

Transforming Treatment Options for Alcohol Use Disorder

August 23rd, 2023

Barbara J. Mason, Ph.D.

Pearson Family Professor

Director, NIAAA P60 Alcohol Research Center-of-Excellence (TSRI-ARC)

Director, Pearson Center for Alcohol and Addiction Research

Department of Molecular Medicine



Scripps Research



Barbara J. Mason, PhD

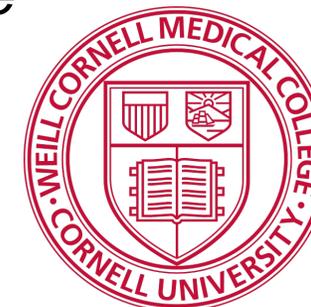
Professor and Pearson Family Chair, Department of Molecular Medicine

Long Island University PhD, Clinical Psychology

Weill Cornell University Medical College

Dissertation, post-doc in Psychopharmacology, Assistant Professor

Mason et al. A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. JAMA. 1996; 275(10):761-7. PMID: 8598592



University of Miami School of Medicine, Professor with tenure

Seminal work showing nalmefene (Selincro), a mu/delta/kappa opioid receptor antagonist, has therapeutic potential for alcohol dependence.

Mason et al. A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. Arch Gen Psychiatry. 1999; 56(8):719-24. PMID: 10435606

UNIVERSITY OF MIAMI
MILLER SCHOOL
of **MEDICINE**



Overall Principal Investigator for the 21-center pivotal trial conducted in support of FDA approval of acamprosate (Campral) for the treatment of alcohol dependence (2004).



Recruited to Scripps Research, La Jolla, CA

Recruited by **Floyd Bloom, M.D.**, Chair of the Department of Neuropharmacology, with assistance from **Ernie Beutler, M.D.**, Chair of the Department of Molecular and Experimental Medicine.

Dr. Bloom's goal was to make Neuropharmacology a fully translational department aimed at medication development for substance use disorder.

My goal is to influence the practice of medicine by developing novel medications to improve treatment of alcohol use disorder (**AUD**) in collaboration with the outstanding basic scientists working in the addiction space at Scripps Research.



Floyd Bloom



Ernest Beutler

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for ALCOHOL & ADDICTION RESEARCH



Mark Pearson

Founding donor: **Mark Pearson**

“My gift is in memory of my family members and friends whom I have lost to alcoholism and addiction, and on behalf of other family members and friends who have suffered indirectly from the devastating consequences of this disease.

It is my hope that by generating greater public awareness and additional financial support for biomedical and clinical research, future generations of families will be spared from the devastating effects of alcoholism and addiction.”

www.pearsoncenter.org



What is Alcohol Use Disorder (AUD)?

AUD is characterized by an **impaired ability to stop or control** alcohol use despite adverse social, occupational or health consequences.

Considered a **brain disorder** and is **on a spectrum of severity**: mild, moderate or severe.

Lasting changes in the brain caused by **untreated AUD** can make individuals **vulnerable to relapse**.

Understanding the **neurobiology of AUD** can guide the development of **novel, safe and effective treatments**.

Prevalence and Impact of Alcohol Misuse

29.5 million Americans met criteria for past year Alcohol Use Disorder (AUD) (*SAMHSA, 2020*)

Costs the U.S. economy \$250 billion annually (*HHS, 2016*)

- Lost productivity, medical care, law enforcement

140,557 alcohol-related deaths per year (**2015-2019**) (*CDC, 2022*)

- Liver or cardiac disease, car crashes, suicide

< **10%** of Americans with AUD get any treatment for AUD (*NSDUH, 2019*)

< **3%** of Americans with AUD are prescribed an FDA-approved medication to treat AUD: disulfiram, naltrexone, acamprosate (*Han et al., 2021*)

FDA-approved Drugs for AUD

Disulfiram

(Antabuse) 125-500mg/day orally, FDA-approved 1951

- Inhibits the metabolism of alcohol; acetaldehyde quickly builds up
- Rapid onset of flushing, nausea and palpitations
- Acts as a psychological deterrent

Naltrexone

(Generic) 50mg/day orally, FDA-approved 1994

(Vivitrol) 380mg/month extended-release injectable, FDA-approved 2006

- A pure μ -opioid receptor antagonist
- Decreases rewarding effects of alcohol

Acamprosate

(Campral) 1998mg/day orally, FDA-approved 2004

- Restores homeostasis in NMDA-mediated glutamatergic neurotransmission
- Reduces craving associated with protracted withdrawal and promotes abstinence

Neurobiological Framework for AUD



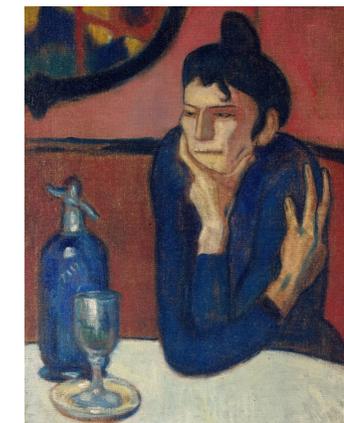
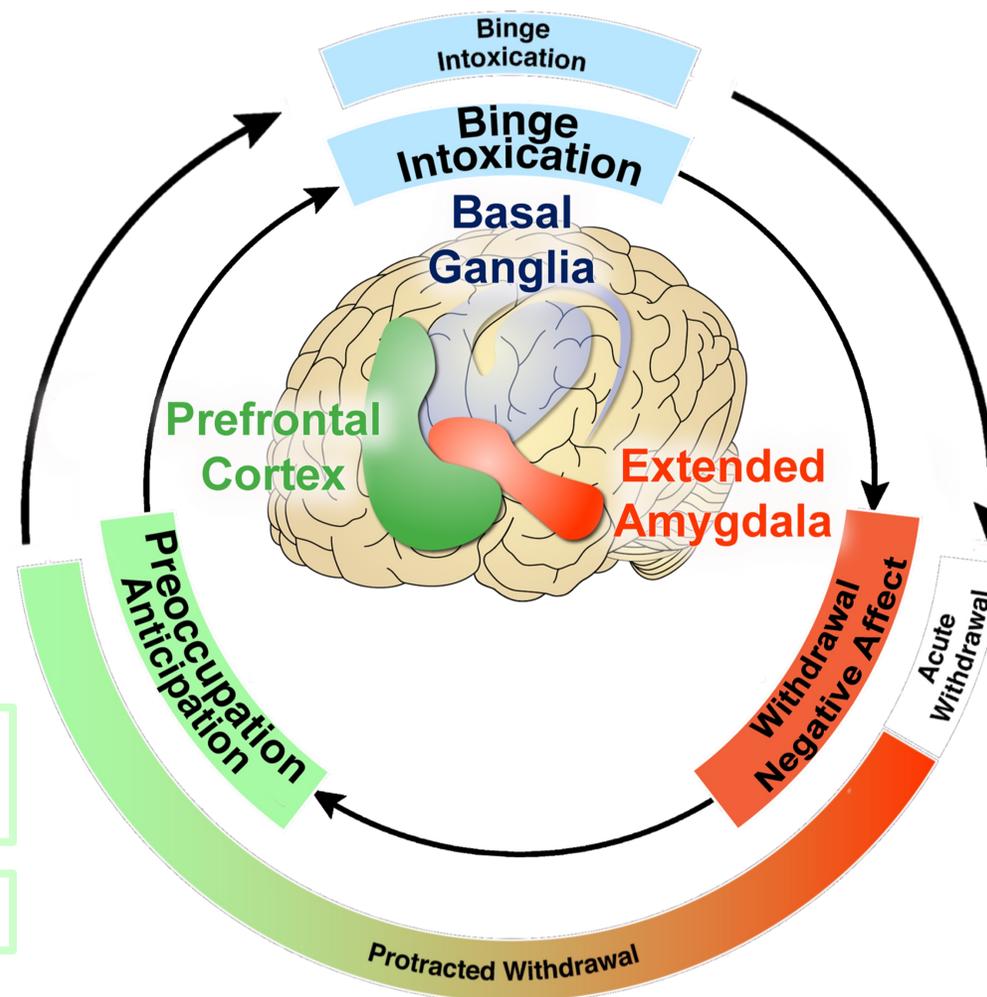
George Koob

