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# Cortisol awakening response in PTSD treatment: Predictor or mechanism of change

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ABSTRACT

PTSD is associated with abnormalities in hypothalamic-pituitary-adrenal (HPA) axis activity. This includes enhanced HPA axis negative feedback, attenuated cortisol awakening response, and attenuated cortisol response to personal trauma script. Whether HPA axis function predicts treatment response or treatment related symptom reduction in PTSD remains unclear. In addition, the relative effects of different treatment modalities (i.e., medication and psychotherapy) on HPA axis is unclear. To address this gap in knowledge, the PROGrESS study examined cortisol awakening response across treatment in Veterans with chronic PTSD randomized to receive Prolonged Exposure + Placebo (PE + PLB), Sertraline + PE (SERT + PE) or Sertraline + Enhanced Medication Management (SERT + EMM). Salivary cortisol awakening response (CAR) was assessed at baseline, mid-treatment (week 6 and 12), post-treatment (week 24) and follow-up (week 36 and 52). Among males at baseline, combat veterans with PTSD showed lower CAR Area Under the Curve Increase (AUCi; $M = 3.15$, $SD = 9.57$) than Combat controls ($M = 7.63$, $SD = 9.07$; $p = .02$), demonstrating combat veterans with PTSD have a less responsive system than combat controls. Higher PTSD severity was also related to lower CAR AUCi ($r = -0.52$, $p = .03$). When controlling for PTSD severity, higher baseline CAR AUCi was related to attenuated reduction in PTSD and lower likelihood of high treatment response over treatment ($z = -2.06$, $p = .04$).

PTSD is a major public health challenge. Soldiers returning from Afghanistan and Iraq show PTSD rates between 12–20 % (Hoge et al., 2004), with significant associated psychological, physical, and economic burden. Abnormalities in hypothalamic-pituitary-adrenal (HPA) axis activity, including specifically enhanced HPA axis negative feedback (Liberzon et al., 1999), attenuated cortisol awakening response (CAR) (Neylan et al., 2005), and attenuated cortisol response to personal trauma script (Pitman et al., 2012; Walsh et al., 2013), have been found with PTSD.

Patients with PTSD have consistently been shown to have enhanced glucocorticoid receptor sensitivity leading to enhanced negative feedback and, less consistently, hypocortisolemia (Elzinga et al., 2003; Liberzon et al., 1999; Yehuda et al., 2006) and flattened diurnal cortisol rhythms (Yehuda et al., 2007). Research supports that trauma survivors who have lower cortisol in the acute aftermath of trauma exposure may be at a higher risk of PTSD at long term follow-up (Pitman et al., 2012; Walsh et al., 2013). Recent research supports that this effect may be moderated by prior trauma exposure (i.e., Klaassens, 2010; van Zuiden et al., 2011). Preliminary studies with cortisol administration in the acute period following trauma suggest that this HPA axis hormone can potentially impact recovery: PTSD rates have been reported as lower with cortisol administration compared to placebo in some studies

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(Pitman et al., 2012; Schelling et al., 2004; Walsh et al., 2013). Indeed, experimental studies of fear have found that administration of cortisol prior to exposure exercises resulted in significantly larger reductions in phobic avoidance and attenuated skin conductance with exposure to phobic situations than placebo (Soravia et al., 2014). In a pilot study of combat Veterans with PTSD randomized to PE with hydrocortisone or PE plus placebo, however, Yehuda and colleagues found increased retention in the augmented condition but no overall difference in post treatment PTSD severity (Yehuda et al., 2015). In a similar study design augmenting exposure therapy with dexamethasone, Maples-Keller et al. found the opposite regarding retention, with greatly increased treatment dropout in the augmentation arm compared to placebo, plus a suggestion of PTSD symptom worsening (Maples-Keller et al., 2019). These discrepancies may be attributed to differences in the mechanisms of action with hydrocortisone acting both centrally and peripherally, whereas dexamethasone acting mainly peripherally. Additional work on administration of cortisol is needed.

