Beyond Treating Acute Alcohol Withdrawal: New Medications for Post-Withdrawal Relapse and Recovery

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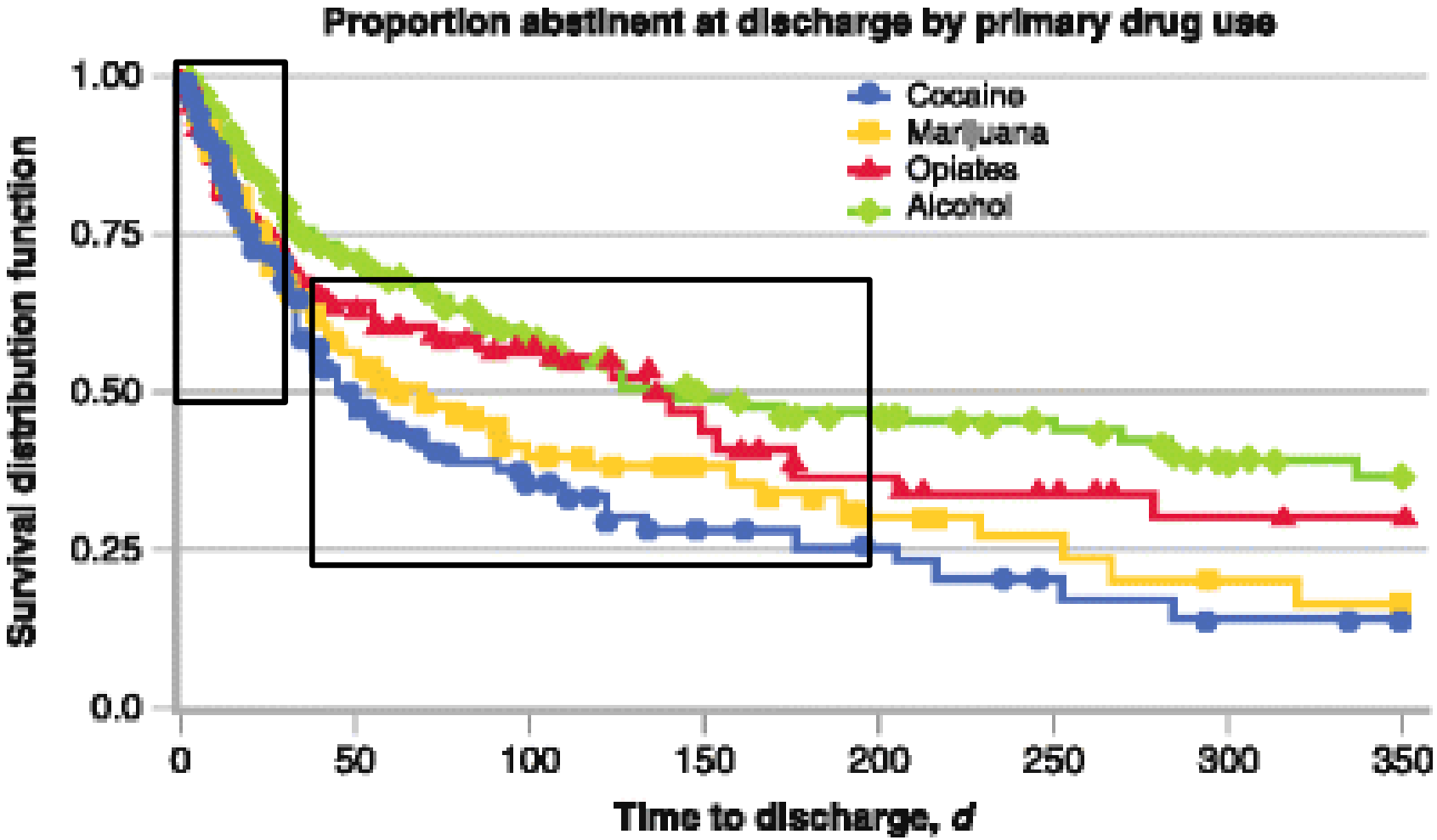
Session Learning Objectives

At the end of the session, you will be able to:

- Articulate key clinical prognostic markers of high alcohol relapse risk and poor treatment response.
- Define some stress pathology biomarkers associated with AUD that characterizes high severity of AUD.
- Identify 1-2 therapeutic compounds that reverses stress pathology in patients with high AUD severity and improves drinking outcomes.



Data from 878 outpatients classified on the basis of primary drug of abuse (cocaine, marijuana, opioid, alcohol). Survival distribution function is shown on the y axis, which represents the proportion of patients in treatment surviving relapse and remaining abstinent over the 350 days assessed.

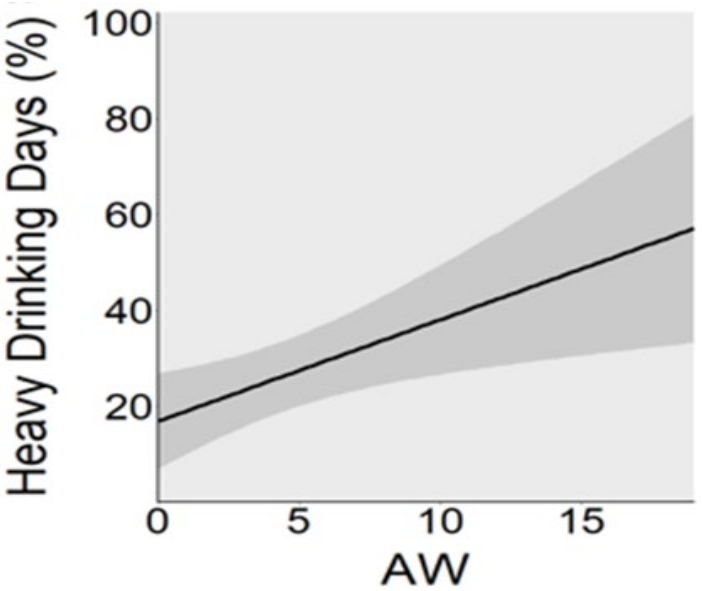
Sinha R, Current Psych. Rep. 2011

Current State of Treatment

- Inpatient treatment for acute medical withdrawal – referral to aftercare.
  - Strict criteria of eight or more acute alcohol withdrawal symptoms
- Outpatient pharmacologic and behavioral treatment to cut back and reduce to healthy drinking or abstinence based on patient goals.
- Self-help groups

Are withdrawal and abstinence symptoms an indicator of stress pathophysiology?

