Investigating the Effect of Hydrocortisone on Depressive Symptom Severity: A Double-Blind, Placebo-Controlled, Crossover Study

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Title: Investigating the Differential Impact of Hydrocortisone on Depressive Symptoms: A Double-Blind, Placebo-Controlled, Crossover Study

Abstract:

Research Question: The study investigates: "Will depressed patients experience a reduction in depressive symptoms, measured by the Quick Inventory of Depressive Symptomatology (QIDS), when treated with hydrocortisone as opposed to a placebo?"

Background: Major depressive disorder (MDD), characterized by altered cortisol levels, has been a subject of extensive research. Recent studies, such as those conducted using the UK Biobank data, have shown that both systemic and inhaled glucocorticoid use is associated with changes in brain volume and white matter microstructure, impacting cognitive and emotional outcomes .[28] This study is an interim, secondary analysis of a double-blind, placebo-controlled clinical trial with treatment crossover, examining the effects of hydrocortisone on the human hippocampus (NCT03896659). This manuscript is focusing on an interim secondary analysis of a larger trial. While the main study is interested in understanding whether hydrocortisone has a differential effect on the hippocampus of depressed versus non-depressed individuals, we are investigating if depressed patients will experience a reduction in depressive symptoms, measured by the Quick Inventory of Depressive Symptomatology (QIDS), when treated with hydrocortisone as opposed to a placebo. A meta-analysis highlighted the importance of HPA axis dysregulation in the onset and maintenance of depressive symptoms, suggesting that targeting this dysregulation could advise therapeutic strategy.[4] The manipulation of cortisol levels has been shown to have a significant impact on depression symptoms. According to DeBattista et al. (2000), acute hydrocortisone infusion significantly reduced the severity of depression in patients with major depression, suggesting that cortisol modulation may be of therapeutic benefit in depression.[12]

Methods: This study is an interim, secondary analysis of an NIH-funded (5R01MH115932-05) double-blind, placebo-controlled clinical trial with treatment crossover, examining the effects of hydrocortisone on the human hippocampus (NCT03896659). Eligible participants were allocated into two groups based on their baseline QIDS-C: the “depressed” arm (QIDS-C 11-20), consisting of individuals diagnosed with Major Depressive Disorder (MDD), and the “healthy control” arm (QIDS-C ≤ 5), individuals with no history of MDD diagnosis. Of the 54 potentially eligible participants, 12 participants were lost to follow up or screen failed. Therefore, a total of 42 participants were included in this study. For each group, participants were randomized by a statistician to receive either hydrocortisone (160 mg tablet) or a matching placebo tablet for three days, followed by MRI and cognitive testing, with a subsequent washout period and treatment cycle repeat. The study was conducted over a total of five visits.

Results: Building on existing research indicating altered brain structures and cognitive functions in glucocorticoid users, this study's preliminary insights suggest a nuanced response to hydrocortisone in the modulation of depressive symptoms. The expected outcomes, based on initial data, indicate that depressed patients might exhibit a more significant change in QIDS scores following hydrocortisone treatment compared to placebo, aligning with clinical trial findings. However, our results revealed no significant difference in QIDS-C scores when treated with hydrocortisone versus the placebo among the depressed cohort.

Conclusion: This study aims to augment the understanding of cortisol's role in depression. While final results are pending, the interim secondary analysis may enhance understanding of the role cortisol plays in depression. Our results highlight the complexity of the HPA axis feedback mechanism and its role in depression. This is further supported by evidence suggesting variability in glucocorticoid receptor sensitivity among individuals.[36] Additionally, both high and low cortisol states have been associated with depressive disorders.[40] The study's design is anticipated to yield robust, generalizable data, influencing future clinical practices and psychoneuroendocrinology research.

Research Question

In participants with major depressive disorder (MDD), does treatment with hydrocortisone, compared to placebo, reduce depressive symptoms when measure by the Quick Inventory of Depressive Symptomatology scale (QIDS-C)?

