Hello again, colleagues!

Alcohol use disorder (AUD) is a disease that affects one in seven people.[1] *And while treatment options exist, more of them, with more efficacy, are needed. Prazosin has been studied for treatment of nightmares in PTSD and for alcohol use disorder (AUD), two conditions with frequent overlap. The results for alcohol use have been mixed.* ***This paper makes a strong case that the presence of low-level alcohol withdrawal predicts the effectiveness of prazosin in AUD.*** *This may help to untangle the inconsistencies in the existing body of evidence, and reinvigorate the quest to take advantage of alpha blockade in AUD treatment.*

While it's not time to offer clinical guidance based on this study, the effect of 16mg/day of prazosin found here draws attention. With prazosin, there was a 50% reduction in drinking days (OR 0.5 P<0.01) and 76% reduction in heavy drinking days (OR 0.23, p <0.0004) among people with mild alcohol withdrawal symptoms, while no effect of prazosin was seen in people with fewer or no alcohol withdrawal symptoms. Could it be that we've had a highly effective option in our midst but we didn't know who to use with? Maybe. It's worth thinking about the findings here as we reabsorb prior- and look to future- research, including one just out on prazosin and alcohol use in active duty soldiers (referenced below for eager readers[2]*). I hope this un-patented medication that shows promise for a subset of people with AUD can find its way into quality studies that further elucidate its role.*

Thank you for reading,

Andrea

Andrea Truncali, MD MPH

Title: Prazosin may reduce drinking in study volunteers with AUD who had mild alcohol withdrawal symptoms compared to those with no alcohol withdrawal.

Citation: Sinha R, Wemm S, Fogelman N, Milivojevic V, Morgan PM, Angarita GA, Hermes G, Fox HC. Moderation of Prazosin's Efficacy by Alcohol Withdrawal Symptoms. Am J Psychiatry. 2021 May 1;178(5):447-458. doi: 10.1176/appi.ajp.2020.20050609. Epub 2020 Nov 19. PMID: 33207935; PMCID: PMC8119326.

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8119326/ (free access)

And follow up editorials:

https://pubmed.ncbi.nlm.nih.gov/34033270/

https://pubmed.ncbi.nlm.nih.gov/34551219/

https://pubmed.ncbi.nlm.nih.gov/33979539/

Funding/Conflicts:

No conflicts disclosed. Funded by NIAAA and State of Connecticut.

METHODS

Study Design

This was a randomized double-blind placebo-controlled trial of prazosin in people with AUD aiming to discontinue alcohol use. The authors prespecified that alcohol withdrawal would modify the effect of prazosin. That is, that in the presence of alcohol withdrawal, prazosin would influence drinking outcomes, but would not do so in people without alcohol withdrawal.

From 2012-2017, community dwelling adults were recruited via media or through direct referral from addiction treatment in the greater New Haven, CT area. Included were people who met DSM-IV for alcohol dependence and could read and write English. Excluded were those with other SUDs (except nicotine and caffeine), current use of psychoactive medication except SSRIs and current use of naltrexone or disulfiram, severe medical or psychiatric conditions, pregnancy or BP <90/60.

Patients were assessed by trained staff with a CIWA-Ar, and if eligible based on inclusion/exclusion, randomized to placebo or prazosin 16mg/day. No pretreatment abstinence was required though a negative breathalyzer was required for assessment.

Primary outcomes were number of heavy drinking days and drinking days. Secondary outcomes included drinks/day as well as craving and mood outcomes.

Intervention

After assessment, patients could choose outpatient treatment only or initial inpatient (x3-4wks!) followed by outpatient. Anyone deemed to require medically assisted withdrawal was recommended the inpatient-first option. Study medication was started only after medically assisted withdrawal.