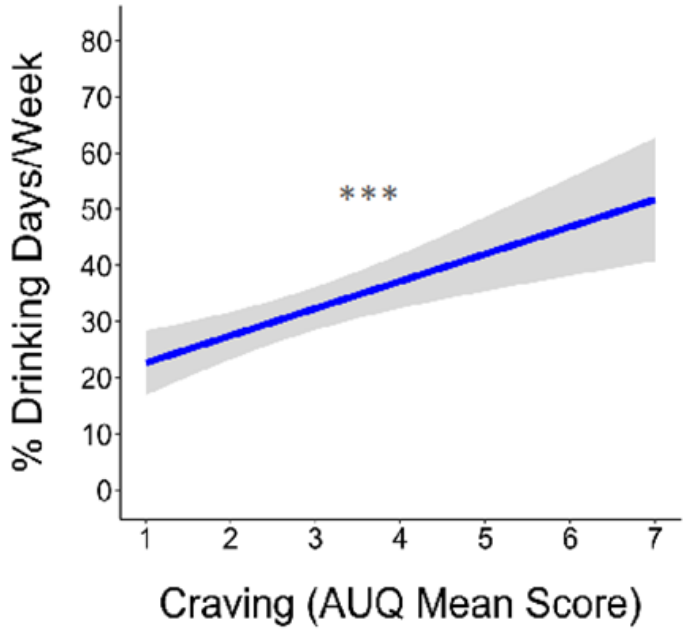
- Tremors
- Tension, Anxiety
- Agitation, Irritability, Aggression
- Sweating
- Nausea, Vomiting
- Headaches, Abdominal pain, Cramps
- Tactile, Visual and Auditory Hallucinations
- Orientation
  - *Note: High autonomic tone (HR, BP) and HPA dysfunction are not included in the CIWA*

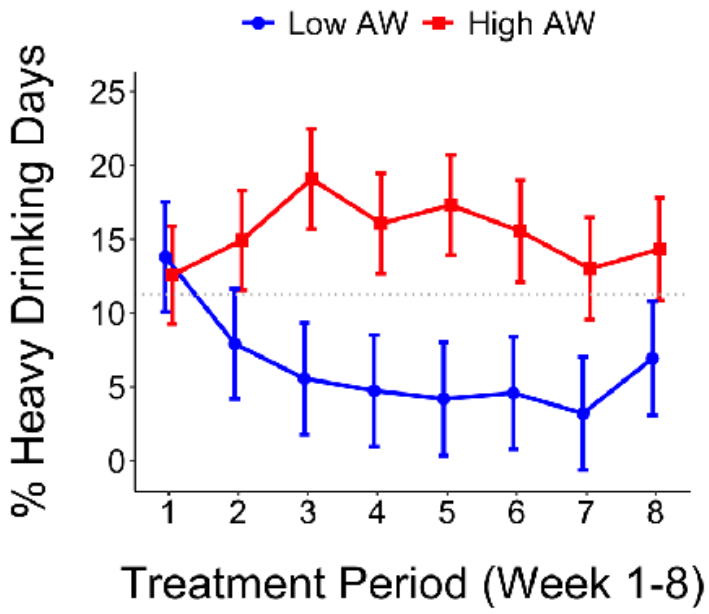


Higher AW symptoms (CIWA scores) at intake prospectively predicted higher 2-week drinking during early treatment (Percent heavy drinking days – HDD%: (b=2.11, 95%, CI[.57, 3.66], p<.01); Error bands are ± SEM

Alcohol Withdrawal (AW) Clinical Institute of Withdrawal from Alcohol – Revised (CIWA-Ar scores) , Sullivan et al., 1989.
Sinha et al., Addiction Biology, 2021

Alcohol Craving and Withdrawal (AW) Predicts Future Outpatient Treatment Outcomes (N=80)





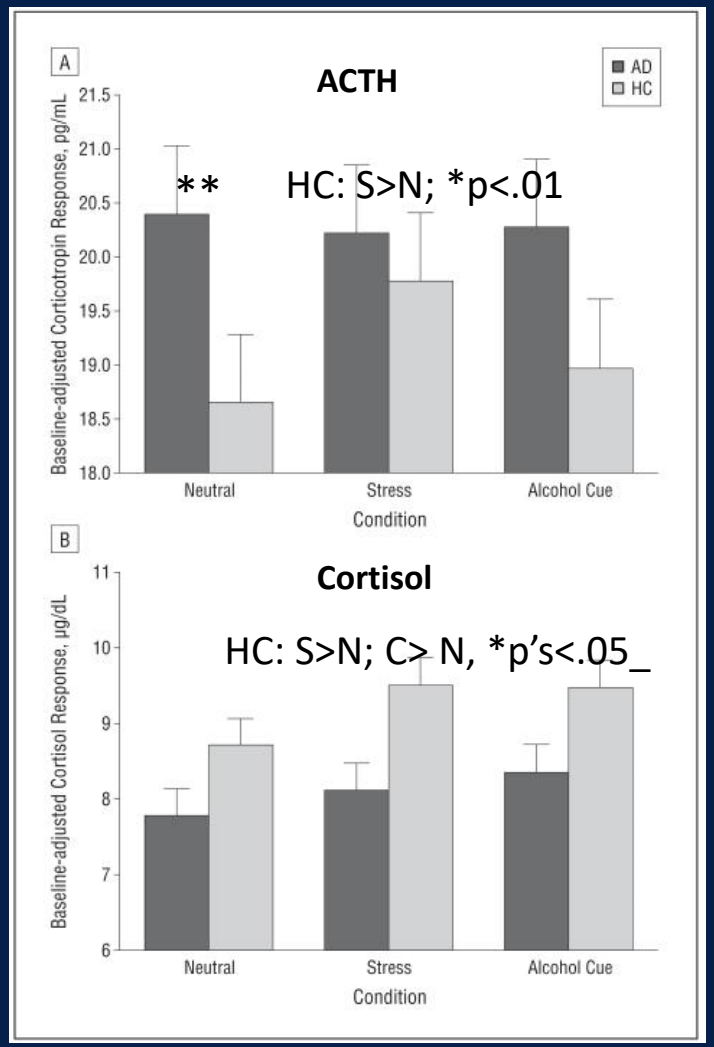
Higher Craving (Alcohol Urge Q) and AW symptoms (CIWA-Ar scores) at intake prospectively predicted greater alcohol use outcomes with NIAAA manualized relapse prevention treatment (Percent heavy drinking days – HDD%: Craving - $p<.001^{***}$, AW - $p<.01^{**}$; For AW - error bands are ± SEM; covarying for baseline drinking, abstinent days, demographic variables.

