New Vistas for Medications to Treat Alcohol Use Disorder

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Conflicts of Interest

Altimmune: Consultant

Imibrium: Consultant

Awakn: Consultant

Prevalence and Impact of Alcohol Misuse

29.5 million (10%) Americans met criteria for past-year Alcohol Use Disorder (AUD; *NSDUH, 2022*)

178,000 alcohol-related deaths per year (*CDC, 2020 -2021*)

- **Liver disease, car crashes, suicide**

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

< 2% of Americans with AUD are prescribed an FDA-approved medication to treat AUD: disulfiram, naltrexone, acamprosate (*Han et al. 2021)*

Development of a broader range of drugs to treat AUD is a public health priority (*Surgeon General's Report on Alcohol, Drugs and Health 2016*).

Widely Approved Drugs for AUD

Disulfiram (Antabuse) 125-500mg/day, taken orally

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

Naltrexone (ReVia) 50mg/day, taken orally; (Vivitrol) intramuscular injection, taken monthly

- A mu opioid receptor antagonist
- Decreases rewarding effects of alcohol

Nalmefene (Selincro) 20 mg, taken orally, 2 h prior to an anticipated drinking occasion

- A mu, delta and kappa opioid receptor antagonist
- Decreases rewarding effects of alcohol and the discomfort of abstinence

Acamprosate (Campral) 1998mg/day, taken orally

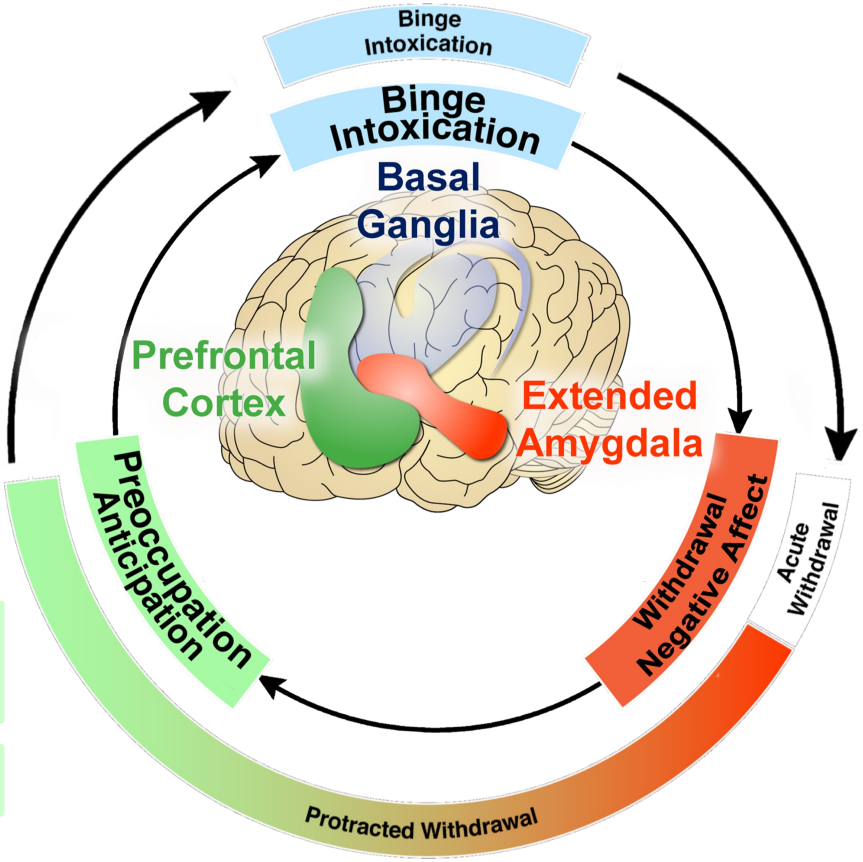
- Restores homeostasis in NMDA-mediated glutamatergic neurotransmission
- Reduces craving associated with protracted withdrawal and promotes abstinence