Binge Intoxication

**Disulfiram
Naltrexone**

**Preoccupation
Anticipation**

Acamprosate



**Withdrawal
Negative Affect**

Brain Stress Systems

- Corticotropin Releasing Factor
- Dynorphin/KOR
- Glucocorticoid
- Hypocretin/orexin

Neuroinflammation



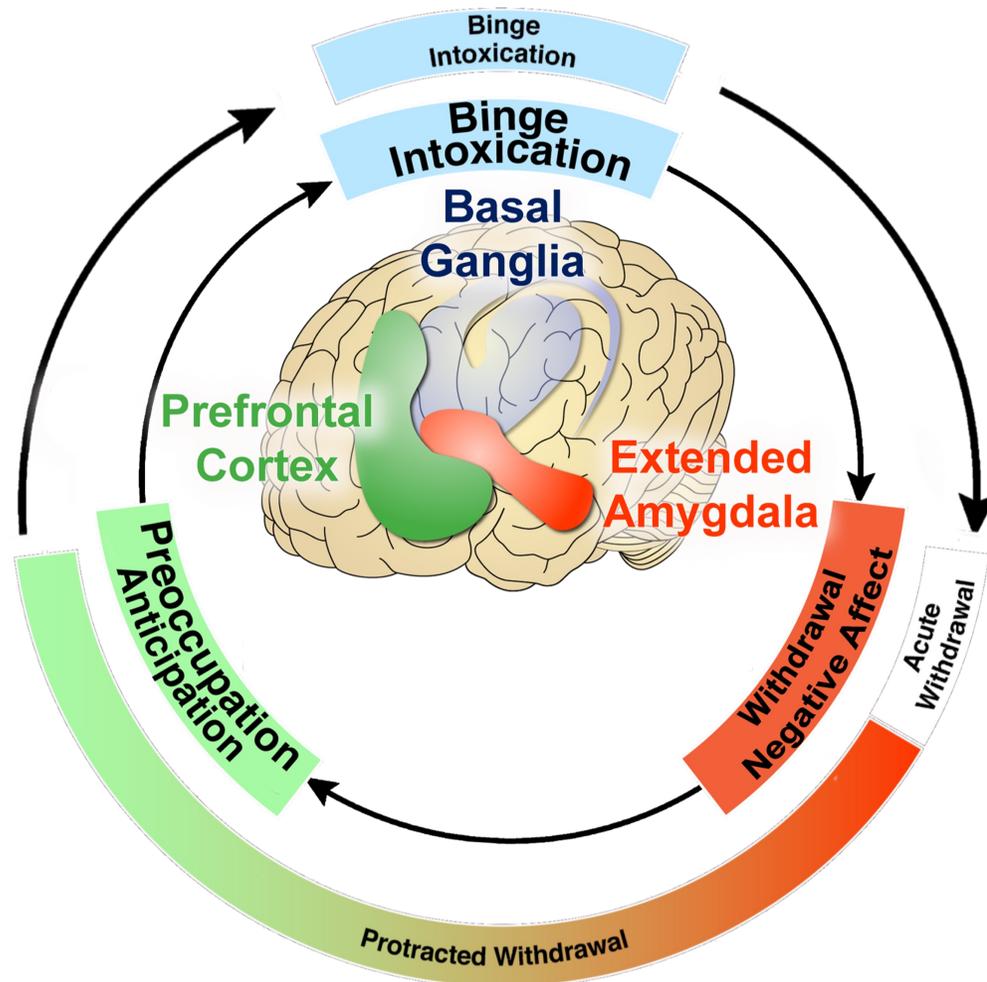
TSRI-ARC/Mason Lab: Promising Medications to Treat Alcohol Use Disorder

	Mechanism of action <i>for AUD</i>
Gabapentin	GABAergic modulator
Mifepristone	Glucocorticoid receptor antagonist
Apremilast	Anti-inflammatory
Suvorexant	Dual hypocretin/orexin antagonist
CORT118335	Glucocorticoid/mineralocorticoid receptor antagonist
MAP4343	Microtubule stabilizer

The challenge: Unlike most substances of abuse, there is no alcohol receptor in the brain! AUD drugs do not have a common mechanism of action, which underscores the complicated nature of AUD.

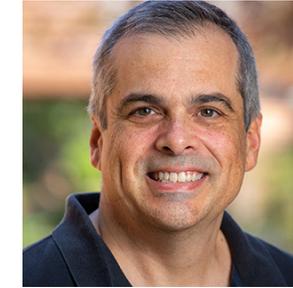


Potential Drug Targets



Withdrawal Negative Affect

- Brain Stress Systems**
- Corticotropin Releasing Factor
 - Dynorphin/KOR
 - Glucocorticoid
 - Hypocretin/orexin
 - Neurosteroids
 - Neuroinflammation**



Eric Zorrilla & Luísa Bertotto



Rémi Martin-Fardon & Francisco Flores Ramirez



Candice Contet Olivier George

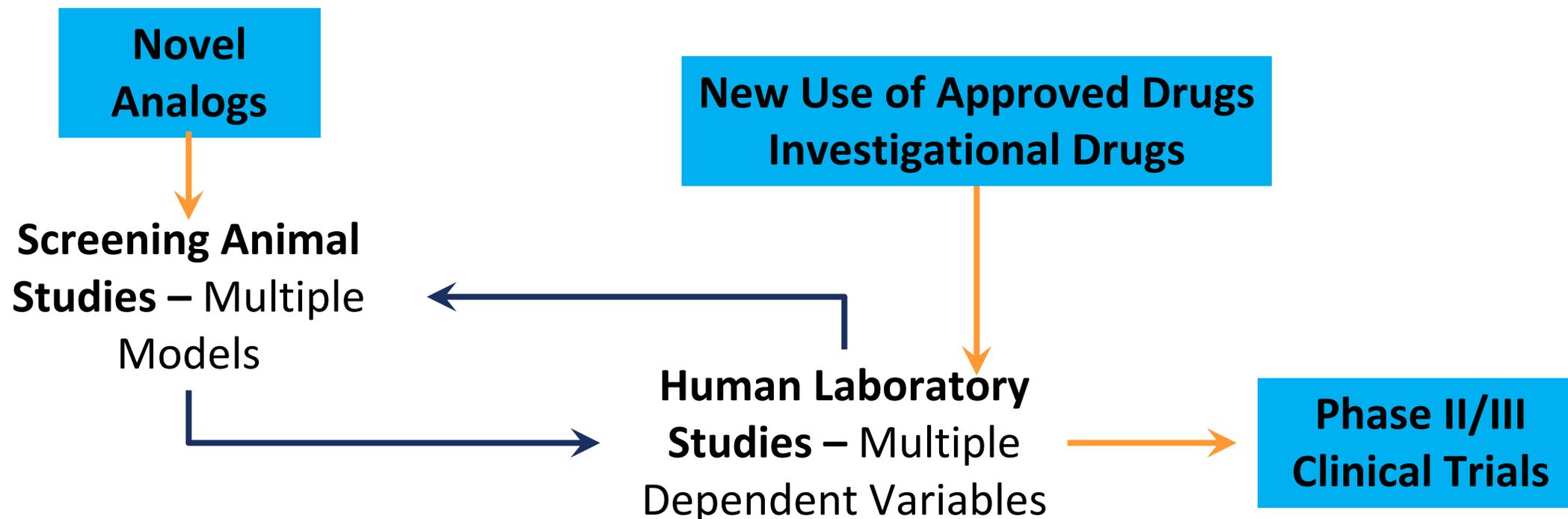
Goals of TSRI-ARC/Mason Lab

Overall goal of TSRI-ARC: To identify neurobiological mechanisms mediating AUD by bringing a multi-disciplinary focus to the less well-understood persisting **heightened neurobiological stress** response and **impaired cortical control** that drive relapse in early recovery.

Overall goal of the Mason Lab: To **translate** TSRI-ARC's basic research findings to the identification and **clinical evaluation** of medications that target the stress response and the associated symptoms of anxiety, dysphoria, insomnia and craving that heighten relapse risk in early recovery.