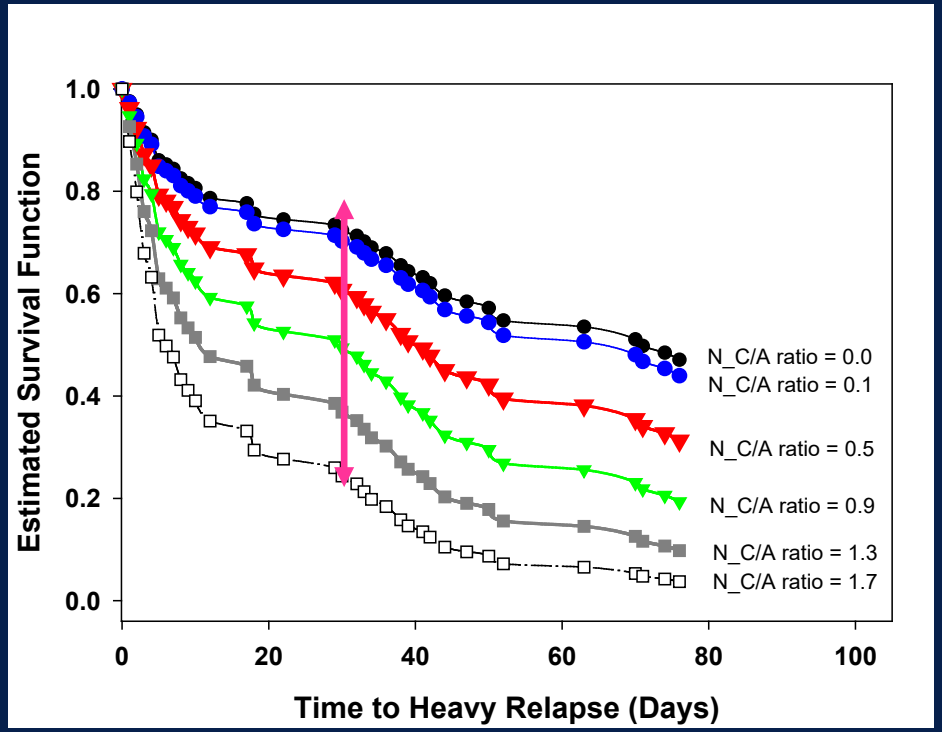
Martins, Fogelman, Wemm, Sinha, DAD, 2022

Disrupted HPA axis Responses and Greater the Likelihood of Alcohol Relapse

ACTH: Group X Condition: F(2,135)=5.64, P<.004;

Cortisol: Group X Condition: F(2,135)=3.25, p<.04.

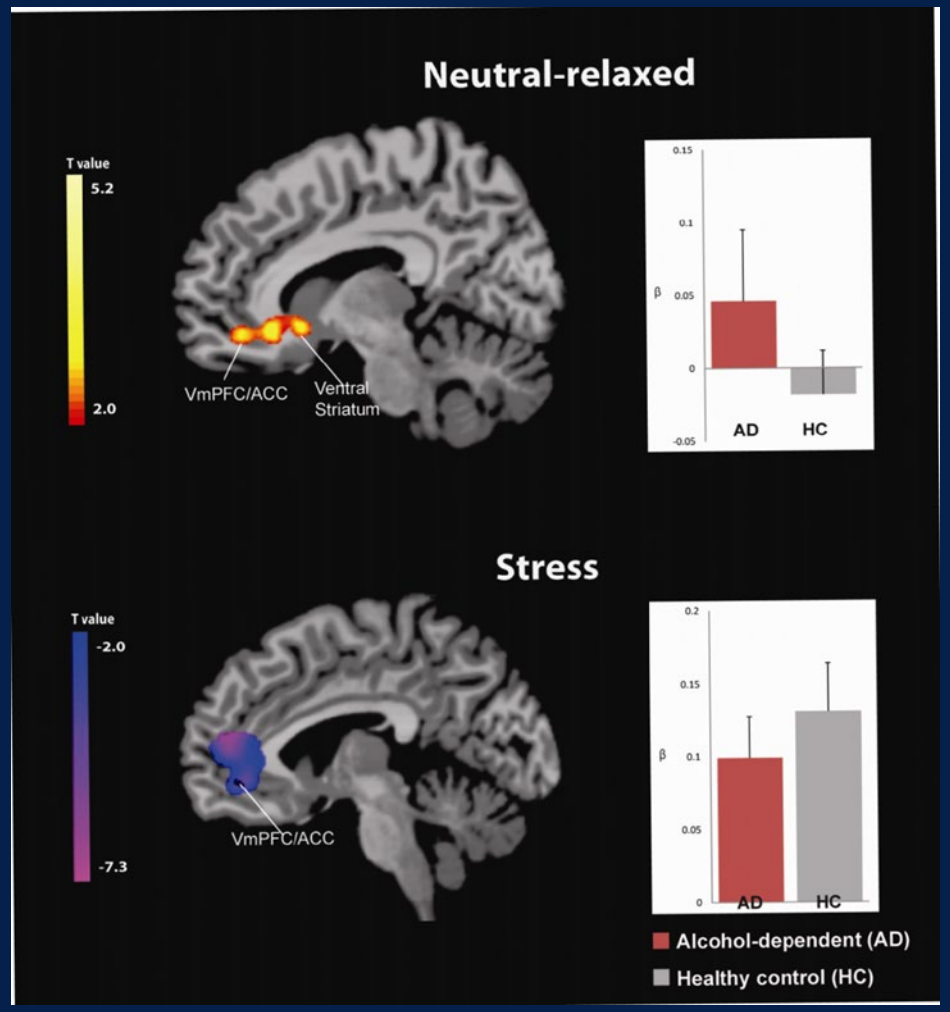


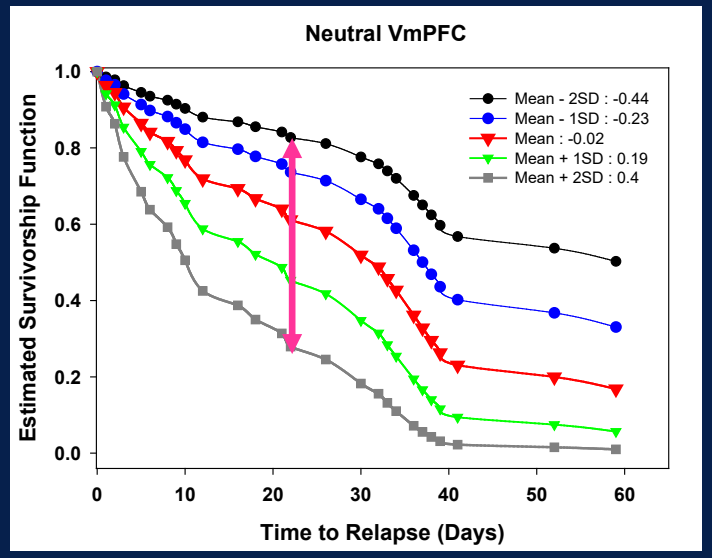


Cox Proportional Hazards Regression: Cort/ACTH ratio during neutral (X^2=7.24, p<.007; HR: 2.16) predicted future time to alcohol relapse.