Specific aims

1. Evaluate the effect of hydrocortisone treatment on depressive symptoms in participants with MDD, as measured by QIDS-C. This aim seeks to determine whether hydrocortisone can effectively reduce symptom severity among the depressed cohort when compared to the placebo.
2. Understand the role of cortisol modulation in the treatment of MDD. Due to the HPA axis dysregulation in MDD, this aim is focused on determining the impact of modifying cortisol levels on clinical symptomatology through the treatment with hydrocortisone.

Introduction

Pathophysiology of Depression

The pathophysiology of major depressive disorder (MDD) involves a complex interplay between genetic, biochemical, environmental, and psychological factors. While the exact mechanisms are not fully understood, advancements in research have provided insight to several key theories. The dysregulation of neurotransmitters is fundamental in understanding the etiology of depression.[16] The deficiency of serotonin (5-HT) has been linked to the development of prevalent psychiatric diseases, such as depression and anxiety. Whereas dopamine, norepinephrine, and epinephrine play a role in behavior regulation.[15] Research indicates that the transport of dopamine is altered in patients with depression. Furthermore, evidence suggest that imbalances in glutamate and γ-aminobutyric acid (GABA) can also contribute to the development of depression.[17] For example, a meta-analysis revealed that depressed patients had lower GABA levels when compared to non-depressed participants.[1]

The Hypothalamic–pituitary–adrenal (HPA) axis, directly involved in the body's stress response, is notably dysregulated in individuals living with depression. As a result of stress, corticotropin-releasing hormone (CRH) is released from the hypothalamus, stimulating the production of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, consequently increasing glucocorticoid (cortisol) production and secretion from adrenal glands. To restore homeostasis, glucocorticoids bind to their receptors in several target tissues, such as the HPA axis, where they inhibit ACTH and CRH production in the pituitary and hypothalamus, respectively.[25] However, the reduced sensitivity to glucocorticoid receptors in depression leads to abnormally elevated cortisol levels due to HPA axis overactivity, consequently altering negative feedback mechanisms.[21,29]

Depression is also associated with structural changes within the brain. Research has focused primarily on the brain-derived neurotropic factor (BDNF), which serves as marker for nerve growth and 5-HT neuron function.[15] BDNF levels in the hippocampus are believed to be reduced in stress-induced depression, but have been found to improve with antidepressant treatment.[21] The decreased levels of BDNF are thought to impair the process of neurogenesis, contributing to the pathogenesis of depression.[15,21] Furthermore, neuroimaging studies have visualized changes within the hippocampus and prefrontal cortex in depressed patients.[3]

It is also important to note the genetic and environmental effects on MDD. Studies involving twin and adopted participants revealed a genetic and environmental component explaining the etiology of depression, with a heritability rate up to 42%.[18,19] However, environmental factors specific to individuals have also been found to substantially contribute to the development of MDD.[30] Moreover, gene-environment interactions are implicated as a risk for MDD, specifically exposure to adverse life events.[30,31] For example, increasing evidence shows that traumatic childhood experiences are implicated in HPA axis dysfunction as a result of stress.[32]

Inflammatory Hypothesis

Inflammation is hypothesized to play an important role in the growth and progression of depressive disorders. Previous studies revealed a greater incidence of depression among patients with systemic inflammatory diseases such as autoimmune disorders.[23] Increasing evidence indicates that depressed individuals have elevated levels of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), and C-reactive protein (CRP).[10] As demonstrated by Haapakoski et al., increased inflammatory markers were identified in MDD patients, suggesting a potential causal relationship.[5] Dowlati et al.'s study also observed similar elevations in cytokine levels among depressed individuals, further strengthening the association between inflammation and depression.[6]

There are a number of underlying mechanisms that link inflammation to depression. Evidence indicates that proinflammatory cytokines may disrupt neurotransmitter metabolism, resulting in reduced levels of serotonin and dopamine, both of which are crucial to mood regulation.[5,6] Depressive symptoms are strongly influenced by this neurochemical change, as discussed earlier. Furthermore, inflammation can disrupt the HPA axis, resulting in the cortisol imbalances we observe in depression. Chronic inflammation has also been associated with structural and functional changes in brain regions involved in mood regulation, such as the hippocampus and prefrontal cortex.[7,8]