Our Translational Approach for Medication Development to Reduce Relapse Risk





Our Clinical Strategy for Medication Development to Reduce Relapse Risk

We test the most promising small molecules directed at neurobiological targets for protracted withdrawal using:

- **Phase 2a** a proof-of-concept human laboratory model of protracted withdrawal in non treatment-seekers with AUD
- **Phase 2b** randomized, placebo-controlled clinical trial in treatment seekers with AUD who also receive evidence-based counseling

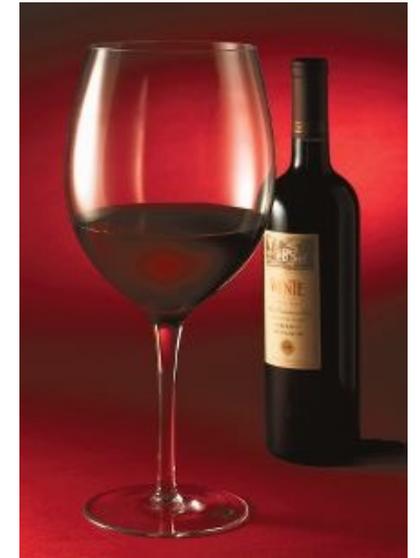
Human Lab Model of Risk Factors for Relapse in Protracted Withdrawal

Subjects: Non treatment-seeking male and female volunteers with AUD, abstinent 3 days prior to testing on the last day of dosing

Design: Double-blind, placebo-controlled, random assignment, dosing duration based on pharmacokinetics (1-2 weeks)

Procedure:

- Affective priming of emotions associated with relapse.
- The individual's preferred alcoholic beverage is presented
- The individual views and smells the beverage for 90 seconds and does not drink it
- Primary outcome: Visual Analogue Scale (VAS) measures of craving.



Selecting Potential Medications to Treat AUD

Small molecules that cross the blood-brain barrier

No abuse potential

No alcohol x drug interactions, e.g., impaired alertness or motor coordination

Good safety profile, e.g., no hepatotoxicity

Good tolerability, e.g., adverse events are mild-moderate and not associated with treatment discontinuation

Good patient acceptability, e.g., route of administration and dosing regimen

FDA has granted an IND or a waiver of an IND



Gabapentin (Neurontin)



Rationale for Gabapentin as a Treatment for Alcohol Use Disorder

FDA-approved for epilepsy and pain, taken orally

Used off-label to treat symptoms associated with protracted withdrawal 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

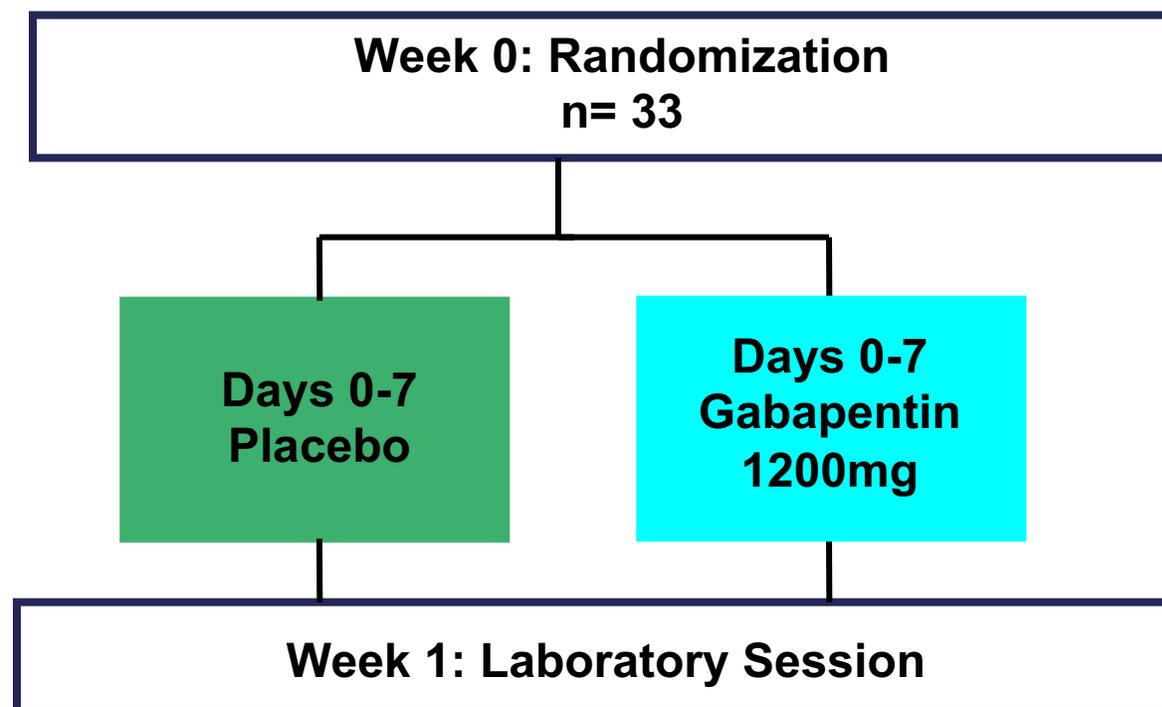
- Not metabolized in the liver

Modulates GABAergic activity to restore homeostasis in brain stress systems; showed efficacy in animal models of excessive drinking during withdrawal (*Roberto et al., 2008*)