Neurobiological Framework for AUD

George Koob

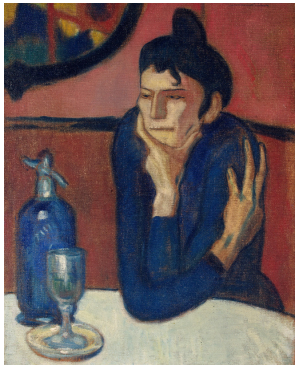
Binge Intoxication

Disulfiram
Naltrexone
Nalmefene



Preoccupation Anticipation

Acamprosate



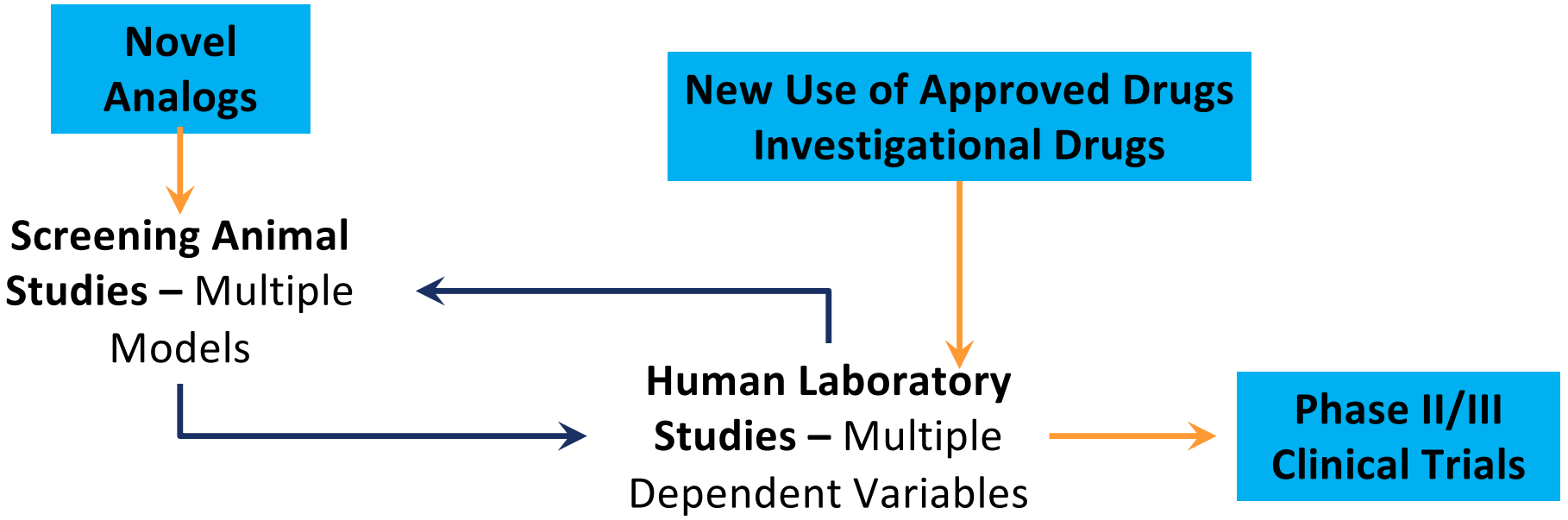
Withdrawal Negative Affect

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

Neuroinflammation

Adapted with permission from: Koob GF, Volkow ND. *Neuropsychopharmacol Rev*, 2010

Our Translational Approach for Medication Development to Reduce Relapse Risk



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

Grant number R01 AA012602; 1999 – 2019

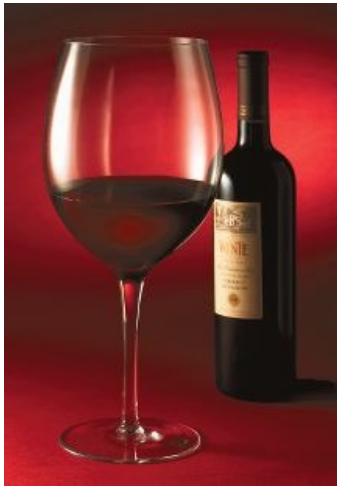
Human Lab Model of Risk Factors for Relapse in Protracted Withdrawal

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.



