Better Living Through Physics?

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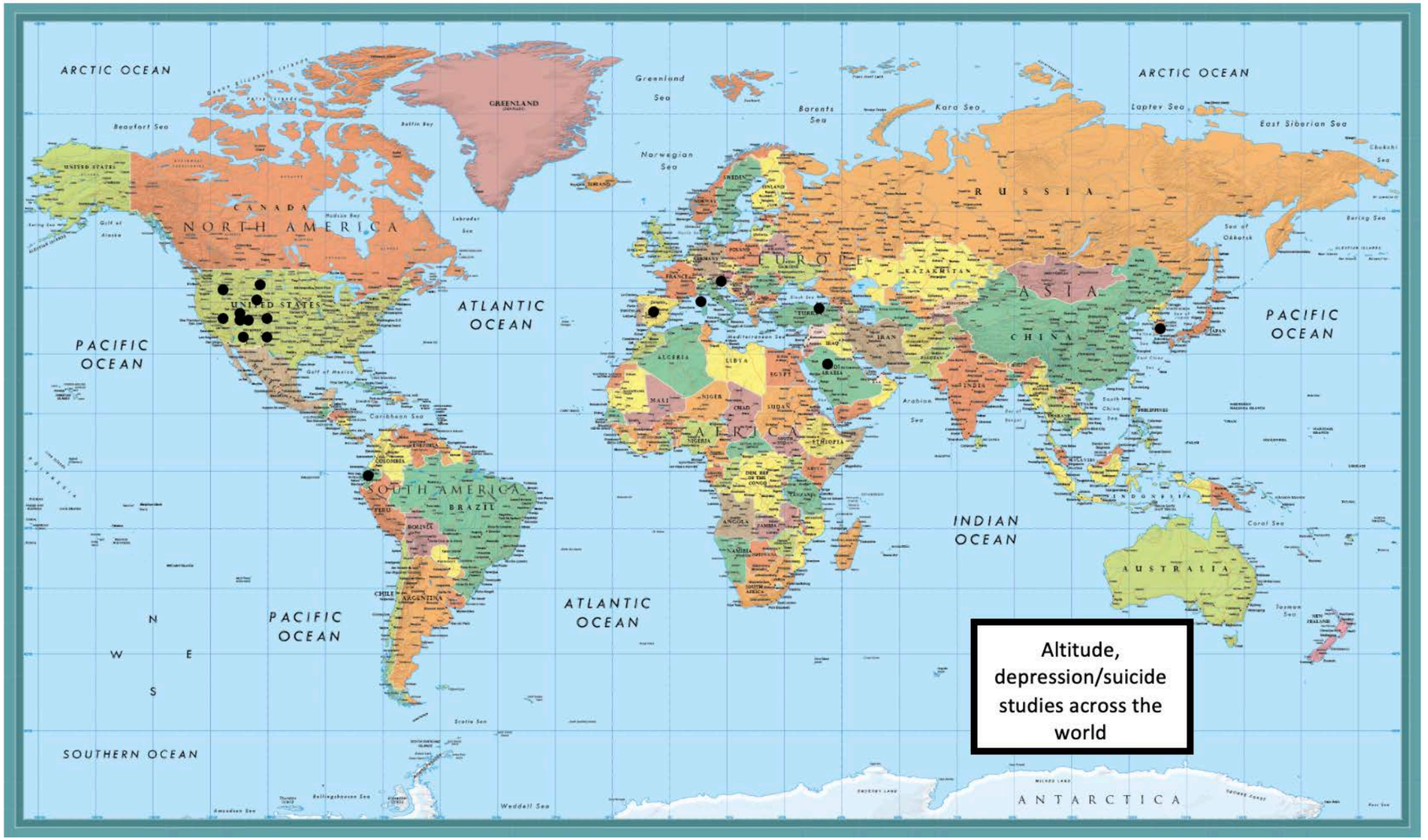
THE THEORY OF EVERYTHING



FUNDING SOURCES

University of Utah Seed Grant Funding

Utah Science, Technology, and Research initiative (USTAR)

Veteran's Affairs Rocky Mountain Mental Illness, Research, Education, and Clinical Center

Big Pharma

Little Pharma

CAVEAT EMPTOR!

- I file patents (~27 issued). But these are all assigned to my academic employer.
- I work with and occasionally for pharma, biotechs, and natural product companies. But I am expected to do this by USTAR.
- I do not pitch proprietary products or give drug company talks.
- I do not practice clinically. But I completed my general psychiatry residency at the MGH.

IN THE FOOTSTEPS OF GIANTS: MILDRED COHN, BRITTON CHANCE, JOHN LEIGH

UNIVERSITY OF PENNSYLVANIA

Mildred Cohn (1913-2009)

Britton Chance (1913-2010)

John S. Leigh (1939-2008)

