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Placebo Effects across Self-Report, Clinician-Rating, and Objective Performance Tasks among Women with PTSD: Investigation of Placebo Response in a Pharmacological Treatment Study of PTSD

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Abstract

Purpose/Background—For a drug to acquire Food and Drug Administration approval, it must significantly outperform placebo treatment. In recent years, the placebo effect seems to be increasing in neuropsychiatric conditions. Here we examine placebo effects across self-reported, clinically rated, and performance based data from a trial using a corticotropin releasing hormone receptor type 1 (CRHR1) antagonist for treatment of post-traumatic stress disorder (PTSD).

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Disclosures

In the past five years, Dr. Iosifescu has consulted for Avanir, Axome, CNS Response, INSYS Therapeutics, Lundbeck, Otsuka, Servier, and Sunovion and he has received grant/research support through the Icahn School of Medicine at Mount Sinai from Alkermes, Astra Zeneca, Brainsway, Euthymics, Neosync, Roche, Shire.

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Dr. Harvey has received research support from Takeda. He has served as a consultant to Allergan, Boehringer-Ingelheim, Otsuka Digital Health, Sanofi, Sunovion, and Takeda.

Methods/Procedures—Women with chronic PTSD were randomized to treatment with either GSK561679, a CRHR1 antagonist, or placebo. Prior to randomization, participants completed self-report scales, clinician-rated measures of PTSD and depression symptoms, and objective tests of cognition and functioning. Differences in change scores on measures were compared between GSK561679 and placebo-treated participants.

Findings/Results—GSK561679 failed to produce any significant improvement in the participants. A substantial placebo effect was observed in both self-report and clinical rating scales, with effect sizes up to 1.5 SD. No single variable predicted placebo-related changes. Notably there was an improvement on objective performance measures of cognition that exceeded previous standards for practice effects.

Implications/Conclusions—Participants in this trial manifested retest effects on performance-based measures of cognition. Notably, they had minimal prior experience with performance-based assessments. Experiencing the structure and support of a clinical trial may have contributed to significant reductions in subject-reported and clinician-rated PTSD symptom levels. The improvement seen across all assessment domains was consistent with that seen in previous studies where the active treatments separated from placebo. Investigators conducting clinical trials treating PTSD patients should expect placebo effects and design studies accordingly.

Keywords

clinical trial; post-traumatic stress disorder; women; child abuse; placebo; adrenocorticotrophic hormone

Introduction

The placebo-controlled randomized control trial (RCT) has been the gold standard in evaluating medications since World War II (1). In order to receive US Food and Drug Administration (FDA) approval, generally a drug treatment must be more efficacious than a placebo. It is thought that response to placebo is a complex behavioral phenomenon often beyond patient control, producing significant improvement with biological correlates (2). This phenomenon is known as the ‘placebo effect.’

The placebo effect has always had a significant presence in mental health research trials, but now seems to be increasing in both clinician-rated and self-reported measures. Trials for selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine showed considerable efficacy for major depressive disorder as well as many anxiety disorders in the 1980’s and 1990’s. Since the time of the first approvals for SSRIs, the drug-placebo difference, even for previously approved treatments, has steadily declined on average and the number of failed trials has increased (3, 4). The cause of this increase remains largely unknown, although it has been suggested that changing characteristics of patients entering clinical trials over the past 30 years may be associated with an increase in placebo effects. An alternative suggestion has been that efforts to recruit patients who meet entry criteria may have led to biased rating with inflation of clinical symptoms at baseline.

Psychiatric patients may be particularly likely to demonstrate placebo effects in clinical trials. Recent depression studies report placebo response rates of 25% to 60% on the primary

outcomes measures (5). In contrast, hypertension studies typically show an improvement in blood pressure readings of approximately 5% from baseline while taking a placebo (6). This discrepancy of placebo effect magnitude across diseases emerges in part from the lack of an objective biomarker for depression; clinical assessments are clearly more prone to multiple sources of bias compared to an objective measure such as blood pressure.

Posttraumatic stress disorder (PTSD) is an illness marked by a variety of re-experiencing, avoidance, mood, and cognitive symptoms following exposure to a traumatic event, as defined in the DSM-V. The lifetime prevalence of PTSD in the United States is estimated to be 6.8%, with women more often affected than men (8). Patients with PTSD suffer from decreased functioning across a broad spectrum of psychosocial domains, including occupational and interpersonal relationships (9). Studies have revealed a significant correlation between self-reported functional impairment and self-reported distress (10). Further, PTSD has a high rate of comorbid substance abuse and depression (11). Given the high degree of comorbidity, it is difficult to assess the specific impact of PTSD on the functionality and well-being of a patient.

Since PTSD was first recognized as a psychiatric disorder, treatment has revolved around psychotherapeutic techniques. Cognitive-processing therapy and prolonged exposure therapies are forms of cognitive behavioral therapy (CBT) proven to have efficacy for treating PTSD, though rates of treatment nonresponse reach 50% (12). Pharmacologic options for PTSD remain limited. Currently, SSRIs, sertraline and paroxetine, are the only FDA-approved pharmacotherapies for PTSD. Remission rates from SSRI treatment for PTSD are typically below 30% (13). Clearly, more research and development is needed to improve PTSD treatment outcomes.