Gabapentin (Neurontin)

Rationale for Gabapentin as a Treatment for Alcohol Use Disorder

FDA-approved for epilepsy and pain, taken orally

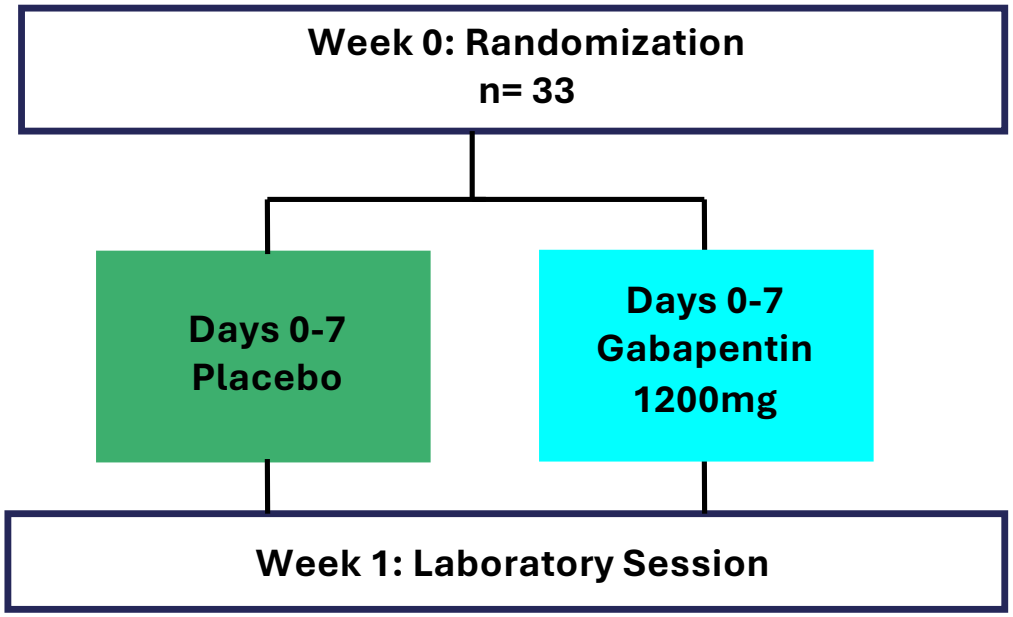
Used off-label to treat symptoms associated with protracted withdrawal and risk of relapse

- Depression
- Anxiety
- Insomnia: Decreased stage 1 sleep and arousals; increased slow wave sleep and sleep efficiency (*Bazil et al., 2005*)