Consistent with the hypothesized role of cortisol, Bentz et al. (Bentz et al., 2010) proposed that glucocorticoids may enhance inhibitory learning, or specifically enhance the consolidation of "safety" information in feared situations and inhibit retrieval of learned fear. As such, altering exposure procedures to tap into processes that enhance inhibitory learning and/or recall, as opposed to simply tolerating distress, may enhance treatment outcome; cortisol may be a salient "player" in these processes. However, few studies have examined the relevance of endogenous cortisol secretion on treatment outcomes or how these processes change over a full course of treatment in PTSD patients. Variability in results from studies examining HPA axis function is partially due to the complexity and sensitivity of the system, such that slight variations in paradigm or method of collection can have a significant impact on results across studies. For instance, studies using very brief personal trauma scripts have shown an association between increased cortisol in response to the brief script and PTSD treatment response (Rauch et al., 2015a,2015b), while studies using longer personal trauma scripts found the opposite relationship (Norrholm et al., 2016). This difference suggests that the brief script may be more effective at testing system effectiveness of avoidance. Specifically, with a brief script, patients with HPA systems that are effective at avoidance are able to NOT react while those that are less able to quickly engage avoidance show reactive process. These people are then more able to quickly respond in exposure-based treatments. When the script is longer, then this difference may not appear as fewer people with PTSD are able to avoid effectively as the script continues and they all react. Thus, the magnitude of response will not discriminate those who will do well in exposure-based treatment.

Based on such sensitivity and the resulting variability, better clarity in what exactly is tested is necessary. CAR is thought to reflect reactivity of the HPA axis to the standardized stressor of waking and has the potential to be a cost effective and practical tool should it prove to be a significant biomarker for differential treatment outcome. To date, however, the evidence linking CAR with PTSD symptom severity has been equivocal. In a sample of police officers, greater current PTSD symptom severity was strongly associated with attenuated CAR (Neylan et al., 2005), whereas an elevated response has been associated with higher depressive symptoms (Pruessner et al., 2003a,2003b). In one study examining CAR in PTSD, Pacella et al. (2014) found that higher baseline CAR was associated with lower PTSD symptom severity at post-treatment, but CAR did not change with trauma focused psychotherapy or medication (Pacella et al., 2014). In another study examining symptom response 6–8 months post treatment, Rapcencu et al. (2017) found both reduction in CAR over time (for those treated and untreated) and an association between baseline higher CAR and PTSD symptom reduction in male combat veterans with PTSD (Rapcencu et al., 2017).

Given the inconsistent pattern of results additional mechanistic studies examining cortisol longitudinally over the course of therapy are thus needed to determine whether these markers predict response to treatment or track specific symptom/function changes essential to recovery. To examine HPA function over treatment, the current study focused on CAR (a general measure of HPA activity) due to ease of collection, association with perceived stress (Pruessner et al., 1999) and psychiatric symptoms. We examined CAR as a candidate biomarker of PTSD treatment response using salivary cortisol collected from participants of a large randomized clinical trial comparing PTSD symptom changes across three PTSD treatment conditions (Rauch et al., 2019). Salivary cortisol was collected at baseline, mid-treatment (6-weeks), post-treatment (12-weeks) and follow-up (24-weeks) in response to awakening across the study conditions: Prolonged exposure + placebo (PE + PLB), Sertraline + enhanced medication management (SERT + EMM), and Prolonged exposure + sertraline (PE + SERT).

## 1. Method

The PROlonGed ExpoSure and Sertraline Trial (PROGrESS) is a randomized controlled trial (RCT) approved by site IRBs and DOD Human Research Protection Office (HRPO) and registered at ClinicalTrials.gov (NCT01524133). The current study presents planned mechanistic analyses examining CAR. PE occurred in the first 13 weeks with pills administered for 24 weeks. Follow-up occurred at 36 and 52 weeks. Readers are referred to the previously published in depth methods paper (Rauch et al., 2018) and the primary outcomes paper for details (Rauch et al., 2019). The three conditions showed no significant differences in PTSD severity at post-treatment (week 24) or follow-up.

### 1.1. Participants

Four sites [VA Ann Arbor Healthcare System (VAAAHS), VA San Diego Healthcare System (VASDHS), Ralph H. Johnson VA Medical Center (RHJVAMC), and Massachusetts General Hospital (MGH)] recruited 207 (178 from randomized and 29 from combat control group) patients who completed CAR between 2011 and 2016. Of them, 195 (172 men and 23 women) provided saliva that allowed for calculation of baseline CAR area under the curve increase (AUCi). Due to gender differences in HPA axis function (Verma et al., 2011) and the small number of women in our sample, we restricted all analyses to men (N = 172).