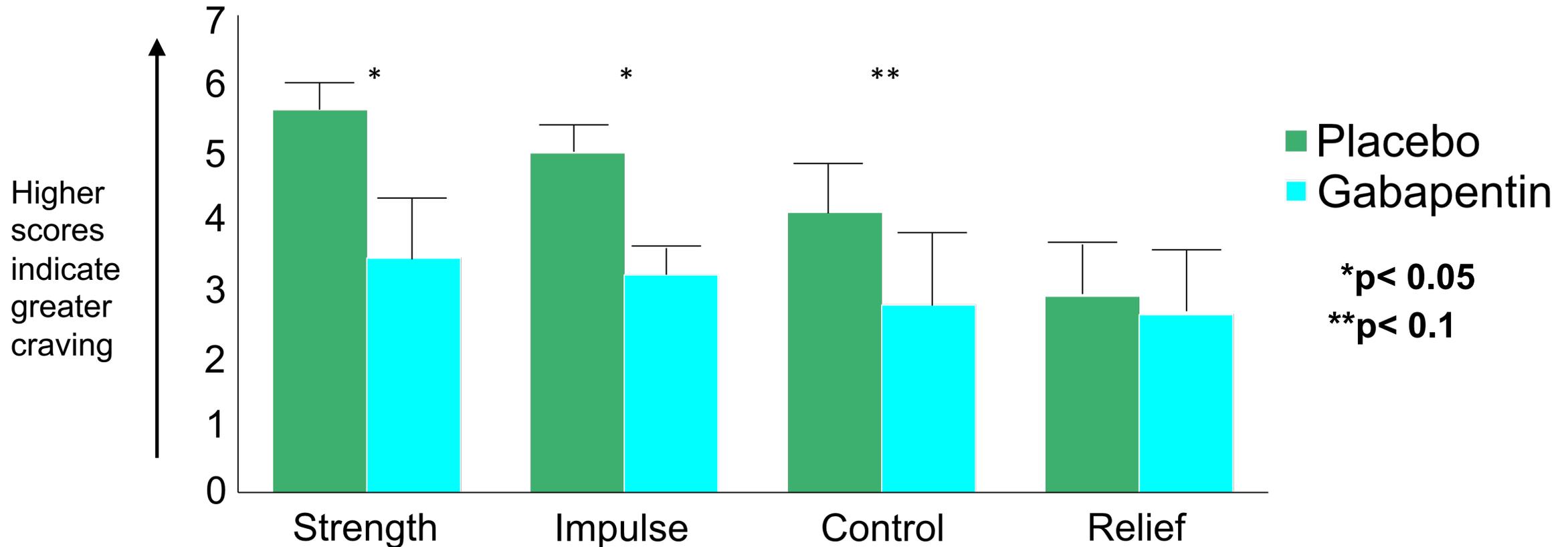


*Marisa Roberto
Front Row 8/22*

Phase 2a Human Laboratory Study: Oral Gabapentin 1200mg/d vs Placebo



Oral Gabapentin 1200mg/d Decreased VAS Craving Scores Relative to Placebo

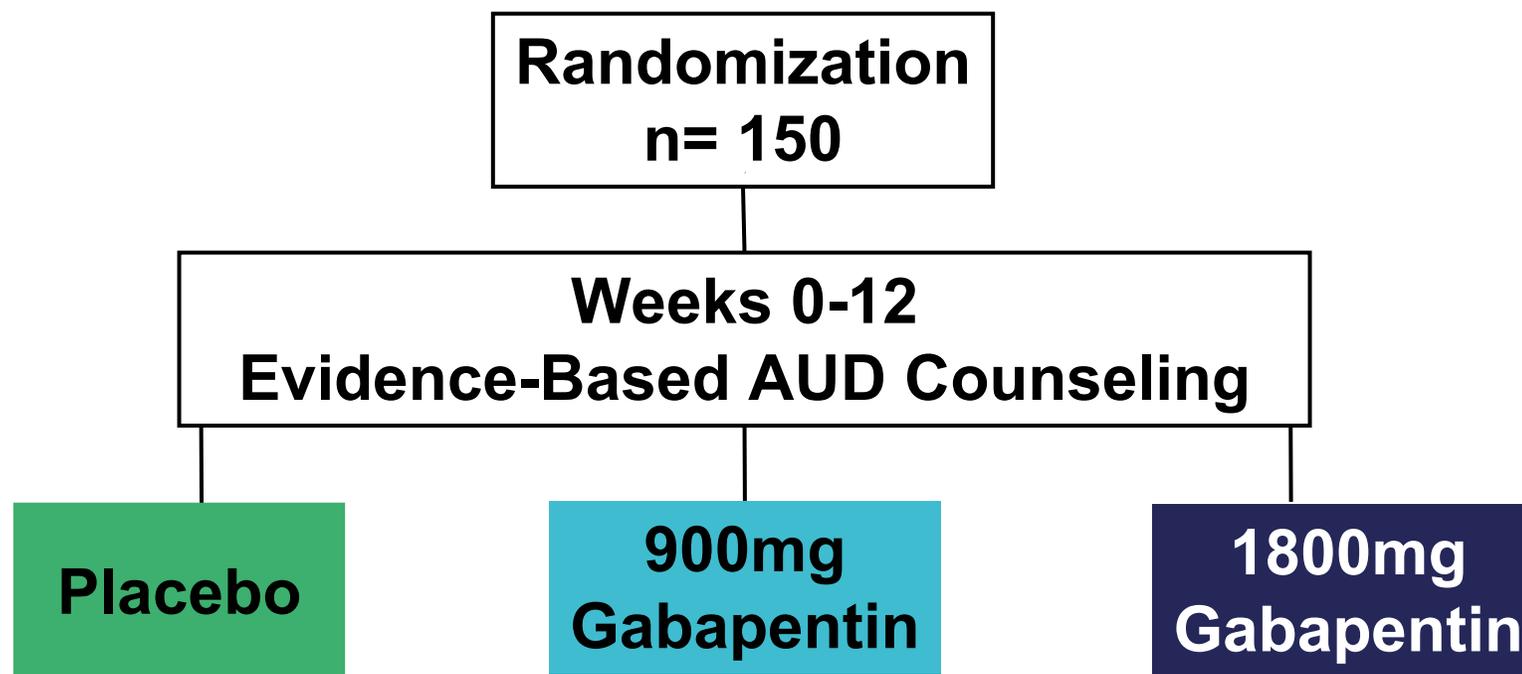


Note: Gabapentin also significantly improved sleep quality, sleep latency and sleep efficiency relative to placebo, with no elevation in next day drowsiness.

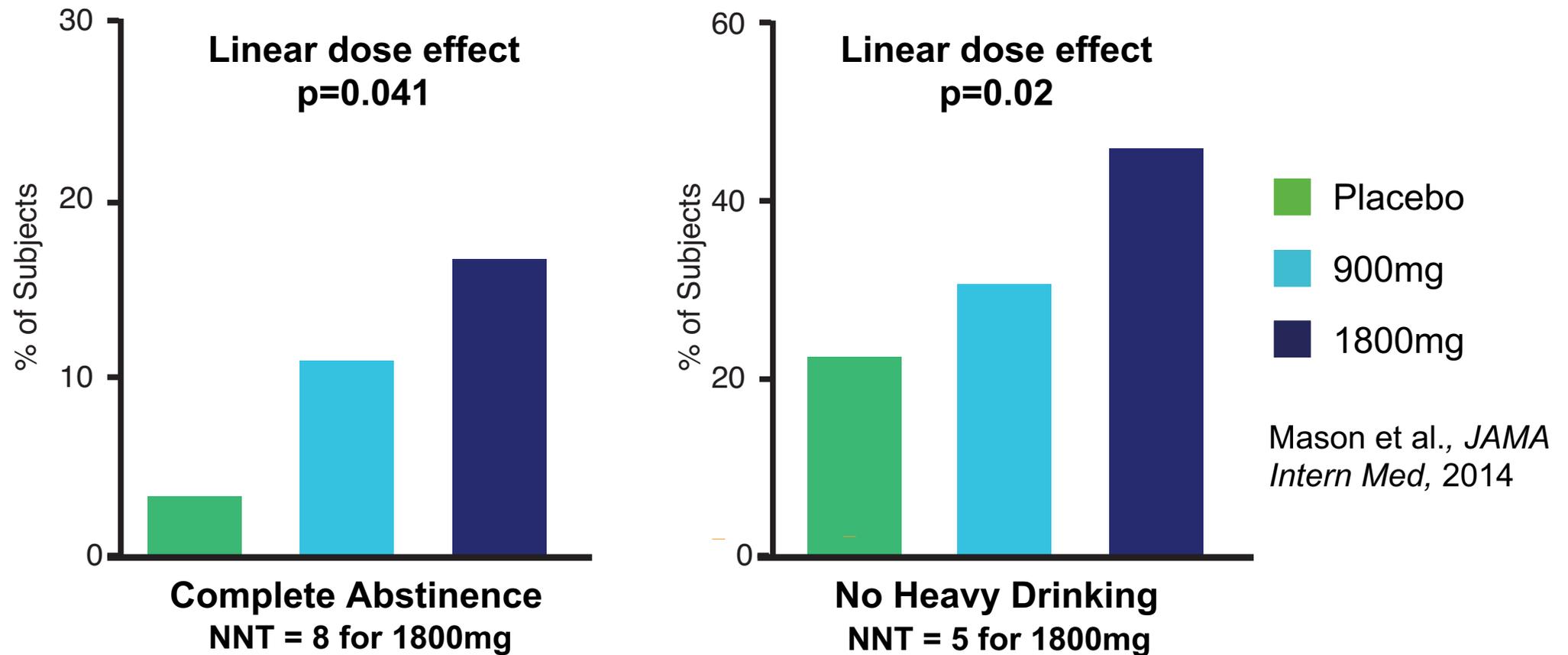
Mason et al.,
Addict Biol, 2008



Phase 2b Double Blind, Placebo Controlled, 12-week Dose-ranging Clinical Trial of Oral Gabapentin in 150 Outpatients with AUD



Gabapentin Increased Rates of Complete Abstinence and No Heavy Drinking Over the 12-week Study (N=150)



Gabapentin also showed significant linear dose-related reductions on measures of mood, sleep and craving.

Clinical Impact

Practice Guideline for the Pharmacological Treatment of Patients with Alcohol Use Disorder (APA, 2017)

Included the recommendation that gabapentin be offered to patients as a treatment for AUD.

Gabapentin is now available as a treatment for AUD in the VAMC formulary and reimbursable as a treatment for AUD under many insurance plans.



Mifepristone (Korlym)



Rationale for Mifepristone as a Treatment for Alcohol Use Disorder

Mifepristone functions as a glucocorticoid receptor antagonist and blocks overactivation of the brain's stress systems.

Administering mifepristone following acute alcohol withdrawal may normalize the brain stress axis, thus protecting against drinking relapse.

