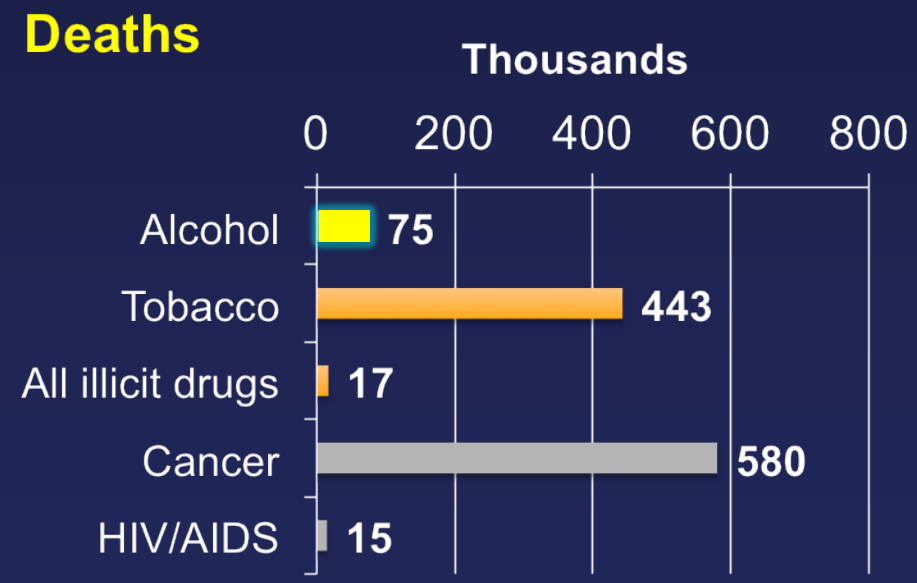
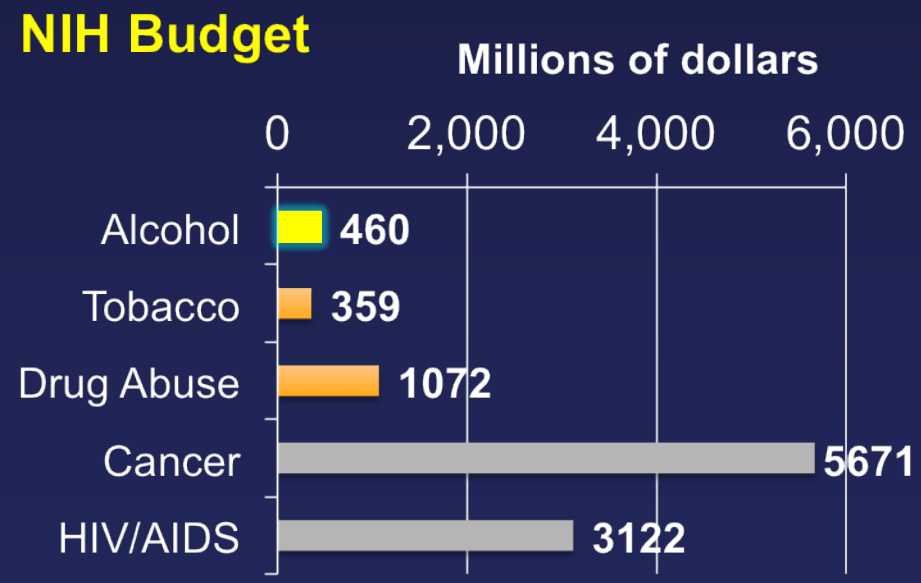
Dr. Mason has no conflicts of interest to disclose

Cost and Scope of Substance Use Disorder









Source: NIH, CDC

What is Alcohol Use Use Disorder?

DSM V = 2 of 11 sx, moderate+ severity = 4+ sx

Also called:

- **Alcohol Addiction**
- **Alcohol Dependence (DSM IV, ICD 10, draft ICD 11)**
- **Alcoholism**

Defined as a chronic, relapsing disorder that involves:

- **Compulsive alcohol seeking and drinking**
- **Loss of control over drinking**
- **Tolerance and physiological withdrawal**
- **A protracted *motivational* withdrawal syndrome**
  - **negative emotional state (dysphoria, anxiety, irritability)**
  - **sleep disturbance**

Current Status of Pharmacotherapies for Alcohol Use Disorder

FDA-approved medications are limited

- **disulfiram (Antabuse), 1951, FDA-approval**
- **naltrexone (ReVia, Vivitrol), 1994, 2006, FDA-approval**
- **acamprosate (Campral), 2004, FDA-approval**

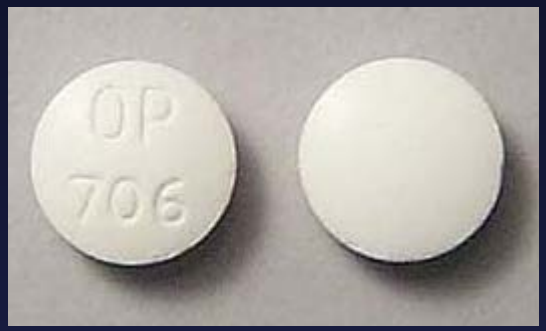
FDA-approved medications are under-utilized

- **Prescribed for < 9% of 8.4m Americans with alcohol use disorder**

Relapse rates are high following non pharmacological treatment

- **80% relapse 1+ times during year following treatment**

FDA-approved Medications for AUD



Disulfiram
(Antabuse)
125-500mg orally
$18/month generic
FDA approved in 1951

Mechanism: the alcohol-disulfiram interaction

- Inhibits the metabolism of alcohol
- Acetaldehyde quickly builds up
- Rapid onset of flushing, nausea and palpitations
- A psychological deterrent to alcohol use

Efficacy

- Medication compliance tends to be poor
- Optimized with supervised administration and compliant participants who want to quit drinking completely

Safety

- Should not be given to someone in a state of alcohol intoxication, or without their full knowledge.
- Hepatotoxicity, drowsiness

FDA-approved Medications for AUD

Naltrexone (Revia, generic)
50mg orally, $27/month
FDA approved 1994

Naltrexone (Vivitrol)
380mg extended-release Injectable, FDA approved 2006
$1372/month

Mechanism

- A pure opioid receptor antagonist
- If alcohol consumption is less rewarding, drinking will decrease.