Inclusion criteria for PROGrESS were service members or Veterans of Iraq/Afghanistan wars with combat-related PTSD and significant impairment (Clinicians Administered PTSD Scale (CAPS) ≥50) of at least three months duration. Exclusion criteria were: 1) current, imminent risk of suicide, 2) active psychosis, 3) alcohol or substance dependence (past 8 weeks), 4) inability to attend weekly appointments for the treatment period, 5) prior intolerance or failure of adequate trial of PE or SERT, 6) medical illness likely to result in imminent hospitalization or contraindication to study treatments, 7) serious cognitive impairment (e.g., confusion, inability to track discussion), and 8) concurrent antidepressants or antipsychotics, benzodiazepines, prazosin, and sleep agents (e.g., zolpidem); they were allowed if the dose was stable for 2 weeks by baseline. Veterans with mild traumatic brain injury were not excluded. For the combat controls, inclusion criteria were: 1) absence of any history of PTSD symptoms (CAPS < 20), related to any type of trauma; 2) exposure to Criterion A Combat Trauma with Combat Exposure Scale (CES; (Keane et al., 1989)) score ≥ 17 (e.g., at least moderate exposure) during OEF/OIF/OND involvement. Otherwise, the same inclusion/exclusion criteria apply for the CC group as that used for the PTSD patient group noted above. See Table 1 for demographics and descriptive analyses of the participants included.

### 1.2. Procedures

Veterans and service members were recruited, consented and completed symptom and diagnostic assessments prior to randomization.

**Table 1**
Baseline Demographic and Mental Health Symptom Characteristics of male CAR Cohort ($N$ = 172).

| | Randomized Groups ($N$ = 144) | | | Combat |
|---|---|---|---|---|
| | Sertraline + EMM<br>$N$ = 57 | PE + placebo<br>$N$ = 43 | PE + Sertraline<br>$N$ = 44 | Control<br>$N$ = 28 |
| Age, mean (*SD*) | 33.6 (8.7) | 33.7 (8.4) | 34.9 (9.0) | 33.9 (8.1) |
| Race | | | | |
| White | 37 (64.9 %) | 26 (60.5 %) | 26 (59.1 %) | 22 (78.6 %) |
| Black | 15 (26.3 %) | 9 (20.9 %) | 13 (29.6 %) | 2 (7.1 %) |
| Other | 5 (8.8 %) | 8 (18.6 %) | 5 (11.4 %) | 4 (14.3 %) |
| Hispanic or Latino Ethnicity[1] | 12 (21.1 %) | 5 (11.6 %) | 6 (13.6 %) | 1 (4.2 %) |
| Marital Status[2] | | | | |
| Married | 31 (55.4 %) | 28 (65.1 %) | 21 (47.7 %) | 12 (42.9 %) |
| Never Married | 17 (30.4 %) | 6 (14.0 %) | 9 (20.5 %) | 13 (46.4 %) |
| Divorced/Separated | 8 (14.3 %) | 9 (20.9 %) | 14 (31.8 %) | 3 (10.7 %) |
| Education | | | | |
| High School (or equivalent) | 25 (43.9 %) | 17 (39.5 %) | 15 (34.1 %) | 2 (7.1 %) |
| Some College (13−15 years) | 24 (42.1 %) | 17 (35.9 %) | 20 (45.5 %) | 9 (32.1 %) |
| Bachelor's or Above (16+) | 8 (14.0 %) | 9 (20.9 %) | 9 (20.5 %) | 17 (60.7 %) |
| Work Status | | | | |
| Full Time | 29 (50.9 %) | 24 (55.8 %) | 22 (50.0 %) | 17 (60.7 %) |
| Part Time | 6 (10.5 %) | 8 (18.6 %) | 6 (13.6 %) | 1 (3.6 %) |
| Not Working | 22 (38.6 %) | 11 (25.6 %) | 16 (36.4 %) | 10 (35.7 %) |
| Served in Iraq | 45 (79.0 %) | 36 (83.7 %) | 35 (79.6 %) | 23 (82.1 %) |
| Served in Afghanistan[3] | 26 (45.6 %) | 24 (55.8 %) | 22 (51.2 %) | 11 (39.3 %) |
| CAPS, mean (*SD*) | 74.2 (15.5) | 81.5 (11.9) | 76.3 (14.2) | 2.2 (3.9) |
| CAPS subscale B, mean (*SD*) | 19.4 (6.4) | 20.8 (6.9) | 18.9 (6.6) | 0.6 (1.1) |
| CAPS subscale C, mean (*SD*) | 28.3 (8.1) | 31.9 (7.2) | 29.9 (7.2) | 0.4 (1.3) |
| CAPS subscale D, mean (*SD*) | 26.5 (5.3) | 28.9 (4.3) | 27.5 (4.8) | 1.2 (2.7) |
| Major Depressive Disorder | 34 (59.7 %) | 33 (76.7 %) | 30 (68.2 %) | 0 (0%) |
| Panic Disorder | 9 (14.0 %) | 5 (11.6 %) | 5 (11.4 %) | 0 (0%) |
| Agoraphobia | 14 (24.6 %) | 10 (23.3 %) | 8 (18.2 %) | 2 (7.1 %) |
| Alcohol Abuse yes[4] | 7 (14.6 %) | 6 (14.6 %) | 5 (12.2 %) | 2 (7.1 %) |
| Substance Abuse yes[5] | 1 (1.8 %) | 0 (0%) | 2 (4.6 %) | 0 (0%) |
| High responders[6] | 22 (40.7 %) | 10 (30.3 %) | 17 (42.5 %) | NA |
| Low to moderate responders[7] | 28 (51.9 %) | 20 (60.6 %) | 18 (45 %) | NA |
| Numerically increased[8] | 4 (7.4 %) | 3 (9.0 %) | 5 (12.5 %) | NA |