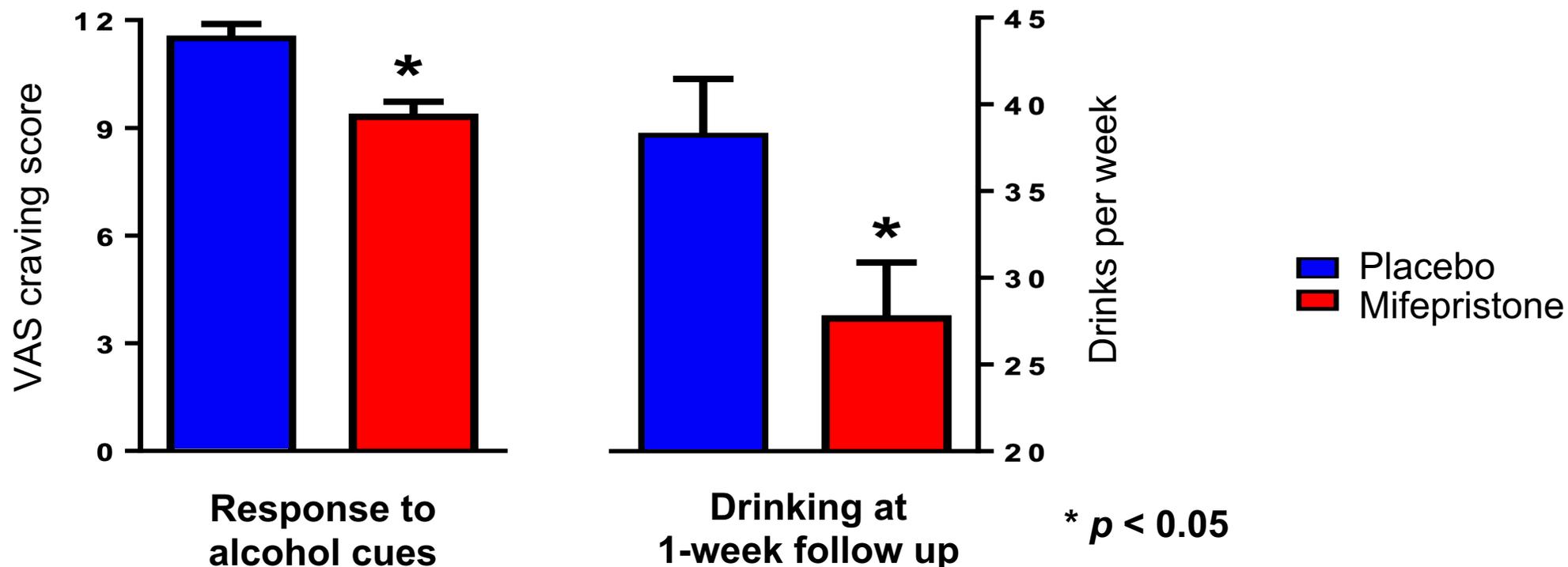


Leandro Vendruscolo



Olivier George

Oral Mifepristone 600mg/day for 1-week Decreased VAS Craving Scores and Subsequent Drinking Relative to Placebo (N = 50)



Phase 2b Double-Blind, Placebo-Controlled Trial of Oral Mifepristone for the Treatment of AUD (N=103)

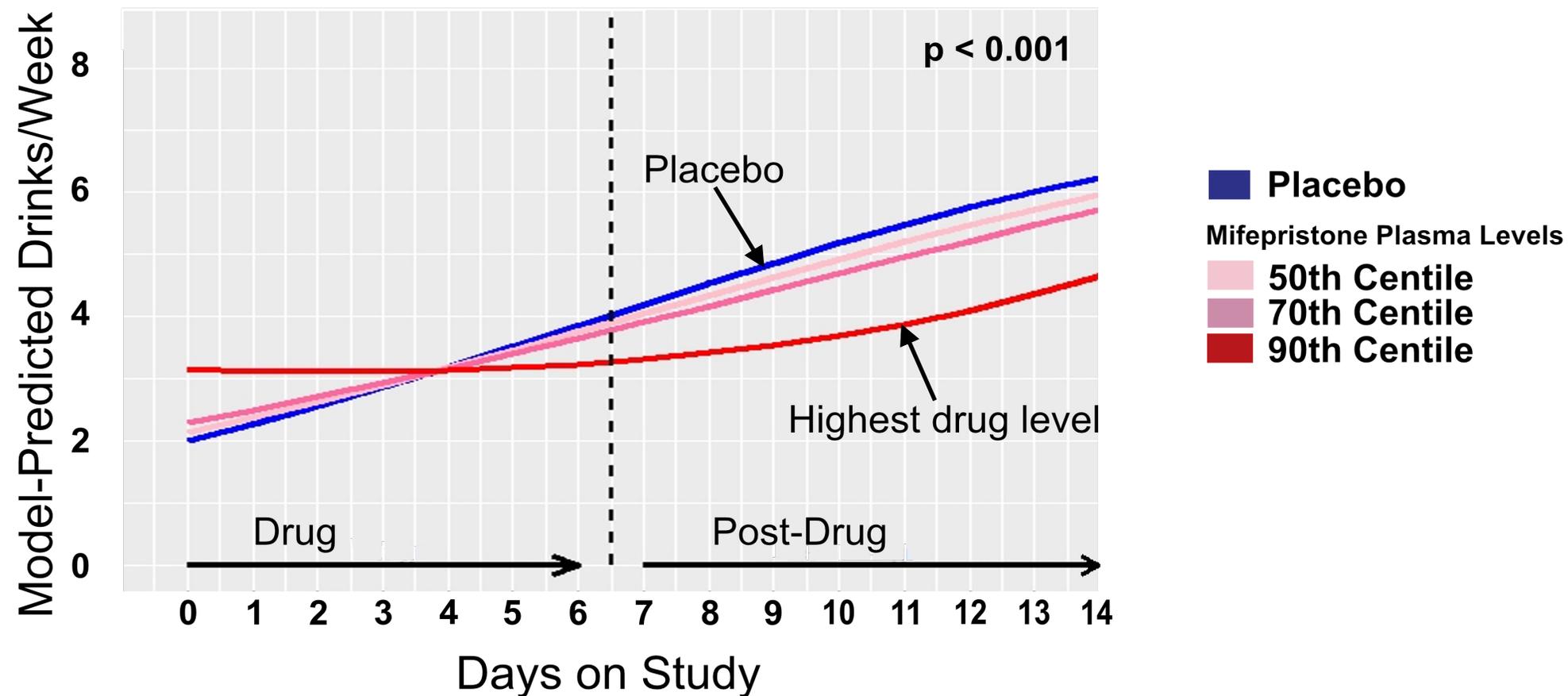
Aim: Extend findings from the human laboratory study to outpatients seeking treatment for AUD and identify predictors of response.

***A priori* predictors:** Plasma mifepristone level, treatment goal of abstinence or non-abstinence, sex.

Potential advantages: Mifepristone has a half-life of ~85 hours and requires ~12-15 days for elimination following chronic dosing.

Hypothesis: 1-week of treatment with mifepristone (up to 1200mg/d) will reduce drinking and symptoms of protracted withdrawal significantly more than placebo, *given in conjunction with 8 weeks of evidence-based AUD counseling.*

Higher Mifepristone Plasma Concentrations Predicted Lower Levels of Drinking (N=50)



Higher mifepristone plasma concentrations also predicted greater reductions in mood and sleep disturbance.



Apremilast (Otezla)

Rationale for Apremilast Treatment of AUD

Apremilast (Otezla) is FDA-approved for psoriasis, 60mg/d, taken orally

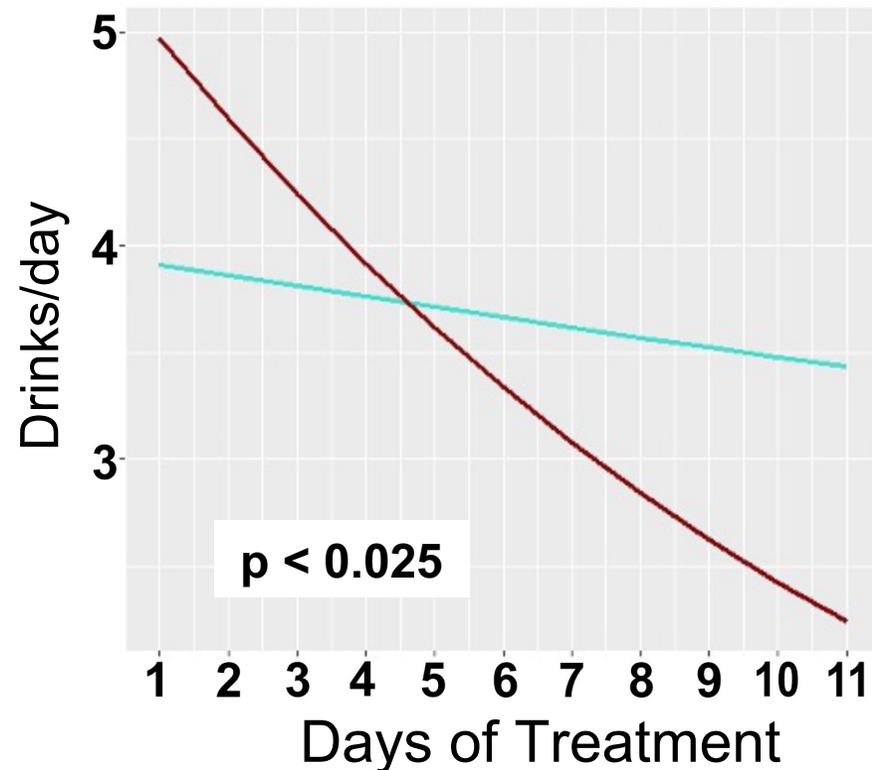
A selective phosphodiesterase type 4 (PDE4) inhibitor that acts on immune system targets (IL-10) to reduce inflammation