Efficacy

- Increases rates of no heavy drinking (NNT = 8.6 - 12)
- Compliance problems with oral daily dosing
- Vivitrol once-monthly extended-release intramuscular injection

Safety

- Do not give to patients with current prescribed or illicit opiate use, as it will induce acute opioid withdrawal.
- **Hepatotoxicity**

FDA-approved Medications for AUD

Acamprosate
(Campral)
1998mg orally
$108/month
FDA approve 2004

Mechanism

- Heavy drinking and withdrawal dysregulate the balance between neuronal excitation (glutamatergic) and inhibition (GABAergic).
- Restores homeostasis in NMDA-mediated glutamatergic neurotransmission.

Efficacy

Increases rates of abstinence in studies up to 1 year long (NNT = 7.5 - 12)

Safety

- Not metabolized in the liver, excreted renally
- Safe in patients with hepatic impairment.

When, How, What Drug to Prescribe to Treat AUD: Disulfiram, Acamprosate, Naltrexone?

- Consider medication especially if there is an inadequate response to counseling
- Review package insert, NIAAA Clinician's Guide, talk with colleague
- Review drug pros and cons with patient, keeping in mind their health status, motivation to be abstinent, and their preference
- In case of inadequate response, meds may be used sequentially or in combination, and can be restarted in case of relapse

FDA-approved drugs to treat AUD have the following characteristics:

- Not a cure
- Not alcohol-substitution drugs
- Not addictive or habit forming
- Should be prescribed in conjunction with counseling
- Have better drinking outcomes (with counseling) than placebo (with counseling)
- Efficacy higher with initial abstinence: 4-7days

Study of Investigational Drugs in Humans Requires an Investigational New Drug (IND) Application Accepted by the FDA

An IND contains data to determine if a drug is safe to test in humans and includes:

- Animal, pharmacology and toxicology studies
- Chemistry and manufacturing info
- Clinical protocols, Investigator credentials, Informed Consent and IRB approval

Also required for:

- New Indication
- Change in approved route of administration or dose
- Change in approved patient population

Clinical Studies Required for Regulatory (FDA) Approval of an Experimental Drug

Phase I: assesses safety and pharmacokinetics (absorption, metabolism, excretion) in healthy paid volunteers, across a range of doses (~30% failure rate)

Phase II: assesses safety and efficacy in patients with the indicated disorder, using randomized, double-blind, placebo-controlled trials (RCTs) involving up to several hundred patients (~66% failure rate)

Phase III: 6-month RCTs involving several hundred to 1000s of patients (10 - 30% failure rate)

Post-marketing Surveillance (Phase IV) Trials are conducted after drug approval

Measures of Alcohol Consumption

Patient Reported Outcomes

- Timeline Follow-Back Interview
  - Calendar-based retrospective estimates of daily drinking
  - Psychometrically evaluated and field tested
- Ecological Momentary Assessment (EMA)

Objective Outcomes

- Direct measures: BAC, alcohol glucuronide
- Indirect measures: GGT, CDT
- Biosensors

Abstinence outcome: Not a single drink during a 6-month RCT or after a pre-specified grace period