Abbreviation: NA is not applicable. : [1]Fourpersons in Combat Control group with missing Hispanic status are not included in the percentage calculation.; [2]Excludesone Sertraline group person with missing marital status.; [3]Excludesone PE + Sertraline group person with missing Afghan deployment information.; [4]Doesnot include alcohol dependence because that was an exclusion criterion.; [5]Doesnot include substance dependence because that was an exclusion criterion.; [6]High responders are defined as those with 50 % reduction from baseline CAPS to Week 24; those without any follow-up CAPS assessments were not included in the percentage calculation and N = 54, 33, and 40 for Sertraline, PE + placebo and PE + Sertraline arm, respectively.; [7]Lowto moderate responders are defined as those with less than 50 % reduction from baseline CAPS to Week 24; [8]Numericallyincreased are defined as those with at least one point increase from baseline CAPS to Week 24;

Self-report and clinician administered clinical measures occurred at weeks 0 (intake), 6, 12, 24, 36, and 52. Evaluators blind to treatment condition completed all structured interviews.

### 1.3. Measures

CAPS (CAPS; Blake Weathers, Nagy, & Kaloupek, 1995) and Mini International Neuropsychiatric Interview (MINI (Sheehan et al., 1998)) were used to determine diagnostic status and comorbidities at intake. Interrater reliability was conducted throughout the study period on 20 % of randomly selected CAPS and MINI assessments and is reported elsewhere (Rauch et al., 2019). Primary outcome was PTSD severity (past month total CAPS). Since the study was initiated prior to DSM5, DSM-IV-TR PTSD criteria were used. High responder was defined as reduction from pre to posttreatment (week 24 or last available) of at least 50 % in CAPS. Low to moderate responder was defined as pre to posttreatment (week 24 or last available) of less than 50 % in CAPS. Numerically increased was defined as pre to posttreatment (week 24 or last available) at least one point increased over baseline CAPS.

CAR assessed salivary cortisol. The current study was initiated prior to publication of the consensus guidelines for CAR (Stalder et al., 2016) but still complied with most of the requirements (control of sampling accuracy through self-report diary, participant clear instructions with confirmed checklist of exclusionary behaviors, influence of covariates minimized through statistical control in models and exclusion for illness. Assessment of CAR used three post waking collections, and data reporting included AUCi, AUCg examined but not the CAR measure). Subjects received instructions with timing logs and three salivettes for collection of the saliva samples at awakening, 30 min, and 45 min post awakening. Saliva was collected by cotton swabs placed in the mouth for 30 s for each collection. Veterans were instructed to refrain from eating, drinking, brushing their teeth, or smoking for at least one hour before sampling. The logs included recording of all collection times and yes/no responses required for each unwanted morning behavior (smoking, brushing teeth, eating, drinking, etc.). They were instructed to collect and bring the samples to their study assessment the same day. Cortisol is assayed using Immulite™ (Siemens, Inc.), a rapid and highly sensitive and precise semi-automated chemiluminescent assay and has an intra-assay variability of < 5 %. CAR was calculated as the area under the curve with respect to increase over baseline (AUCi; (Pruessner et al., 2003a,2003b) to show whether cortisol response to awakening is predictive of treatment response or related to magnitude of response. Based on previous studies showing CAR outcome in PTSD treatment using AUCi but not AUCg (area under the curve with respect to ground), we focused analyses on AUCi (Pacella et al., 2014; Rapcencu et al., 2017).