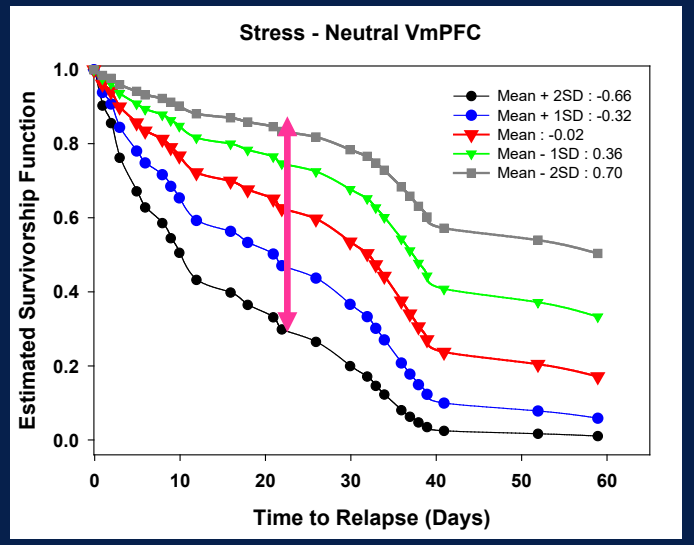
Sinha et al., Archives of General Psychiatry, 2011

Disrupted Ventromedial Prefrontal Response to Stress, Greater the Likelihood of Alcohol Relapse





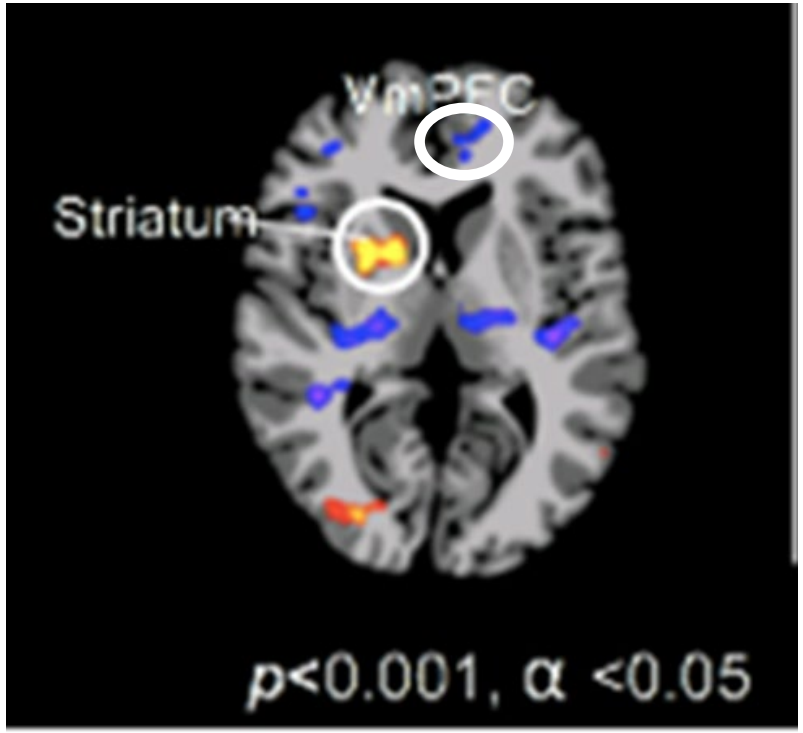
p<.002; Hazard ratio (HR): 6.6

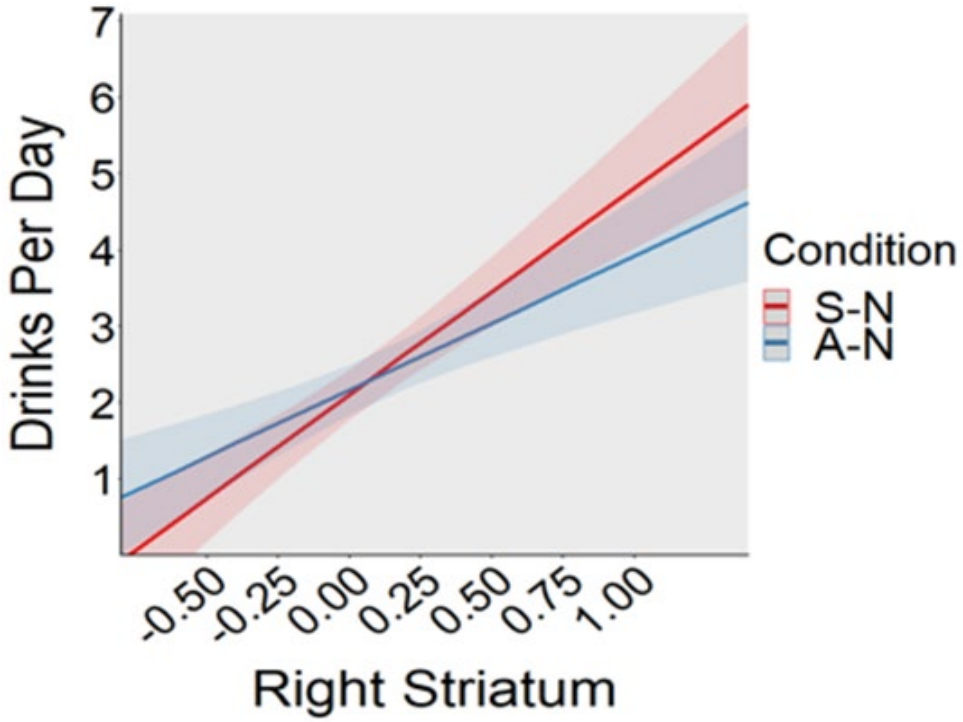


p<.02, HR: 0.25 (75%)

Seo et al., JAMA Psychiatry (2013)

Alcohol Withdrawal (Aw)-related Prefrontal-Striatal Disruption Predicts Future Drinking in Early Treatment

