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Short Communication

A history of early life parental loss or separation is associated with successful cognitive-behavioral therapy in major depressive disorder

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ABSTRACT

Background: There is a clinical need for evidence-based psychotherapy response biomarkers in major depressive disorder (MDD). Based on previous studies, we hypothesized that lower 24-h urinary cortisol levels and a history of early life stress/trauma would predict an improved antidepressant response to cognitive-behavioral therapy (CBT).

Methods: 50 currently depressed MDD subjects were enrolled. 24-h urine was collected and measured for cortisol levels by radioimmunoassay (RIA). Subjects were also administered early life stress/trauma measures at baseline: Global Perceived Early-Life Stress (GPELS), The Early Life Trauma Inventory (ELTI) and Klein Loss Scale (KLS). The efficacy of a twelve-week course of once-weekly CBT was evaluated by the primary outcome measure, the 24-item Hamilton Depression Rating Scale ($HDRS_{24}$), at baseline and every four weeks, and the Beck Depression Inventory at baseline and weekly thereafter. 42 subjects had at least one complete follow-up visit (≥ 4 weeks of CBT), and 30 subjects completed the full 12-week course.

Results: Baseline 24-h urinary cortisol levels did not correlate with CBT's antidepressant response. Higher KLS scores, a measure of early life parental loss or separation, correlated with delta $HDRS_{24}$ ($r_s = -0.39$, $p_{adjusted} = 0.05$). Complementary general linear model analysis revealed enhanced CBT efficacy in patients with a history of early life parental loss or separation [$F_{(1,35)} = 6.65$, $p = 0.01$].

Limitations: Small sample size, Treatment-naïve population.

Conclusions: Early life parental separation or loss positively correlated with CBT's antidepressant efficacy in our sample and may warrant further study in larger clinical samples.

1. Introduction

Major depressive disorder (MDD) is a heterogeneous neuropsychiatric condition with the highest worldwide morbidity across all sociodemographic strata (Kessler et al., 2003; Ormel et al., 2008; Ustun et al., 2004). Standard interventions for unipolar depression include antidepressant medications, somatic therapies, and psychotherapy. Instead of a more personalized approach targeting the patient's specific behavioral profile, history, or underlying pathophysiology, treatment selection is often based on subjective factors such as patient preference and the theoretical orientation of the treating clinician. Unfortunately, many patients do not have a beneficial antidepressant response with this approach to treatment selection. As a result, there is critical need to identify treatment response biomarkers to facilitate treatment modality selection and assess response.

Abbreviations: BDI, Beck Depression Inventory; ELL, Early Life Parental Separation or Loss (as detected by the Klein Loss Scale); ELTI, Early Life Trauma Inventory; GPELS, Global Perceived Early Life Stress; HAM-A, Hamilton Anxiety Rating Scale; HDRS24, 24-item Hamilton Depression Rating Scale; MDE, Major Depressive Episode

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The two manualized psychotherapies with the largest evidence base in MDD are interpersonal psychotherapy (IPT) and cognitive-behavioral therapy (CBT). Both psychotherapies are recommended as first-line treatments in the 2010 American Psychiatric Association's (APA) MDD practice guideline (American Psychiatric Association., 2000). Additionally, when compared to antidepressant medications, CBT is associated with a lower risk of relapse once a patient achieves remission (Evans et al., 1992; Gloaguen et al., 1998; Simons et al., 1986; Thase et al., 1992). Although a multi-site study initially suggested that CBT was less effective in patients with severe depression (Elkin et al., 1989), a subsequent meta-analysis did not find evidence to support this claim (DeRubeis et al., 1999). As baseline illness severity does not appear to be a reliable means of predicting antidepressant efficacy, several studies have turned to depressive subtypes as potential predictors. Stewart et al. (1998) reported that atypical depression responded more robustly to cognitive therapy than other depressive subtypes. In addition, hypothalamic-pituitary-adrenal (HPA) axis dysfunction (a biometric of melancholic depression) predicted a poorer treatment response to CBT and other psychosocial interventions (Robbins et al., 1989; Thase et al., 1996). Yet, due to discrepancies in the literature (Thase and Friedman, 1999), there is currently insufficient evidence to support depressive subtypes as a reliable predictor of antidepressant response.

Due to prior reports of a positive correlation between cognitive-based psychotherapy efficacy and history of early life stress/abuse (Kuyken et al., 2015; Nemeroff et al., 2003), we similarly hypothesized that a history of early life stress would correlate with CBT's antidepressant efficacy. Also, based on the aforementioned studies of HPA axis dysfunction/melancholic depression correlating with reduced antidepressant response to CBT (Robbins et al., 1989; Thase et al., 1996), we predicted that subjects with decreased baseline 24-h urinary cortisol (indicative of lower HPA axis activity/non-melancholic depression) would have an enhanced antidepressant response to CBT.