The relationship between stress and inflammation is also a critical component of this hypothesis. It is known that psychological stress can trigger inflammatory responses, suggesting a bidirectional relationship between psychological stress, inflammation, and depression.[9] Psychological stress has been found to induce the production of proinflammatory cytokines in a progressive manner, leading to neuroinflammation.[9] It is important to consider the implications of the inflammatory hypothesis for the treatment of depression, as clinical trials have shown that anti-inflammatory drugs, such as NSAIDs and cytokine inhibitors, can have antidepressant effects.[10]

Cortisol's Impact on Depression

The HPA axis regulates the production of cortisol, a key stress hormone, within the body. Cortisol plays an important role in regulating various physiological systems, and its dysregulation is strongly associated with depression. It is believed that chronic exposure to excess cortisol can lead serotonin deficiency due to decreased levels of it’s precursor, tryptophan.[26] According to Belvederi Murri et al. (2014), patients with depression exhibit hyperactivity of the HPA axis as evidenced by elevated levels of cortisol and altered cortisol awakening responses.[7] The authors of Burke et al. (2005) also conducted a meta-analysis on the correlation between cortisol levels and psychological stressors in depressed individuals. While baseline and stress cortisol levels were similar in depressed and non-depressed individuals, depressed participants exhibited significantly higher cortisol levels during the recovery period, indicating a dysregulated stress response.[8]

The body's inflammatory response is also regulated by cortisol. An increase in pro-inflammatory cytokines in depressed patients suggests a link between cortisol, inflammation, and depression.[5,6] Therefore, glucocorticoids, such as hydrocortisone, have been studied for their

role in managing depression symptoms in a few clinical trials. In a double-blind, placebo controlled study by DeBattista et al. (2000), participants treated with a 15 mg hydrocortisone infusion (n=6) demonstrated a 37% reduction in Hamilton Depression Rating Scale scores, suggesting that cortisol modulation may be of therapeutic benefit in depression.[12] In another controlled trial by Arana et al., 37% of patients given a 4-day course of oral dexamethasone (4mg/day) experienced a significant reduction in depressive symptoms when compared to placebo, as measured by the Hamilton Depression Rating Scale.[33] It is thought that the treatment with a glucocorticoid serves as a negative feedback on the release of CRH from the hypothalamus, reducing the HPA axis hyperactivity.[33] Another theory suggests that glucocorticoids can increase dopaminergic activity, addressing the deficit observed in MDD.[12] Conversely, there is evidence to suggest that depression is also associated with a hypocortisolemic state.[40] Current therapies, antidepressants, are often evaluated by the effects on cortisol secretion. Due to varying mechanisms of action and chemical structures, they modulate the HPA axis differently.[26] Consequently, understanding cortisol in depressed individuals, especially given the neurodegenerative implications, may help predict treatment efficacy.

Rationale for the Study

The rationale for investigating the effects of hydrocortisone in depression is driven by the significant role of the HPA axis and cortisol dysregulation in depression.

1. **HPA Axis Dysregulation in Depression:** A dysfunctional HPA axis and the resulting abnormalities in cortisol are well-established characteristics of depression. A meta-analysis highlighted the importance of HPA axis dysregulation in the onset and maintenance of depressive symptoms, suggesting that targeting this dysregulation could advise therapeutic strategy.[4]
2. **Effectiveness of Cortisol Modulation:** Given cortisol's pivotal role in depression, further understanding the effects of hydrocortisone in depressed and healthy controls is logical. The manipulation of cortisol levels has been shown to have a significant impact on depression symptoms, as evidence by DeBattista et al. and Arana et. al's study.

Study Objectives and Impact

This manuscript is focusing on an interim secondary analysis of a larger trial. While the main study is interested in understanding whether hydrocortisone has a differential effect on the hippocampus of depressed versus non-depressed individuals, we are investigating if depressed patients will experience a reduction in depressive symptoms, measured by the Quick Inventory of Depressive Symptomatology (QIDS), when treated with hydrocortisone as opposed to a placebo. As a translational research study, this project will contribute to our understanding of stress and cortisol's effects on the brain. It is not a treatment study.

