The Impact of Living at Altitude on Depression and Antidepressant Function in Utah Women: The Need for Novel Antidepressants

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Abstract
Objectives: Utah has the highest rates of depression and suicide in the US, despite high rates of antidepressant prescriptions. People living at altitude are exposed to chronic hypobaric hypoxia, which may disrupt brain serotonin and bioenergetic function, to worsen depression and reduce selective serotonin reuptake inhibitor (SSRI) function. We therefore (1) used an animal model to study altitude-related depression, and (2) evaluated novel therapeutics in depressed Utah women.

Methods: We examined depression and SSRI function in rats housed at altitude. In treatment-resistant women, we tested antidepressant potential of compounds which correct hypoxia-induced brain deficits: creatine monohydrate (CrM) for bioenergetics or 5-hydroxytryptophan (5HTP) for serotonin deficit.

Results: At altitude, female rats exhibit increased depression and lack of antidepressant response to SSRIs (except sertraline). In treatment-resistant women, adjunctive CrM and 5HTP+CrM improves depression status and bioenergetic function.

Conclusions: With significantly lower basal brain serotonin levels than men, women are likely more susceptible to altitude-related depression. Targeted treatment may be required: sertraline, CrM or 5HTP+CrM show promise in improving mood and reducing suicidal ideation in women living at altitude or with hypoxic diseases.

Introduction
Major depressive disorder (MDD) affects over 16.5% of the US population, with lifetime prevalence of up to 12% in men and 25% in women (Trivedi, 2008). Depression affects women more severely than men, potentially due to several biological and psychosocial mechanisms (Dalla, 2010). MDD is linked to poor serotonergic neurotransmission, and healthy women exhibit 52% lower rates of brain serotonin synthesis than men (Nishizawa, 1997), reduced serotonin receptor binding and higher excretion of serotonin metabolites (Dalla, 2010). Poor basal serotonin transmission may contribute to greater vulnerability to MDD in women.
Living at altitude is demographically linked to heightened risk for MDD (DelMastro, 2011) and suicide (Brenner, 2011; Haws, 2009; Kim 2011), the most negative outcome of unresolved depression. Living at altitude involves chronic exposure to hypobaric hypoxia (the low partial pressure of oxygen-ppO2- at altitude). People with chronic hypoxic disorders (COPD, asthma, cardiovascular disease, smoking) similarly exhibit higher rates of MDD and suicide, vs. those with other chronic diseases (osteoporosis, diabetes) (Goodwin, 2003; Webb 2012). Chronic hypoxia may therefore worsen MDD status and suicidal behavior (Young, 2013), implying a role in treatment-resistant depression (TRD).
Living at altitude may be linked to a brain serotonin deficit. Rats exposed to extremes of altitude (1-14days, 20,000-25,000ft) show reduced brain serotonin levels (Kumar, 2011). Serotonin is synthesized in two steps: the rate-limiting first step requires tryptophan hydroxylase 2 (TPH2) and

molecular oxygen to convert tryptophan to 5-hydroxytryptophan (5HTP). 5HTP is then converted to serotonin in an oxygen-independent second step. Chronic hypobaric hypoxia decreases TPH2 activity, lowering levels of brain 5HTP and serotonin. Hypoxia may also compromise efficacy of selective serotonin reuptake inhibitors (SSRIs), the most widely prescribed of antidepressants (Preskorn, 1996). SSRIs improve depression status by blocking the serotonin transporter to increase synaptic serotonin concentrations. However, in animal models of low brain serotonin, SSRIs can lose antidepressant efficacy (Durkin, 2008; Kulikov, 2011). By reducing brain serotonin, hypobaric hypoxia may thus simultaneously impair depression status and exacerbate SSRI-treatment resistance.

Living at altitude is also linked to brain hypometabolism. 1Hydrogen or 31Phosphorus-magnetic resonance spectroscopy (1H-MRS or 31P-MRS) scans allow in vivo measurement of brain biomarkers for cellular energy production (Kondo, 2011a). 1H-MRS neuroimaging of age- and gender-matched healthy residents living at moderate altitude (4,500 ft, Salt Lake City, UT) vs. those at sea level (Belmont, MA or Charleston, SC) identified a deficit in forebrain levels of the bioenergetic marker creatine (Cr) in those at altitude (Renshaw, 2012). A similar deficit in forebrain Cr was found in female rats after housing at an altitude of 10,000ft for a week, implying that hypobaric hypoxia can induce this deficit (Bogdanova 2014). Cr plays an important role in regulating energy metabolism, and low Cr is representative of cellular hypometabolism (Kondo, 2011a). A bioenergetic deficit is similarly seen in key depression-linked brain regions in MDD patients, which improves with effective treatment, but remains unchanged in non-responders (Iosifescu 2008). Living at altitude could thus increase vulnerability to MDD by causing brain deficits in serotonin and Cr levels.