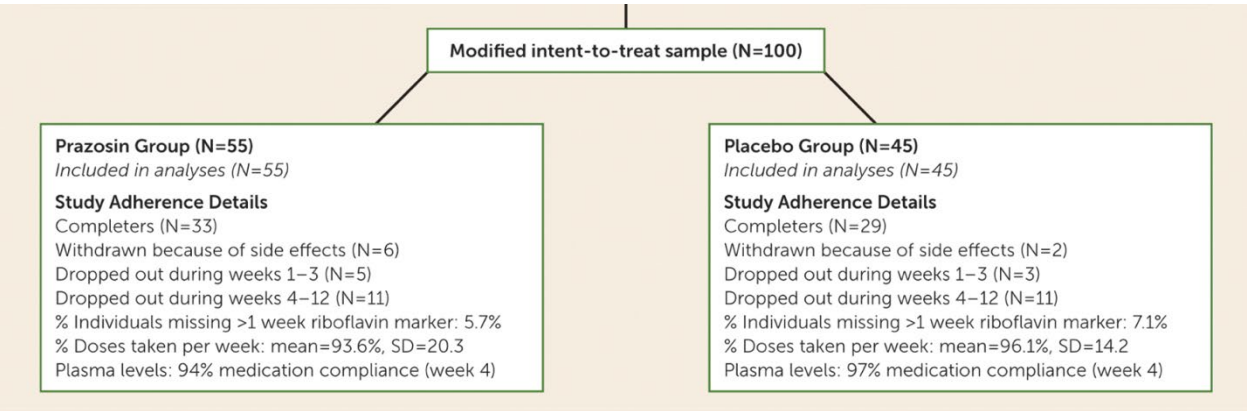
Patients were titrated over two weeks to a total daily dose of prazosin 16mg /day, divided into three doses 5mg/5mg/6mg . Starting dose was 1mg qhs x2days. Patients were maintained at 16g/day for 9wks then tapered over 5days on week 12. Med adherence was supported by blister packaging and TID reminders by smartphone app or interactive voice response. Medication included riboflavin to help assess adherence.

Study visits were twice per week. Behavioral support, focused on 12-step facilitation and relapse prevention, was provided weekly. Attendance was incentivized by a fishbowl contingency management. Med adherence was assessed with twice weekly urine observation (for riboflavin discoloration) and prazosin blood level at week 4. Participants responded each night to a 4-5min survey about drinking that day as well as a weekly timeline follow-back assessment. Urine was tested for ethyl glucuronide (EtG).

MAIN RESULTS

Population and follow up

112 patients were randomized. Of these, 12 did not start the study (4 prazosin, 8 placebo) and analysis was conducted on the remaining 100. 60% (n=33) of the prazosin group completed the trial vs 64% (n=29) placebo.



As shown above, medication adherence measures were high. Patients were 65% male, mean age 40, an even mix of Caucasian and African American race.

9-15% were treated with the inpt-outpt option. Lifetime anxiety including PTSD was 26-29%. Mean education was 13yrs, mean BP was 133-134/77-79. Patients had been drinking an average 17yrs, mean CIWA-AR was = 4 and average drinks/day = 6. About 2/3 of days were drinking days, and ½ of all days were heavy drinking days. Under 10% of the sample was using marijuana; similar for cocaine. No significant differences were found between the placebo and prazosin groups at baseline.

Patients were divided into high alc withdrawal (HAW) vs low alc withdrawal (LAW), based on the median CIWA-Ar (=3) at assessment such that HAW included those with CIWAs of 3 or more. *Note: CIWA < 8 is considered minimal withdrawal, 9-19 mild to moderate, and 20+ severe.*

Means for HAW vs LAW (see here for complete published table)

	HAW N=56	**LAW N=44**
CIWA-ar	8	0.9
BP	139/80	129/76
Tremor	75%	23%
Nervous/anxiety	68%	20%
Tactile, visual or auditory disturbances	N = 4-7	N = 2

Primary Outcomes

As is often the case in alcohol trials, there was a significant reduction in alcohol use from wk 0-1 in both groups. Wk 0-1 data were excluded from analysis, such that week 1 was the new baseline.