Suicide and Geographic Diversity

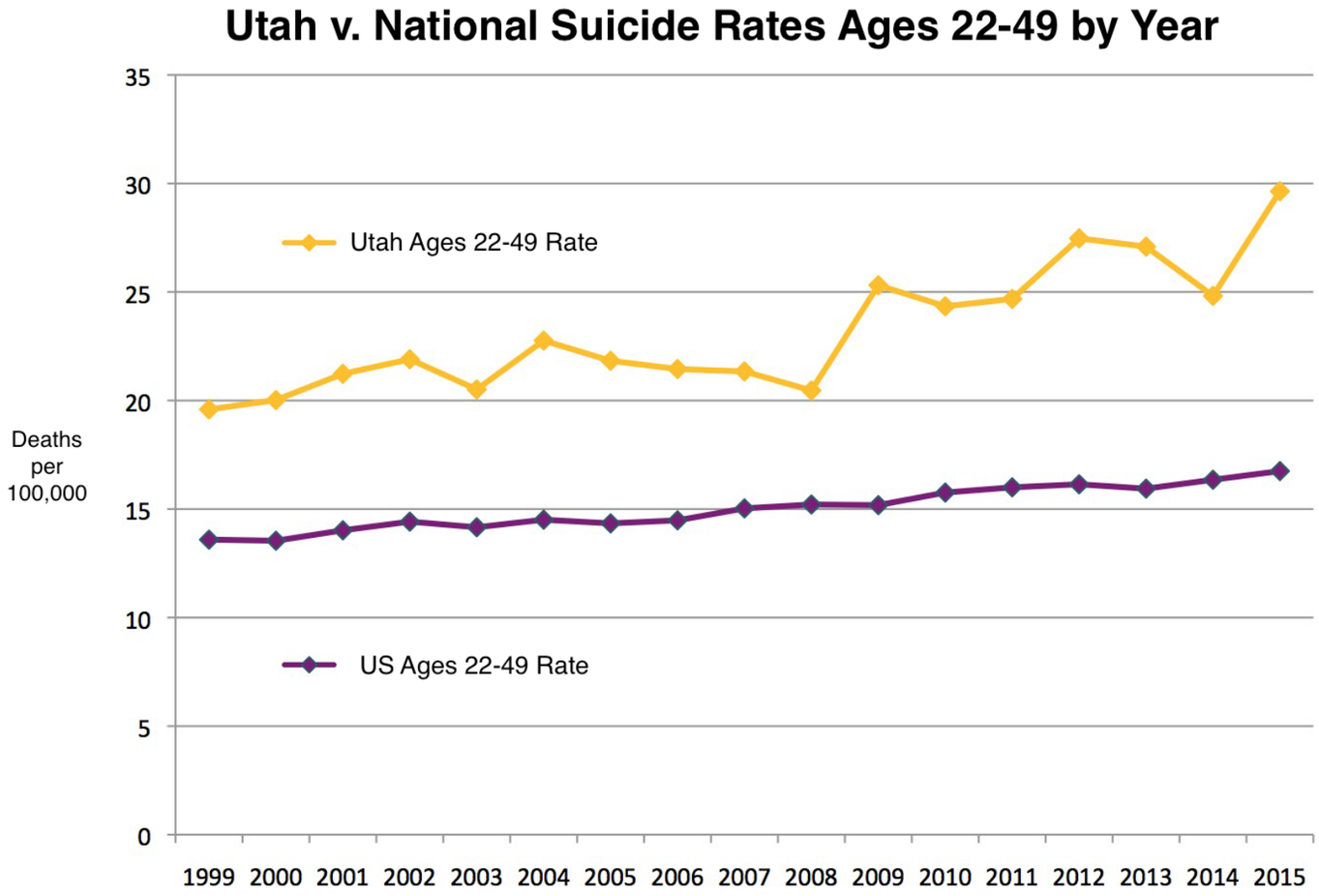
The Salt Lake Tribune

Utah has one of the highest suicide rates in nation

By Julia Lyon
Published: February 19, 2012

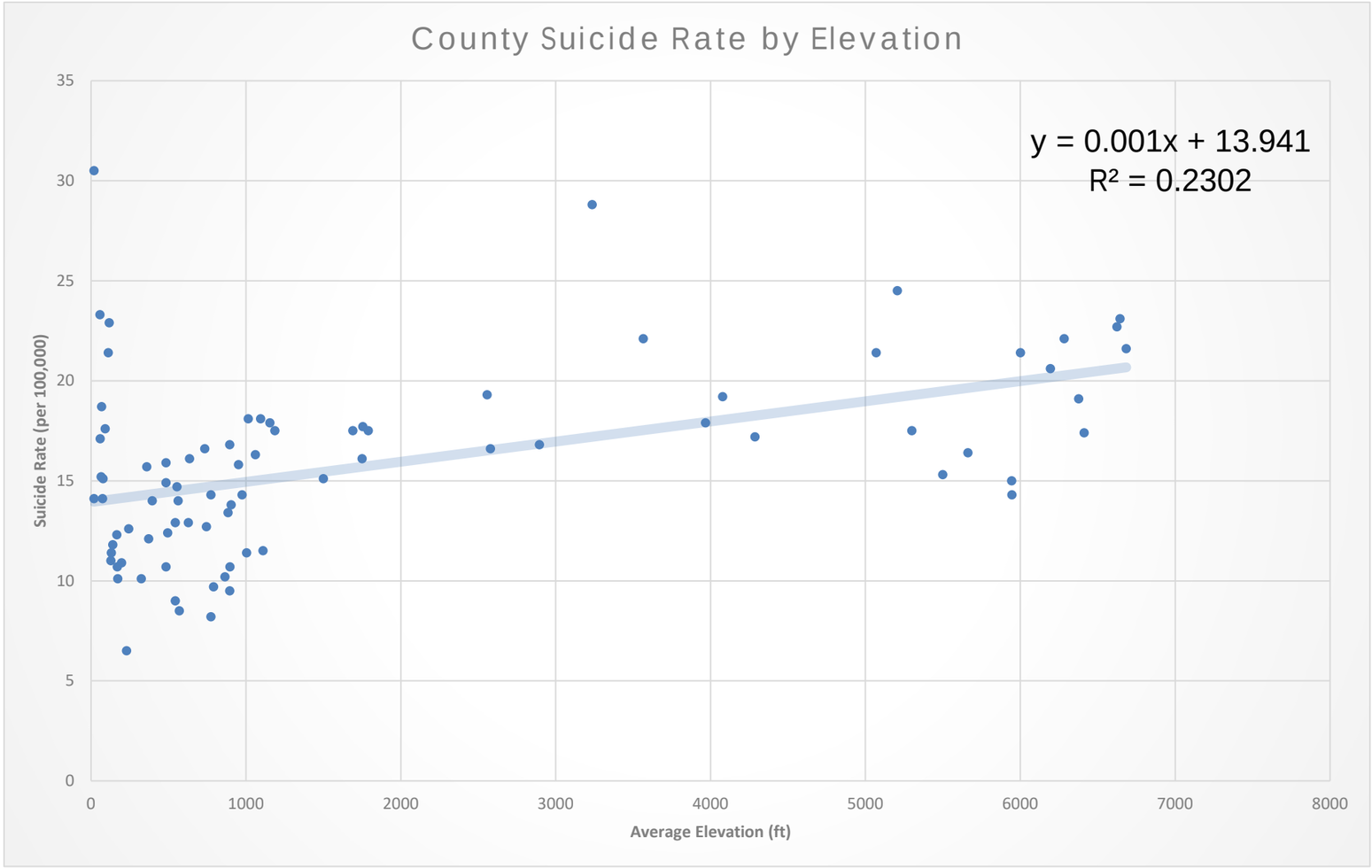
The number of suicides in Utah continues to climb, making it-once again-home to one of the highest suicide rates in the country. According to preliminary data from the Office of Vital Records and Statistics, 495 Utahns took their own lives in 2011, compared with 455 in 2010. Because Utah's population rose during the same time period, state officials do not consider the increase statistically significant. But they acknowledge suicide remains a major problem. A recent Centers for Disease Control and Prevention study of 2008 and 2009 data found that Utah had the highest percentage of adults with suicidal thoughts—6.8%-- compared with 2.1% in Georgia, the nation's lowest.

UTAH SUICIDE RATE BY ELEVATION



The above data is publicly available from the Centers for Disease Control and Prevention at http://www.cdc.gov/injury/wisqars/

NORTH CAROLINA SUICIDE RATE BY ELEVATION



HOW UTAHNS ARE DIFFERENT.. BUT SIMILAR TO SOUTH KOREANS, AUSTRIANS, SPANIARDS, SAUDI ARABIANS, TURKS, CHILEANS, AND PERUVIANS

↓Lithium in Drinking Water (Austria but not US)

↓ **PO_2**

15% at U of U

God

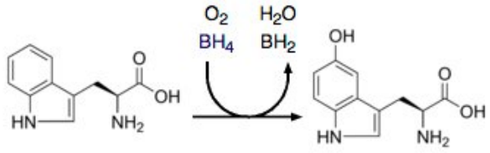
Phosphocreatine

$PCr + ADP \rightleftharpoons Cr + ATP$

Hachachka, 1996
Prescot, ongoing

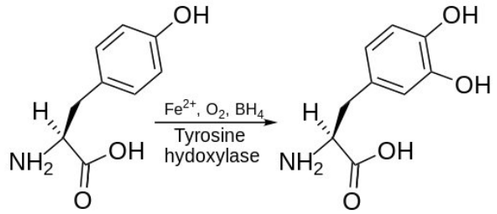
↓ 5HT

Tryptophan Hydroxylase



Katz, 1980

Dopamine/ Norepinephrine



Ray, 2010

Suicide and Altitude

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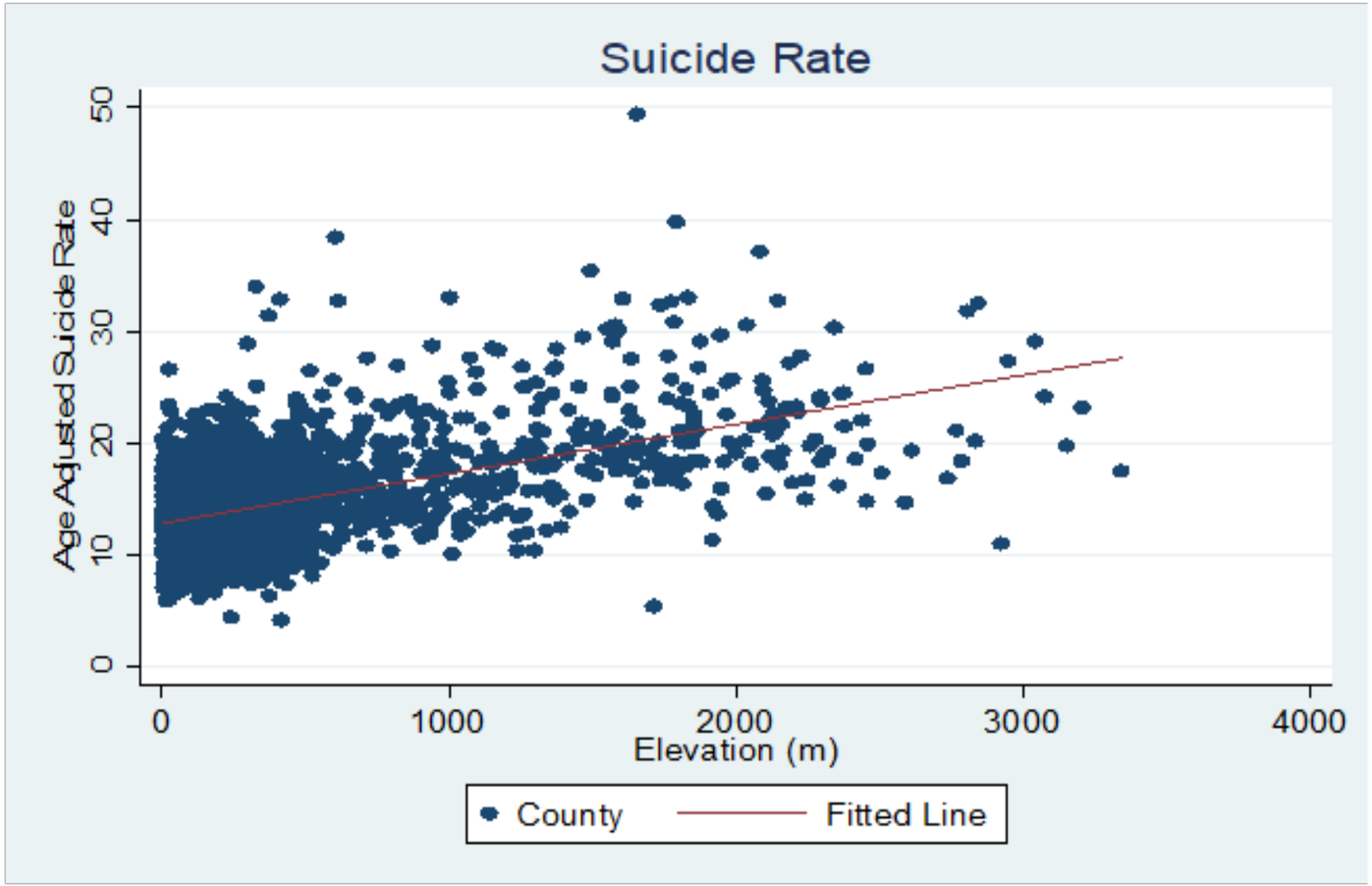
AGE-ADJUSTED SUICIDE RATE VS. MEAN ELEVATION OF EACH U.S. COUNTY