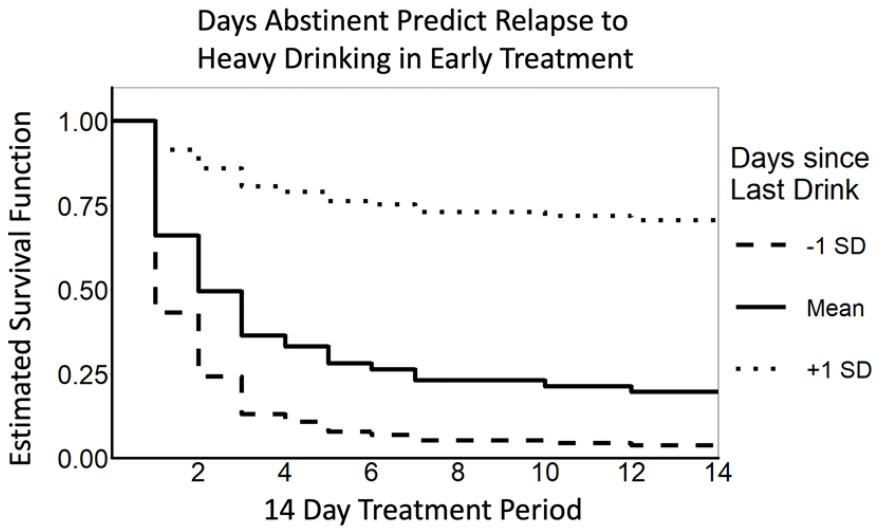


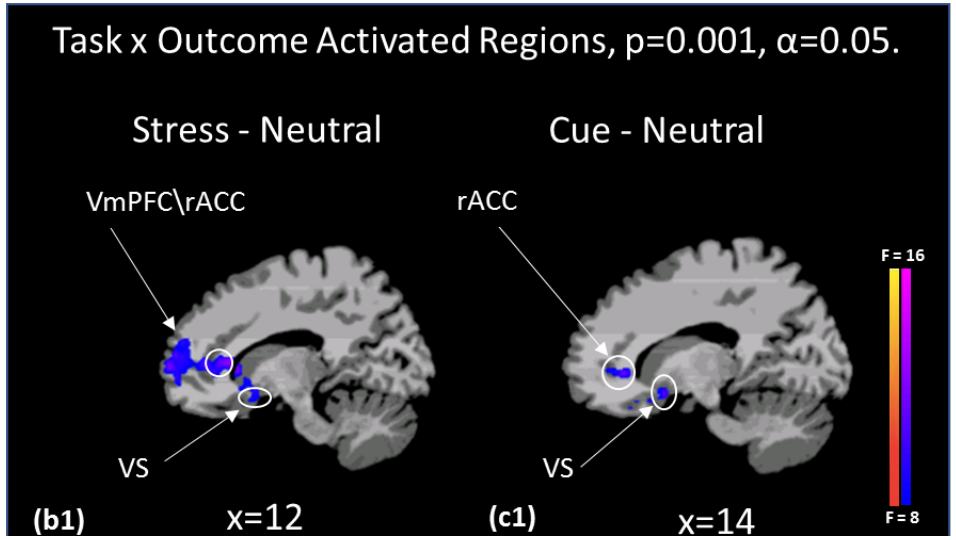


S-N: Stress relative to neutral; A-N: alcohol cue relative to neutral;
Red/yellow: increased activation; blue: decreased activation

Sinha et al., Addiction Biology, 2021

Less Abstinence at Treatment Entry Predicts Stress- and Cue- Brain Responses and Heavy Drinking Days (HDD) in Treatment





Low days of abstinence, greater percent HDD in early treatment; Lower Stress-induced VmPFC and ventral striatal response (shown in blue), predict future higher HDD during early recovery in treatment.

Blaine et al., Am. J of Psychiatry (2020)

Moderators/Biobehavioral Markers to Enhance Precision Medicine

- Disease Pathophysiology (Severity, acute withdrawal and drug abstinence)
- Early Trauma, Stress/Trauma-related Pathophysiology
- Sex differences
- Lifespan effects – developmental and aging effects
- Co-morbidities (Depressive Disorders; Co-Occurring Substance Use Disorders, medical conditions)
- Genetic and pharmacogenomic effects

What About Current Addiction Medications? Do Any Target the Stress Pathophysiology of Addiction?

- FDA Approved Medications:
  - Alcohol: Naltrexone, Acamprosate, Disulfiram
  - Opioids: Methadone, Buprenorphine, Naltrexone
- Non-Approved/Off label and Treatment Development:
  - *Noradrenergic agents: Alpha – 2 Adrenergic Agonists (Lofexidine, Clonidine, Guanfacine) ; Alpha – 1 Antagonists (Prazosin)*
  - GABAergic Agents: Gabapentin, Topiramate
  - Glutamatergic agents: Topiramate, Modafinil
  - Cannabinoids: Dronabinol, Cannabidiol, FAAH inhibitors?

Prazosin: Alpha1-Antagonist and Old Anti-Hypertensive Drug

- Rescues repeated stress related impairment in the prefrontal cortex (Arnsten, et al., 2012).
- Reduces alcohol withdrawal behavioral symptoms and alcohol intake in dependent animals (Walker et al., 2008; Rasmussen et al., 2009)
- Prazosin (16 mg/day, t.i.d) decreases stress-induced craving, normalizes HPA axis (Fox et al., 2012) and reduces drinking in alcohol dependent individuals (Simpson et al., 2009, 2015).

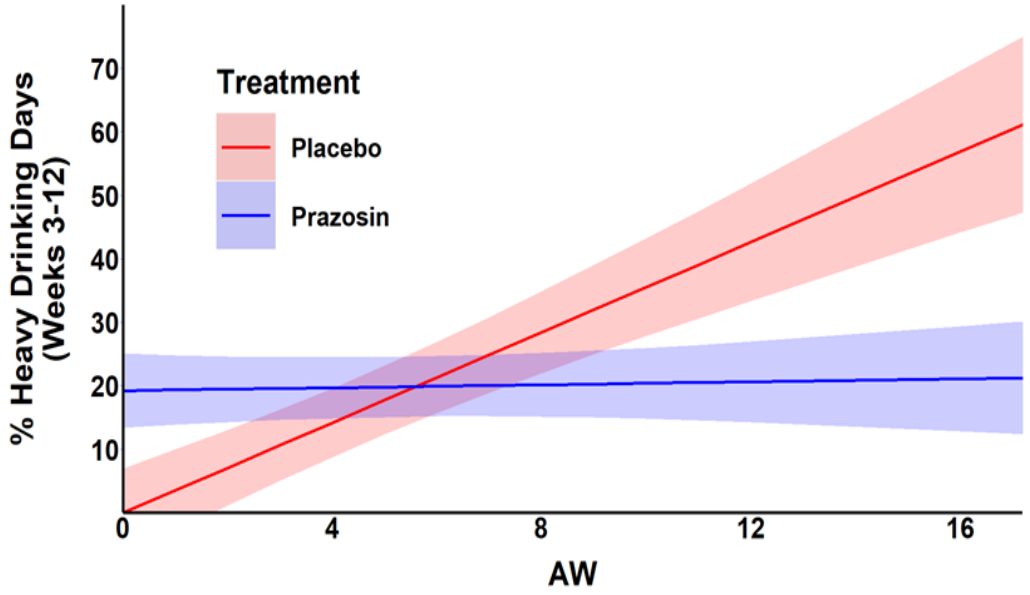
Prazosin Versus Placebo RCT: Influence of Alcohol Withdrawal (AW)

