Sex-based Animal Model Studies identifying Effective Antidepressants for SSRI-resistant Depression at Altitude 🐼 🎇 📴 🖽 🖽





- Hypoxia

has the Highest rates of Depression & Suicide in the US despite also having the highest Antidepressant Prescription Rates

Living at Altitude (4,500ft) alters Human Physiology vs Sea Level: 1. Blood oxygen levels are significantly lower at Altitude 2. Forebrain Bioenergetic Markers are lower at Altitude

ANIMAL MODEL FOR DEPRESSION AT

After 2wks at sea level, 4,500ft or 10,000ft, rats are tested for depression-like behavior & SSRI efficacy in the Forced Swim Test



At Altitude, both males and females show increased Depressive symptoms in the FST

SSRIs at Altitude: Prozac, Paxil, Lexapro lose efficacy at altitude in both sexes, Zoloft does work.

Shami Kanekar, Robert Ettaro, Michael D Hoffman & Perry F Renshaw

• Living at Altitude: chronic exposure to Hypobaric

• MDD & Suicides 1 in Chronic hypoxic disorders (COPD, asthma, CVD disease, smoking)





MDD-linked regions: **PFC- prefrontal cortex** STR- striatum **HIP- hippocampus BST-** brainstem

↓Dopamine Males:

getics at Altitude MF: **↓** Creatine

Rodent brain levels of the Bioenergetic Marker Creatine decrease with time at Altitude



RESULTS: 5HTP-Pilot Study









Dietary 5HTP

- Only the highest dose improved **Brain** Serotonin
- No Antidepressant function

Was detrimental to Feeding & Weight gain

Dietary 5HTP studies were stopped after pilot tests

USTAR, Huntsman Mental Health Institude, University of Utah School of Medicine, VISN19 MIRECC & US Department of Veterans Affairs

Dietary CyCR (1%, 3wks) vs. food





1. Male and Female Rats at 4,500ft were given

• Dietary 5HTP (0.2-2%, 3wks)

Dietary CR (4%, 5wks)





Dietary CR: • **↑** Brain Energetics

- ↑ Female Serotonin
- **J** Male Serotonin

- **Dietary CyCR:**

CONCLUSIONS

- The serotonin precursor 5HTP was not Antidepressant at Altitude
- - **CR and CyCR improve Brain Energetics in a sex-based manner**





METHODS

We tested dietary treatments to correct brain deficits and improve depressive symptoms at altitude • 5-hydroxytryptophan (5HTP): intermediate Serotonin precursor- to correct serotonin deficit • Bioenergetic Drugs: Creatine (CR), Cyclocreatine (CyCR)- to correct energy deficit

- 2. Food consumed & weight gain measured wkly
- 3. Rats were tested for depressive symptoms in the **Forced swim (FST) and Sucrose preference tests**
- 4. Brain & Serum tested for CR, CyCR or Serotonin.

LTS: BIOENERGETIC COMPOUNDS

Bioenergetic Compounds CR & CyCR show sex-based Antidepressant Efficacy at Altitude **Both improve brain serotonin in Female rats, but reduce serotonin in Male** Further studies will evaluate mode of function of CR/CyCR and impact on anxiety at Altitude