Preclinical studies and computational genomic analyses identified PDE4 inhibitors, e.g., rolipram, ibudilast and apremilast, as having therapeutic potential for AUD

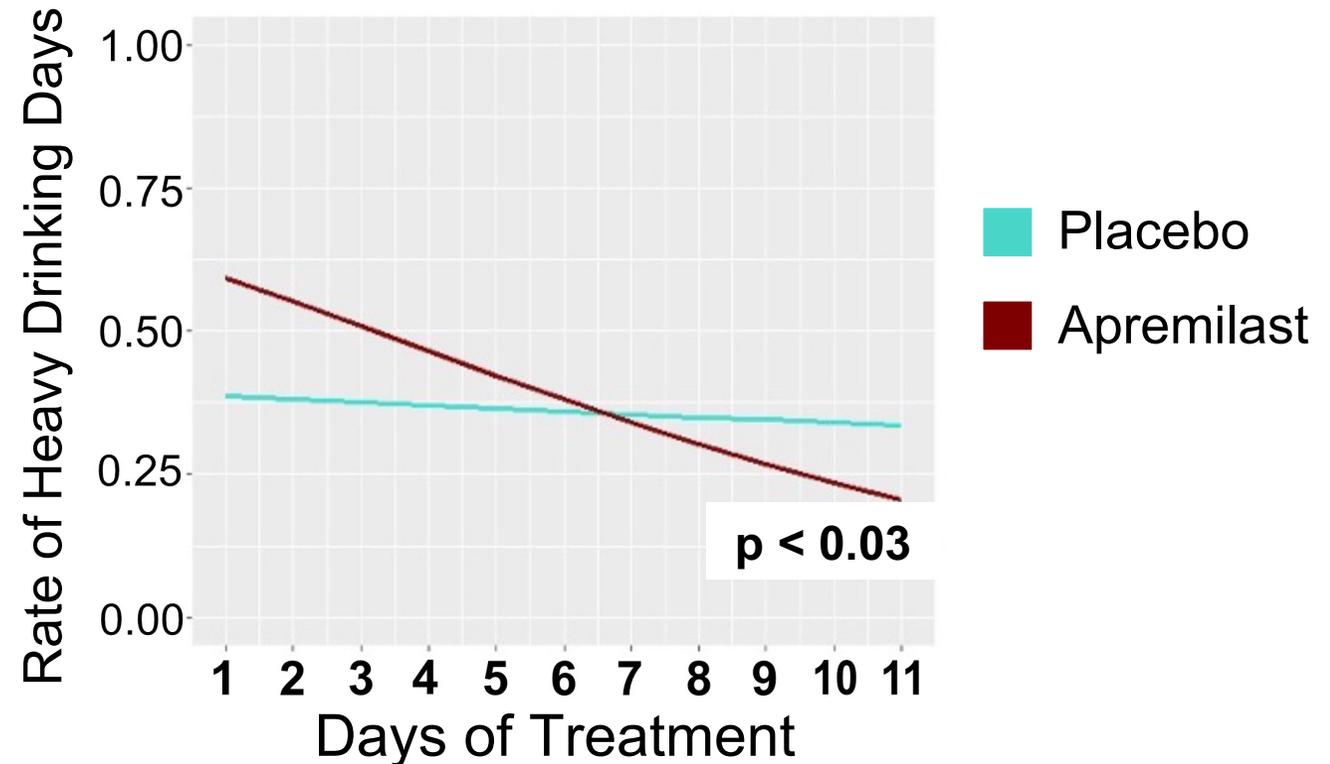
- Apremilast has less severe gastrointestinal side effects than early PDE4 inhibitors such as rolipram and ibudilast and may have better acceptability as a treatment for AUD
- Optimal efficacy for decreased drinking with apremilast was identified in dose-ranging animal models of AUD, which indicated a dose equivalence of 90mg/d for testing in humans with AUD

Oral Apremilast 90mg/d Significantly Reduced Alcohol Consumption Relative to Placebo (N=51)

Number of Drinks Per Day is Significantly Reduced for Apremilast vs. Placebo



Proportion of Heavy Drinking Days is Significantly Reduced for Apremilast vs. Placebo





Summary

Clinical studies of gabapentin, mifepristone and apremilast:

- Reduced drinking relative to placebo
- Reduced negative affect, insomnia and craving
- Were safe and well-tolerated
- Provided clinical validation of preclinical models

Validated the novel conceptual approach of TSRI-ARC

Drug targets from the protracted withdrawal phase that return the brain's stress systems to homeostasis are an exciting and innovative approach to developing medications to treat AUD.

Our Phase 2b clinical trial results support the predictive validity of the human laboratory model as a screen for drugs to reduce relapse in protracted withdrawal.



Transforming Treatment Options for Alcohol Use Disorder

	IND granted	Phase 2a proof-of-concept	Phase 2b efficacy	Phase 3 Multi-center	On formulary for AUD
Acamprosate	√	√	√	√	FDA √ *
Nalmefene	√	√	√		EMA √
→ Gabapentin	waiver	√	√		VAMC √
→ Mifepristone	√	√	√		
→ Apremilast	√	√			
Suvorexant	waiver	√			
CORT118335	√	√			
MAP4343	√				

*Web Annex A. World Health Organization Model List of Essential Medicines – 23rd List, 2023.

Acknowledgements



THE FRONT ROW
at Scripps Research

Appreciation is expressed to the **Scripps Research Institutional Review Board**.
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and the **Pearson Center for Alcohol and Addiction Research**.



Pearson Center
for ALCOHOL & ADDICTION RESEARCH



The Scripps Research Institute
Alcohol Research Center



Adnan Begovic **John Light** **Farhad Shadan**
Alan Beneze **Jenny Miller** **Michael Skinner**
Jessica Bess **Susan Quello**

Michal Bajo **Jolene Diedrich** **Marisa Roberto**
Luísa Bertotto **Jeff Dunning** **Amanda Roberts**
Lieselot Carrette **Rémi Martin-Fardon** **John Yates**
Candice Contet **Francisco Flores-Ramirez** **Eric Zorrilla**
Olivier George



Thank you very much!