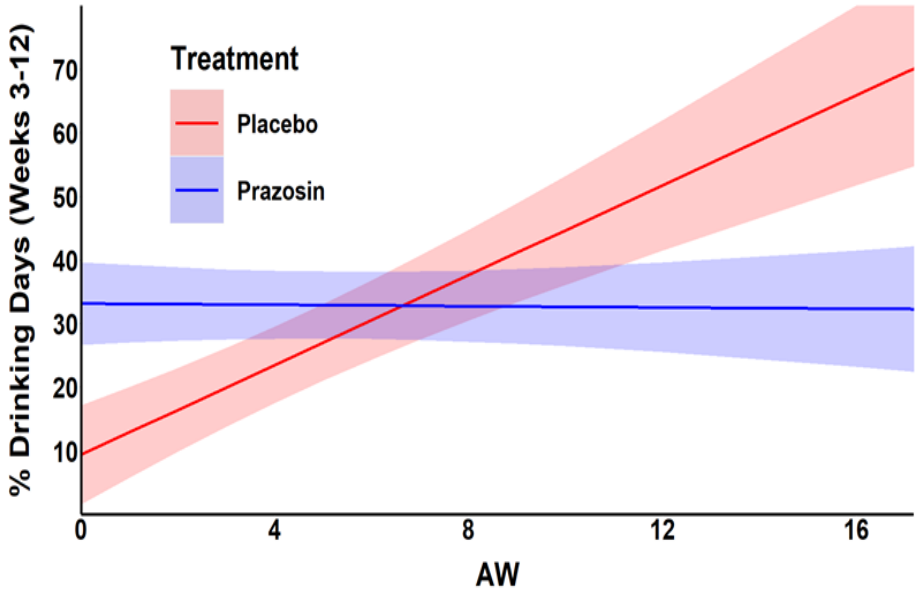
- NIAAA-funded 12-week outpatient clinical trial; 112 patients with AUD enrolled; 100 patients initiated the trial and included in the Intent-to-treat (ITT) analysis.
- CIWA used to assess AW; Drinking outcomes assessed via daily electronic diaries and time-line followback.
- 16 mgs (titrated to 5mg am q; 5mg pm q; 6mg night q , over 2 weeks) – 9 weeks at full dose (16mgs) , week 12, 5-day taper.
- Piecewise mixed effects models used to distinguish treatment effects prior to and after full dose.
- No abstinence days required for treatment initiation.

Sinha, Wemm et al., Am. J. Psych., 2021

Alcohol Withdrawal (AW) Significantly Moderated Prazosin (PZ) Benefit in AUD

Full Dose Period (Post-FD): Weeks 3-12

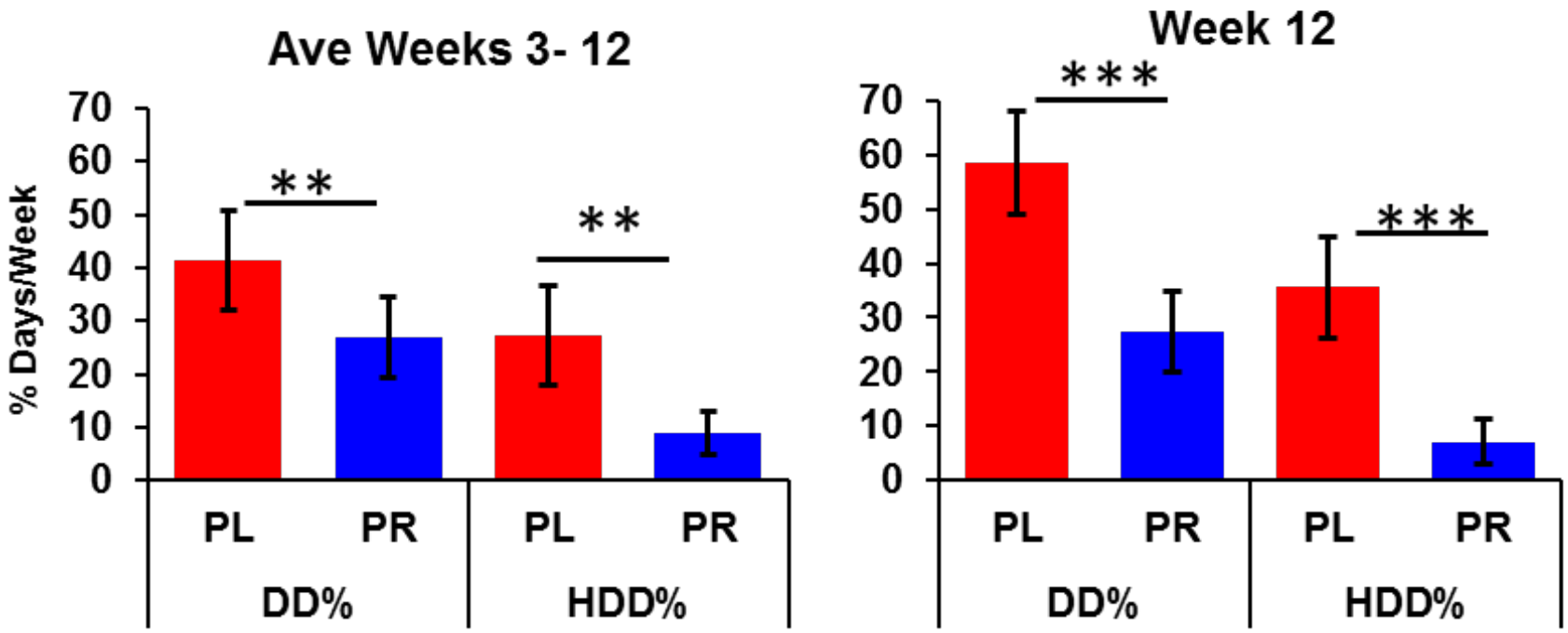




**p<.01; Prazosin vs Placebo in 12-week RCT(16 mg/day) with individual 12-step counseling and contingency management. Greater the alcohol withdrawal scores better the Prazosin treatment response.