1. **Understanding Cortisol's Role in Depression:** The study is designed to enhance understanding of the role cortisol plays in depression. By comparing the effects of hydrocortisone in depressed and non-depressed individuals, the study aims to elucidate how cortisol modulation might differ in these populations. A clinical trial by Young et al. (2004) emphasized the importance of understanding individual variations in cortisol response and its implications for depression treatment.[14]

2. **Impact on Treatment Strategies:** If hydrocortisone is found to be effective in reducing depressive symptoms, particularly in depressed individuals, it could significantly impact depression treatment strategies. This aligns with the shift towards personalized medicine, where treatments are tailored based on individual physiological characteristics, including HPA axis function.
3. **Implications for Future Research:** Further research into HPA axis-targeted therapies for depression may contribute to a deeper understanding of the disorder's neuroendocrine underpinnings and provide more effective treatments.

Materials and Methods

Study Design

This study is an interim, secondary analysis of an NIH-funded (5R01MH115932-05) double-blind, placebo-controlled clinical trial with treatment crossover, examining the effects of hydrocortisone on the human hippocampus (NCT03896659). The primary aim of this study is to evaluate the effects of hydrocortisone on Quick Inventory of Depressive Symptomatology (QIDS-C) scores in non-depressed individuals, when compared to a placebo.

This study was conducted in accordance with the UT Southwestern Institutional Review Board (STU 2018-0360).

Study Participants

Participants included adults (18 to 50 years of age) with at least 20/40 corrected vision, at least 12 years of education, a Baseline Rey Auditory Verbal Learning Test (RAVLT) total words recalled T-score of ≥ 40, and a body mass index (BMI) between 18.5 and 35.0. A detailed list of the exclusion criteria can be found in **Supplementary Table 1**. Eligible participants were allocated into two groups based on their baseline QIDS-C: the "depressed" arm (QIDS-C 11-20), consisting of individuals diagnosed with Major Depressive Disorder (MDD), and the "healthy control" arm (QIDS-C ≤ 5), individuals with no history of MDD diagnosis. Of the 54 potentially eligible participants, 12 participants were lost to follow up or screen failed. Therefore, a total of 42 participants were included in this study.

Exclusion Criteria
History of major psychiatric illness other than MDD for the depressed group, defined as bipolar disorder, posttraumatic stress disorder, schizoaffective disorder, schizophrenia, eating disorders, or MDD with psychotic features. For the control group, a past episode of MDD (per SCID) is also exclusionary
History of drug or alcohol use disorder
History of neurological disorders including seizures, brain surgery, multiple sclerosis, Parkinson's disease
Taking CNS-acting medications (e.g., antidepressants, antipsychotics, lithium, anticonvulsants, sedative/hypnotic/anxiolytics). Thus, the depressed group will be medication free.
History of allergic reaction or medical contraindication to hydrocortisone
Metal implants, claustrophobia, or other contraindications to MRI
Significant medical conditions (e.g., cancer, heart disease, diabetes)
Vulnerable population including pregnant or nursing women, prisoners, and people with intellectual disability, history of special education classes, dementia, or other severe cognitive disorders

Current suicidal ideation, a suicide attempt in the past 12 months or more than one lifetime attempt
History of systemic CS use in the past 12 months, lifetime cumulative use of more than 12 weeks, or recent (defined as past 28 days) inhaled CS use
Women who are using estrogen containing oral contraceptive agents (other contraceptives are acceptable, see Protection of Human Subjects section for a list of acceptable birth control methods) or who are post- or peri-menopausal or with irregular menstrual cycles (i.e., inconsistent menstruation patterns)

Supplementary Table 1. Exclusion criteria for participants.

Data collection

For each participant the following information was collected and stored in REDCap: age, sex, QIDS-C score at each visit, RAVLT at each visit, and treatment assignment at each visit.