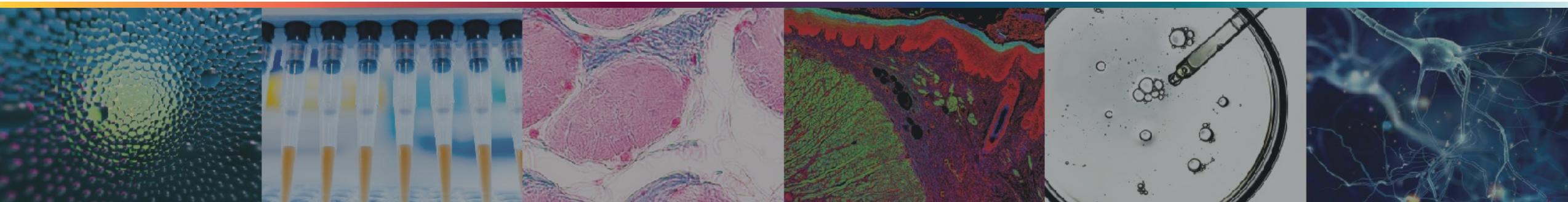
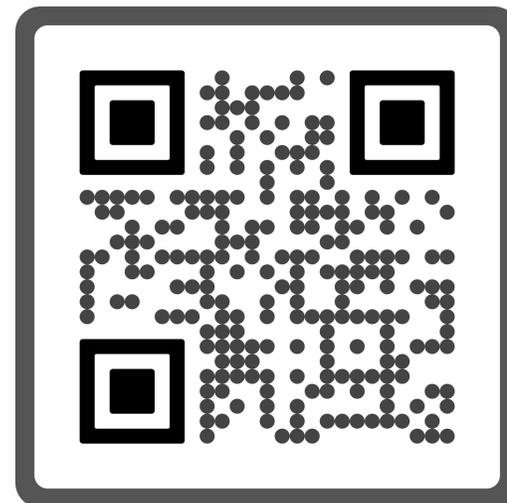
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Facilitating AUD Treatment

The U.S. Preventative Services Task Force

- Recommends AUD Screening, Brief Intervention and Referral to Treatment for all adults aged 18 years and older

The Surgeon General's Report on Alcohol, Drugs and Health (2016)

- Recommends a chronic care management approach to AUD
 - Provide evidence-based behavioral & pharmacological treatments
 - Monitor efficacy, side effects, compliance, relapse at every visit

Subspecialty Certifications in Addiction Medicine & Psychiatry

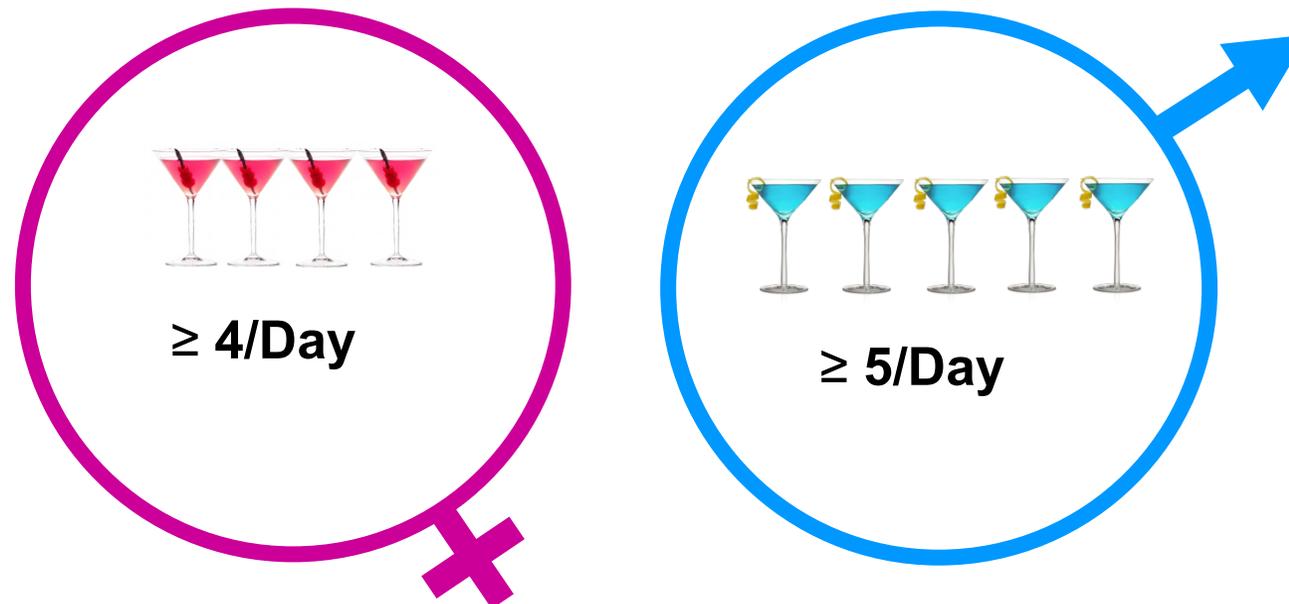
- Have greatly expanded the number of physicians with expertise in treating addiction
- 10,000+ physicians have become certified in one or both of these subspecialties

FDA Guidance for AUD Drug Approval

TWO POSITIVE MULTI-CENTER 6-MONTH TRIALS

RESEARCH DESIGN: Randomized, double-blind, placebo-controlled; drug treatment *given in conjunction with evidence-based behavioral counseling*

OUTCOME MEASURES: Rates of no drinking or no heavy drinking



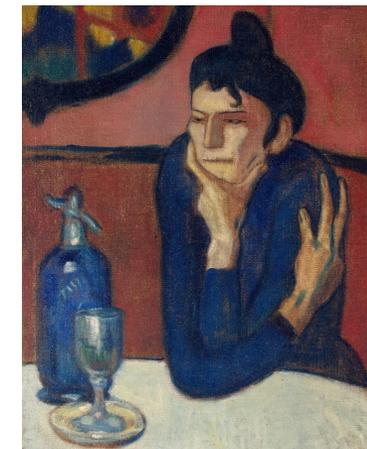
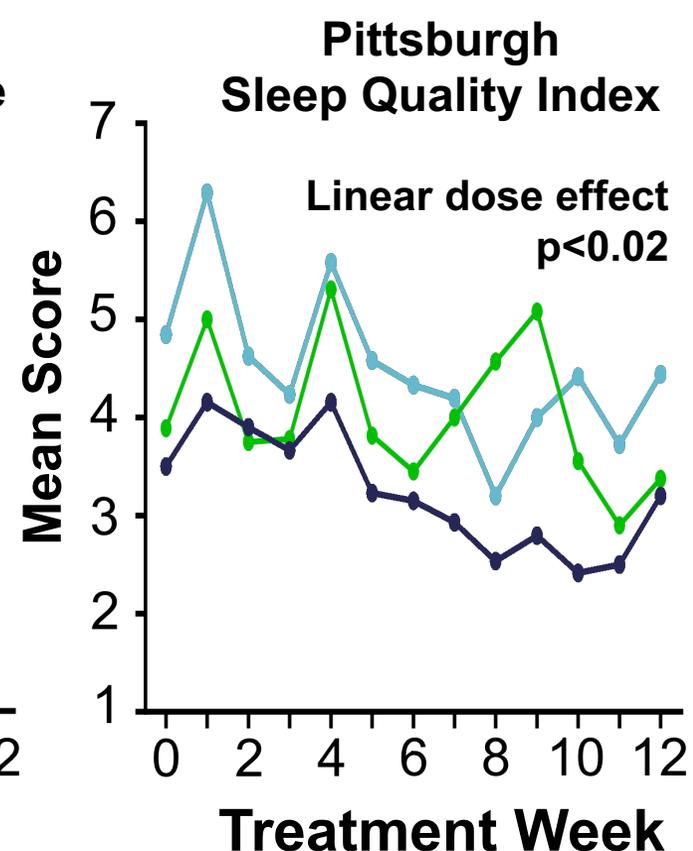
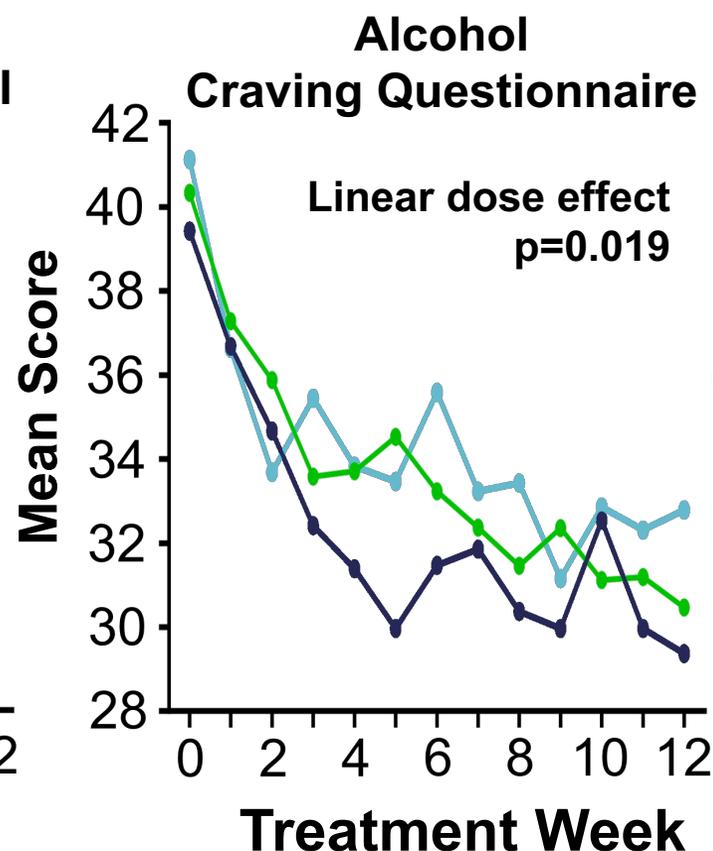
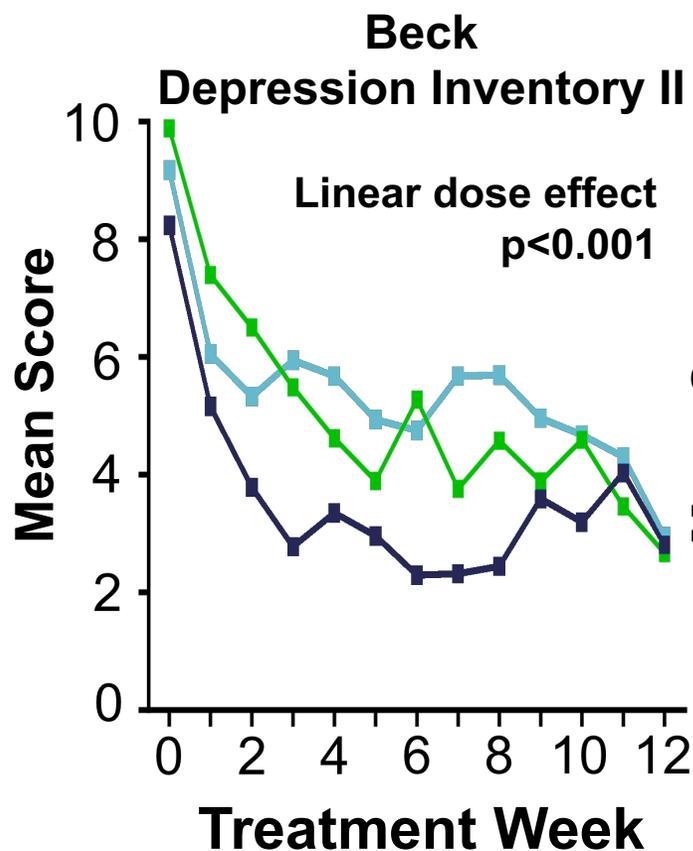
Our Overall Strategy for Medication Development to Reduce Relapse Risk in Protracted Withdrawal