Sinha, Wemm et al., American J of Psychiatry, (2021)

Average Drinking in High Alcohol Withdrawal (AW) Group in Prazosin vs. Placebo

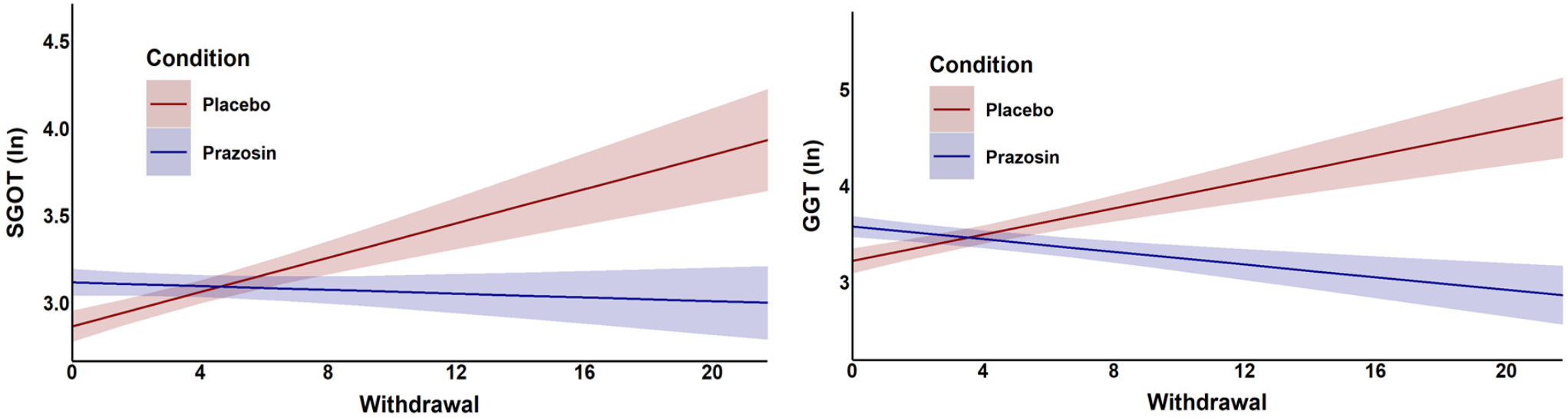


**p<.01; ***p<.001; DD%: Percent Drinking Days; HDD%: Percent Heavy Drinking Days

Also, significant improvements in anxiety, alcohol craving and mood for high AW treated with Prazosin vs. those on Placebo.

Sinha, Wemm et al., American J of Psych. 2021; also see Milivojevic et al., ACER, 2020; Fox et al., ACER 2011

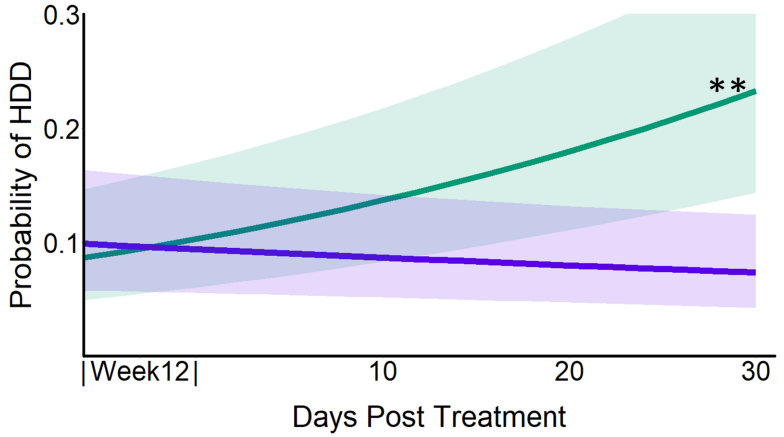
Alcohol Withdrawal (AW) Significantly Moderated Prazosin (PZ) Benefit on Liver Enzymes in AUD



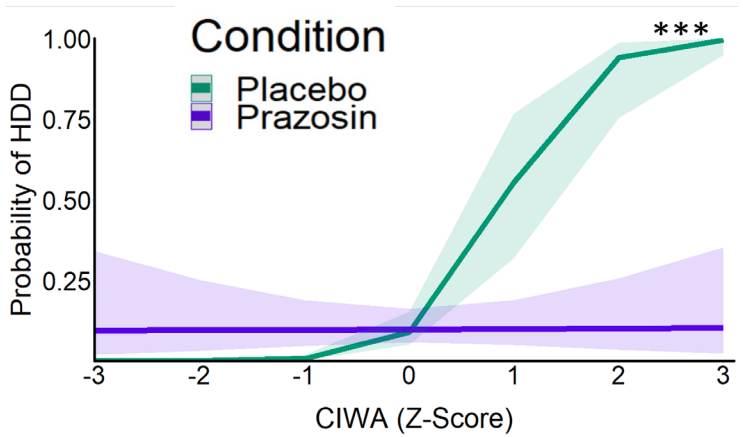
Change in liver function levels (log transformed – ln) from pre-treatment to 12-weeks:
AW X MedGrp Effect: SGOT: F[1,78]=7.86, p<.006; GGTP: F[1,89]=13.24, p<.0004; SGPT: F[1,80]=5.03, p<.03, data not shown; **p<.01;

From the Prazosin vs Placebo in 12-week RCT(16 mg/day) with individual 12-step counseling and contingency management (Sinha et al., AJP, 2021).