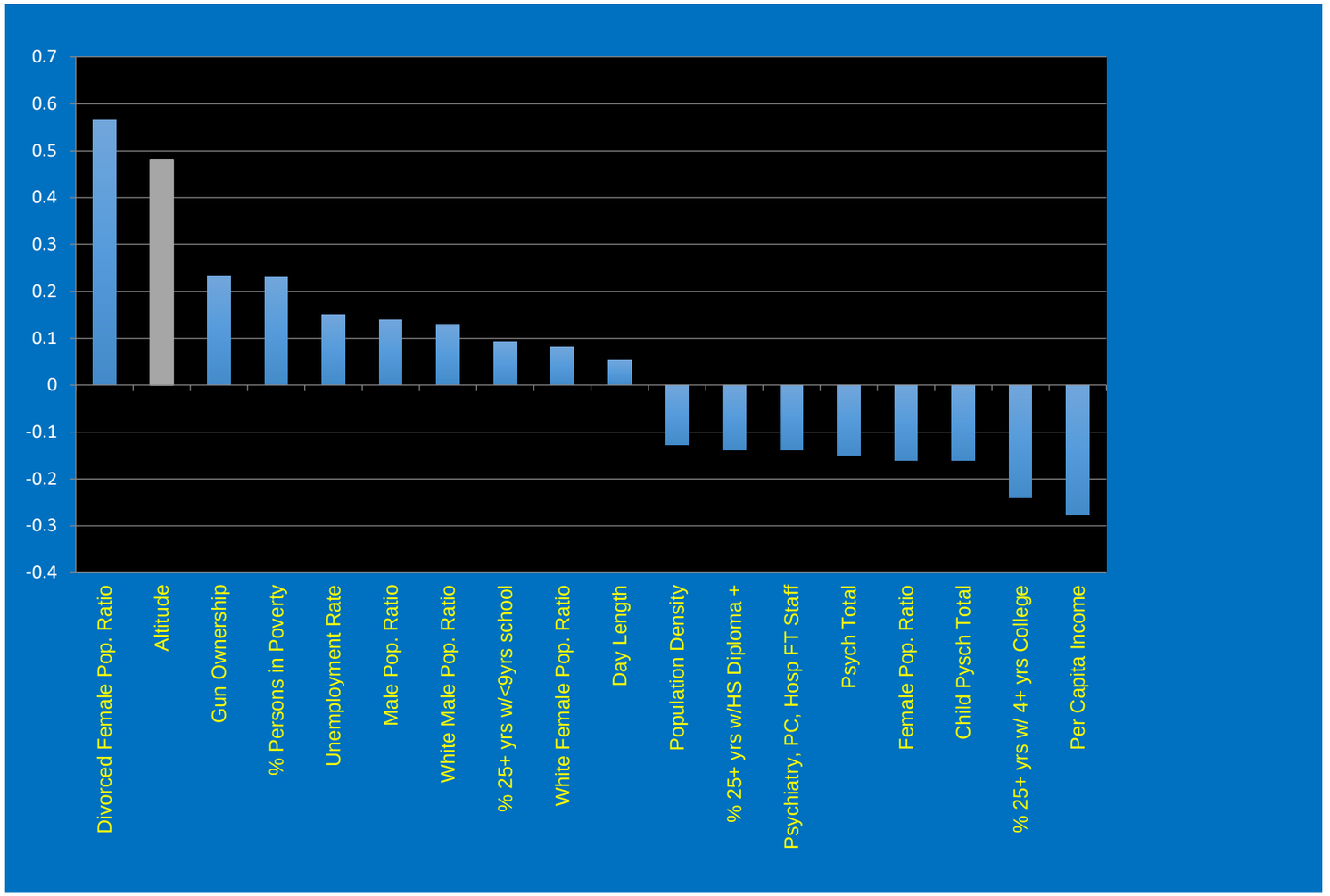
An r value of 0.50 suggests that altitude explains 25% of the variation in suicide rates across the United States....

Source: Kim et al., American Journal of Psychiatry (2011) January;168(1):49-54

BUT, NOTE THAT ALL CAUSE MORTALITY GOES DOWN WITH ALTITUDE!

- In the state of New Mexico, even COPD deaths (they call it “COLD”) were lower (in Caucasian males, at least).
- There’s a JAMA dialysis paper, and one or two others on kidney failure.
- The NEJM published (back in 1977) that coronary artery disease deaths are reduced at altitude.
- Apparently, heart transplant patients have improved survival if they live at > 2,000 feet
- In Switzerland, mortality from both heart disease and stroke is lower with altitude.
- Even heart transplant patients have improved survival at altitude(?!)

CORRELATION BETWEEN SUICIDE RISK FACTOR AND AGE-ADJUSTED SUICIDE RATES



Source: Kim et al. (2010) American Journal of Psychiatry (2011) January;168(1):49-54