Utah is representative of a high altitude state with significant burden of depression and suicidal behavior. Between 2000-2006, Utah exhibited the highest antidepressant prescription rates in the US: 18.4% vs. the US average of 10.8% (Cox, 2008). In Utah, 68% of antidepressants are prescribed for women, and >80% are for SSRIs (Gaskill, 2010). Despite this, Utah showed the highest depression index in the US in 2007, based on four criteria: annual percentage of adults and adolescents reporting a major depressive episode, adults reporting serious psychological distress, and rates of suicide (Mark, 2007). Over 30-40% of MDD patients taking antidepressants do not respond adequately to treatment (Al-Harbi, 2012; Trivedi 2008), and treatment-resistance leads to unresolved depression, and increases suicidal ideation and suicide attempts. The Rocky Mountain States exhibit by far the highest rates of suicidal ideation (5.2% vs. 3.7%, CDC, 2011) and completed suicide (17.7 vs. 11.3 per 100,000) (Mark, 2007) in the US. Of particular relevance, the State of Utah had the highest annual prevalence of suicidal ideation in 2008-2009 (6.8%) – a rate that, incredibly, is more than three times that of Georgia, the US state with the lowest prevalence (2.1%) (CDC, 2011). Moreover, Utah women contend with significantly greater burden of suicidal thoughts than men: 8.1% vs 5.6%, vs. the US average of 3.8% (women) vs. 3.5% (men) (CDC, 2011). Similarly, high rates of suicidal ideation are noted in women in the high-altitude States of Idaho (7%), Nevada (9%) and New Mexico (6%). Suicidal risk factors include cultural and socioeconomic factors (eg., poverty, rural residence, population density) as well as biological ones (eg., age, sex, mental illness), but depression is almost always observed in those who think about and attempt suicide. The poor quality of life inherent in 8% of Utah women expressing suicidal thoughts suggests a critical need for targeted interventions for depression in this population. Here we first describe translational animal model studies of the impact of housing at altitude on depression-like behavior (DLB) and antidepressant function. Further, we describe clinical trials of non-traditional adjunctive treatments to correct hypoxia-linked neurochemical deficits in Utah women with TRD: with creatine monohydrate (CrM) to correct bioenergetics (Kondo 2016; Kondo, 2011) or with combination therapy of 5HTP+CrM to improve both serotonergic and bioenergetic deficits.

Methods

I. Animal Studies:

Animals:

Male and female Sprague Dawley (SD) rats were received from Charles River (Raleigh, NC). All procedures were approved by the Institutional Animal Care and Use Committees of the University of Utah and the Veterans Affairs Salt Lake City Health Care System, and were performed in accordance to the NIH Guide for Care and Use of Laboratory Animals.

Altitude Simulations:

The altitude groups consist of sea level (SL), 4,500ft (4.5K) and 10,000ft (10K), plus a 20,000ft (20K) group in Study 1. Animals were housed in barometric chambers used to alter the ambient pressure at our facility (4,500ft): the hyperbaric chamber mimicked SL conditions (21% ppO2), and the hypobaric chamber mimicked 10K (15% ppO2) and 20K (10% ppO2), while the 4.5K group was housed at local conditions (18% ppO2) adjacent to the altitude chambers.

Forced Swim Test (FST):

The FST is a well-established test for DLB and antidepressant function, widely used in pre-clinical antidepressant development (Bogdanova, 2013). After a week at altitude, rats were tested for DLB in the modified FST (Kanekar 2015). In the FST, a rat is placed in a clear tank (25cm diameter, 65cm tall) filled to 48cm deep water at 25oC (Detke, 1996), and behavior videotaped. The FST is conducted in 2 sessions: a conditioning pretest and 24hrs later, the test FST to assay for DLB.

Treatment:

In study 2, rats were injected with antidepressant or vehicle (C) at 1hr, 19hrs and 23hrs after the pretest FST (Detke 1996). Antidepressants were tested at optimal doses shown to be effective in the FST (Detke 1996): fluoxetine hydrochloride (Prozac®, 20mg/kg), paroxetine hydrochloride (Paxil®, 20mg/kg), escitalopram oxalate (Lexapro®, 20mg/kg), sertraline hydrochloride (Zoloft®,10mg/kg), or the TCA desipramine hydrochloride (8mg/kg, positive control).