Each Contains the same amount of Alcohol (0.6 oz)*

*US Dietary Guidelines

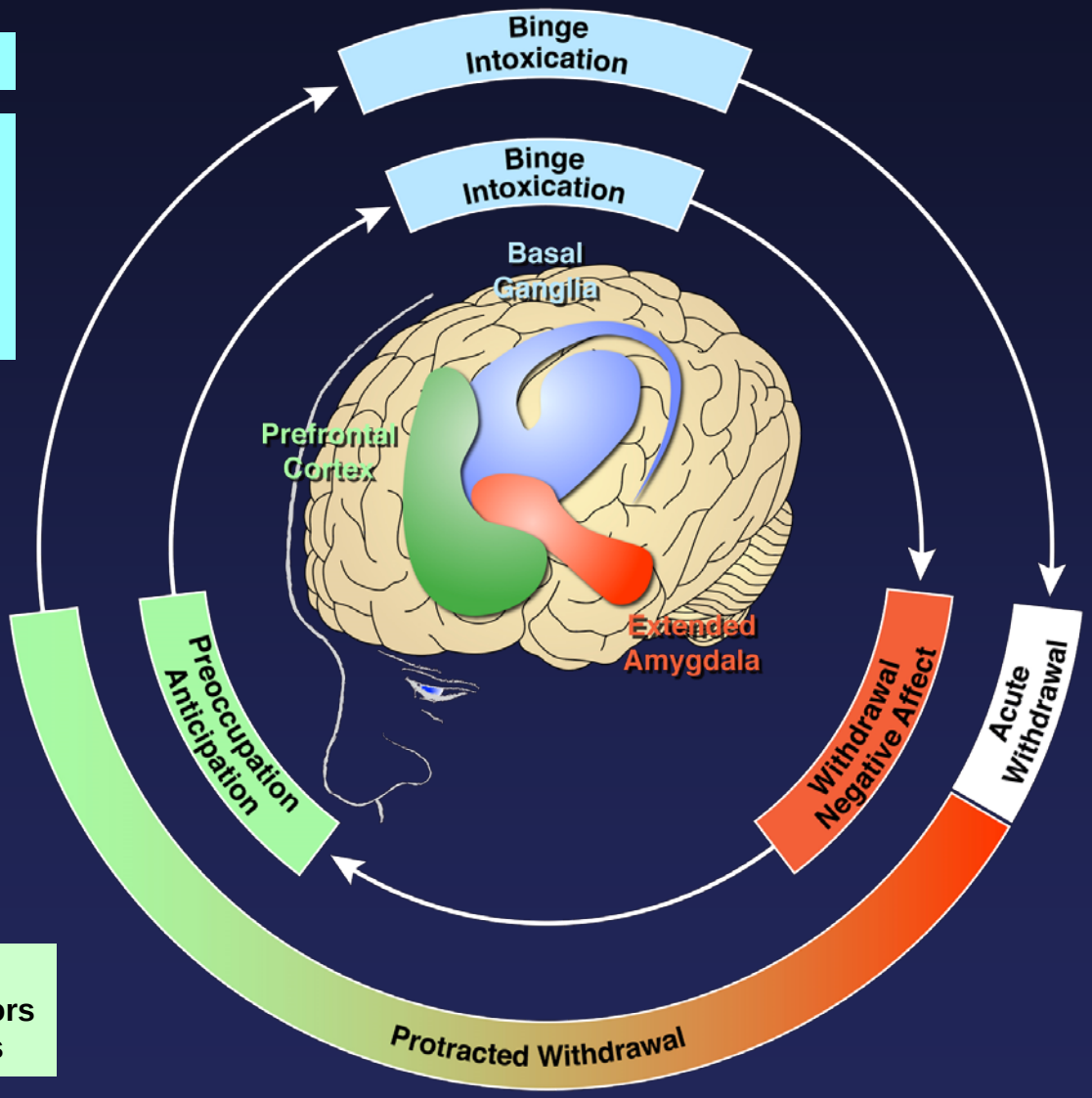
Heavy Drinking Outcome

Binge Drinking: BAC reaches 0.08g/dL within 2 hours

Drug Targets by Stage of the Alcohol Use Disorder Cycle with Corresponding Clinical States

Binge Intoxication

Disulfiram
Naltrexone
Reward Modulators
- Dopamine
- Opioid
- Receptor channels



Withdrawal Negative Affect

Brain Stress Systems
- CRF
- Dynorphin
- Glucocorticoid
- Hypocretin
- Norepinephrine
- Vasopressin

Neuroimmune Brain Anti-stress Systems
- Endocannabinoid
- Neuropeptide Y
- Nociceptin
- Oxytocin

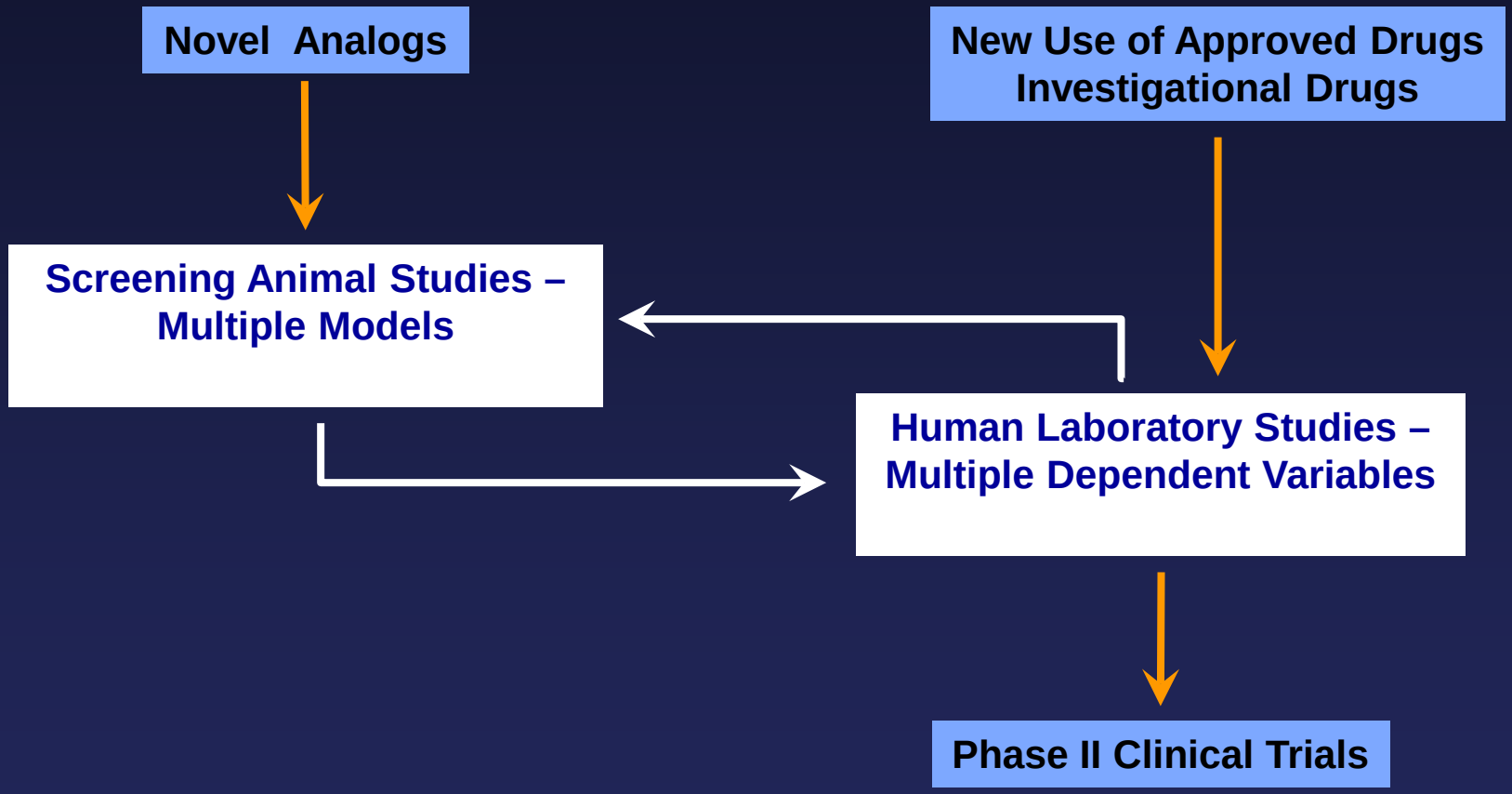
Preoccupation Anticipation

Acamprosate
Glutamate
- AMPA
- Metabotropic
- NMDA

Molecular Cellular
- Transcription factors
- Translation factors

Adapted with permission from: Koob GF, Volkow ND. Neuropsychopharmacol Rev, 2010, 35:217-238; George O, Koob GF. Proc Natl Acad Sci USA, 2013, 110:4165-4166.