Our aim

Restore neurocircuitry changes in the pathophysiology of AUD 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.



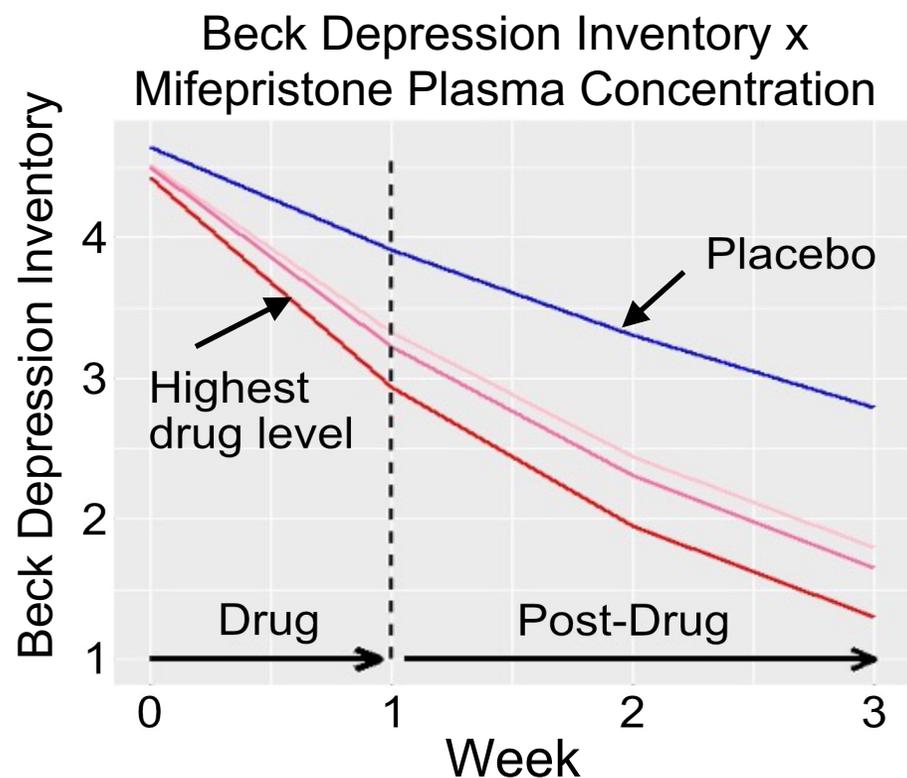
Gabapentin Decreased Symptoms of Protracted Withdrawal (N=150)



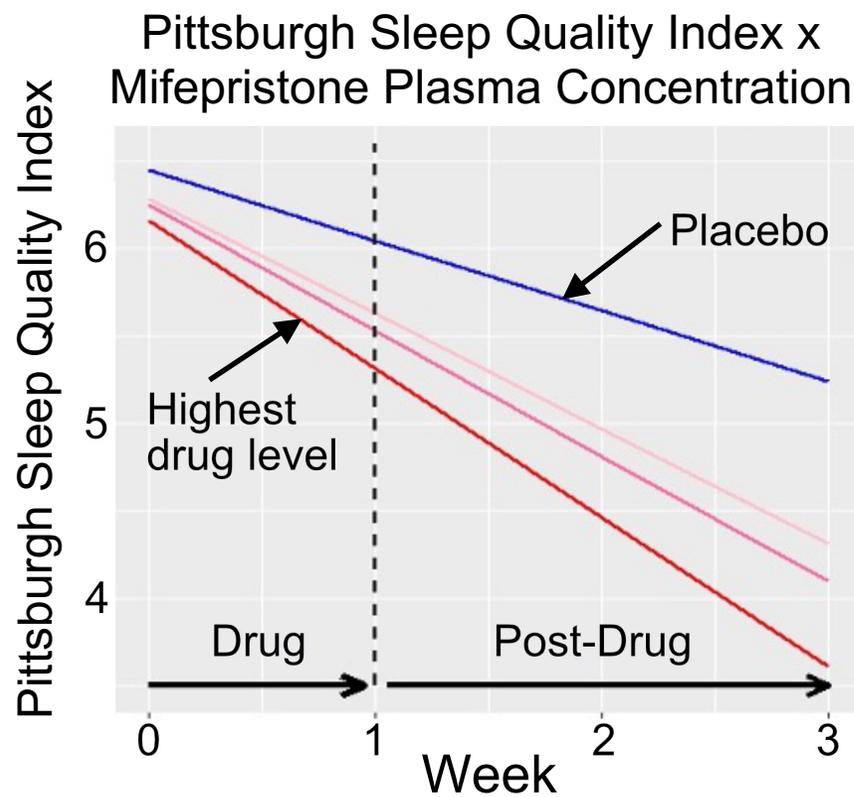
- Placebo
- 900mg
- 1800mg

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

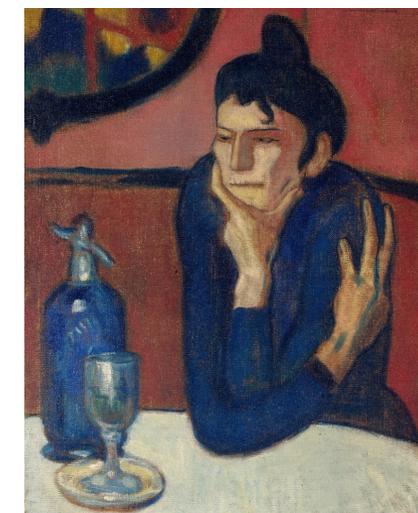
Higher Mifepristone Plasma Concentration Significantly Decreased Mood and Sleep Symptoms



Non-abstinent Treatment Goal



All subjects



- Placebo** (Blue line)
- Mifepristone Plasma Levels**
 - 50th Centile (Light Pink line)
 - 70th Centile (Medium Pink line)
 - 90th Centile (Red line)