SUICIDE RATE AND ELEVATION

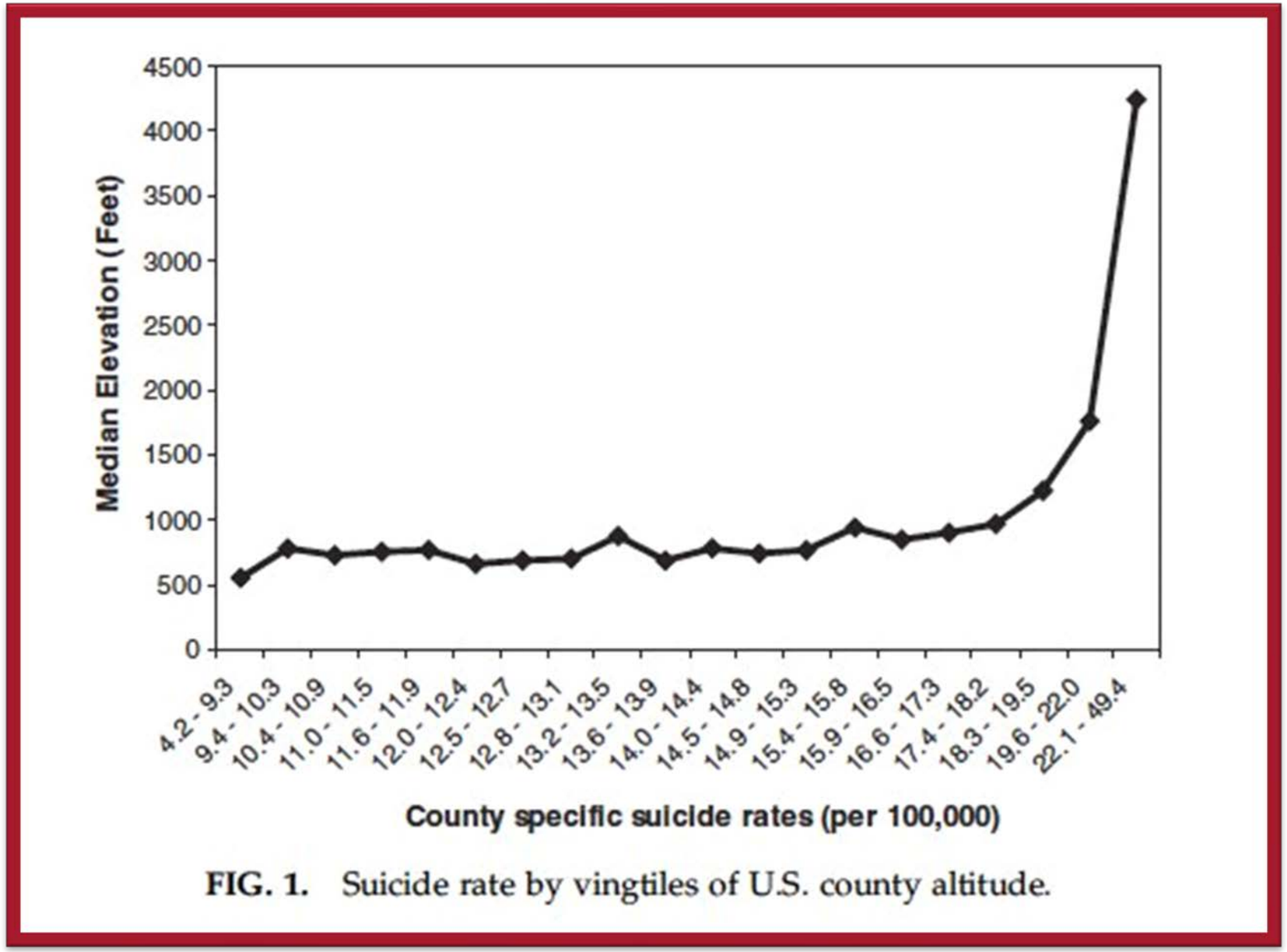


FIG. 1. Suicide rate by vingtiles of U.S. county altitude.

Source: Brenner B, Cheng D, Clark S, Camargo, CA. Positive association between altitude and suicide in 2584 U.S. counties. High Alt Med Biol. 2011; 12(1):31-5.

Depression and Altitude

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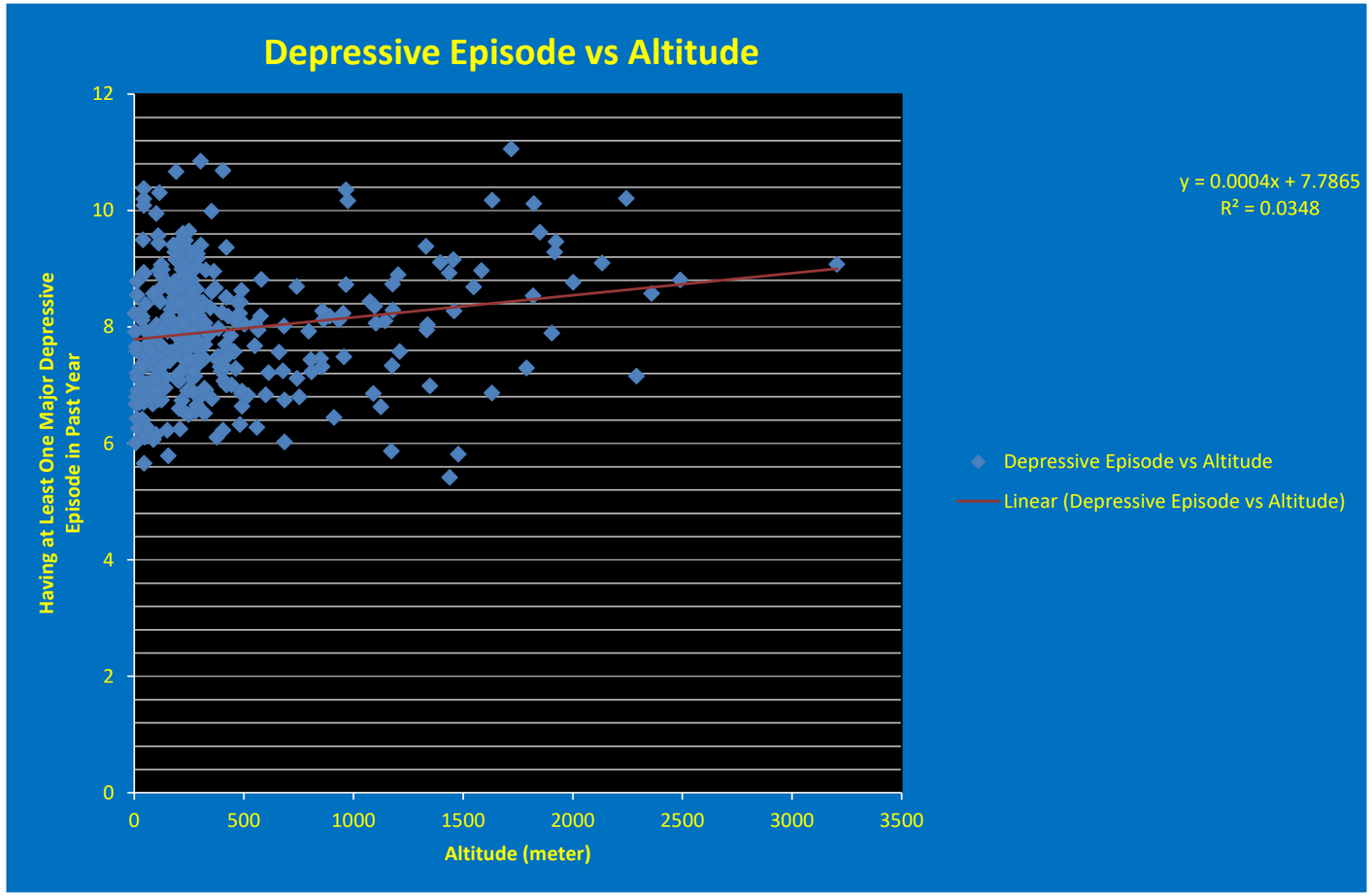
IS THERE A RELATIONSHIP BETWEEN ALTITUDE AND DEPRESSION?

HAVING AT LEAST ONE MAJOR DEPRESSIVE EPISODE IN PAST YEAR VS. ALTITUDE



Correlation r-value = 0.1865;
p-value = 0.0004

Source: DelMastro et al. Journal of Affective Disorders. 2011 Mar;129(1-3):376-9.

Hi Perry,

In 2013-2014 I lived in New Mexico at elevation of 7500 feet. I would often travel to Southern California for work and it had become seemingly apparent that when I returned to the higher elevation that I would "crash" within a few days and immediately fall into a deep depression.

Fast forward to now and I have since moved to Chicago, IL and sought treatment for my serotonin problem. This week I revisited New Mexico, and within a couple days I started to dip again... but what is incredibly fascinating is that I began experiencing the "Brain Zaps" people describe when withdrawing from SSRI's. I am familiar with them as once I missed a dose and experienced them, and once I attempted to lower dosage and experienced the same.

In other words, I have been experiencing withdrawal symptoms at higher altitudes without having reduced my medication. I thought this might add insight to your studies.