Medications Development for Treatment of Alcohol Use Disorder



Koob GF, Lloyd GK, Mason BJ. *Nat Rev Drug Discovery* 2009; 8:500

Grant number R01 AA012602; 1999 – present

Strategies for Medication Development to Reduce Relapse in Protracted Abstinence

The aim is to restore neurocircuitry changes in the pathophysiology of alcoholism to within a homeostatic range of functioning, i.e., block the recruitment of brain stress systems that drive negative reinforcement and provide a powerful motivation for relapse to drinking

1. **A systematic preclinical evaluation of the most promising small molecules directed at neurobiological targets for the Withdrawal Negative Affect and Preoccupation Anticipation stages of protracted withdrawal.**
2. **Clinical testing of compounds with a similar mechanism of action and an IND using:**
    a) **Proof-of-concept human laboratory studies**
    b) **Randomized clinical trials**

Human Lab Model of Protracted Withdrawal

Method: Affective priming, *in vivo* exposure to alcohol

Subjects: Non treatment-seeking males and females with alcohol dependence, abstinent 3 days prior to testing

Design: Double-blind, placebo-controlled, random assignment, dosing based on PK, typically 1-week

Primary outcome: Visual Analogue Scale - craving

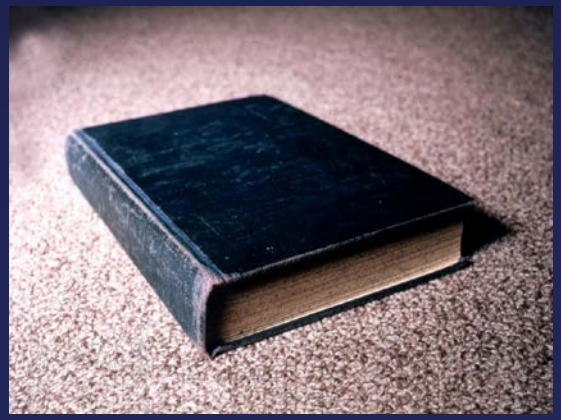
- Confirmatory outcomes: EMG, heart rate, GSR
- Exploratory outcome: sleep, mood, cognition

Safety: Physical exam, labs, vital signs, SAFTEE, ARCI

Mood Induction Methods

- Affective images were selected from the International Affective Picture System (IAPS; CSEA, 1994).
- Images are presented on a monitor in a digitized format.
- 12 images with similar emotional content are presented over a 3 minute period.
- Subjects are asked to look at each picture and try to feel the mood evoked by the picture.

Negative



Neutral

Positive

Beverage Cue Exposure Procedures

- The subject's preferred alcoholic beverage or bottled water are presented in random order for 90 seconds following each mood condition.

- The subject is told to hold and sniff the beverage for 90 seconds and to not drink it.

Primary Outcome: Craving VAS Items*

1. How strong is your craving to drink alcohol ? *STRENGTH*
2. If I could drink alcohol now, I would drink it. *IMPULSE*
3. It would be hard to turn down a drink right now. *CONTROL*
4. Having a drink would make things just perfect. *RELIEF*

* 0 = None, 20 = Extremely Strong

Convergence of Mason Human Lab Results with Drinking Outcomes in AUD Randomized Clinical Trials

	Lab	RCT
Gabapentin	+	+
Naltrexone	+	+
Acamprosate	+	+
Pregabalin	+	+
Duloxetine	–	–
Mifepristone	+	+
Fenofibrate	–	–

Summary of Human Lab Model of Protracted Abstinence

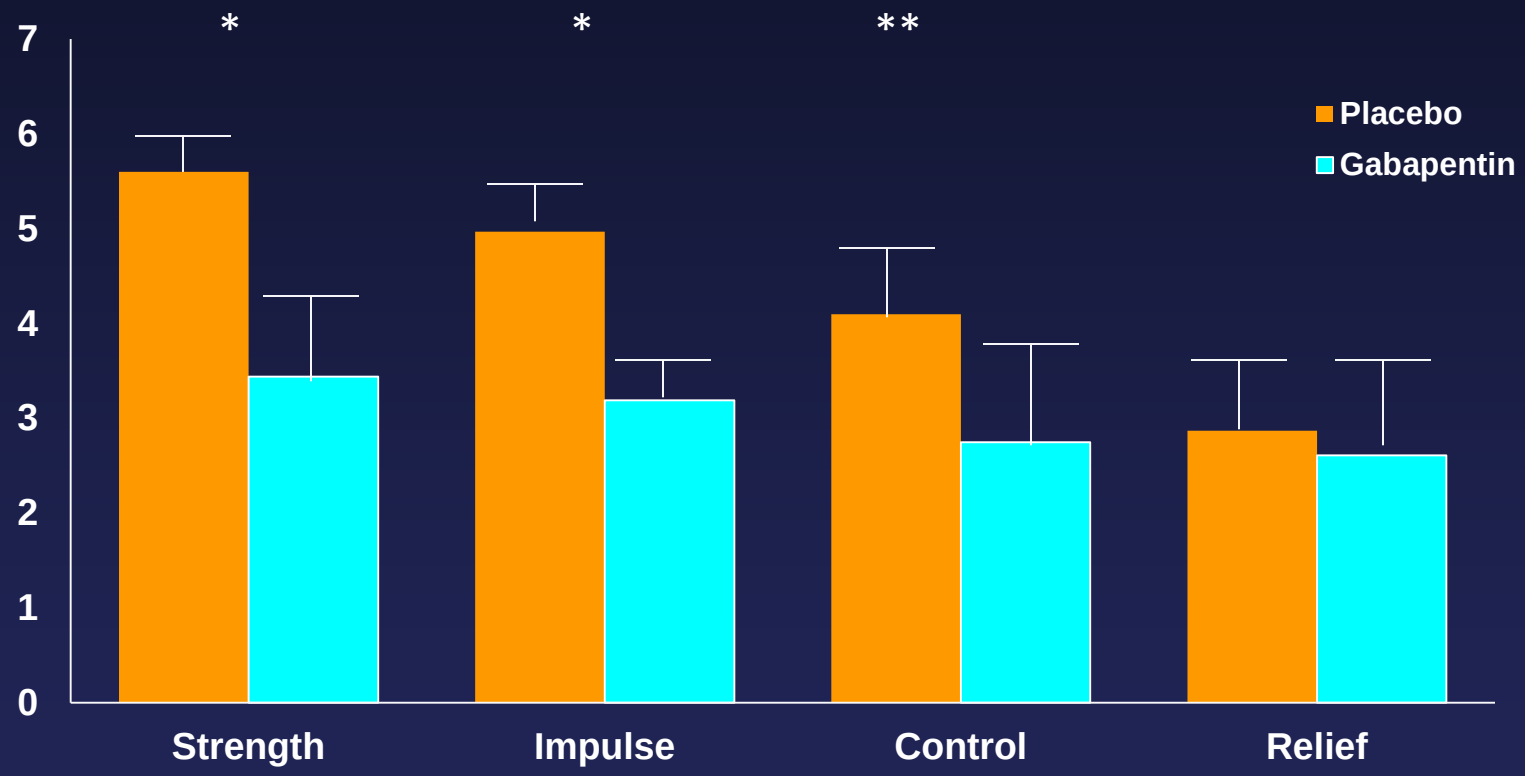
- Uses mood induction and *in vivo* alcohol cues
- Reliably causes craving in abstinent alcoholics
- Decreased drinking is predicted by decreased alcohol-induced craving in the human laboratory model
- Demonstrated predictive validity for drinking outcomes in clinical trials of acamprosate, naltrexone, gabapentin, pregabalin and duloxetine in alcoholics
- Offers a reliable method for POC testing of drugs to treat relapse risk in protracted abstinence in alcohol dependence