FIGURE 2A/B: Percent drinking days and heavy drinking days were significantly impacted by the alcohol withdrawal symptom score in placebo but not in the prazosin group, as shown here:

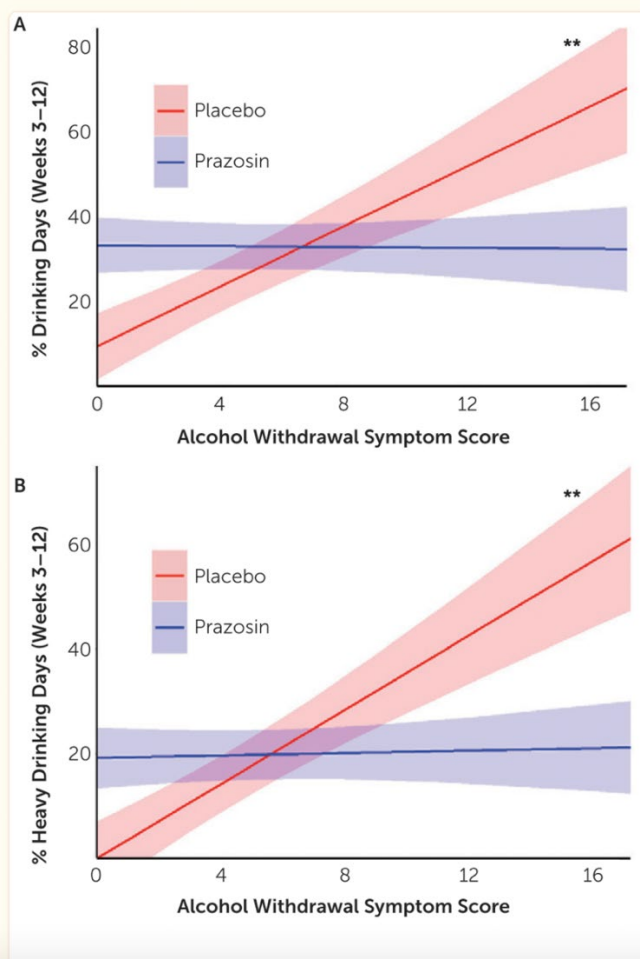
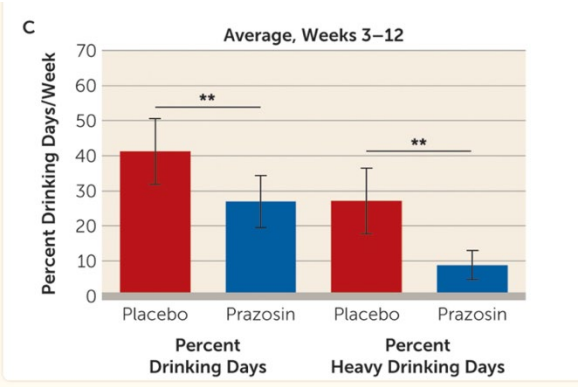


FIGURE 2C: And shown below, **among individuals with HAW**, drinking days and heavy drinking days were lower in prazosin vs placebo. Now difference was found between placebo and prazosin for those in the LAW group.