Acceptable safety and tolerability

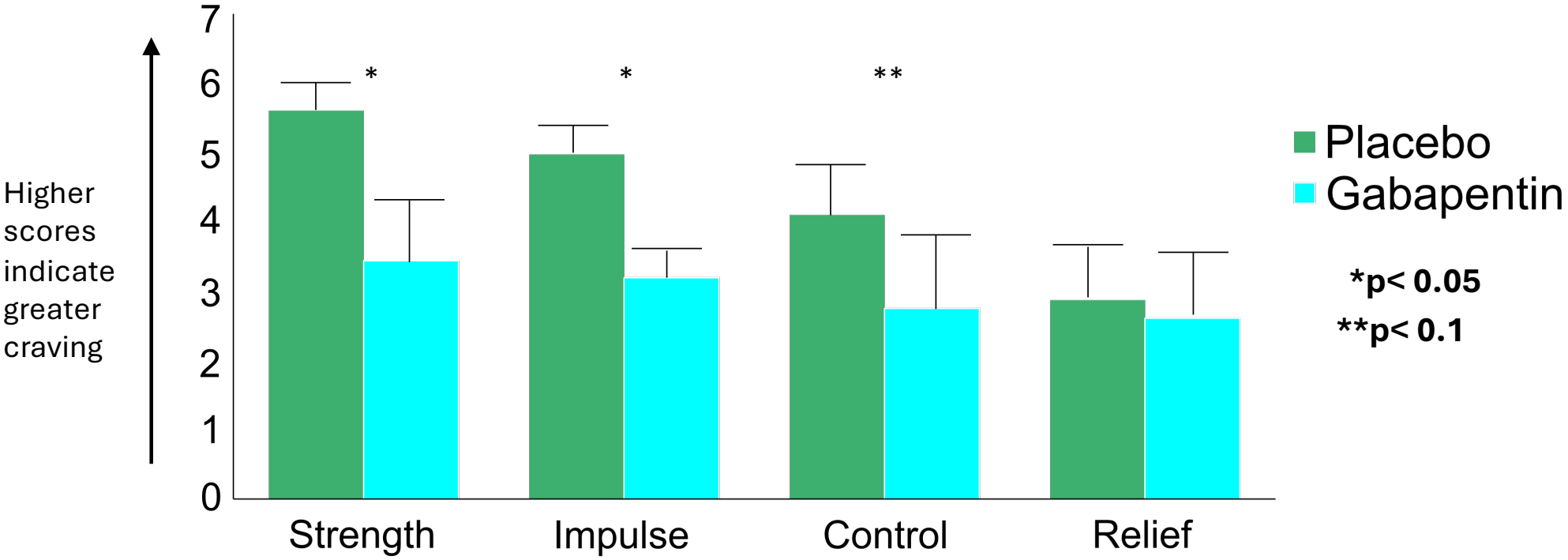
- Not metabolized in the liver

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



Mason et al., *Addict Biol,* 2008

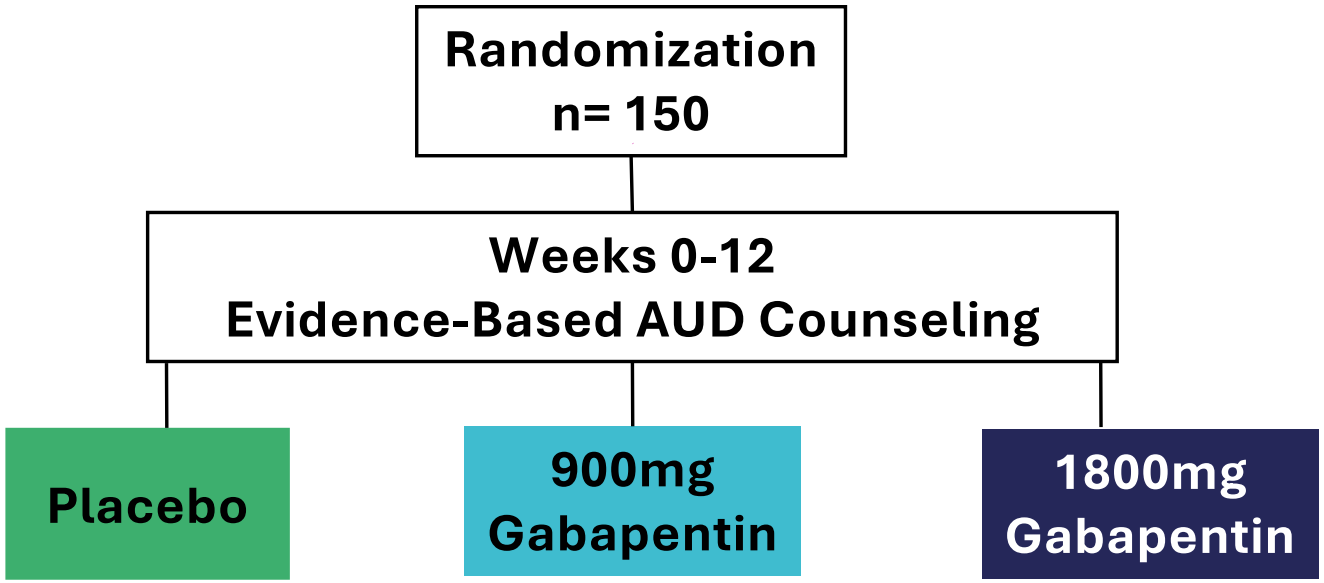
Oral Gabapentin 1200mg/d Decreased VAS Craving Scores Relative to Placebo