Gabapentin

Rationale for Gabapentin (Neurontin) as a Treatment for Alcohol Use Disorder

- FDA-approved for epilepsy and pain
- Associated with modulation of GABAergic activity via action on voltage-gated calcium channels
- Hypothesized to functionally restore homeostasis in brain stress systems dysregulated in protracted abstinence
- Used off-label to treat symptoms associated with protracted abstinence and risk of relapse
  - Depression
  - Anxiety
  - Insomnia: Decreased stage 1 sleep and arousals, increased slow wave sleep and sleep efficiency (*Bazil et al. 2005*)
- Acceptable safety and tolerability
  - Not metabolized in the liver

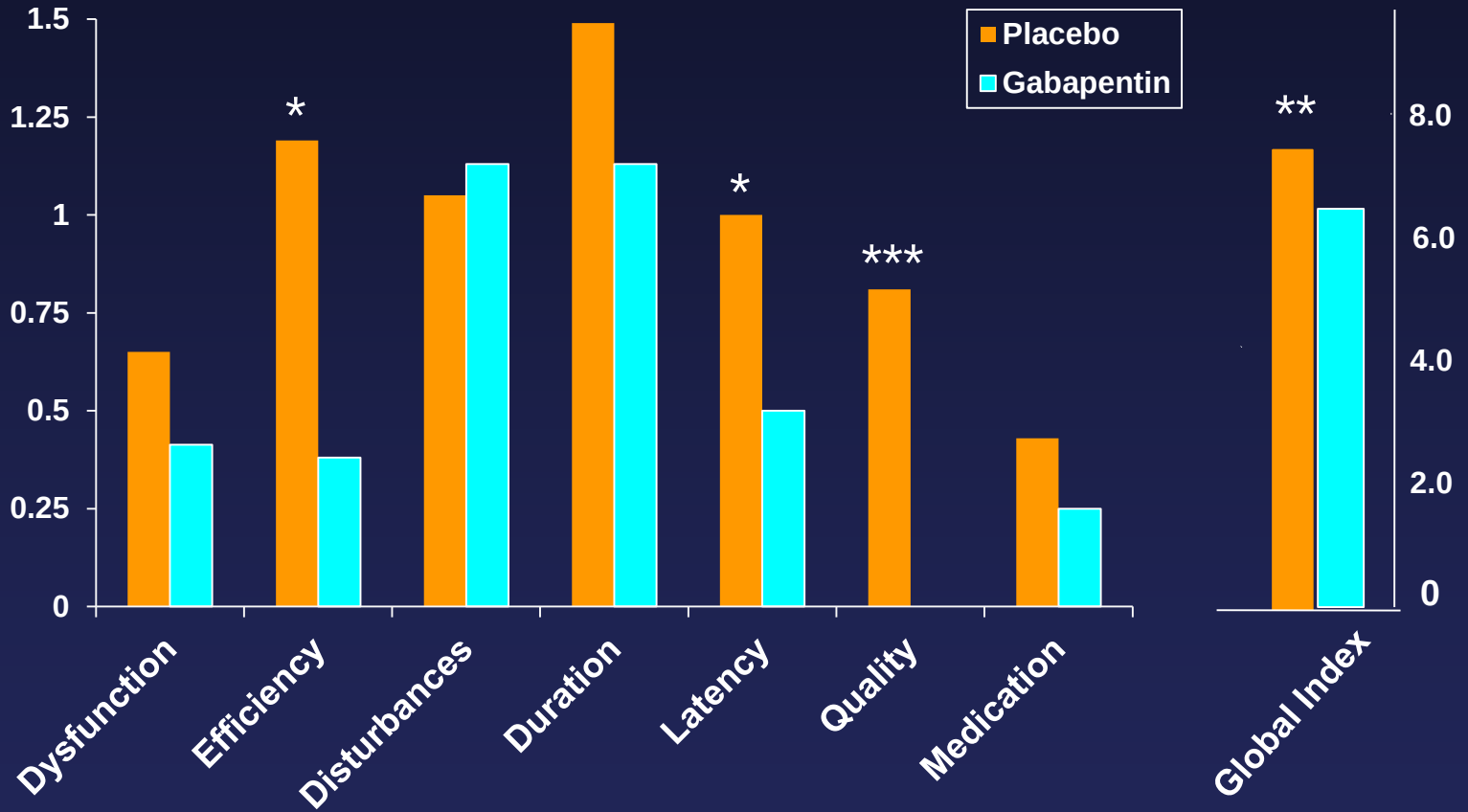
VAS Craving Scores: Alcohol Minus Water



*p< 0.05
**p< 0.1

Mason et al., *Addict Biol*, 2008

Effect of Gabapentin vs. Placebo on Pittsburgh Sleep Quality Index[1]



[1] Higher values indicate greater disturbance; subscale range 0-2
***$p < 0.001$; **$p < 0.05$; *$p < 0.06$