Data Analysis:

FST behavior is presented as percent time spent swimming, climbing or immobile. Latency to immobility (LTI) is the time taken to achieve the first 10sec of immobility (Kanekar 2015). DLB in the FST is a measure of behavioral despair in response to the inescapable stress of forced swim (Bogdanova 2013). Increased immobility and a shorter LTI represent DLB in the FST, and antidepressants reduce immobility and increase LTI by ≥20%. Serotonergic antidepressants (SSRIs) improve DLB by increasing swimming, while noradrenergic/dopaminergic antidepressants (desipramine) increase climbing (Detke 1996).

Data was analyzed by two-way analysis of variance (ANOVA) to investigate effects of altitude and gender (Study 1), or altitude and treatment (Study 2). Data is presented as mean ± standard error of the mean (M±SEM). Statistical significance was determined at $p<0.05$, presented after Bonferroni corrections.

II. Clinical Trials

All studies were approved by the University of Utah Institutional Review Board.

Study 1. Dietary Cr in Treatment-Resistant Adolescent Females:

Inclusion Criteria:

Participants were women between 13-20yrs of age with a primary diagnosis of MDD, with fluoxetine (Prozac®, open-label study) (Kondo, 2011) or equivalent SSRI dose (placebo-controlled study) (Kondo 2016) treatment for ≥8wks with ≥4wks at a dose of ≥40mg/day, and a Children's Depression Rating Scale-Revised (CDRS-R) raw score ≥40 at screening. Exclusion criteria included renal disease, psychotic symptoms or active problematic use of alcohol or illicit drugs. Complete blood count, metabolic panel, and urinalysis were obtained at baseline and at study conclusion.

Treatment and Outcome Analyses:

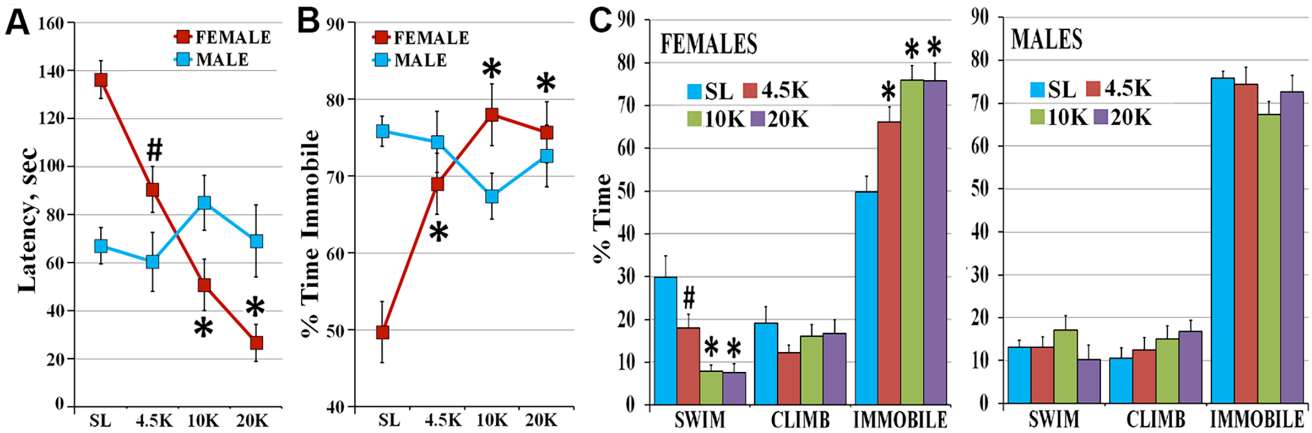
In the open-label study, MDD patients received Creapure® brand CrM (AlzChem AG, Trostberg, Germany), 4g oral daily for 8wks (Kondo, 2011). In the placebo-controlled study, participants were randomly assigned to 2g, 4g or 10g CrM or placebo daily for 8wks (Kondo 2016). Vital signs and adverse signs were recorded at each visit. Rating

scales administered were the CDRS-R, the Clinical Global Impressions scale-Severity (CGI-S) and the Columbia Suicide Severity Rating Scale (C-SSRS). The primary outcome was change in CDRS-R score from baseline. In vivo 31P-MRS neuroimaging was used to measure brain metabolites involved in cellular energy production, including Cr, phosphocreatine (PCr) and -nucleotide phosphates (measuring adenosine triphosphate or ATP), vs. a baseline of total phosphate resonance (TP). 31P-MRS scans were conducted on participants prior to and after treatment, and on age-matched healthy control adolescents.