SUICIDAL IDEATION AMONG PATIENTS WITH MAJOR DEPRESSIVE DISORDER LIVING AT HIGH ALTITUDE

Personal characteristics	No Suicidal Ideation (n=107)		Suicidal Ideation (n=9)		*P* value
	No.	%	No.	%	
Gender:					
Females	89	90.8	9	9.2	0.181
Males	18	100.0	0	0.0	
Age at onset:					
<25 years	21	95.5	1	4.5	
25-50 years	70	93.3	5	6.7	
>50 years	16	84.2	3	15.8	0.341
Residence:					
Jizan	46	97.9	1	2.1	
Aseer	61	88.4	8	11.6	0.061

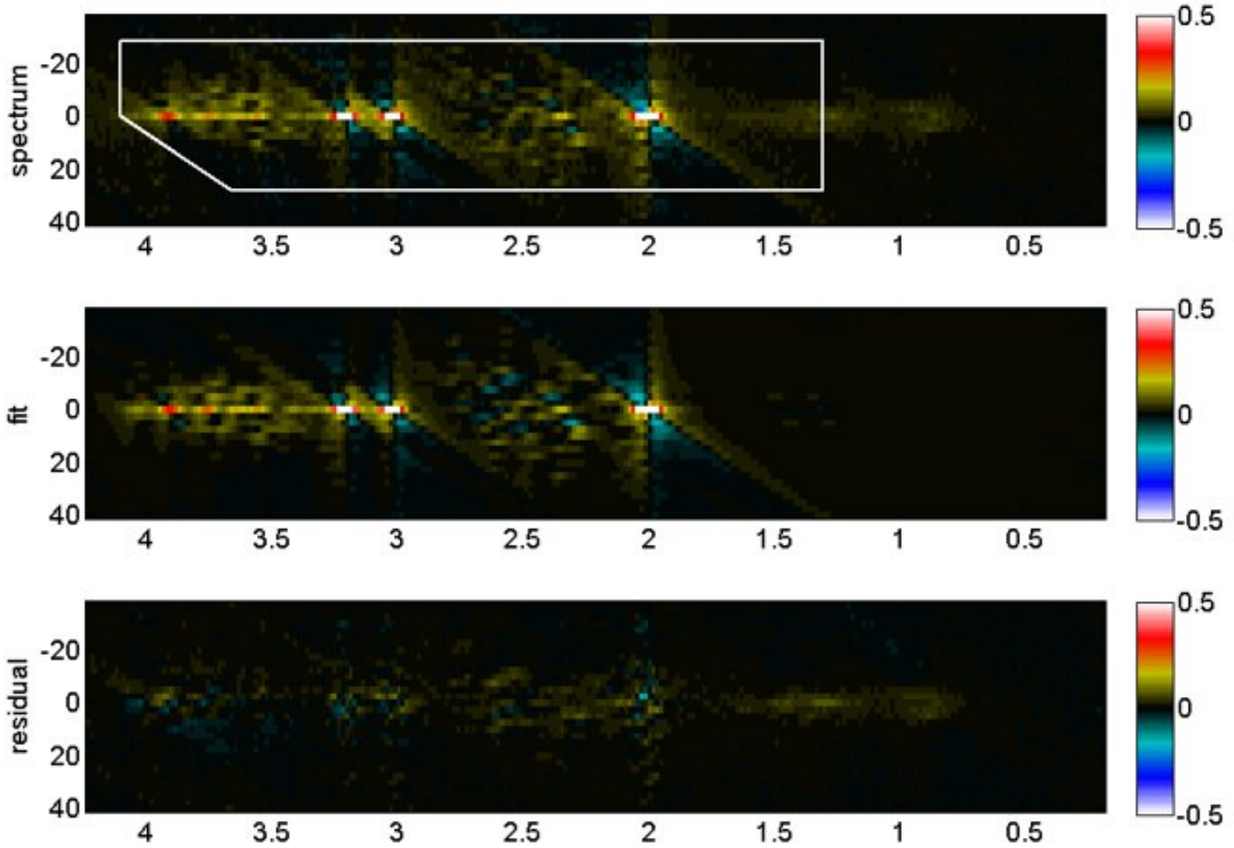
Source: Saeed A. Asiri, M.D. Med. J. Cairo Univ., Vol. 82, No. 2, December: 223-228, 2014

ALTITUDE VS. EQUIVALENT OXYGEN CONCENTRATION AT SEA LEVEL

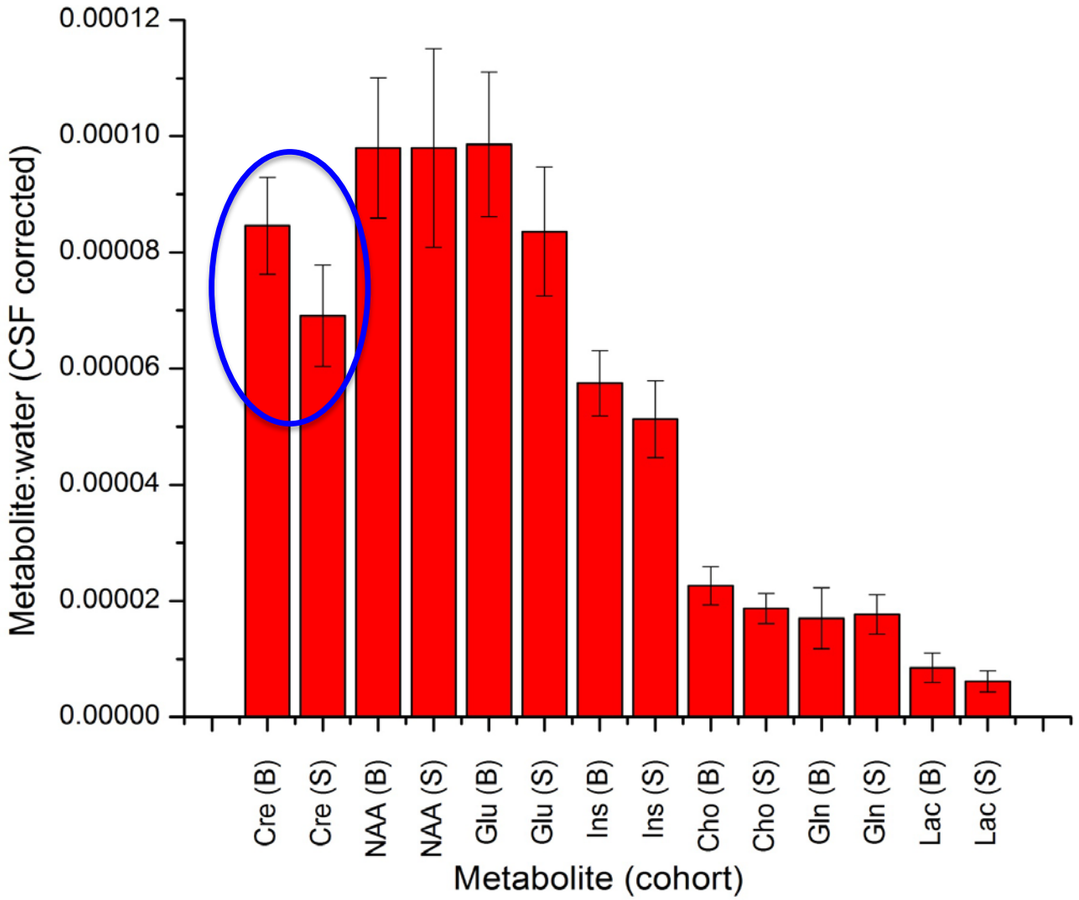
Altitude (Meters)	Altitude (Feet)	Barometric Pressure (P_B)	Partial Pressure of Oxygen (PiO_2)	Equivalent O_2 Concentration at Sea Level (FiO_2)	Decrease In FiO_2
Sea Level	Sea Level	759.6	149.1	0.209	0%
1,000	3,281	678.7	132.2	0.185	12%
1,219	4,000	661.8	128.7	0.180	14%
1,500	4,921	640.8	124.3	0.174	16%
1,524	5,000	639.0	123.9	0.174	17%
1,829	6,000	616.7	119.2	0.167	20%
2,000	6,562	604.5	116.7	0.164	22%
2,134	7,000	595.1	114.7	0.161	23%
2,438	8,000	574.1	110.3	0.155	26%
8,839	29,000	253.0	43.1	0.060	71%

Source: Auerbach PS, Wilderness Medicine, 5th Edition (2007)

1H MAGNETIC RESONANCE SPECTROSCOPY IS A GOOD TOOL FOR LOOKING AT CHANGES IN CEREBRAL METABOLISM IN THE BRAIN



ANTERIOR CINGULATE METABOLITES: SALT LAKE CITY (S) VS. BOSTON (B)