### 1.4. Treatment

Detailed descriptions of study treatment are available in Rauch

et al., 2018. Briefly, veterans were randomly assigned to PE + PLB, SERT + EMM, and PE + SERT. All conditions included pill and therapy. Active treatment began at week 0 and was maintained through week 24.

PE. Participants were scheduled for 13, 90-minute PE sessions to be completed by week 12 with allowance to complete by week 24. PE sessions included recording sessions and *in-vivo* exposure homework (Foa et al., 2007).

Pharmacotherapy. Medication doses of sertraline were flexibly adjusted between 50 and 200 mg/day, with last dose increase at week 10 to ensure stable dosing by week 12. Medication was continued until week 24. After completion of week 24 outcome measures, patients and providers were unblinded and participants were offered referrals for open PE and/or sertraline or other treatment outside of the study, as clinically indicated.

### 1.5. Statistical analyses

We first compared CAR AUCi between combat Veterans with PTSD and combat Veterans without PTSD at baseline using a two-sample *t*-test. We examined whether baseline CAR AUCi is associated with baseline PTSD severity as measured by the CAPS with a regression model with baseline CAR AUCi as the primary predictor. In the randomized sample of combat Veterans with PTSD only, we assessed the influence of baseline CAR AUCi on CAPS pre- to post-treatment change, and on response status, defined as at least 50 % reduction in CAPS from baseline. For baseline CAR AUCi influence on CAPS change, we used a regression model with change in week 24 CAPS score (baseline minus week 24) as the response variable adjusting for baseline CAPS value. Adjusting for baseline CAPS was done to obtain a more precise and unbiased estimate of the relationship between baseline AUCi and CAPS change as baseline CAPS is generally predictive of CAPS change. We also used a longitudinal mixed-effects model with CAPS scores at all follow-up assessments to week 52 as response variables adjusting for a decreasing rate of change in CAPS over time using ln(time + 1) as a predictor. For baseline CAR AUCi influence on treatment response status, we used a logistic regression model with binary response status (high responder vs. not) as the outcome and CAR AUCi as the predictor. We also assessed the change in week 24 CAR AUCi across treatment. Finally, in order to compare our study with the previous Pacella et al. (Pacella et al., 2014) we added the female subsample and assessed if the baseline CAR AUCi influences on week 24 CAPS differed by gender.

## 2. Results

*CAR AUCi and PTSD Severity Within Timepoints.* In a mean comparison of combat Veterans with and without PTSD at baseline, we found significantly lower CAR AUCi in combat Veterans with PTSD ($N$ = 144; $M$ *(SD)* = 3.1( ± 9.6) than controls ($N$ = 28; $M$ *(SD)* = 7.6 ( ± 9.1), $p$ = 0.02). In a regression, we found that lower AUCi was related to higher CAPS (coefficient = -0.52, $p$ = 0.03).

During follow-up, no symptom assessments were made in combat control veterans. At each follow-up, we no longer found a significant relationship between AUCi values and CAPS. Specifically, the coefficients were .11 (p-value = .54), .29 (.21), -.15 (.55), -.05 (.89), and -.07 (.84) at week 6, 12, 24, 36, and 52, respectively.