Study 2. Dietary 5HTP+Cr in Treatment-Resistant Adult Women:
Inclusion Criteria:
Adult women were recruited with moderate-severe MDD at baseline as measured by Hamilton Depression Rating Scale (HAM-D) scores ≥16, with ≥8wks of treatment with an SSRI or serotonin norepinephrine reuptake inhibitor (SNRI) (Kious, 2017).

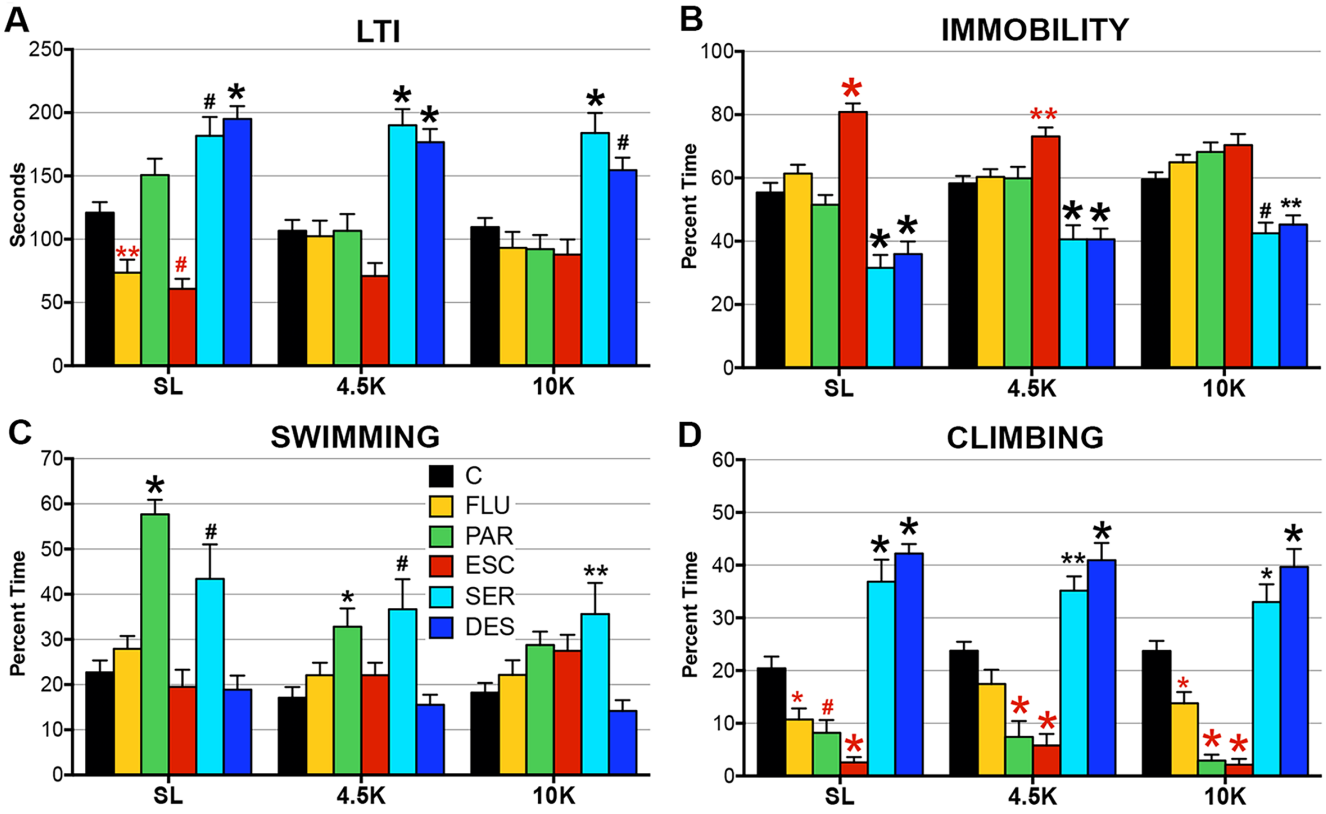
Open-label treatment consisted of dietary 5HTP+CrM for 8wks, with visits at 1wk, 2wks, 4wks, 6wks and 8wks, and 2 post-treatment visits (10wks, 12wks). Participants received 5g of Creapure® and 100mg Fuller Enterprise's 5HTP (Fuller Enterprise Inc., Ontario, Canada) daily for 8wks, to supplement ongoing SSRI/SNRI treatment. Study outcomes were measured by HAM-D, Montgomery-Asberg Depression Rating Scale (MADRS), CGI-S, and Beck Anxiety Inventory (BAI) scales. C-SSRS and Young Mania Rating Scale (YMRS) identified adverse effects. Since 5HTP is linked to serotonin syndrome and/or eosinophilia myalgia syndrome (Turner, 2006), subjects were screened at each visit. Blood tests were conducted at screening and follow up. Primary outcome was a change from baseline HAM-D scores. HAM-D, MADRS and BAI scores were analyzed by repeated-measures linear mixed model, with Sidak correction for multiple comparisons. Statistical significance was defined as $p<0.05$.

