• NE and CRF antagonists reduce the stress response to uncertain stressors and block stress-induced reinstatement of previously extinguished drug-seeking behavior in rodents.
• Our laboratory has helped to validate a human model of stressor reactivity that has:
  • Strong method and measure ties to preclinical literature in rodents & non-human primates.
  • Shown reliable, robust effects of drug administration & drug deprivation in dependent users.
• This stress-reactivity paradigm may be utilized as a surrogate endpoint in Phase 2a RCTs.

Predictable Shock Block (Certain Threat)

Unpredictable Shock Block (Uncertain Threat)

= Electric Shock to Fingers

Stress-Response Dampening Effects: Alcohol Administration Studies In Social Drinkers

• Participants: “Social” drinkers with no significant problems with alcohol use.
• Alcohol dose response (2 experiments): BAC range: 0.00% - 0.16%

Stress-Response Enhancing Effects: Drug Deprivation Studies In Tobacco, Marijuana Or Alcohol Dependent Users

• Smoker Participants: Regular heavy tobacco (Study 1) or marijuana (Study 2) users randomly assigned to one group:
  • Abstain from tobacco 24hrs or marijuana 3days
  • Continue normal ad libitum use prior to study
• Drinker Participants: Abstinent alcoholics 1-8 weeks since last drink and healthy controls (Study 5).
• Results: Drug deprivation increases stress-reactivity, especially during uncertain relative to certain threat.
• Conclusions: Biomarker of sensitized stress-reactivity in addicted individuals during periods of abstinence may reflect:
  • Risk marker for stress-induced relapse.
  • Surrogate endpoint to evaluate treatment efficacy.

Phase 2a Clinical Trial: Screening Prazosin As Treatment Of Stress-Induced Relapse In Alcoholism

Objectives & Aims

• Objective 1: To confirm norepinephrine alpha1 receptor involvement in startle potentiation during unpredictable stressors in humans with alcoholism.
• Objective 2: Evaluate efficacy of initial (2mg) and therapeutic (15mg) dose of Prazosin at reducing stress-reactivity among alcoholics in early abstinence and the relationship of this biomarker to treatment/response outcomes.
• Aim 1: Examine the effects of initial dose Prazosin (2mg vs. placebo) on responses to unpredictable stressors in abstinent alcoholics.
• Aim 2: Examine effects of a therapeutic dose Prazosin (15mg vs. placebo) on responses to unpredictable stressors.
• Aim 3: Examine predictive validity of laboratory biomarkers of stress-reactivity on 2-week relapse outcomes.

Method

• Design: Double-blind, placebo-controlled, mixed design, cross-over study.
• Participants: Abstinent alcoholics 1-8 weeks since last drink.
• Drug: Prazosin is a brain-penetrant norepinephrine alpha1 receptor antagonist.
• Initial Dose: Administer 2mg Prazosin and Placebo on two separate laboratory visits 2-7 days apart (order randomized & counterbalanced within-subjects).
• Therapeutic Dose: Participants titrate to 15mg Prazosin or Placebo (randomized between-subjects) over 2 weeks following 2nd initial laboratory visit.
• Stress-Reactivity Task: Assessed at 2 initial study visits (Aim 1: 2mg vs. Placebo; within-subjects) and 3rd study visit following 2 week titration (Aim 2: 15mg vs. Placebo; between-subjects).
• Treatment Outcome: Relapse to alcohol use is assessed after two weeks of Prazosin (Aim 3).