Randomization and study procedures

For each group, participants were randomized by a statistician to receive either hydrocortisone (160 mg tablet) or a matching placebo tablet.

Participants were instructed to take their assigned treatment daily for three days and the study was conducted over a series of five visits as follows:

- ***Visit 1:*** *This visit served as a baseline assessment. Participants signed the informed consent at this time.*
- ***Visit 2:*** *Initiation of Treatment (Day 1). Participants are prescribed their assigned medication.*
- ***Visit 3:*** *Post-Treatment Assessment (Day 4). This occurs after completion of three-day treatment. Assessments conducted during Visit 1 are repeated to evaluate immediate effects of intervention.*
- ***Visit 4:*** *Second Treatment Phase Initiation (Day 29). This visit is conducted after a 25- day washout period, minimizing potential carryover effects between study phases. Participants are prescribed the second round of medication, the alternate of what was first prescribed at Visit 2.*
- ***Visit 5:*** *Final Assessment (Day 32). This visit mirrors Visit 3. All initial assessments were repeated to compare against participant's baseline and first phase outcomes.*

Instrument	**Baseline (Visit 1)**	**Visit 2**	**2 days (Visit 3 [illegible])**	**Visit 3**	**Washout (25 days)**	**Visit 4**	**2 days (Visit 5 [illegible])**	**Visit 5**
Informed consent	X							
Medical and psychiatric history	X							
Concomitant medication review	X	X		X		X		X
Physical exam	X							

Quick Inventory of Depressive Symptomatology (QIDS-C)	**X**	**X**		**X**		**X**		**X**
Rey Auditory Verbal Learning Test (RAVLT)	X			X				X
Begin 3-day course of hydrocortisone or placebo		X				X		
Follow-up with a clinician		X		X		X		X
Adverse events review		X		X		X		X
Exit survey								X
Approximate time/visit	**3 hr**	**45 m**		**3.5 hr**		**45 m**		**3.5 hr**

Supplemental Table 2. Study procedures table (represents a subset of the study procedures table in the original study, NCT03896659)

Statistical Analysis

Descriptive statistics were calculated for all variables where categorical data is reported as count and percentage, and continuous data as mean and standard deviation. For two group comparisons, paired t-test and Chi-squared test were used for continuous and categorical values, respectively. For repeated measures, linear mixed effect models were calculated where random intercepts for subjects were included to account for within-subject variability across time points. All statistical analysis was performed using R statistical software (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria). Univariate descriptive statistics were calculated for all baseline characteristics including age, sex, smoking status, weight, ethnicity, race, marital status, and employment status. Statistical significance was defined as a p-value of less than 0.05 for all statistical tests.

Results

Of the 54 participants that were screened, 12 did not meet the inclusion criteria. The final cohort included 42 participants, 30 (71.4%) were female and 17 (40.5%) were classified as baseline depressed (BLD).

There was a significant difference in age when participants were stratified by baseline depression (Table 1), with the depressed cohort being older (M=36.5, SD=11.2) compared to the healthy control group (M=27.5, SD=7.51), p=0.008. Marital status was also found to be significantly different (P=0.009) between the two cohorts, with more married or cohabitating participants in the baseline depressed group (52.9%) compared to the healthy controls (34.8%). All other factors were comparable between the two cohorts.

The mean QIDS-C score of the depressed group at baseline was significantly higher (M=13.6, SD=2.00) than the healthy control group (M=1.72, SD=2.09), p<0.001. This finding continued across all subsequent visits (Visit 2-5), with p-values <0.001, indicating persistent depressive symptoms in the depressed cohort.

For the depressed cohort at Visit 3, the QIDS-C total score for participants treated with hydrocortisone (n=10) had a score of 9.70 (SD=3.83), while those receiving placebo (n=7) was 8.86 (SD=5.01), with no significant difference between the groups (p=0.715). After the washout period (Visit 5), depressed participants that switched to the placebo (n=8) had a mean QIDS-C score of 7.00 (SD=3.93) versus 5.33 (SD=3.50) in the hydrocortisone group (p=0.420).