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

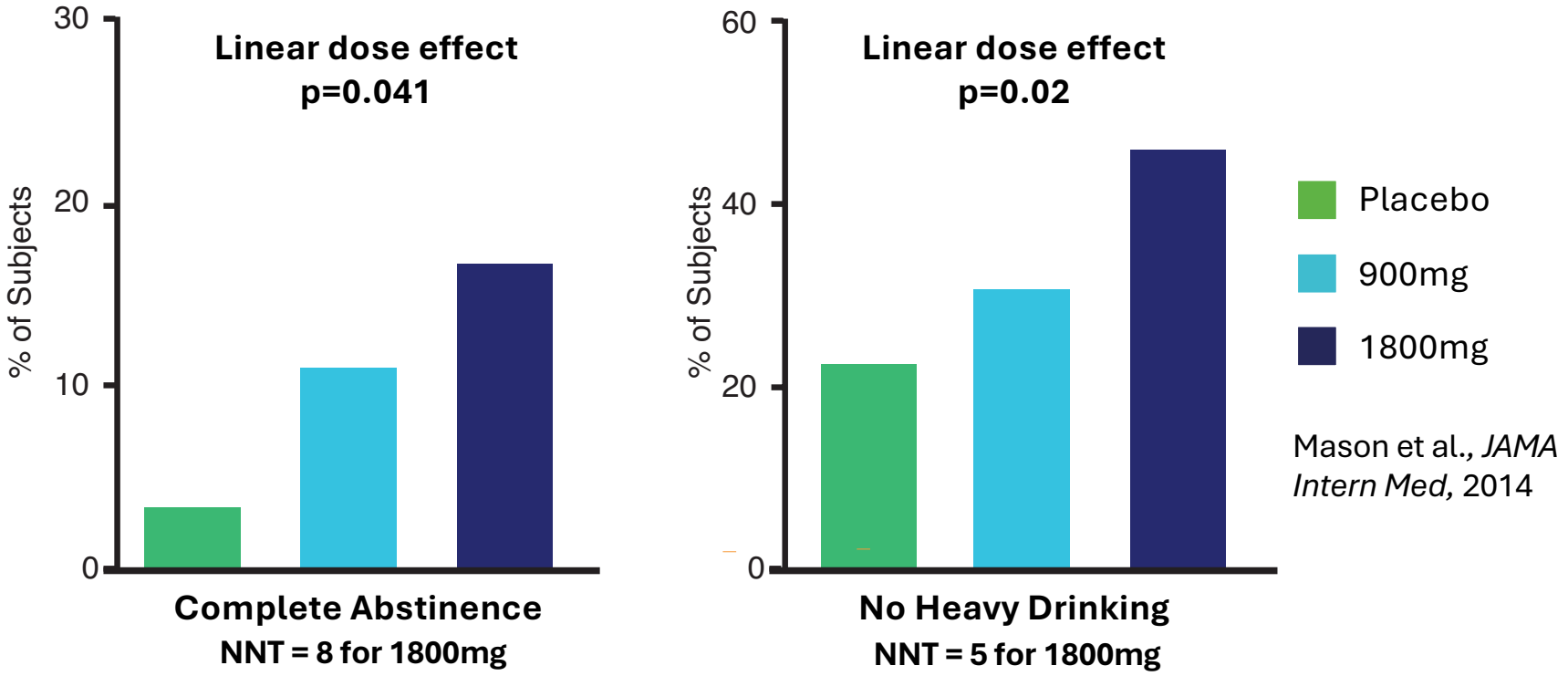
Mason et al., *Addict Biol,* 2008

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



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

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.