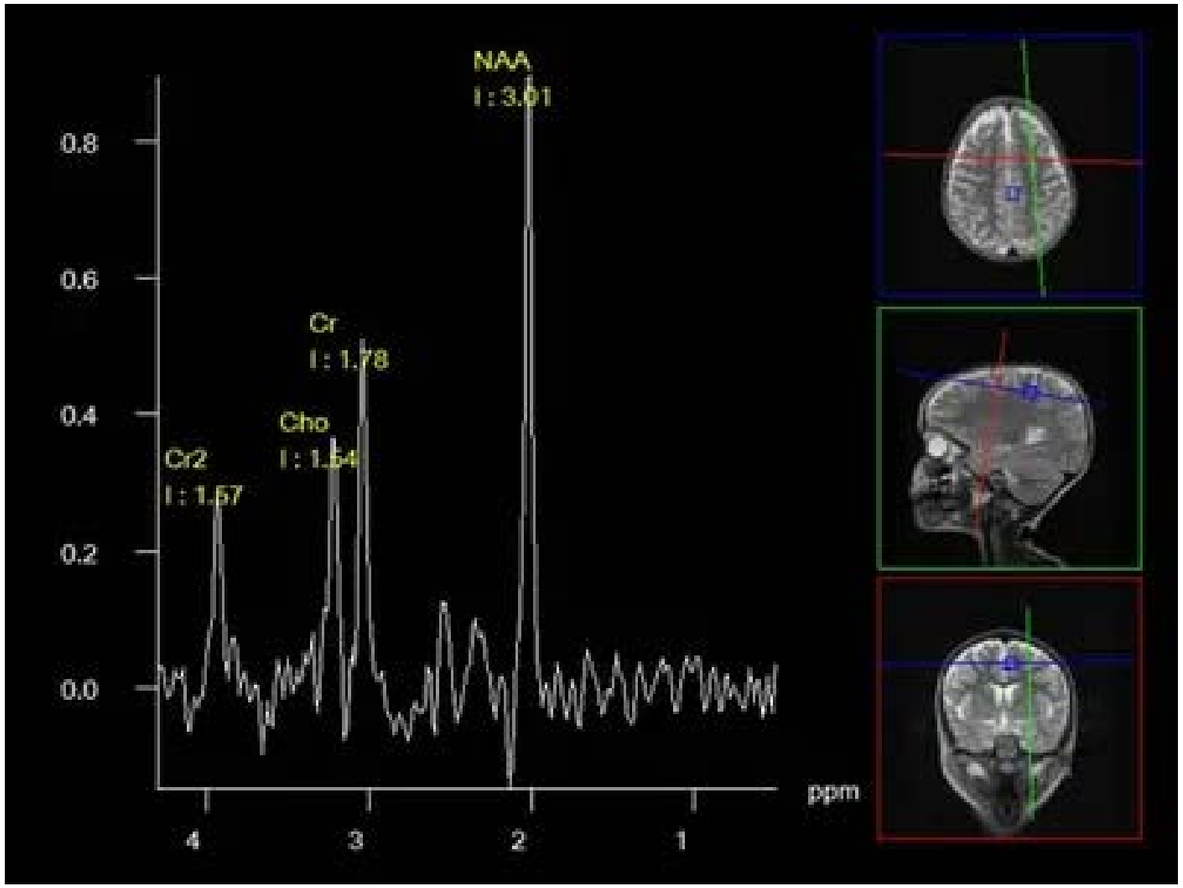
Cre = Creatine; NAA = N-Acetyl Aspartate; Glu = Glutamate; Ins = Myo-inositol; Cho = Choline; Gln = Glutamine; Lac = Lactate

Source: Prescot, unpublished data.

PHOSPHORUS-31

MAGNETIC RESONANCE SPECTROSCOPY

1H AND 31P SPECTROSCOPIES ARE HELPFUL IN UNDERSTANDING DIFFERENT MEASURES



Britannica, The Editors of Encyclopaedia. "magnetic resonance spectroscopy". *Encyclopedia Britannica*, 10 Aug. 2024, https://www.britannica.com/science/magnetic-resonance-spectroscopy. Accessed 5 September 2024.

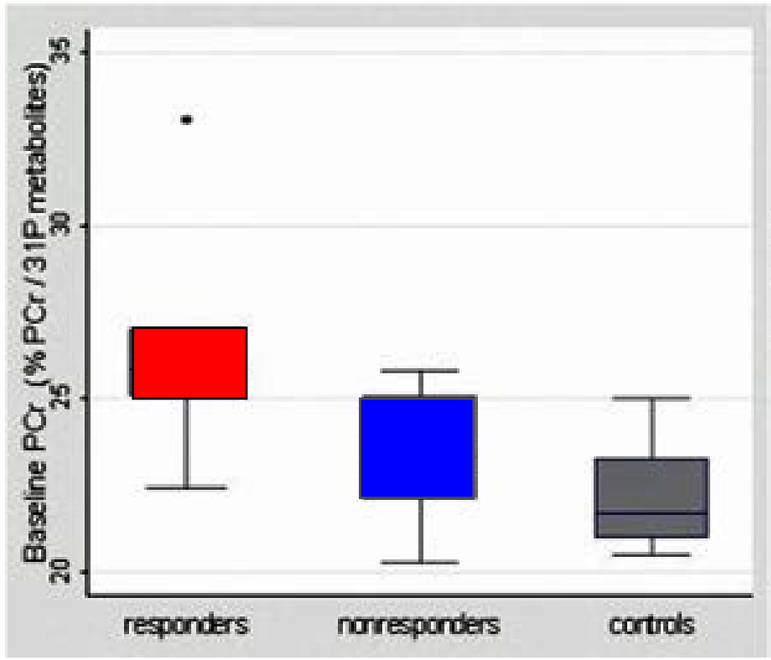
CREATINE KINASE REACTION:

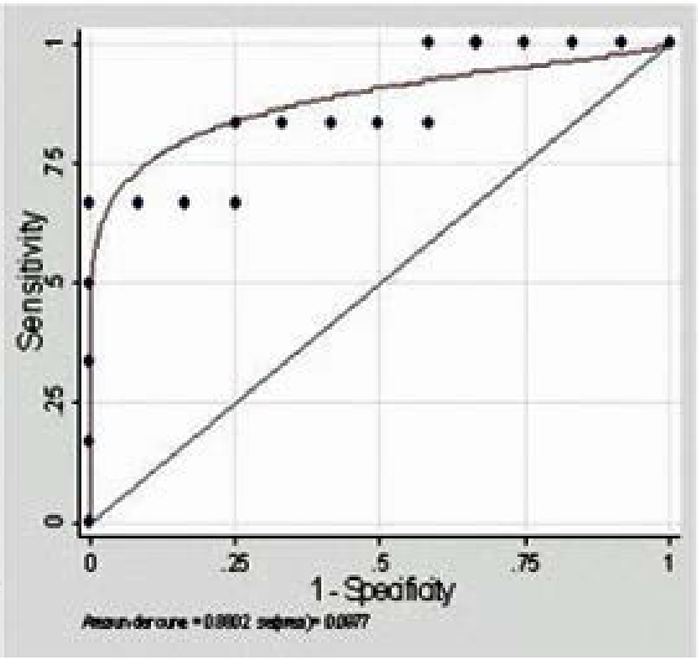
$$PCr^{2-} + ADP^{3-} + H^{+} = Cr + ATP^{4-}$$

Lower Levels of Nucleoside Triphosphate in the Basal Ganglia of Depressed Subjects: A Phosporous-31 Magnetic Resonance Spectroscopy Study

Constance M. Moore, M.Sc., Ph.D., James D. Christensen, Ph.D., Beny Lafer, M.D., Maurizio Fava, M.D., and Perry F. Renshaw, M.D., Ph.D.

