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High reactivity of the cortisol awakening response predicts positive treatment outcome in heterogeneous depressed patients completing an alternate milieu inpatient program

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ABSTRACT

Objective: Delineating clinically meaningful subgroups within heterogeneous depressed populations is a major challenge. As outlined in the Research Domain Criteria Strategy, biomarkers may help to empirically classify such patients. Following this basic strategy, the current pilot study examined whether the cortisol awakening response (CAR) following admission to hospital predicts treatment response in heterogeneous depressed patients completing a 4-week alternate milieu inpatient program.

Methods: The Alternate Inpatient Milieu program at the Centre for Addiction and Mental Health is composed of both individual-based and group-based programming designed to promote a recovery-oriented, collaborative treatment environment. The current sample consisted of 25 consecutive patients with various forms of complex/chronic depression who completed the full program. Saliva samples were collected at 0, 30 and 60 min after awakening on 2 consecutive days following admission. Linear regressions controlling for baseline depression scores were used to assess whether the CAR AUCg (*a*rea *u*nder the *c*urve ground) and/or AUCi (*a*rea *u*nder the *c*urve *i*ncrease) at admission predicted the change in depression scores from admission to discharge based on the Quick Inventory of Depressive Symptoms scale.

Results: The CAR AUCi, but not the CAR AUCg, at admission significantly predicted treatment response over the 4-week hospital stay. In these naturalistic patients with major depressive disorder, high CAR reactivity as assessed using the AUCi was associated with a better treatment response ($t = 2.20$; $df = 2,24$; $P = .039$). The CAR was easy to implement and well accepted by patients and staff.

Conclusion: This pilot study suggests that CAR reactivity at admission may help to identify a subgroup of depressed patients most likely to respond clinically to a 4-week alternate milieu inpatient program.

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1. Introduction

When treating naturalistic, heterogeneous samples of depressed patients, defining clinically meaningful subgroups is a major challenge. *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*)-based classification on its own is limited in this context as most patients will meet criteria for multiple categorically defined diagnoses. Recognizing the limitations of the *DSM* approach in complex patients, the Research Domain Criteria Strategy suggests a more empirical approach to subgroup definition including the use of putative biomarkers where possible. However, finding biomarkers for depression that are both valid and practical in busy hospital settings is a significant challenge on its own.

Recent evidence suggests that the cortisol awakening response (CAR) offers significant promise in this regard. For example, a higher baseline, CAR in adolescents has been associated with an increased risk of developing major depressive disorder (MDD) at 1 year follow-up, even after excluding individuals with MDD at baseline [1]. In adults, both current and remitted MDD patients exhibit a higher CAR AUCg (*a*rea *u*nder the *c*urve ground) than do normal controls, suggesting that total cortisol output may be a trait marker for MDD [2]. On the other hand, in an extension of the latter study in over 800 participants with established MDD, a *blunted* CAR [AUCi (*a*rea *u*nder the *c*urve *i*ncrease) and/or AUCg] has been associated with an unfavorable course trajectory over a 2-year follow-up period [3]. Consistent with the latter finding, the only study looking at the CAR in inpatients showed a blunted rather than exaggerated CAR [4]. Taken as a whole, these various findings thus suggest that the CAR may have clinical utility in predicting both de novo cases of MDD and the longitudinal course of established MDD cases, with the direction of change in these

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relationships evolving over time, i.e., exaggerated responses predicting early pathology and blunted responses predicting chronicity. Indeed, this biphasic model would be consistent with well-established models of acute vs. chronic stress [5].

Given the inherent challenges in identifying meaningful subgroups of complex depressed patients based on categorical diagnoses and the promise of the CAR at both theoretical and practical levels, we performed this pilot study to assess (1) whether CAR measures at admission predict treatment response in heterogeneous MDD patients completing a 4-week alternate milieu inpatient program and (2) whether the CAR would be acceptable to patients and staff in this relatively busy clinical setting.

2. Methods

2.1. The Alternate Milieu Program

The current sample consisted of consecutive patients with major depression admitted to the Alternate Inpatient Milieu (AIM) program for mood disorders at the Centre for Addiction and Mental Health (CAMH), Toronto, Canada. The AIM program is 28 days in duration and is staffed by an interdisciplinary team including qualified psychiatrists, psychologists, nurses, occupational therapists, social workers and recreational therapists. It is designed to promote a recovery-oriented, mutually responsible and collaborative treatment environment including both individual-based and group-based programming. Group therapies focus on skill building, cognitive and dialectical behavior therapy as well as activation, leisure education and general wellness. AIM provides a home-like setting while emphasizing patient empowerment, goal setting, coping, social skills and stress management.