The linear mixed-effects model indicated that hydrocortisone treatment alone (Table 3) did not predict QIDS-C scores (p=0.637) among the baseline depressed group. When age was included as a covariate (Table 4), neither hydrocortisone (*B* 0.37, 95% CI -1.12, 1.85, p=0.623) nor age (*B* 0.08, 95% CI -0.23, 0.08, p=0.345) had a significant effect on QIDS-C scores. Sex alone (Table 5) was found to be a predictor of QIDS-C scores (*B* -4.95, 95% CI -8.97, -0.93, p=0.017), as depressed females exhibited lower QIDS-C scores. However, the interaction effect between treatment and sex (Table 6) was not found to be significant (B -2.69, 95% CI -6.87, -1.49, p=0.203).

Discussion

The primary outcome of this interim analysis was to assess the impact of hydrocortisone on depressive symptoms, as measured by the Quick Inventory of Depressive Symptomatology (QIDS-C). Treatment with glucocorticoids has shown to reduce depressive symptoms, through the modulation of HPA axis dysregulation in MDD.[12,33] However, our results revealed no significant difference in QIDS-C scores when treated with hydrocortisone versus the placebo among the depressed cohort. Despite initial hypothesis that hydrocortisone treatment would reduce depressive symptoms, the study did not observe hydrocortisone as a predictor of QIDS-C score. Our results highlight the complexity of the HPA axis feedback mechanism and its role in depression. This is further supported by evidence suggesting variability in glucocorticoid receptor sensitivity among individuals.[36] Additionally, both high and low cortisol states have been associated with depressive disorders.[40]

A few factors could contribute to the outcome of this study. It is possible that the duration of treatment or the dosage was insufficient to elicit a significant change in QIDS-C score. Patients were treated with 160 mg of oral hydrocortisone for 3 days. Conversely, in the trial conducted by Arana et al., participants were treated with a glucocorticoid, dexamethasone (4 mg), for 4 days orally and experienced a reduction in depressive symptoms.[33] Furthermore, dexamethasone is classified as a long-acting glucocorticoid with a potency that is 25 time greater than short-acting corticosteroids, such as hydrocortisone.[34] Yet, the treatment dose in Arana et al. was less than the equivalent dexamethasone dose (6 mg) to the 160 mg of hydrocortisone in this study. Thus, perhaps the duration of treatment is the more important modifying effect.[37,38]

On the other hand, DeBattista et al. identified a significant effect of low dose (15 mg) IV hydrocortisone on improving symptoms of depressed participants in the acute setting.[12] As also demonstrated by Goodwin et al., infusion of hydrocortisone (7 mg/kg) significantly improved the mood of depressed patients when compared to saline infusion.[39] Thus, it is plausible that the route of hydrocortisone administration, oral versus IV, could explain the difference in outcomes, as it introduces variability in the treatment's bioavailability. Intravenous infusion allows for a more controlled setting to observe immediate effects at 100% bioavailability. Additionally, DeBattista et al. and Arana et al. utilized a different scale, Hamilton Depression Rating Scale, to assess depressive symptomology.[12,33] Thus, the difference in sensitivity and specificity of the Hamilton Depression Rating Scale and QIDS-C scale could also explain different outcomes.

It is also important to consider the implications of various demographic factors on the development of depression and response to treatment. For example, evidence has shown that age-related changes in the HPA axis result in supraphysiological cortisol levels in response to stress.[41-43] Moreover, studies have demonstrated that these age-related changes may also be a biomarker for the development of depression and, in conjunction with a MDD diagnosis, aging may amplify these pathological changes.[43-44] Likewise, sex-related differences in the development and manifestation of depression are widely reported and should be considered in related studies.[35] In this study, the female sex was significantly associated with decreased QIDS-

C scores when controlling for treatment on multivariate analysis however, their interaction was not significant. Similarly, while the baseline depressed cohort was significantly older than the control group, age was not associated with QIDS-C scores when controlling for treatment. Although the efficacy of hydrocortisone in reducing depressive symptoms did not differ among males and females and we did not identify a clear association with age, it is important to consider differential responses to treatment based on these socioeconomic factors.