PHOSPHOCREATINE IS ASSOCIATED WITH TREATMENT RESPONSE IN DEPRESSION





Baseline PCr Levels in:

- MDD Treatment Responders
- MDD Non-Responders
- Controls

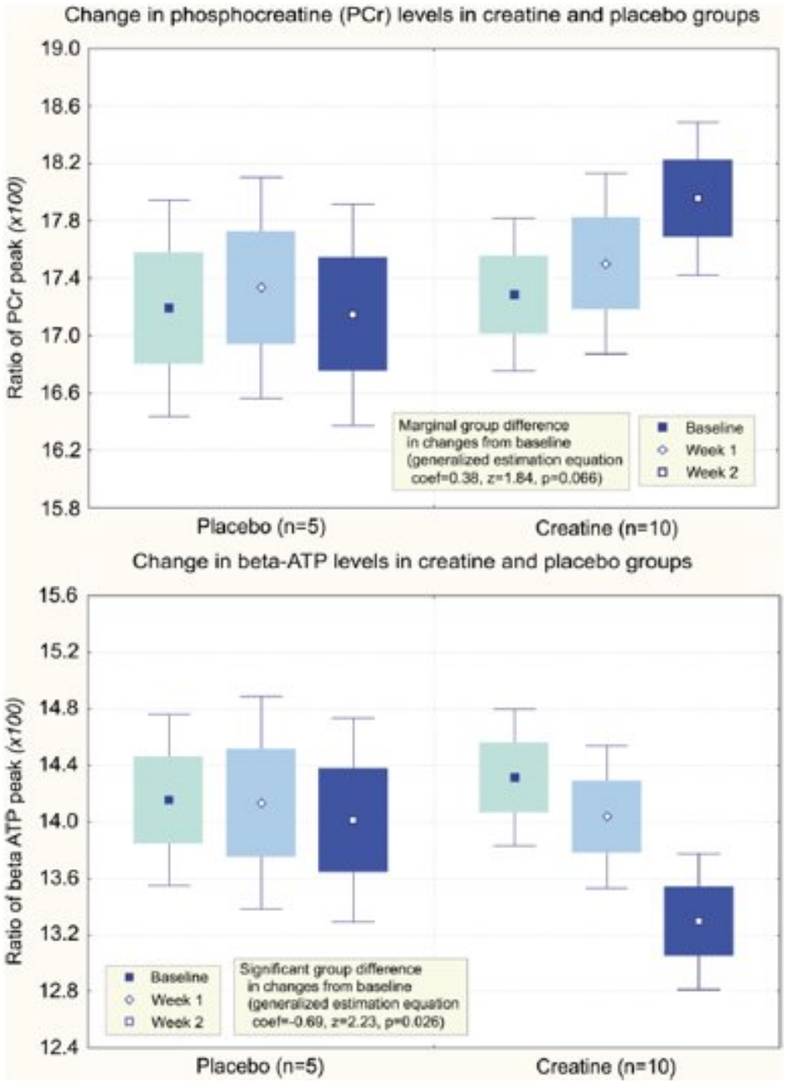
"Baseline PCr" Predicts Treatment Response

- Sensitivity = 83%
- Specificity = 75%

Area under the ROC curve = 0.88

Source: Iosifescu et al., Biological Psychiatry 2008; 63:12)

CREATINE SUPPLEMENTATION SHOWS ANTIDEPRESSANT EFFECTS



Lyoo et al. (2003)

MRS of high-energy phosphate metabolites in human brain following oral supplementation of creatine-monohydrate.

Psychiatry Research 123: 87–100

Δ PCr

Δ β-NTP (ATP)

Source: Lyoo et al. Psychiatry Research: Neuroimaging 2003; 123)

B-NTP IS SIGNIFICANTLY REDUCED IN DEPRESSED PATIENTS

TABLE 1. Concentration of the Phosphate Metabolites and pH in the Basal Ganglia of Patients With Major Depression and Comparison Subjects

	Comparison Subjects (N=18)		Depressed Patients (N=35)		ANOVA (df=1, 51)	
Metabolite	Mean	SD	Mean	SD	F	p
Concentration (%)						
Phospho-monoesters	7.2	3.8	7.5	3.7	0.09	<0.76
Inorganic phosphate	6.8	1.4	6.9	2.0	0.06	<0.80
Phosphodi-esters	26.8	5.3	28.4	4.9	1.15	<0.29
Phospho-creatine	16.0	4.9	16.7	4.5	0.26	<0.61
Nucleoside triphosphate						
γ	12.1	3.1	11.9	3.2	0.04	<0.84
α	16.1	2.9	15.9	2.5	0.02	<0.87
β	15.0	3.7	12.6	3.8	5.07	<0.03
pH	6.99	0.08	6.96	0.08	1.19	<0.28

CREATINE KINASE REACTION:

$$PCr^{2-} + ADP^{3-} + H^{+} = Cr + ATP^{4-}$$

NUTRITIONAL SUPPLEMENT: CREATINE?

Additional evidence for possible treatment of depression with creatine

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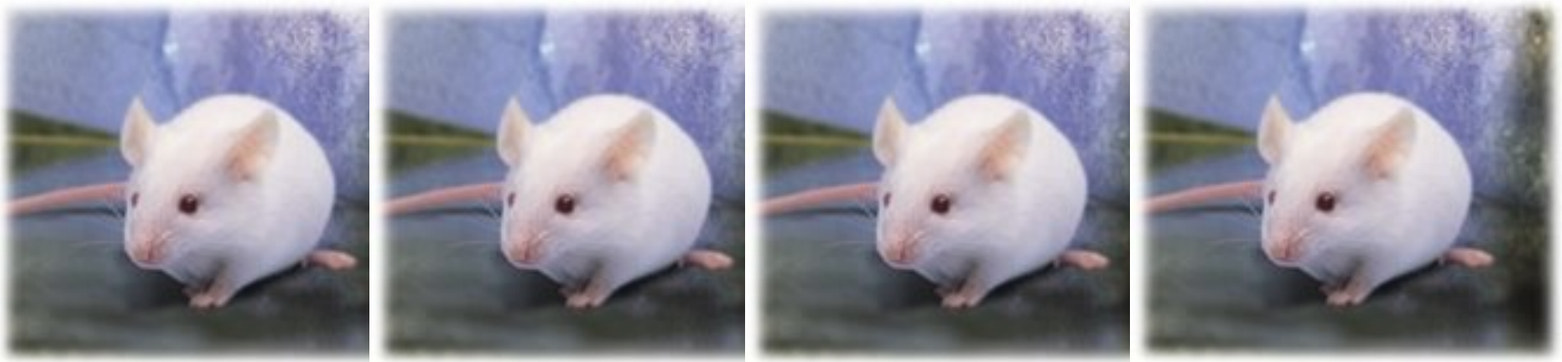
RATS ARE NOT HUMANS WITH AFFECTIVE ILLNESS

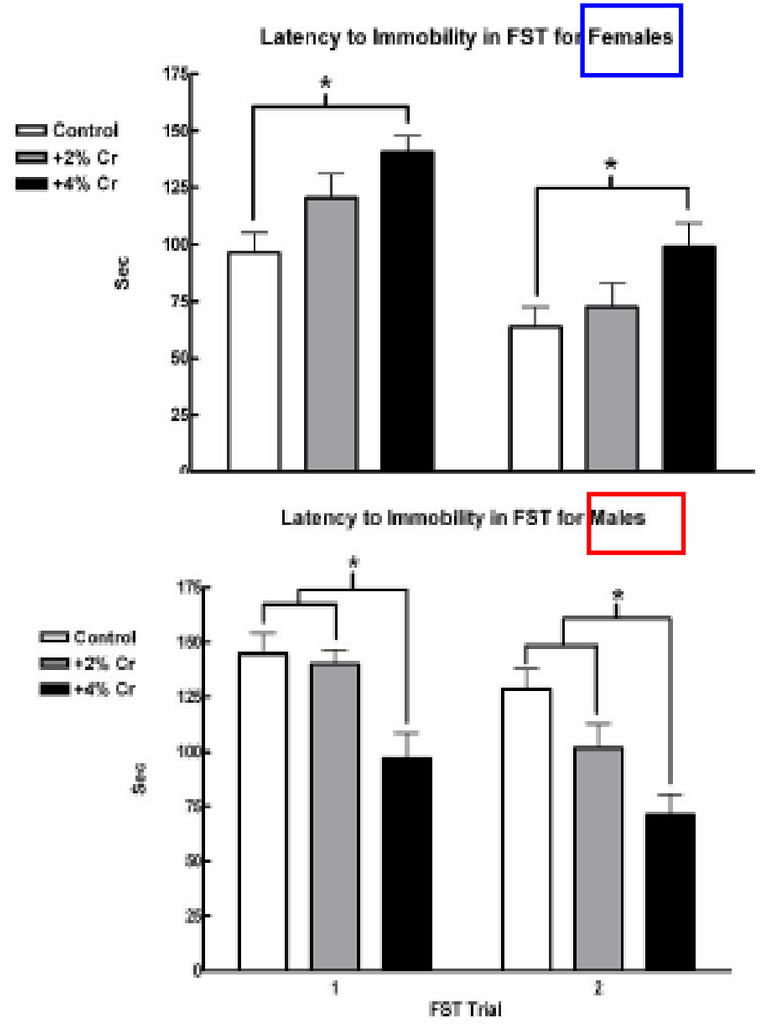


Happy Sad Grumpy Hopeless

Source: Carlezon et al

LEARNING MORE FROM RATS...