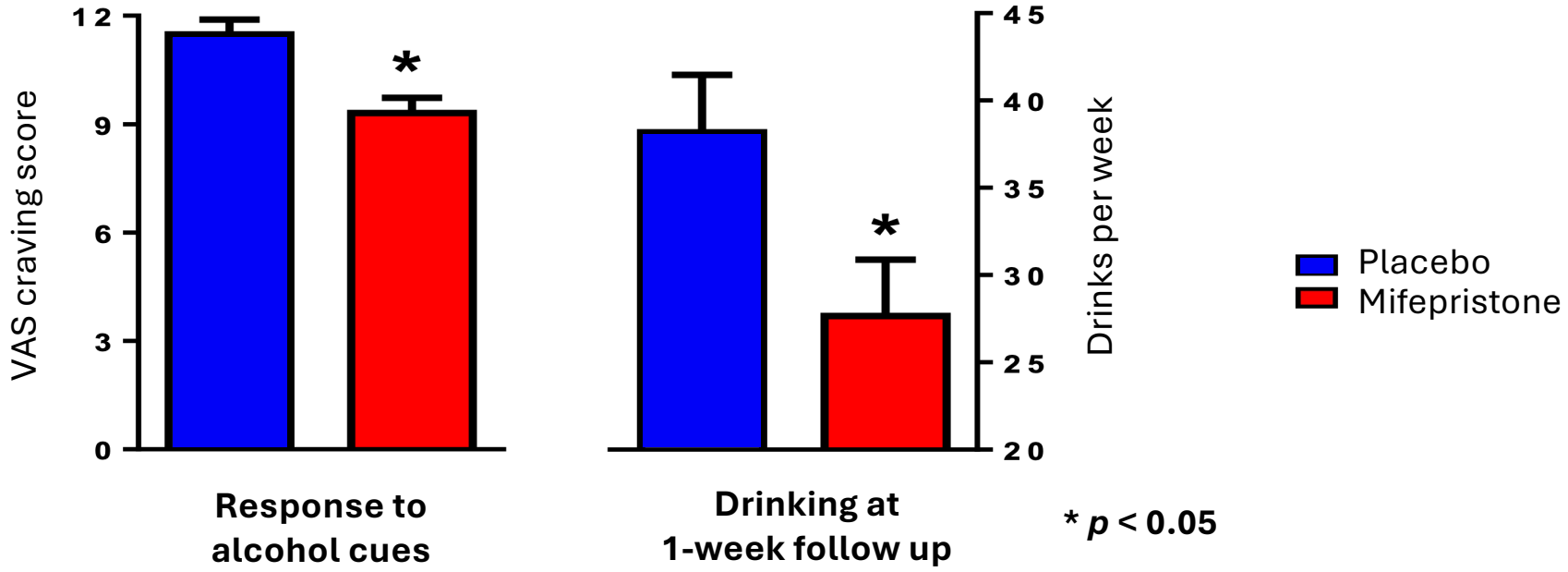
Administering mifepristone following acute alcohol withdrawal may normalize the brain stress axis, thus protecting against drinking relapse.

Leandro Vendruscolo

Olivier George

Vendruscolo et al., J Clin Invest 125(8):3193-3197 (2015)

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



Vendruscolo et al. *J Clin Invest, 2015, 125:3193-3197.*

Apremilast (Otezla)

Rationale for Apremilast Treatment of AUD

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

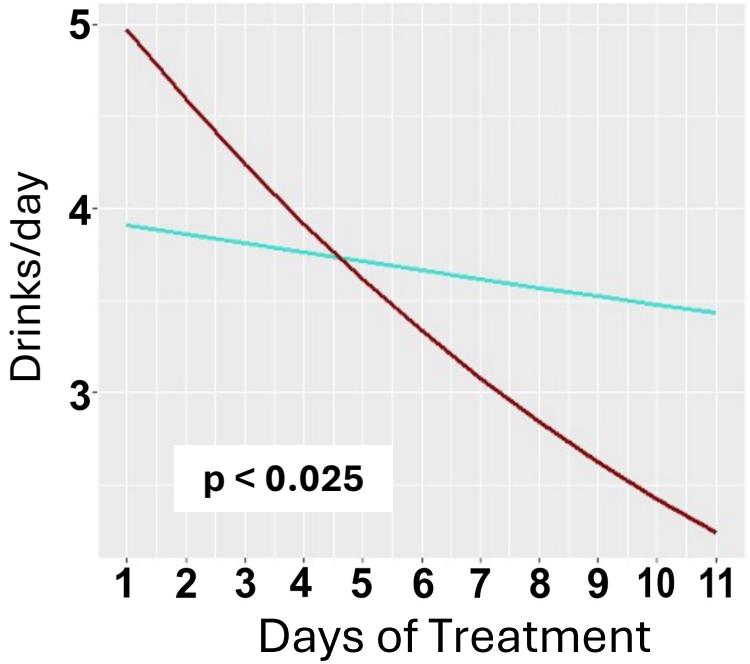
A selective phosphodiesterase type 4 (PDE4) inhibitor that acts on immune system targets (IL-10) to reduce inflammation