Results
I. Animal Studies
Study 1. Altitude and Depression:
Rats were tested for DLB in the FST after a week of housing at SL, 4.5K, 10K or 20K (Kanekar 2015). For LTI, two-way ANOVA showed no effect of gender, a strong effect of altitude ($p<0.0001$) and of their interaction ($F(3,88)=12.8$, $p<0.0001$, Fig 1A, 1C). In females, LTI decreased significantly with altitude ($F(3,44)=28$, $p<0.0001$), but not in males. For immobility, a significant effect was seen of altitude ($p=0.014$) and of the interaction between altitude and gender ($F(3,88)=9.5$, $p<0.0001$). Immobility increased significantly with altitude in females, but not males ($F(3,44)=10.5$, $p<0.0001$, Fig 1B, 1C).



(Figure 1)

Study 2. Altitude and SSRI Function:
After housing for a week at SL, 4.5K or 10K, female rats were treated with the SSRIs fluoxetine, paroxetine, escitalopram or sertraline, or the TCA desipramine and tested for DLB in the FST (Fig 2) (Kanekar, 2018). For LTI, two-way ANOVA showed a main effect of treatment ($p<0.0001$), none of altitude ($p=0.3$) and a significant effect of their interaction ($F(10,266)=2.4$, $p=0.009$, Fig 2A). For immobility, significant effects were seen of antidepressant ($p<0.0001$), altitude ($p=0.01$) and their interaction ($F(10,267)=1.97$, $p=0.03$, Fig 2B). For swimming, significant effects were seen of treatment ($p<0.0001$) and altitude ($p=0.0006$), and of their interaction ($F(10,267)=2.6$, $p=0.004$, Fig 2C). For climbing, a significant effect was seen of antidepressant ($p<0.0001$), but none of altitude or their interaction ($F(10,268)=0.8$, $p=0.67$, Fig 2D).