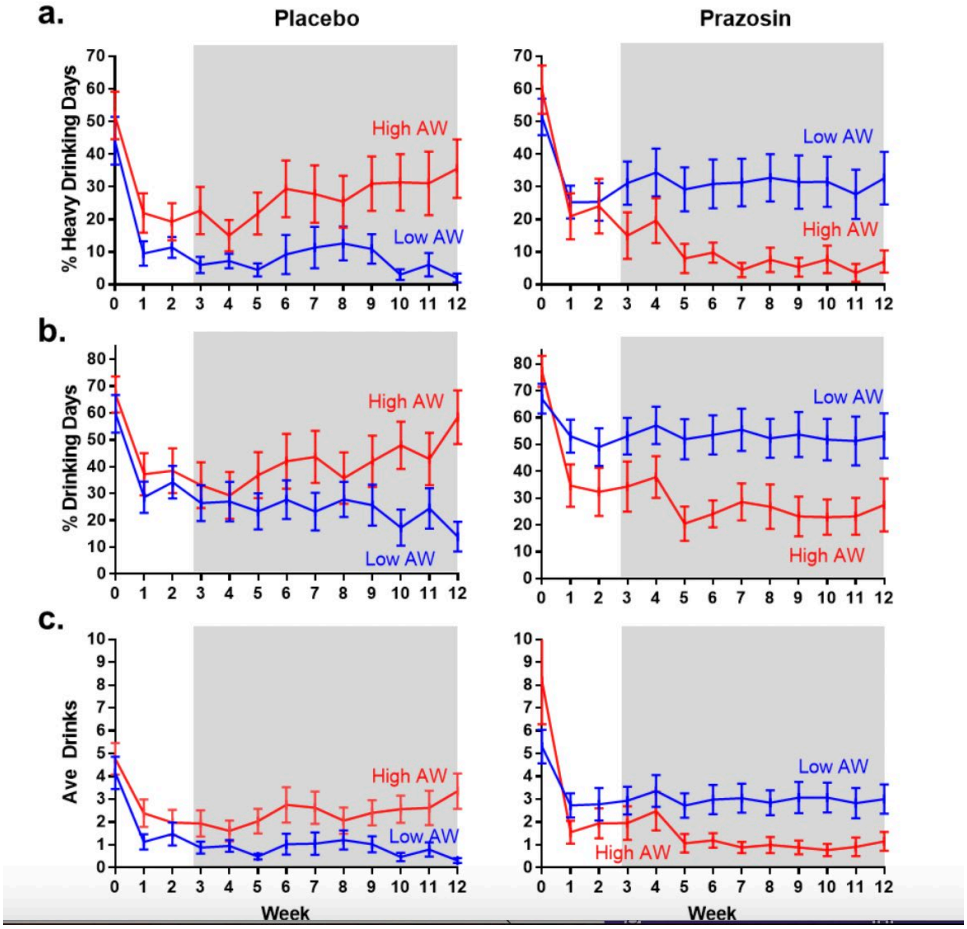


**P<0.001

Among those in the HAW group, this amounts to 41% drinking days in placebo vs 27% for prazosin, (OR 0.5 P<0.01) and for 27% heavy drinking days in placebo vs 9% prazosin (OR 0.23, p <0.0004).

The supplement shows the drinking changes in a different format (below) where the LAW group holds its reduction better in placebo but the HAW group holds its reduction better with prazosin. Note that the LAW prazosin group doesn't seem to have as much initial reduction as placebo.

Alcohol use outcomes at Baseline week 0 and during the trial (weeks 1-12) for Prazosin/Placebo Treatment Groups by High and Low AW (Median Split)



Severe AEs were similar between groups. Dropouts for side effects were 6/55 in prazosin vs 2/45 in placebo.

The secondary outcomes (cravings anxiety, depression and sleep) generated some theories about how prazosin might exert its effects (ie, less through

hyperadrenergic suppression in the locus coeruleus and more through activity at the stress and reward circuits who have derangements in severe & later stage use disorders) - but this is conjecture.

CONCLUSION

Among a study group of people with AUD motivated to stop drinking, the initial presence of mild alcohol withdrawal symptoms predicted effectiveness of prazosin on alcohol use.

COMMENTARY

Prazosin, an alpha 1 adrenergic antagonist has had signals for therapeutic benefit in people with PTSD and AUD, though the results of trials have been mixed. The benefit in AUD is thought mostly due to effects on mild or post-acute alcohol withdrawal symptoms. This study measured and stratified results by CIWA-AR to understand if withdrawal moderates the benefit of prazosin. The observed effect supported the authors' hypothesis, perhaps explaining previous mixed results, and identifies a subgroup for further study, ie those with a CIWA-AR of 3 or more, where prazosin may substantially improve outcomes.