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

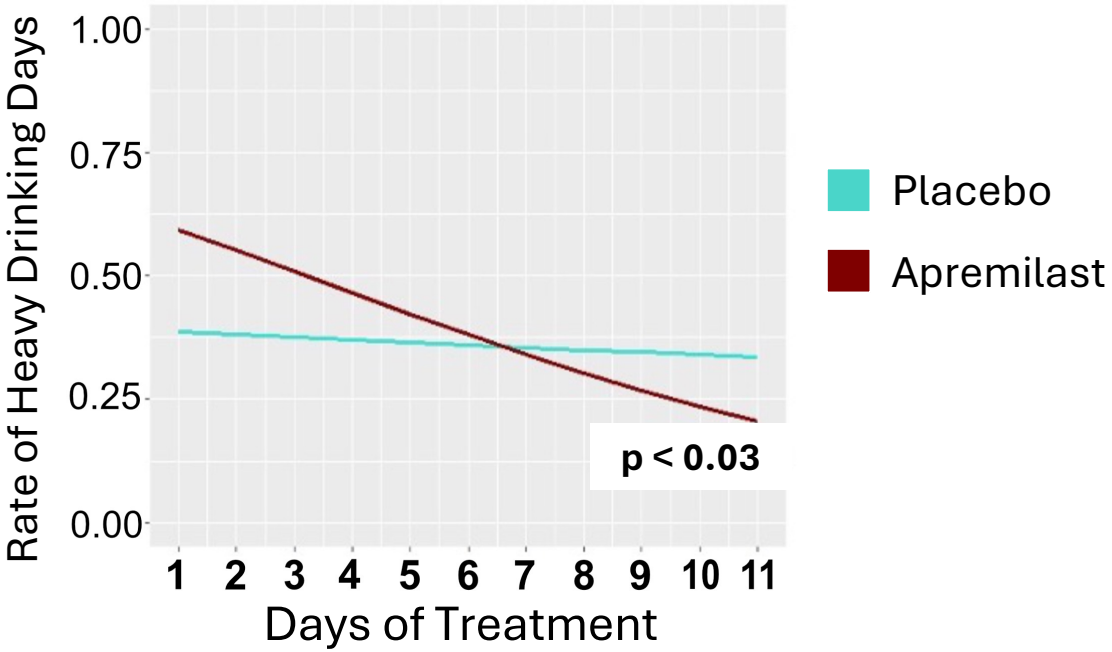
- Apremilast has less severe gastrointestinal side effects than early PDE4 inhibitors such as rolipram and ibudilast and may have better acceptability as a treatment for AUD
- Optimal efficacy for decreased drinking with apremilast was identified in dose-ranging animal models of AUD, which indicated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



Grigsby, et al. Preclinical and clinical evidence for suppression of alcohol intake by apremilast. J Clin Invest. 2023; 133(6):e159103. PMID: 36656645

Summary

Clinical studies of gabapentin, mifepristone and apremilast:

- Reduced drinking relative to placebo
- Were safe and well-tolerated
- May offer a broader range of drugs to treat AUD
- Provided clinical validation of preclinical models of AUD

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.

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Thank you very much!

The Scripps Research Institute
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