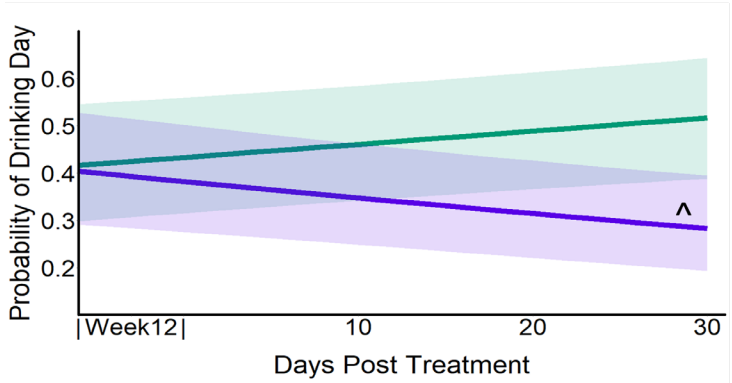
Short-term Enduring Effects of Prazosin (PZ) Benefit Post-treatment Over 30 days



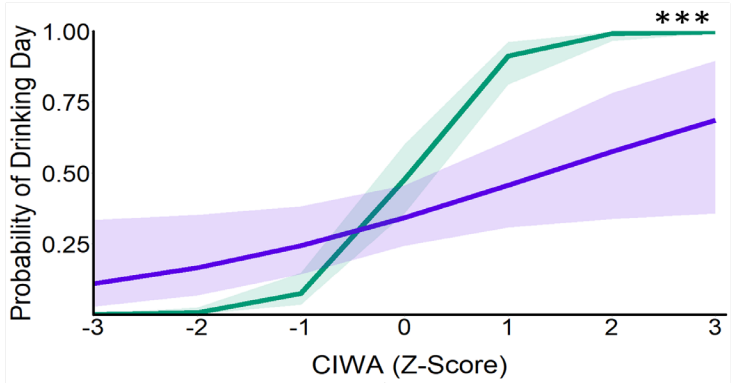
Condition x Day: $\chi^2(1) = 7.9$, $p < 0.005$



CIWA x Condition: $\chi^2(1) = 8.1$, $p < 0.005$



Condition x Day: $\chi^2(1) = 4.6$, $p < 0.033$



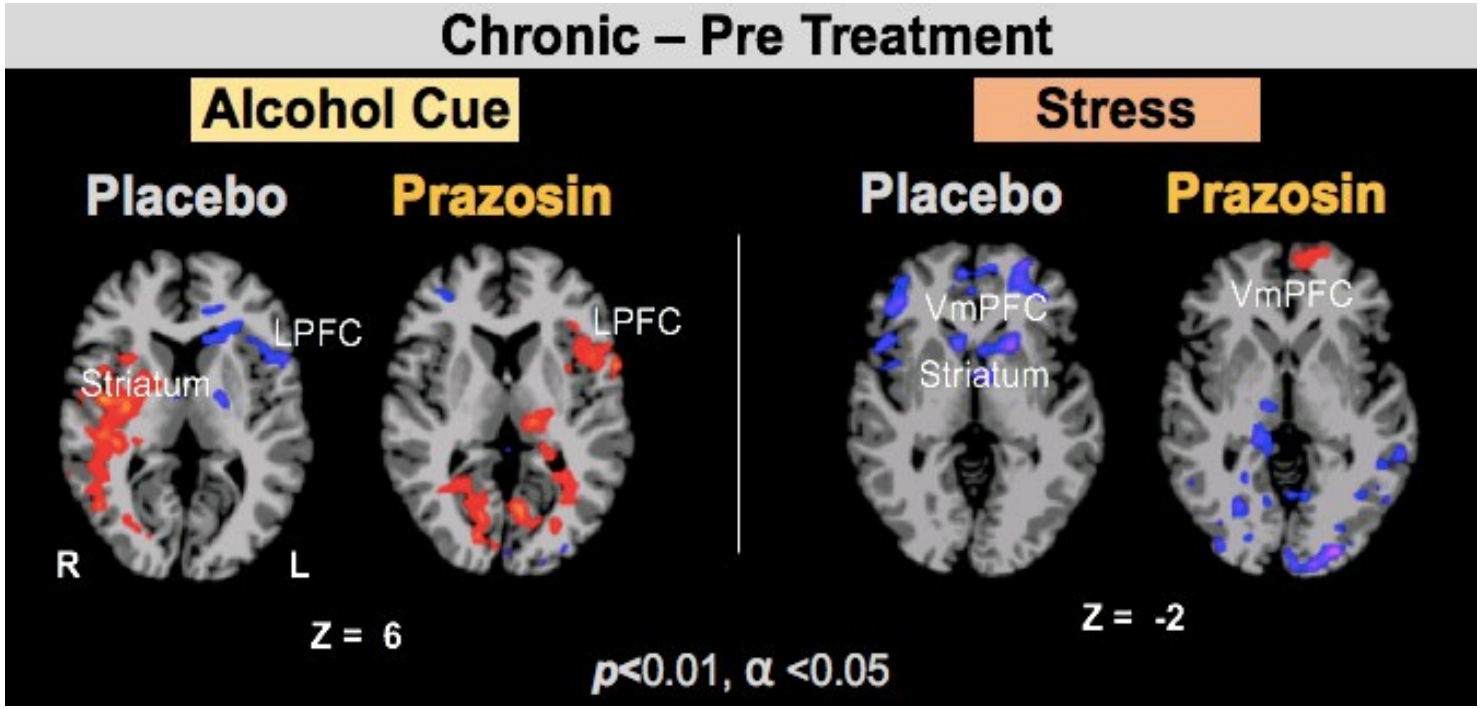
CIWA x Condition: $\chi^2(1) = 6.2$, $p < 0.013$

From the Prazosin vs Placebo in 12-week RCT(16 mg/day) with individual 12-step counseling and contingency management

^p < 0.1, *p < 0.05, **p < 0.01, ***p < 0.001

Fogelman et al., RSA Conference, 2019; Sinha et al., AJP, 2021

Chronic Prazosin Treatment (9-10 weeks) Significantly Improved Brain Prefrontal-Striatal Functional Pathology



Chronic > Pre: Increase

Chronic < Pre: Decrease

The Prazosin group showed improved VmPFC function with chronic treatment during stress (shown in red) not seen in the Placebo group; while the Placebo group showed increased R Striatum response (shown in Red) and blunted PFC (shown in blue) response during stress and alcohol cue challenge not seen in the Prazosin group.

Sinha et al., ACER,2018; Sinha et al., Addiction Biology, 2022

Final Takeaways

- There are chronic alcohol-and stress/trauma-related peripheral and neural adaptations in stress pathways associated with increased distress symptoms, drug craving, reduces behavioral and cognitive control, and that promote relapse risk to jeopardize recovery.

- ***Utilize specific biobehavioral & clinical prognostic markers of SUD relapse and treatment failure in initial assessment:*** Continued validation of prognostic markers of relapse/treatment failure is warranted.

- ***Precision Medicine Goal 1:*** Identify those are most vulnerable to risk of relapse during early recovery.

- ***Precision Medicine Goal 2:*** Develop specific treatments to address stress pathophysiology to improve relapse outcomes.

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