*Baseline CAR AUCi and Change in PTSD Symptom Severity.* In the 144 combat Veterans with PTSD, we found higher baseline CAR AUCi to be associated with lower week 24 symptom improvement (Table 2, $N$ = 103, coefficient = -0.55, $p$ = 0.02) adjusting for baseline CAPS. In general, the longitudinal model of CAPS severity including all follow-up data ($N$ = 144 persons, 678 observations) showed significant symptom improvement over the one year follow-up period in our subsample ($p$ < .001) consistent with the overall study (Rauch et al., 2019). However, although marginally significant, higher baseline CAR AUCi was associated with an attenuated rate of symptom improvement over follow-up (as indicated by the coefficient of 0.12 ($p$ = 0.06) for the interaction term of ln(week + 1) by baseline CAR AUCi (Table 3). These relationships were significant when baseline symptom severity was entered as a covariate in the analysis. We further explored the relationship by comparing baseline AUCi across the three response groups defined by post-treatment symptom change: (1) high responders, (2) low to moderate responders, and (3) numerically increased. Post hoc ANOVA found that baseline AUCi differed significantly across response groups [F (2, 127) = 3.94, p = 0.02] with means of 0.46 (SD = 10.5), 8.44 (SD = 8.82) and 3.93 (SD = 9.08) in each group, respectively. Results from the logistic regression model with binary treatment response (defined as at least 50 % change in CAPS) as the dependent variable showed higher baseline CAR AUCi ($OR$ = 0.89, $p$ = 0.05) in PE + PLB arm, and African American racial status (OR = 0.19, p = 0.003) was associated with lower odds of treatment response ($N$ = 127, Table 4). Lastly, when we examined if the relationship between baseline CAR AUCi and week 24 CAPS differed by sex, we found no significant difference between low and high responders in week 24 CAR AUCi for men or women; of note, this is contrary to the findings of Pacella et al. (Pacella et al., 2014).

**Table 2**
Regression model of week 24 symptom improvement (CAPS change calculated as "baseline – week 24") in Combat Veterans with PTSD (n = 103).

| Week 24 CAPS change | Coef. | SE | t | p-value | 95 % Conf Limit |
|---|---|---|---|---|---|
| Baseline AUCi | −0.55 | 0.22 | −2.43 | 0.02 | −0.99, −0.10 |
| Baseline CAPS | 0.07 | 0.16 | 0.45 | 0.66 | −0.25, 0.39 |
| Constant | 27.11 | 12.47 | 2.17 | 0.03 | 2.37, 51.84 |

*CAR AUCi Change* vs *PTSD Symptom Severity Change.* Although CAPS scores decreased significantly (baseline, CAPS M = 77.0, SD = 13.3; Week 24, CAPS M = 45.5, SD = 25.9, p < .001) in all three arms in men, CAR AUCi did not significantly change in a longitudinal data model with CAR AUCi as the response variable and ln(week + 1) as the main predictor (p = 0.36). Combined across the three arms, mean CAR AUCi was 3.1, 3.9, 2.4 and 4.8 at baseline, week 6, week 12, and week 24 in men. We did not find decreasing or increasing patterns over time in CAR AUCi in any of the three arms despite PTSD symptom improvement. Further evaluation of the relationship between baseline to week 24 change in CAR AUCi vs. CAPS baseline to week 24 symptom change did not show any meaningful relationships.

## 3. Discussion

In the current study we replicated previous findings of lower CAR at baseline in PTSD patients, as well as baseline CAR relationships with PTSD symptom severity. This is important as it shows that previous studies with non-veteran samples are consistent with veterans in a relatively large sample, and validates the procedures and the potential generalizability of this finding. Specifically, finding that combat veterans with PTSD have lower cortisol than combat veterans without PTSD is an important contribution suggesting that it is not just combat/trauma exposure but PTSD itself that is linked to lower cortisol. On the other hand, we did not find that CAR correlated with symptom change across the study, suggesting it might have limited utility as a biomarker of treatment change. We did find the suggestion that CAR (potentially reflecting endogenous cortisol reactivity) may represent a pre-treatment biomarker predicting lower response to sertraline, prolonged exposure therapy, and their combination. Specifically, across all three treatment groups, those with greater CAR at baseline, had both less reduction in PTSD symptoms over the treatment period and greater likelihood of being poorer responders. This finding is somewhat counterintuitive as higher CAR at baseline predicted lower baseline PTSD symptom severity. Larger studies are needed to establish whether these relationships indeed represent separate mechanisms at play (for

**Table 3**
Longitudinal data model of symptom (CAPS) over the 12 months of intake, treatment and follow-up period in Combat Veterans with PTSD (N = 144 persons, 678 observations).