This study has some limitations. First, the sample size was not have provided sufficient power to observe subtle effects. A larger cohort would allow for subgroup analyses, considering heterogeneity of depressive disorders or responses to treatment. Participant allocation was also a limitation, as there were fewer depressed males in the study population. The study also did not consider psychosocial factors that could influence cortisol levels, mitigating the response to treatment. For example, we found a significant difference in marital status between the depressed cohort and healthy control but did not measure the effect on QIDS-C score. An additional limitation of the study is that we did not measure plasma hormone levels which have been shown to be significantly associated with depressive symptoms in literature.[12,39]

Future Direction

Future research should consider stratifying by age and psychosocial factors that impact cortisol levels when selecting the cohort. Additionally, future trials should consider the duration of treatment, along with pharmacokinetic and pharmacodynamic implications. Incorporating the measures of cortisol levels at baseline and post-treatment could also provide further insight.

Conclusion

In conclusion, the interim analysis did not observe a significant difference in QIDS-C score among depressed individuals treated with hydrocortisone versus placebo. Unlike previous studies, treatment with glucocorticoids did not have a therapeutic effect on depressive symptoms. Thus, this study serves to further our understanding around cortisol's nuanced role in depression, as it highlights the complex relationship between the HPA axis and the development of MDD. Additionally, our observations offer insight to the heterogeneity of depressive disorders and challenges we face when targeting the HPA axis to improve symptoms. Furthermore, given the influence of demographic factors, such as age and sex, that we observed in this study, our findings emphasize the importance of an individualized approach to studying and treating MDD.

Compliance Plan

The Institutional Review Board must approve the consent form and protocol. I have completed UT Southwestern credentialing and IRB CITI Training in accordance with the site and institutional requirements. The UT Southwestern Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. Patient information will be de-identified, and each participant will be assigned a computer-generated subject identification number. Data will be stored in a password-encrypted database. Only research personnel working on this study will have access to this information.

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Table 1. Descriptive Statistics of Cohorts Stratified by Baseline Depression

	Healthy Control ***N=25***	**Baseline Depressed** ***N=17***	**P-value**
Age	27.5 (7.51)	36.5 (11.2)	**0.008**
Female	16 (64.0%)	14 (82.4%)	0.187
Weight (lbs)	168 (40.9)	179 (49.6)	0.495
Race:			0.381
Caucasian/White	19 (79.2%)	11 (64.7%)	
African American	2 (8.33%)	3 (17.6%)	
Asian	2 (8.33%)	1 (5.88%)	
More than 1 race	0 (0.00%)	2 (11.8%)	
American Indian/Alaskan Native	1 (4.17%)	0 (0.00%)	
Ethnicity:			1.000
Not Hispanic/Latino	15 (62.5%)	11 (64.7%)	
Hispanic/Latino	9 (37.5%)	6 (35.3%)	
Marital status:			**0.009**
Single	15 (65.2%)	4 (23.5%)	
Married/Living with Someone	8 (34.8%)	9 (52.9%)	
Widowed	0 (0.00%)	2 (11.8%)	
Divorced/Separated	0 (0.00%)	2 (11.8%)	
Education:			0.782
Some high school	0 (0.00%)	1 (5.88%)	
Graduated high school	1 (4.35%)	1 (5.88%)	
Technical or trade school	2 (8.70%)	1 (5.88%)	
Some college	3 (13.0%)	5 (29.4%)	
Associate's degree	2 (8.70%)	2 (11.8%)	
Bachelor's degree	8 (34.8%)	3 (17.6%)	
Master's degree in progress/did not graduate	3 (13.0%)	2 (11.8%)	
Master's degree	2 (8.70%)	2 (11.8%)	