CHRONIC CREATINE SUPPLEMENTATION ALTERS DEPRESSION-LIKE BEHAVIOR IN RODENTS IN A SEX-DEPENDENT MANNER



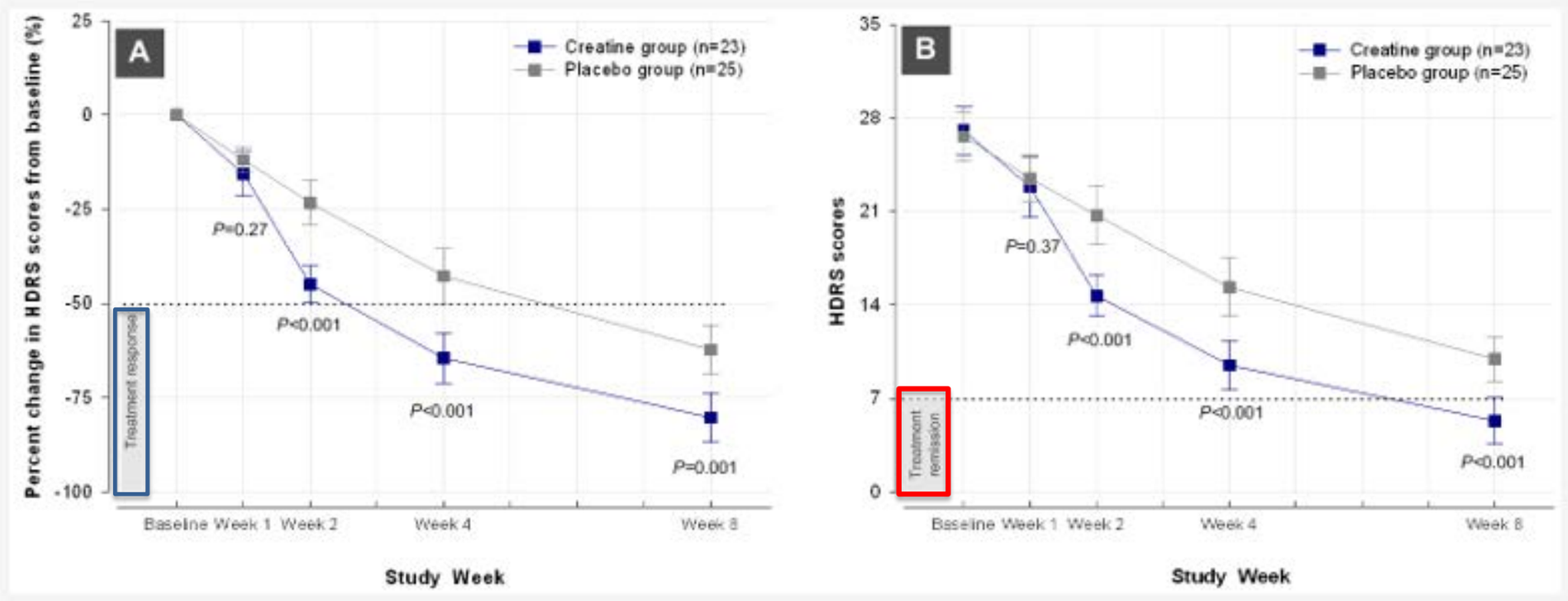
FEMALES

MALES

Rats were housed overnight at reduced PO_2

Source: Allen et al., 2010

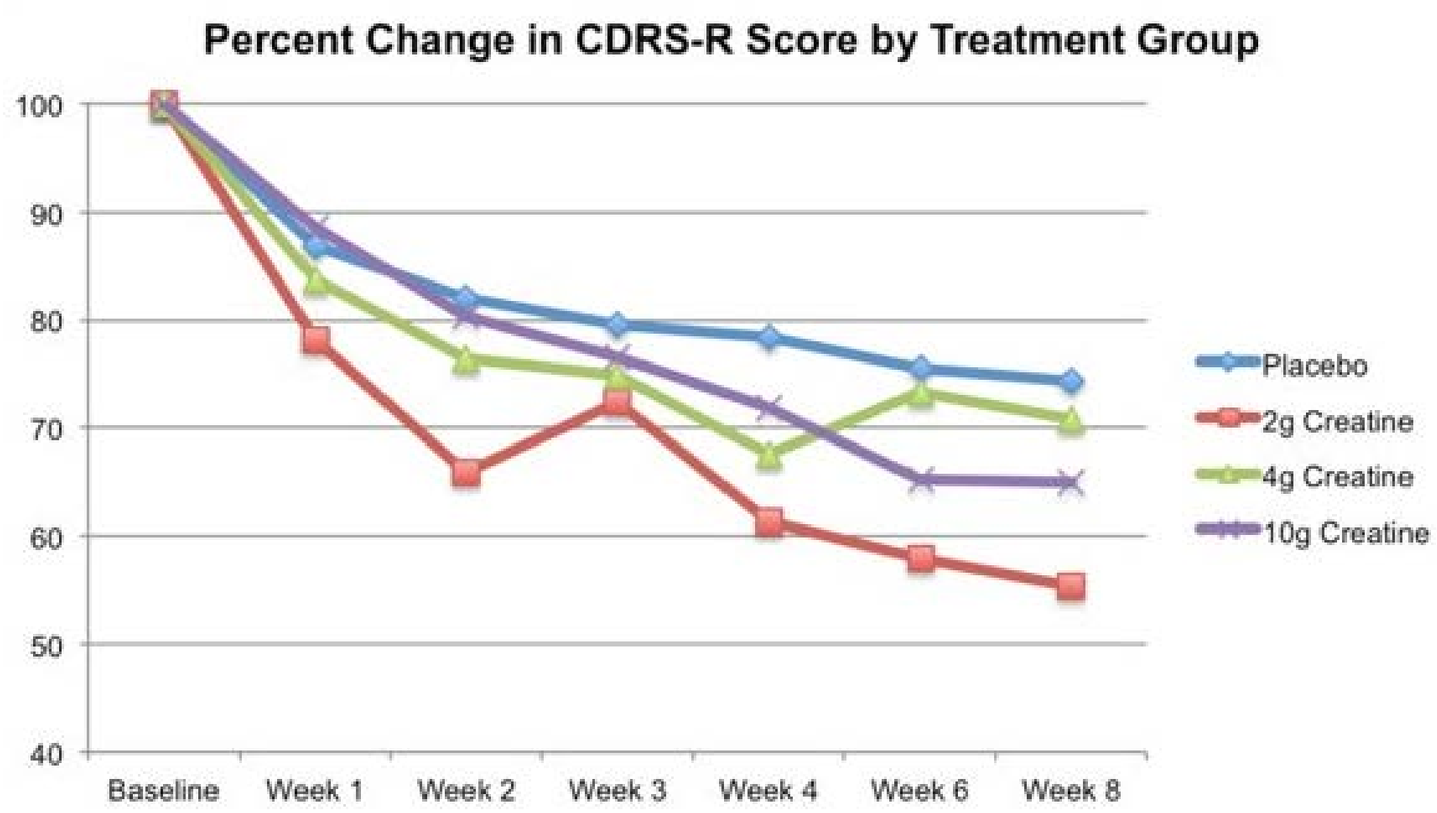
SSRI AUGMENTATION IN ADULT FEMALE MAJOR DEPRESSION: RCT OF CREATINE VS. PLACEBO ADDED TO LEXAPRO®



[A] **CLINICAL RESPONSE:** Percent decrease in Hamilton Depression Rating Scale scores (RESPONSE = ⇓50%)

[B] **CLINICAL REMISSION:** Change in HDRS scores from baseline to 8 weeks (REMISSION < 7)

PERCENT CHANGE IN CHILDREN'S DEPRESSION RATING SCALE-REVISED (CDRS-R) SCORES FROM BASELINE TO WEEK 8, DISPLAYED BY TREATMENT GROUP



CONCLUSION

- Understanding CNS energy utilization has important implications for understanding and treating suicide and depression.
- Animal and human studies have shown evidence that creatine demonstrates effective treatment outcomes.

CURRENT AND FUTURE DIRECTIONS

- Continued investigation of mitochondrial dysfunction and bioenergetics in mood disorders.
  - Ex: Using dual-coil 1H-31P MRS
- Translating methods to study bioenergetics using 7Tesla Magnetic Resonance Imaging
- Additional studies of creatine supplementation
  - In combination with different supplements
  - In other populations (anxiety, PTSD)

Questions?