| CAPS | Coef. | SE | z | P-value | 95 % Conf. Limit |
|---|---|---|---|---|---|
| Ln(week + 1) | −8.81 | 1.18 | −7.48 | < 0.001 | −11.13, −6.51 |
| Arm | | | | | |
| Sert + EMM vs. PE + PLB | −10.44 | 3.24 | −3.23 | 0.001 | −16.78, −4.10 |
| PE + SERT vs. PE + PLB | −6.02 | 3.44 | −1.75 | 0.08 | −12.75, 0.72 |
| Arm by Ln(week + 1) | | | | | |
| PE + PLB by Ln(week + 1) | 0.97 | 1.51 | 0.64 | 0.52 | −1.98, 3.92 |
| PE + SERT by Ln(week + 1) | −0.40 | 1.59 | −0.25 | 0.80 | −3.52, 2.72 |
| Baseline AUCInc[1] | −0.09 | 0.14 | −0.59 | 0.55 | −0.37, 0.20 |
| Baseline AUCInc[1] X Ln(week + 1) | 0.12 | 0.06 | 1.92 | 0.06 | −0.00, 0.24 |
| Constant | 80.67 | 3.76 | 21.47 | < 0.001 | 73.31, 88.04 |

Note: The model included random intercepts and slopes (of ln(week + 1)) and was also adjusted for study sites. Decrease in symptom over time is modeled using ln (week + 1) to reflect the slowly decreasing rate of symptom improvement during the one year of treatment and follow-up period.
[1] Baseline AUCInc values are centered at 2.8.

**Table 4**
Logistic regression model of treatment response (N = 127).

| Response | OR | Std. Err. | z | p-value | 95 % Conf. Limit |
|---|---|---|---|---|---|
| Baseline AUCinc | 0.89 | 0.05 | −1.99 | 0.05 | 0.80, 1.00 |
| Arm | | | | | |
| Sert + EMM vs. PE + PLB | 2.48 | 1.39 | 1.62 | 0.11 | 0.82, 7.45 |
| PE + SERT vs. PE + PLB | 2.99 | 1.77 | 1.86 | 0.06 | 0.94, 9.51 |
| Arm by baseline AUCInc | | | | | |
| Sert + EMM vs. PE + PLB | 1.08 | 0.07 | 1.26 | 0.21 | 0.96, 1.23 |
| PE + SERT vs. PE + PLB | 1.12 | 0.08 | 1.64 | 0.10 | 0.98, 1.28 |
| African American vs. White | 0.19 | 0.11 | −2.98 | 0.003 | 0.07, 0.57 |
| Other vs. White | 1.42 | 0.89 | 0.56 | 0.58 | 0.41, 4.84 |
| _cons | 0.38 | 0.18 | −2.00 | 0.05 | 0.14, 0.98 |

example, one mechanism linked to symptom severity and the other predicting their “malleability”) or not. Examination of whether this may be explained by lower baseline CAPS resulting in a smaller window for potential reduction in CAPS with treatment is warranted in a larger sample; however, our results did not change even after adjusting for baseline CAPS.

As stated above, we did not see a significant change in CAR across treatment in any of the treatment conditions. This finding was also surprising and not consistent with the previous study comparing two psychotherapies (Rauch et al., 2015a,2015b) that found PE was specifically associated with increased CAR compared to Present Centered Therapy. There are several potential reasons for this difference in results. It may be due to the more robust CAR measure used, or to the larger sample size in the current study. Alternatively, baseline measures of HPA axis may reflect more durable and trait-like qualities of system function that may preexist trauma exposure or PTSD and thus may not change with treatment. Finally, this may be due to a difference in treatment modality or in patient attribution of change due to all veterans having taken a pill in the current design. Such attribution may be reflected in changes in biological processes, such as HPA response, based on whether the patient perceives control over change or perceives medication is responsible for the change alone. Indeed, in another publication from the current study examining the impact of trauma related thoughts on symptom change, patterns of change and attribution of change may have altered psychotherapeutic processes as well (Rauch et al., 2020).

There are several limitations to our findings. First, the study did not include a large enough sample of female veterans to thoroughly examine whether the patterns hold for women. With the exception of the one analysis run specifically to compare to the previous study (Pacella et al., 2014), all other analyses were run on male veterans only. Second, only those veterans willing to be randomized to the study conditions that included both medication and prolonged exposure were included. Despite these limitations, the strengths of the study (large, multi-site sample in a comprehensive treatment outcomes and mechanisms design) support the utility of our findings.

In summary, the current study confirms the link between PTSD severity and diagnosis with HPA reactivity as assessed by CAR. On the other hand, our findings do not support a potential role for CAR as a robust predictor or index of treatment response.

## 4. Disclosures

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