Mason et al., *Addict Biol*, 2008

Summary of POC Human Lab Study of Gabapentin for Alcohol Dependence

Gabapentin 1200mg/d vs placebo was associated with

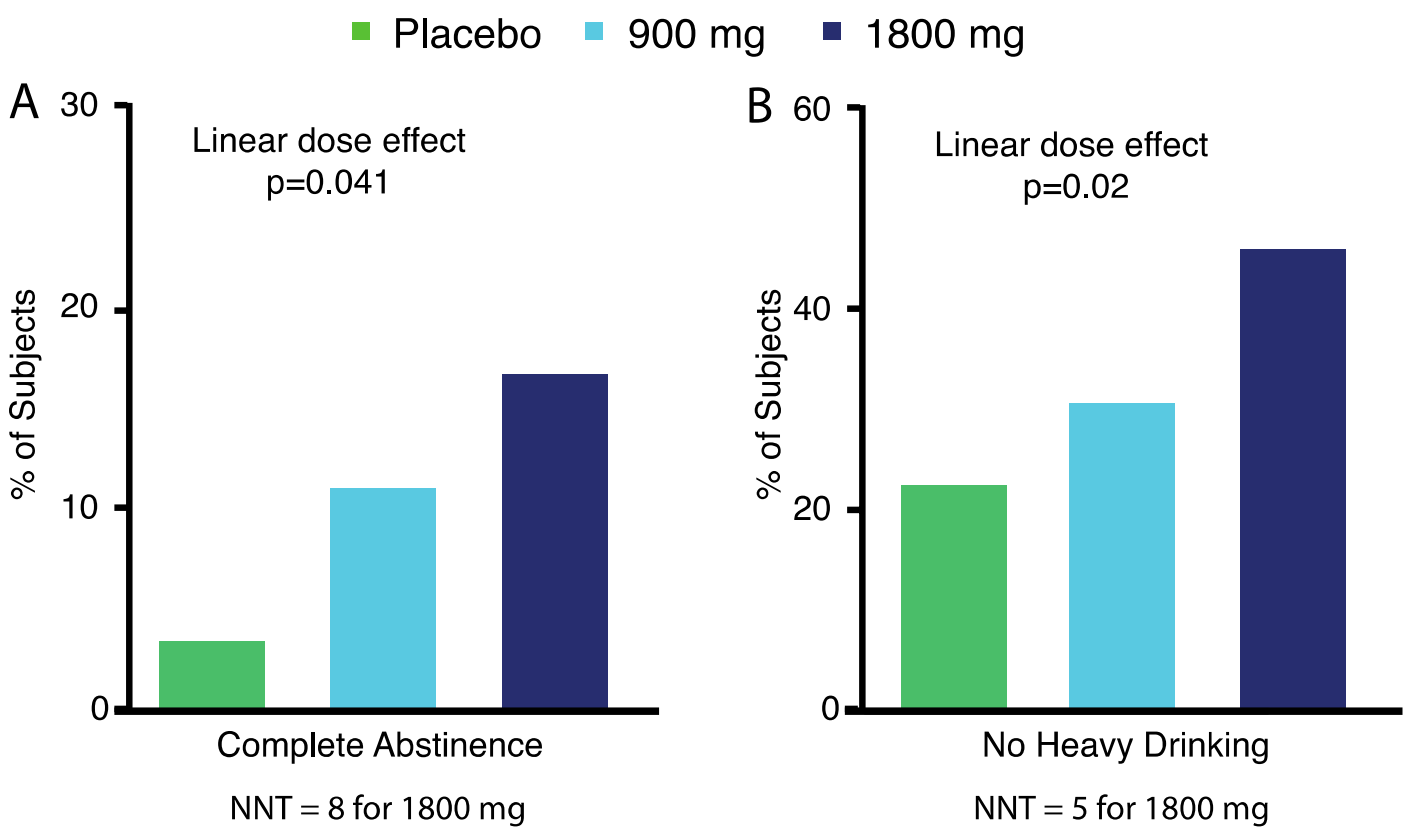
- **Decreased craving ($p < .05$)**
- **Improved sleep ($p < .05$)**
- **Good safety and tolerability**
- **No evidence of abuse potential**

A randomized controlled trial (RCT) to evaluate the efficacy of gabapentin for relapse prevention in alcohol dependence is warranted.

Mason et al., *Addict Biol*, 2008

Rates of Complete Abstinence and No Heavy Drinking on Study

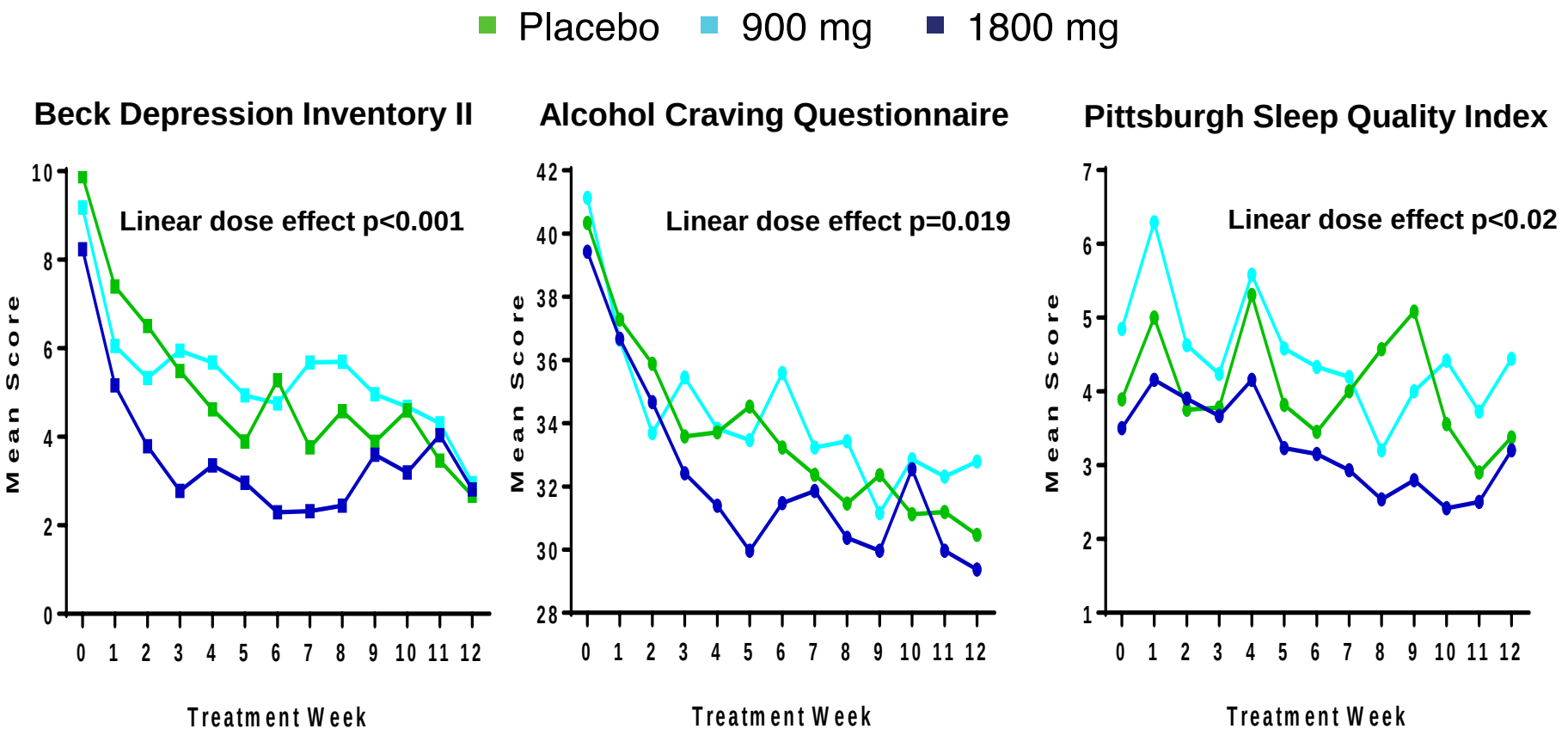
Over the 12-week Study in the ITT Population (N=150)