Internal Validity

Major limitations to consider here:

- The question of unblinding – do people on 16mg /day prazosin really not know they are taking that? Maybe - the study suggested 11 prazosin vs 4% reported lightheadedness or dizziness but the placebo group reported more sedation. Knowing you got the study medication could affect how likely it is to help but (opinion..), probably has a relatively small impact given the compulsive nature of AUD.
- Loss to follow up/Missing data – the 40% dropout is significant. The loss was similar in both groups but we don't know what the reasons were. The timing of loss is similar in the two groups which argue against a differential loss to follow (and favors validity). However, its not clear how missing data was handled or that sensitivity analyses were done. (which does not favor validity).
- Patients were not randomized within the CIWA-Ar groups. It's a a bit of a mind bender to understand the impact of that but the CIWA-ar may carry

confounders like motivation to stop drinking that interacts with the treatment- but that seems to be the point of the study.
- It was peculiar that the LAW prazosin group reduced their drinking less in week one than did the LAW placebo group. Is this because the up to 6mgs of prazosin given in week 1 contributed to early differential drop out? It raises a little concern.
- I also wonder about why EtG and breathalyzers data is not included, even in the supplement.

External Validity

This was very much a research study. Patients entered with stated motivation to quit drinking. Overall the disease burden seemed relatively light, with only 9-15% of people requiring or choosing inpatient treatment and CIWA median of 3. Negative breathalyzers were required for entry. The incidence of polysubstance use was, by design, minimal.

And the study was unlike the 'real world'. There was a prolonged inpatient option for those at risk for severe withdrawal. Patients received blister packaged meds and three-time daily medication reminders. They received rewards for attendance along with twice weekly visits, weekly behavioral counseling and encouragement to report (and probably reflect upon) their drinking every night. While the reminders and blister packaging would tend to inflate the benefit of medication in comparison to a real-world setting, the other features might be effective in both groups, potentially masking medication benefits in situations where there are fewer resources.

And how do we think about this CIWA-ar score and who it brings in? In this study the "high" alcohol withdrawal group had a mean CIWA-AR of 8. That degree of withdrawal is considered rather mild. Also, the CIWA was assessed prior to randomization and medication, but we don't know when it was assessed relative to last drink. And so we wonder a bit whether it reflects motivation, severity or a little of both. Ie, motivated patient stops drinking a few days prior to enrollment, develops mild withdrawal, scores 4 on CIWA, vs person with severe AUD, less motivated, doesn't drink the morning of the evaluation, but also scores a 4. (We don't, however, think there are many of the latter folks in the study given all we've gathered through other channels.)

Overall

The question of loss to follow up and missing data raise a major question about study validity. However, if this loss was for similar reasons in both groups, the findings would be compelling, and would help us to rethink data on alpha adrenergic blockade in AUD. Hopefully studies will be forthcoming that focus on the subgroup identified and confirm if and how prazosin adds to AUD treatment options.

References

1. Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, Pickering RP, Ruan WJ, Smith SM, Huang B, Hasin DS. Epidemiology of DSM-5 Alcohol Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiatry. 2015 Aug;72(8):757-66. doi: 10.1001/jamapsychiatry.2015.0584. PMID: 26039070; PMCID: PMC5240584
2. Raskind MA, Williams T, Holmes H, Hart K, Crews L, Poupore EL, Thomas RG, Darnell J, Daniels C, Goke K, Hendrickson R, Terry G, Mayer C, Simpson T, Saxon A, Rasmussen D, Peskind ER. A randomized controlled clinical trial of prazosin for alcohol use disorder in active duty soldiers: Predictive effects of elevated cardiovascular parameters. Alcohol Clin Exp Res (Hoboken). 2023 Feb;47(2):348-360. doi: 10.1111/acer.14989. Epub 2023 Feb 21. PMID: 36809662.