The typical patient admitted to the AIM unit is referred by an outpatient psychiatrist for treatment optimization and improved overall functioning. Vast majority are on long-term medication and have had depression for several years with varying degrees of treatment resistance and disability. As our primary goal was to identify a biomarker tied to clinical outcome in naturalistic, heterogeneous patients, our inclusion/exclusion criteria were relatively broad though designed to limit major confounds for salivary cortisol where possible. We thus included consecutive patients who met *DSM, Fourth Edition*, criteria for a current major depressive episode as assessed using the MINI [6]. All patients completed informed consent as approved by the CAMH research ethics board. The majority of patients had unipolar MDD, while three had a primary diagnosis of bipolar II disorder, depressed phase. All consenting patients were screened for inclusion and exclusion criteria by a trained research assistant to determine their suitability.

The main exclusion criteria are standard for work on the HPA axis and included serious medical illness, active suicidal ideation, psychosis, having a diagnosis of anorexia nervosa and/or bulimia nervosa, recent substance abuse, being pregnant or lactating or taking steroid medications.

At the time of admission, the vast majority of our depressed patients have been on one or psychotropics on a long-term basis. While it is acknowledged that this has the potential to confound cortisol measures, prior studies suggest that this may not be the case in more chronically depressed samples [7,8]. This, and the ethical and practical issues related to discontinuation of ongoing treatment, led us to include medicated patients while controlling for this statistically.

2.2. Clinical Ratings

Depression severity was assessed at admission and discharge using the self-report Quick Inventory of Depressive Symptoms (QIDS) (16SR) [9].

2.3. Cortisol Assays

Upon admission, participants were asked to collect 2 consecutive days of morning cortisol samples. Vast majority of patients are admitted on weekdays and only weekday samples were collected to avoid the potential confound of weekend sampling. A full set of instructions was provided and saliva was collected by the patients themselves using salivette tubes (Sarstedt, Germany). Participants were asked to maintain a regular sleep/wake schedule throughout their hospital stay that was further supported by the hospital staff. Participants were asked to provide salivary samples immediately upon waking and 30 and 60 min after awakening. Participants recorded what time they went to bed, when they awoke and when they performed each sample in a journal that was provided. Participants were advised not to eat, drink (including caffeinated beverages), smoke, brush their teeth or take medications during the first hour of awakening.

Samples were stored in a −74°C freezer on site at CAMH and assays were performed at St. Joseph's Healthcare Centre in Hamilton Ontario using high-sensitivity enzyme-linked immunosorbent assays. Both the intravariability and intervariability of these assays was less than 10%.

2.4. Calculation of CAR

The equations outlined in Pruessner et al. [10] were used to calculate AUCi and AUCg for the CAR. The AUCi factors out the initial cortisol value and is a measure of HPA axis reactivity. The AUCg includes the first cortisol measure and measures total cortisol output. As these equations assume regular time intervals between samples, participants were asked to record the specific clock times at which they completed each sample as delays exceeding 15 min have been shown to effect the CAR [11]. It was decided a priori that samples collected more than 10 min late of the suggested sampling time would be excluded from the analysis.

Based on the prior literature and past experience, it was anticipated that some salivary cortisol samples would be unusable due to low salivary volumes and/or untimely sampling. To help mitigate this problem, mean cortisol values across the 2 sampling days were used in the CAR calculations; when only one of the two samples for a given time point was available, only single sample values were used in the CAR calculations.

2.5. Data Analysis

All analyses were done using SPSS-16 software. Prior to addressing the specific study questions outlined above, the normality of the clinical self-report measures and CAR data was first assessed using the EXPLORE function of SPSS. Study variables with a Kolmogorov–Smirnov statistic at $P > .01$ were considered normally distributed.

2.6. Potential Confounding Variables

To examine potential confounding variables, we first examined whether age, body mass index (BMI), gender, time of awakening, baseline QIDS, Beck Anxiety Inventory and Childhood Trauma Questionnaire Scores smoking (yes/no) and/or psychotropic medication regimen at admission were associated with either the primary outcome variable (percentage change in the QIDS from admission to discharge) or the primary independent variables (CAR AUCi and AUCg). This was done using univariate logistic or linear regression as appropriate.

For completeness, a series of separate univariate logistic regressions were done for the following psychotropic medication groupings based on current use at the time of admission as summarized in Table 1: use of any antidepressant, any selective serotonin reuptake inhibitor (SSRI), any selective norepinephrine reuptake inhibitor (SNRI), an antipsychotic, a mood stabilizer (lithium or an anticonvulsant), any benzodiazepine or use of more than one psychotropic.

2.7. Primary Analysis

To test our main hypothesis, two separate linear regressions predicting the percent change in QIDS scores from admission to discharge were completed, controlling for baseline QIDS. In one case, the

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