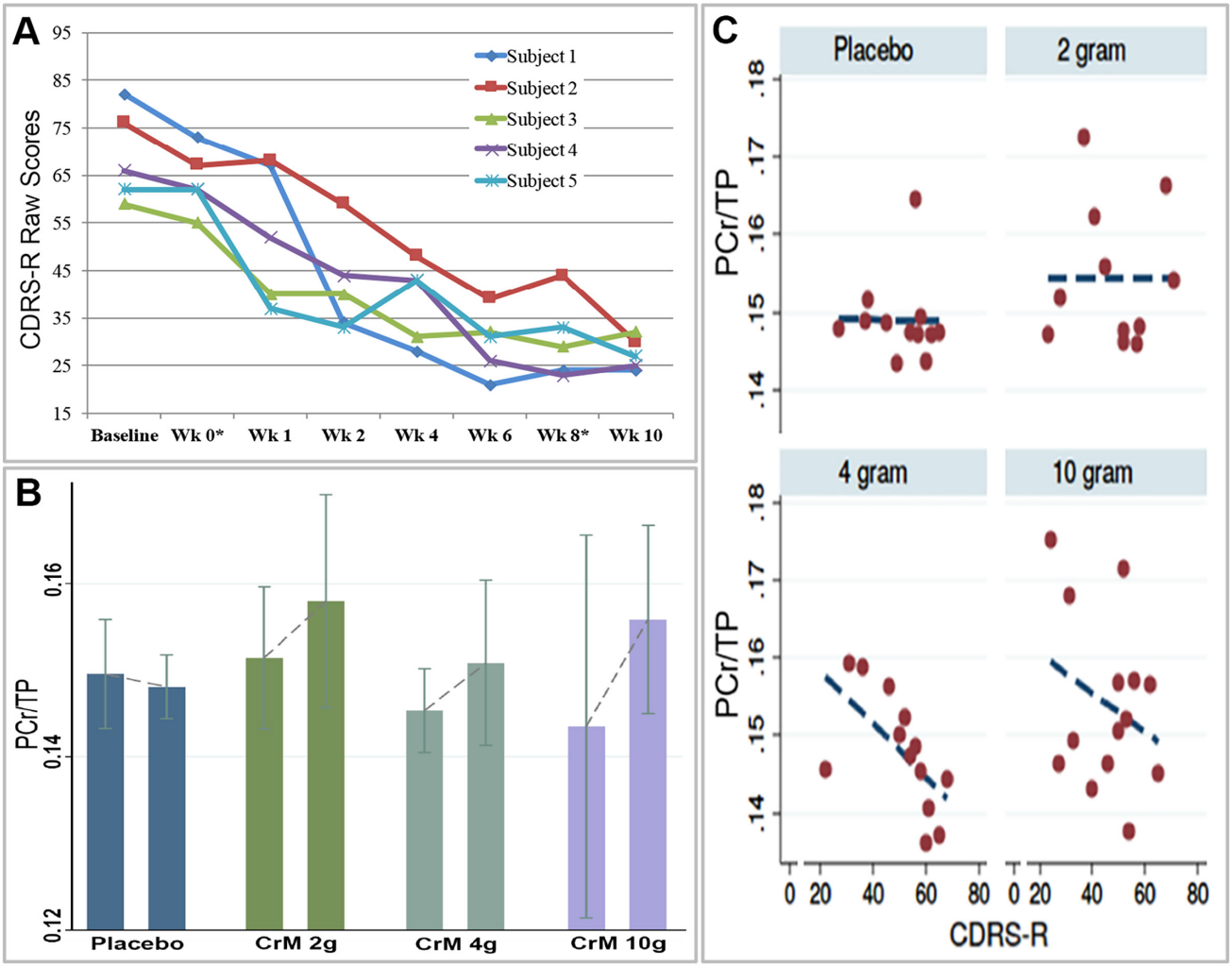


(Figure 2)

II. Clinical Trials
Study 1. Dietary CrM in Treatment-Resistant Adolescent Females:
Five patients completed 8wks of adjunctive CrM and 31P-MRS scans in the open-label study, with no adverse effects seen in vital signs, laboratory tests or behavior (Kondo, 2011). Mean CDRS-R score decreased by an average of 56% from 69±9 (M±SD) to 31±8 after treatment (Fig. 3A). After 8wks treatment, depressed adolescents exhibit a significant increase in forebrain PCr/TP ($p=0.02$, paired t-test) vs. healthy controls. Participants' CDRS-R scores inversely correlated with the change in PCr/TP ($p<0.04$). Four of 5 MDD patients endorsed a history of suicidality: 4 had suicidal ideation, and two attempted suicide prior to this study. During treatment, two reported no suicidal ideation, while suicidal ideation resolved during the study in others, and remained absent at the 10wk follow-up visit.

In the placebo-controlled dose-ranging study, participants were randomized to receive placebo or CrM at 2g, 4g or 10g daily for 8wks (n=6-

8/treatment). A drop in CDRS-R scores was seen across treatment groups (Kondo 2016). Pre- and post-treatment 31P-MRS scans revealed higher frontal lobe PCr/TP levels after CrM treatment, but not in placebo controls (Fig 3B): PCr/TP increased by 4.6% at the 2g dose, 4.1% with 4g, and 9.1% with 10g, while the placebo group showed a 0.7% drop. Lower depression scores correlated to higher fore-brain PCr/TP ($p<0.02$, Fig 3C).