Mason et al., *JAMA Intern Med*, 2014

Gabapentin Effects on Symptoms of Protracted Abstinence

Over the 12-week Study in the ITT Population (N=150)



Mason et al., *JAMA Intern Med*, 2014

Summary

- Gabapentin dose dependently, significantly improved
  - rates of complete abstinence and no heavy drinking
  - drinking quantity and frequency
  - GGT
  - alcohol craving
  - sleep disturbance
  - negative affective symptoms
- Gabapentin was well-tolerated with no serious or unexpected drug-related adverse events or evidence of abuse potential

Clinical Implications

- Gabapentin may offer a cost- effective treatment for AUD
- Effect sizes for rates of abstinence and no heavy drinking were equivalent or superior to approved drugs, with unique benefits re: mood and sleep
- Effects of gabapentin on drinking and symptoms of protracted abstinence lend support to the role of neuromodulating drugs that target brain stress systems to treat AUD
- AUD is found – and gabapentin is widely used – across medical specialties. Reported benefits of gabapentin for AUD may result in a broader interest in AUD treatment across diverse medical settings

Mifepristone

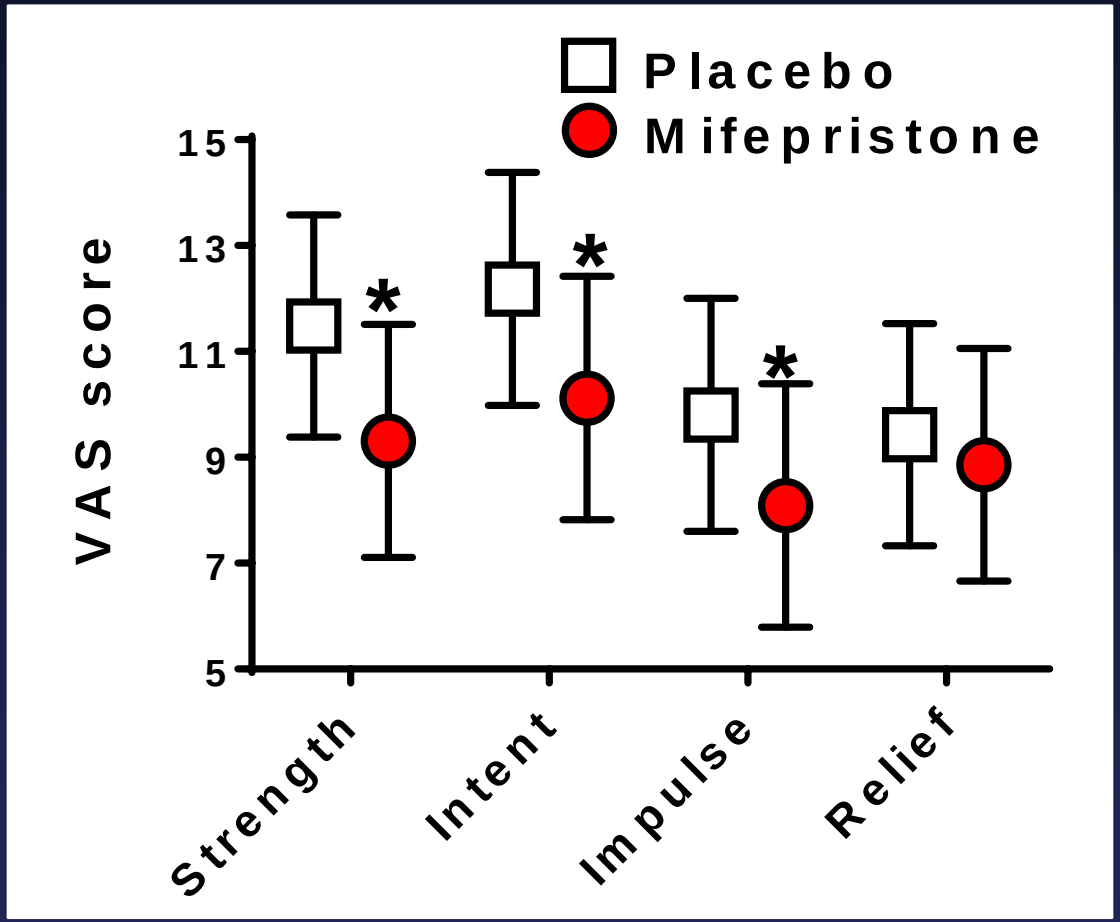
Rationale for Glucocorticoid Antagonism as a Treatment for Alcohol Dependence

- Heavy alcohol use and withdrawal dysregulate the balance between brain stress and reward systems
  - Abnormal HPA axis activity and glucocorticoid receptor feedback, and sensitization of CRF in the amygdala

- Mifepristone, a Type II glucocorticoid receptor antagonist, is available for re-purposing: FDA-approved to control hyperglycemia secondary to hypercortisolism in adults with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance (Korlym, Corcept Theraputics)