	Healthy Control *N=25*	Baseline Depressed *N=17*	P-value
Doctorate degree in progress/did not graduate	2 (8.70%)	0 (0.00%)	
Income (recoded):			0.391
Less than $15,000	3 (13.0%)	2 (11.8%)	
$15,000 - $49,999	11 (47.8%)	4 (23.5%)	
$50,000 - $99,999	5 (21.7%)	5 (29.4%)	
$100,000 or above	4 (17.4%)	6 (35.3%)	
How much alcohol do you drink on a typical day?:			0.782
None	13 (56.5%)	9 (52.9%)	
Occasional drink	9 (39.1%)	6 (35.3%)	
1-2 drinks	1 (4.35%)	2 (11.8%)	
How much do you smoke in a day?:			1.000
None	22 (95.7%)	16 (94.1%)	
0 - 1/2 pack	1 (4.35%)	1 (5.88%)	
QIDS-C Total Score (Baseline)	1.72 (2.09)	13.6 (2.00)	**<0.001**
QIDS-C Total Score (Visit 2)	1.92 (2.43)	10.4 (3.10)	**<0.001**
QIDS-C Total Score (Visit 3)	1.44 (1.78)	9.35 (4.23)	**<0.001**
QIDS-C Total Score (Visit 4)	2.70 (2.87)	8.87 (4.64)	**<0.001**
QIDS-C Total Score (Visit 5)	1.95 (2.38)	6.29 (3.71)	**0.001**

Table 2. QIDS Total Score in Baseline Depressed Individuals Treated with Hydrocortisone versus Placebo at Specified Visits

	Visit 3		
	Placebo (n=7)	**Hydrocortisone (n=10)**	**P-value**
QIDS Total Score	8.86 (5.01)	9.70 (3.83)	0.715
	Visit 5		
	Placebo (n=8)	**Hydrocortisone (n=6)**	**P-value**
QIDS Total Score	7.00 (3.93)	5.33 (3.50)	0.420

Table 3. Linear Mixed Effects Model Estimating the Effect of Treatment on QIDS

Predictors	**Estimates**	**CI**	**P-value**
(Intercept)	8.74	6.87 – 10.61	**<0.001**
Hydrocortisone	0.35	-1.13 – 1.84	0.637
Random Effects			
σ^2	8.26		

$\tau_{00\ record\_id}$	10.09
ICC	0.55
$N_{\ record\_id}$	17
Observations	63
Marginal R^2 / Conditional R^2	0.002 / 0.551

Table 4. Linear Mixed Effects Model Estimating the Effect of Treatment and Age on QIDS

Predictors	Estimates	CI	P-value
(Intercept)	11.50	5.41 – 17.58	**<0.001**
Hydrocortisone	0.37	-1.12 – 1.85	0.623
Age	-0.08	-0.23 – 0.08	0.345
Random Effects			
σ^2	8.24		
$\tau_{00\ record\_id}$	10.26		
ICC	0.55		
$N_{\ record\_id}$	17		
Observations	63		
Marginal R^2 / Conditional R^2			

Table 5. Linear Mixed Effects Model Estimating the Effect of Treatment and Sex on QIDS

Predictors	Estimates	CI	P-value
(Intercept)	12.80	9.12 – 16.49	**<0.001**
Hydrocortisone	0.43	-1.05 – 1.90	0.566
Sex	-4.95	-8.97 – -0.93	**0.017**
Random Effects			
σ^2	8.17		

$\tau_{00\ record\_id}$	7.34
ICC	0.47
$N_{\ record\_id}$	17
Observations	63
Marginal R^2 / Conditional R^2	0.175 / 0.566

Table 6. Linear Mixed Effects Model Estimating the Effect of Treatment, Sex, and Treatment * Sex on QIDS

Predictors	**Estimates**	**CI**	**p**
(Intercept)	12.00	8.02 – 15.98	**<0.001**
Hydrocortisone	2.75	-1.13 – 6.62	0.161
Sex	-3.95	-8.35 – 0.46	0.078
Hydrocortisone * Sex	-2.69	-6.87 – 1.49	0.203
Random Effects			
σ^2	7.93		
$\tau_{00\ record\_id}$	7.87		
ICC	0.50		
$N_{\ record\_id}$	17		
Observations	63		
Marginal R^2 / Conditional R^2	0.190 / 0.594		