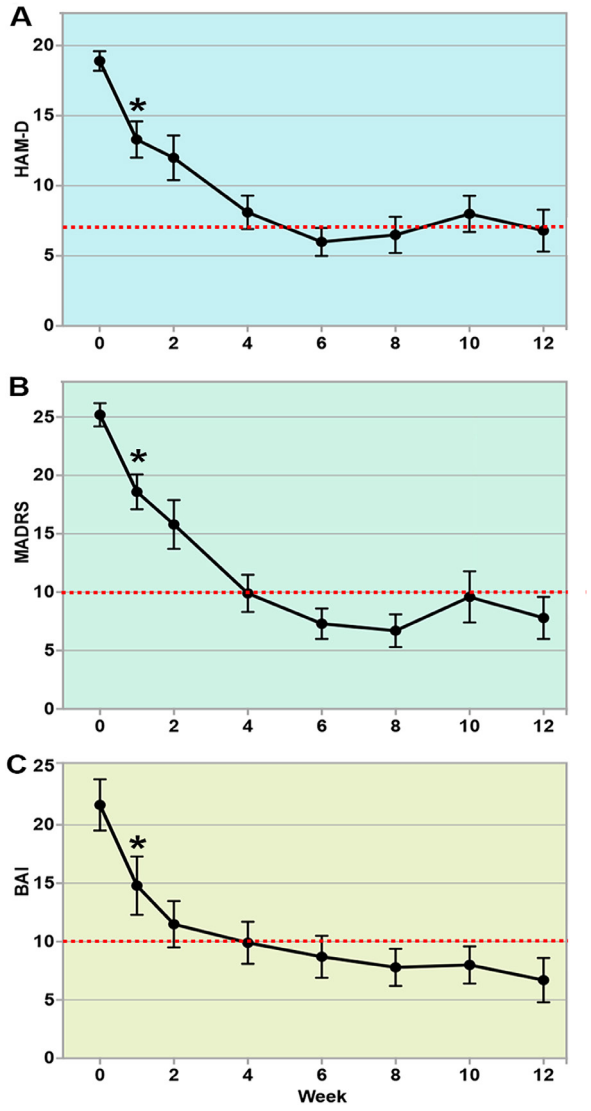
(Figure 3)

Study 2. Dietary 5HTP+CrM in Treatment-Resistant Adult Women:

Twelve women (average age of 34±11yrs) completed the study (Kious, 2017), 10 were on SSRIs and two were on SNRI. 5HTP+CrM was safe and well tolerated, with no evidence of serotonin syndrome, eosinophilia myalgia syndrome or other adverse effects. No treatment-emergent mania or hypomania (by YMRS scale) was seen, or nor was treatment-emergent suicidal ideation identified based on C-SSRS.

At baseline, participants exhibit moderate-severe MDD with mean HAM-D score of 19±2, MADRS score of 25±4 and CGI-S score of 4±0.3. After 8wks treatment, HAM-D scores reduced by 60% to an average of 7.5±4 (Fig 4A), with response criteria (≥50% reduction) met by 10 patients and remission criteria (score ≤7) met by 7 patients. Mean MADRS scores decreased by 65% to 9±6 (Fig 4B), with 12 patients meeting response criteria and 8 patients meeting remission criteria (score<10). Anxiety levels improved, with a 60%

drop in BAI scores from 22.7±9 to 9.3±6 (Fig 4C). Depression severity in the CGI-S improved from 4.1±0.4 to 1.9±1. Significant improvements were seen within a week of treatment ($p<0.00001$, Fig 4).



(Figure 4)

Conclusions: (1) CrM supplementation of SSRI-treated treatment-resistant adolescent women improved depression status and suicidal ideation over 8wks, paralleled with improved forebrain bioenergetics. (2) 5HTP+CrM augmentation of SSRI/SNRI-treated treatment-resistant adult women improved MDD and anxiety status, with a good safety profile.

Discussion

In our animal model, housing at altitude induced increased depression in female rats (Kanekar 2015). Female rats at altitude did not respond to the SSRIs fluoxetine, paroxetine and escitalopram (Kanekar, 2018), which are primarily serotonergic (Damsa et al., 2004). The SSRI sertraline functioned well at altitude, potentially due to its ability to enhance dopaminergic as well as serotonergic neurotransmission (Kanekar, 2018; Page 1999). In recent studies, rat brain serotonin levels decrease with housing at altitude, particularly in the striatum and prefrontal cortex, brain regions involved in mood regulation (C.S. Sheth, unpublished observations). We also find that anxiety and anhedonia (the inability to derive pleasure from pleasurable activity) increase in female rats at altitude (Sheth, 2018). These studies thus suggest that living at altitude or with chronic hypoxic diseases may decrease brain serotonin levels to worsen the status of depression and anxiety disorders, and may also render SSRIs ineffective. Since SSRIs form over 80% of the US market for antidepressants and anxiolytics, this likely worsens rates of unresolved mood disorders at altitude, and may be responsible for the heightened rates of suicidal ideation seen in women in the Rocky Mountain States. Given the significantly lower basal brain serotonin in women vs. men, women living at altitude or with chronic hypoxic disorders may be particularly vulnerable to worsened mood and SSRI treatment-resistance. Women in the high-altitude Rocky Mountain States, Utah included, may thus suffer from unresolved mood disorders despite attempts to medicate with antidepressant use, thus suggesting the need for novel non-traditional therapeutics for altitude-related mood disorders.

