

# Effects of Acute Prazosin Administration on Startle Potentiation During Unpredictable Versus Predictable Stressors in Humans

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## Background & Aims

Initial excitement for prazosin as a promising treatment for Posttraumatic Stress Disorder (PTSD) and Alcohol Use Disorder (AUD) has recently been tempered by larger clinical trials that failed to detect efficacy to improve clinical outcomes<sup>1,2</sup>. Prazosin is a brain-penetrant norepinephrine alpha1 receptor (NE- $\alpha$ 1) antagonist. Extensive preclinical research implicates NE and NE- $\alpha$ 1 in the stress response. However, efforts to repurpose prazosin for PTSD and AUD have proceeded largely in the absence of basic psychopharmacology research in humans.

Understanding if and how prazosin affects stress reactivity in humans can provide important insights to guide future research in this area. We conducted the current study to examine how prazosin acutely affects stress reactivity in humans in a well-validated translational psychophysiology paradigm, the No Shock, Predictable Shock, Unpredictable Shock (NPU) task<sup>3,4</sup>. Startle potentiation during unpredictable (vs predictable) stress has been proposed as potentially sensitive to both NE manipulations and stress system perturbations in PTSD and AUD<sup>5</sup>. This is the first study to our knowledge, to examine the impact of prazosin on objective measures (e.g., electromyography) of the startle response in humans.

**Preregistered Hypotheses** (<https://osf.io/fdig9/>): Acute administration of prazosin, a NE- $\alpha$ 1 antagonist, would have a larger effect on reducing stress reactivity during unpredictable (vs predictable) stressors in the NPU task. Our primary outcome measure was startle potentiation and secondary outcome was self-reported fear/anxiety in the NPU task.

## Methods & Measures

**Design:** Double-blind, placebo-controlled, cross-over randomized controlled trial.

**Participants:** Healthy adults (n = 64, 32 female) completed two study visits separated by 1-3 weeks.

**Drug Administration:** Single acute administration of 2mg prazosin at one visit and placebo at one visit. Drug/placebo order counterbalanced between-subjects.

**Task Timing:** Following drug administration, participants complete a resting (baseline) general startle reactivity task (80 minutes) and the NPU Task (90 minutes).

**Startle Response** (primary outcome): The eyeblink startle response was measured with Ag/AgCl EMG sensors over the orbicularis oculi muscle. Acoustic startle probes (50ms, 102dB) were presented at 4.5s post-cue onset in NPU task. Startle response was quantified as the peak magnitude 20-100ms post-probe onset.

**Self-report Anxiety** (secondary outcome): After the NPU task participants report their subjective fear/anxiety (1 to 5 likert scale) during each NPU condition cue.

## No Shock, Predictable Shock, Unpredictable Shock (NPU) Task

### Predictable Shock Condition



⚡ = Electric Shock to Fingers

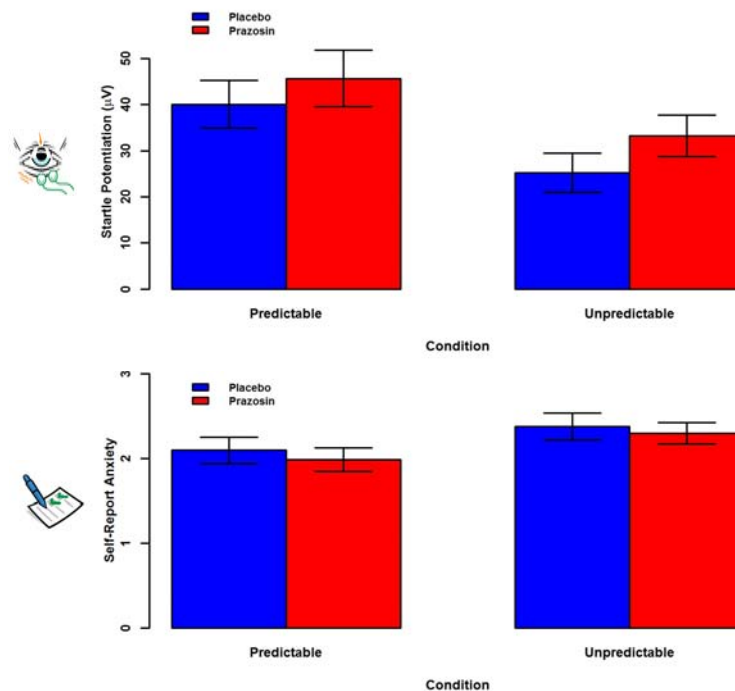
**Predictable shock:**  
Shock occurs during cues only

### Unpredictable Shock Condition



**Unpredictable shock:**  
Shock occurs at any time.

## Results



## Acute prazosin did not selectively reduce startle potentiation or self-reported anxiety to unpredictable vs. predictable stressors.

Our preregistered hypotheses were not supported, as indicated by a non-significant Drug (prazosin vs. placebo) X NPU Condition (unpredictable vs. predictable shock) interaction for startle potentiation (top,  $\eta_p^2 = .006$ ,  $b = 2.4 \mu\text{V}$ ,  $t(63) = 0.64$ ,  $p = .526$ ) and self-report (bottom,  $\eta_p^2 < .001$ ,  $b = 0.03$ ,  $t(63) = 0.18$ ,  $p = .857$ ).

Exploratory analysis suggest that prazosin may actually increase overall startle potentiation, Drug main effect  $\eta_p^2 = .107$ ,  $b = -8.0 \mu\text{V}$ ,  $t(61) = -2.71$ ,  $p = .009$ , but this was not observed for self-report,  $\eta_p^2 = .008$ ,  $b = 0.09$ ,  $t(63) = .70$ ,  $p = .484$ .

Prazosin did not affect baseline general startle reactivity,  $\eta_p^2 = .010$ ,  $b = -3.8 \mu\text{V}$ ,  $t(63) = -0.81$ ,  $p = .421$ .

## Open Science

Preregistered design & analysis plan: <https://osf.io/m8imp/>

Data and analysis code to be posted: <https://osf.io/un6h6/>

## Summary & Future Directions

Single acute dose of prazosin does not reduce stress reactivity in a healthy adult sample. We found this across three measures:

- 1) NPU task startle potentiation
- 2) NPU task self-reported anxiety
- 3) General startle reactivity.

Exploratory follow up analysis suggests that prazosin may acutely increase, rather than decreased, overall startle potentiation during threat of shock in the NPU task.

Future studies should examine the effects of chronic higher therapeutic dosing of NE- $\alpha$ 1 in patient samples (PTSD/AUD) on stress reactivity outcomes.

These findings join recent failures to replicate treatment effects of prazosin for PTSD and AUD, and suggest that targeting stress reactivity mechanisms via NE- $\alpha$ 1 antagonism may be less promising than originally hoped.

## References

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