- Clinically, administering mifepristone in alcoholics following acute withdrawal may normalize HPA axis dysregulation and thereby protect against relapse during protracted withdrawal

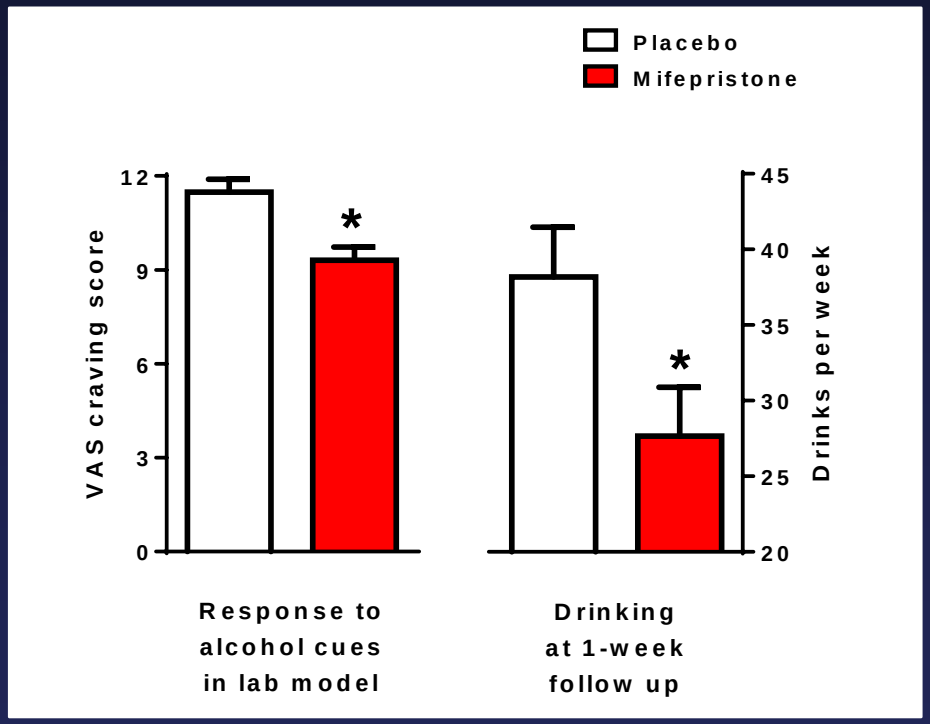
Alcohol-Cued Craving: Visual Analogue Scale (VAS) Scores



* p<0.05

Vendruscolo LF, Estey D, Goodell V, Macshane LG, Logrip ML, Schlosburg JE, McGinn MA, Zamora-Martinez ER, Belanoff JK, Hunt HJ, Sanna PP, George O, Koob GF, Edwards S, and Mason BJ, *J Clin Invest.,* 2015

Craving Response to Alcohol Cues and Subsequent Drinking: Mifepristone 600mg/d vs. Placebo (N = 50)



* $p < 0.05$

Vendruscolo, Estey, Goodell, Macshane, Logrip, Schlosburg, McGinn, Zamora-Martinez, Belanoff, Hunt, Sanna, George, Koob, Edwards, Mason. J Clin Invest, 2015, 125:3193-3197.

Summary of Mifepristone Results

- Mifepristone, relative to placebo, was associated with significantly less
  - Alcohol-induced craving in the lab
  - Alcohol consumption during 1-week of treatment and 1-week post treatment
- Mifepristone was well-tolerated
  - 52% reported no adverse events (AE's)
  - All AE's were of ≤ moderate severity
  - No serious or unexpected AE's
  - No discontinuation due to AE's
  - No evidence of abuse potential
  - Compliance by return pill count was high (mifepristone=100%, placebo=99%).

Discussion

- Reductions in craving, drinking and LFT's relative to placebo suggest mifepristone has therapeutic potential for alcohol dependence.

- Mifepristone was well-tolerated, with no concerns re: safety, abuse potential, non-compliance or rebound following drug discontinuation.

- Positive outcomes for mifepristone
  - provide clinical validation of preclinical studies showing glucocorticoid antagonism reduces reinstatement of ethanol seeking and intake
  - lend support to the role of drugs that target abstinence-related dysregulation in brain stress systems for the treatment of alcohol dependence.

1-week of treatment with mifepristone to re-set the HPA-axis in protracted withdrawal, in conjunction with a course of psychosocial treatment, may offer a novel treatment paradigm that optimizes healthcare resources.

Tool Kit of Web-based Treatment Resources for Alcohol Use Disorder

Behavioral Therapies Used in Pharmacotherapy Trials

AlcoholFree.today
http://alcoholfree.today
• Patient and therapist materials from the U.S. multi-site acamprosate study

COMBINE Monograph Series
Volume 2: Medical Management Treatment Manual
https://pubs.niaaa.nih.gov/publications/combine/Combine%202.pdf
• Treatment issues specific to pharmacotherapy trials in AUD

Project MATCH Monograph Series
https://pubs.niaaa.nih.gov/publications/projectmatch/matchintro.htm
• Motivational Enhancement Therapy (MET)
• Cognitive-Behavioral Coping Skills Therapy (CBT)

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Diagnosis and Treatment Information

Assessing Alcohol Problems: A Guide for Clinicians and Researchers
https://pubs.niaaa.gov/publications/AssessingAlcohol/index.htm

NIAAA Navigator
https://alcoholtreatment.niaaa.nih.gov
• To identify local evidence-based AUD treatment options

The Surgeon General's Report on Alcohol, Drugs and Health
https://addiction.surgeongeneral.gov/surgeon-generals-report.pdf

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Pharmacotherapy Guidance

The A.A. Member – Medications & Other Drugs
https://www.aa.org/assets/en_US/p-11_aamembersMedDrug.pdf
• Developed by physician members of A.A. to guide prescription use in AUD

American Psychiatric Association Practice Guidelines for the Pharmacological Treatment of Patients with Alcohol Use Disorder
https://psychiatryonline.org/doi/book/10.1176/appi.books.9781615371969

Incorporating Alcohol Pharmacotherapies Into Medical Practice
https://store.samhsa.gov/shin/content//SMA13-4380/SMA13-4380.pdf

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Mifepristone and matched placebo was provided by Corcept Theraputics

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