We therefore conducted clinical trials of compounds directed at improving altitude-related deficits in bioenergetics (CrM) and serotonin (5HTP). Supplementing CrM in SSRI-resistant adolescent women improved depression status and brain bioenergetics (Kondo 2011, 2016). Improving brain bioenergetics is proposed as a mechanism for enhancing antidepressant response (Iosifescu 2008), and dietary CrM was initially shown

to improve brain bioenergetics in healthy adults (Lyoo, 2003). Also, CrM augmentation of escitalopram-treated women improved SSRI response vs. escitalopram+placebo (Lyoo 2012). CrM treatment may thus enhance brain bioenergetics, to hasten antidepressant response and enhance clinical remission in depressed women. Our current study suggests that CrM improves response and remission criteria in TRD women. Additionally, CrM-linked enhancement in forebrain PCr/TP correlates with improved depression scores, suggesting a mechanism of action (Kondo 2016). A placebo-controlled study of 10g CrM for treatment-resistant adolescent women is currently in process.

Our study of 5HTP+CrM augmentation in depressed treatment-resistant adult women is the first trial of combination therapy simultaneously targeting bioenergetics and serotonin synthesis (Kious, 2017). The intermediate metabolite in serotonin synthesis, 5HTP is readily converted to serotonin (Turner 2006). In clinical trials, dietary 5HTP showed antidepressant efficacy in an average of 56% of MDD patients within 2-4wks (Turner 2006). Our clinical trial is a small scale open-label study without placebo control, yet it suggests that 5HTP+CrM therapy may be a feasible new approach to TRD in women. A placebo-controlled study of 5HTP+CrM is currently in progress in SSRI/SNRI-resistant adult women.

These clinical studies show that novel antidepressant therapeutics targeted to improving hypoxia-related brain deficits in bioenergetics and serotonin may serve as more effective antidepressants for those living at altitude or with chronic hypoxic diseases.

While the consequences of extreme high altitude exposure (>18,000ft) have been studied for decades with regards to mountaineering, only recently has living at moderate altitudes (2000ft-10,000ft) been suggested to impact human mood and quality of life (Brenner, 2011; Maa, 2010). The human brain consists of about 2% of our body weight, but utilizes 20% of the body's energy at rest. With the high basal oxygen needs of the brain, neurological symptoms including headaches, sleep disruption and mood disorders are prevalent in the chronic hypoxia experienced at altitude (Maa, 2010). As more people move to reside or vacation at moderate altitudes, addressing the physiological consequences of long-term altitude exposure becomes critical. The studies we describe here are an initial effort to understand the impact of living at moderate altitudes, such as in Utah, Colorado, and the other Rocky Mountain states, on brain physiology, mood status and antidepressant function.

Hypoxia exposure can alter brain neurochemistry to promote biomarkers for depression and suicidal behavior (Gould, 2017). In animal models, hypoxia disrupts neurotransmitter balance, increases inflammation and cell stress, and lowers metabolic function in key brain regions involved in mood disorders (Gould, 2017; Kumar, 2011). In animal models, hypoxia is linked to low brain serotonin levels. Low brain serotonin in humans is implicated in greater depression, anxiety, impulsivity, risk-taking behavior and aggression, each of which is also linked to suicidal behavior. Further studies with our animal model may thus be of high relevance in studying hypoxia-related brain and behavioral deficits which may alter susceptibility to suicidal behavior, and, combined with clinical trials, will help us critically evaluate novel potential therapeutics for MDD in chronic hypoxia.

Health Implications

Chronic hypoxia exposure may worsen MDD and impair antidepressant function. With greater vulnerability to hypoxia, women living at altitude or with chronic hypoxic diseases likely suffer from a greater burden of MDD-linked health issues, poor quality of life and suicidal ideation, suggesting a critical need for effective antidepressant interventions in this population. Targeted therapeutics may be required for depressed women at altitude: the current studies identify sertraline, adjunctive CrM or 5HTP+CrM as promising antidepressant therapeutics for women exposed to chronic hypoxia. Given the high rates of depression and suicidal behavior documented in women living in the high-altitude Rocky Mountain States, the success of these studies are likely to be of considerable beneficial impact.

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