2. Methods

All subjects provided written informed consent prior to any research-related procedures. The Yale School of Medicine Institutional Review Board/Human Investigation Committee approved all portions of the protocol.

2.1. Study design

The methods have been described previously (Abdallah et al., 2014). In brief, medication-free currently depressed outpatients presented to the Yale Depression Research Program for initial screening and evaluation. After consenting, subjects received baseline clinical assessments from licensed psychiatric clinicians, and trained research staff completed rating scales and trauma inventories. Then, participants received structured CBT (Beck et al., 1987). The psychotherapy consisted of once-weekly 50-minute individual sessions for up to 12 weeks.

2.2. MDD subjects

18–65 year old subjects in a current major depressive episode met Diagnostic and Statistical Manual-IV-Text Revision (DSM-IV-TR) criteria for MDD. Diagnosis was determined by in-person psychiatric evaluation via Structured Clinical Interview for DSM-IV Disorders (SCID)(First et al., 1995). Exclusion criteria were as follows: a current or past diagnosis of MDD with psychotic features; active suicidal ideation; history of suicidal behavior in the preceding two years; current use of psychotropic medications; history of, or currently uncontrolled, serious medical or neurological illness; illicit substance use disorder within the preceding six months; current illicit substance use (detected by urine toxicology); history of psychiatric illness due to confirmed general medical condition(s), history of primary personality disorder, and history of psychotic spectrum illness. Pre-defined exit criteria were defined as a 25% increase over baseline Beck Depression Inventory (BDI)(Beck et al., 1961) score during weekly ratings, or an increase in passive suicidal thinking or the onset of active suicidal ideation. No subjects were terminated for clinical deterioration.

2.3. Ratings and urinary cortisol levels

At baseline, all participants completed a battery of clinician-administered psychiatric assessments including the primary outcome measure, the 24-item Hamilton Depression Rating Scale ($HDRS_{24}$) (Hamilton, 1967), and the following self-administered scales: BDI, Global Perceived Early-Life Stress (GPELS) (Carpenter et al., 2004), The Early Life Trauma Inventory (ELTI) (Bremner et al., 2000), and Klein Loss Scale (KLS) (Lizardi et al., 1995). Thereafter, the $HDRS_{24}$ was repeated every 4 weeks and the BDI weekly to monitor clinical response.

Patients were provided collection containers and portable refrigerated units for 24-h urine collection. Subjects were informed to flush the first specimen of the morning, noting the time, and then to continue collecting each urine sample for the next 24 h. Samples were processed for storage within 6 h after collection was complete. Urinary free cortisol concentrations were determined in duplicate in a single batch using a commercially available radioimmunoassay (RIA) kit (Coat-a-Count, DPC, Los Angeles, CA) with a within-assay variation of $< 10\%$.

2.4. Statistical analysis

Prior to model entry, the distribution of each outcome measure was examined using probability plots and Kolmogorov–Smirnov test statistics. Antidepressant response was defined as a $\geq 50\%$ $HDRS_{24}$ score reduction from the trial entry baseline. Paired *t*-test and related-samples Wilcoxon Signed Rank tests were used to examine pre- and post-treatment changes. Non-parametric (Spearman's Rank Order) test statistics were used for correlational analyses. General linear model (GLM) repeated-measures analyses were constructed as needed. Age and sex were considered as covariates in all models. All tests were two-tailed, with a significance level set at $p \leq 0.05$. False Discovery Rate correction for multiple comparisons was used when appropriate (as indicated by $p_{adjusted}$).

3. Results

A total of 50 subjects were enrolled [30 women, mean age 42.6 ± 11.4]. Of these, 42 subjects had at least one complete treatment follow-up visit (≥ 4 weeks of CBT), and 30 subjects completed the full 12-week course. As presented in our initial report in an intent-to-treat analysis (Abdallah et al., 2014), following 12 weeks of treatment, CBT response was associated with antidepressant efficacy on both clinician-administered and self-reported measures ($p < 0.001$), resulting in an average 41% reduction from baseline $HDRS_{24}$ scores and 38% response rate ($\geq 50\%$ reduction from baseline $HDRS_{24}$).

Mean observed urinary free cortisol excretion was 34 ± 25.6 μg/24 h. Baseline 24-h urinary cortisol levels, and ELTI and GPELS scores did not correlate with $HDRS_{24}$ change (all $p_{adjusted} > 0.1$). However, higher KLS, a measure of parental loss or separation, scores were correlated with delta $HDRS_{24}$ ($r_s = -0.39$,