The analyses reported herein are based on data collected from participants in a clinical trial for a novel drug treatment for PTSD, NCT01018992. PTSD, along with other anxiety-related illnesses, may be associated with chronically increased activity of central nervous system circuits utilizing corticotropin releasing hormone (CRH). A broad literature implicates elevated CRH activity in PTSD (14). CRH signaling drives activation of the hypothalamic-pituitary-adrenal (HPA) axis resulting in increased release of adrenocorticotropin and cortisol, which may have adverse psychiatric effects when sustained. In response to stress, corticotropin-releasing factor (CRF) is released from the hypothalamus, and goes on to activate the HPA axis. CRF binds in the pituitary gland to stimulate the release of adrenocorticotropin (ACTH) which enters the systemic circulation and stimulates the adrenal cortex to release cortisol. Cortisol then typically has a negative feedback effect on the HPA axis. In PTSD patients, the levels of circulating ACTH and cortisol seem to be low, thus elevating CRF levels. CRF receptors are numerous in the amygdala, where activation induces a fear response. Intracerebroventricular administration of CRH produces anxiety-like behaviors in animal models, including features particularly relevant to PTSD such as sleep disturbance, enhanced acoustic startle response, and increased conditioned fear response (14). To target the HPA axis, this trial evaluated GSK561679, a CRH type 1 receptor antagonist versus placebo (15).

Animal models suggest that CRHR1 antagonists may have therapeutic value in the treatment of stress-related disorders, but these agents had not previously been investigated in patients with PTSD. Functional activity and in vitro binding assays indicate that GSK561679 is a potent CRHR1 antagonist. GSK561679 is an investigational drug and is not currently FDA-approved for any indication. Commonly reported adverse events in human studies of GSK561679 have included headache, fatigue, somnolence, dizziness, nausea, nasal congestion, upper respiratory tract infection, influenza, and acne and have been mild in nature. However, in human studies degenerative changes of the testes were observed in rats, dogs, and cynomolgus monkeys, though the change was reversible after a period of drug withdrawal. This concern has led to the exclusion of men from clinical trials using GSK561679 (14).

The main results of the study were negative in that GSK561679 was essentially indistinguishable from placebo, as outlined in the primary results paper from the trial (15). The baseline scores on the CAPS and other tested measures were comparable to other positive trials for PTSD, such as those with venlafaxine, suggesting that the failure of GSK561679 was not a result of symptom severity or placebo responsiveness. Further, there is data suggesting that the CRF pathway is not associated with anxiety-related disorders. The failure of the trial may have been a result of a poor target (15).

Herein we focus on placebo effects in this negative study across self-reported, clinician-rated, and performance based assessments. We assumed that the three assessment modalities would have different degrees of susceptibility to the placebo response. Potential drivers of placebo effects on self-report measures include optimism about treatment efficacy and potentially over-endorsing symptoms at entry into the study in order to ensure inclusion. The clinician assessment via clinician-administered ratings could possibly reduce response bias in terms of both baseline symptoms and clinical change, though clinician-based assessments still depend on the participants' verbal responses (3, 16). However, clinician ratings may also be particularly prone to placebo effects, as evidenced by increased placebo response over time in depression trials using clinical ratings as the outcome measure. Performance-based measures such as cognitive tests seem to be least likely to be susceptible to expectation bias. Although there is a controversy as to whether PTSD patients manifest impairments in cognitive performance that exceed premorbid functioning (17), cognitive assessments have been shown in other conditions to have placebo effects that are relatively small, on the order of 0.1 to 0.2 SD at a single retesting (18). In this study, we also included a measure of response bias which examined tendencies toward endorsing symptoms not part of the PTSD syndrome, previously used to detect exaggerated symptom reporting (10). This measure was examined for its correlation with both baseline and change scores across the different assessment modalities. We hypothesized that the self-reported measures and clinician rated measures would be most susceptible to placebo effects and cognitive test performance least susceptible. Additionally we hypothesized that tendencies toward higher baseline scores on the measure of response bias would be correlated with greater placebo response across all three assessment strategies.

Methods

Participants

Full details of the study protocol have been published previously and are reviewed briefly here (14). The trial randomized 128 women, with 96 completing the 6-week treatment period. The demographic and clinical characteristics of the randomized sample are presented in Table I. Men were excluded from this trial due to preclinical data suggesting adverse effects of GSK561679 on the male reproductive tract. Participants were recruited across four sites: University of California San Francisco; Emory University School of Medicine, Atlanta; Mount Sinai School of Medicine, New York; Michael E. DeBakey VA Medical Center/Baylor College of Medicine, Houston. Key inclusion criteria were a diagnosis of chronic PTSD according to the DSM-IV criteria and at least moderately severe PTSD symptom severity, indicated by a Clinician-Administered PTSD Scale (CAPS) past-week and past-month scores ≥ 50 (19). Exclusion criteria included a diagnosis of a psychotic disorder, bipolar disorder, OCD, anorexia nervosa, bulimia, substance abuse or dependence (in the past 90 days), high current suicide risk, being pregnant or nursing, taking psychoactive medication (other than non-benzodiazepine hypnotics), active legal issues related to PTSD or trauma exposure, or participating in structured psychotherapy targeting PTSD symptoms. All study procedures were done in compliance with the Declaration of Helsinki and its amendments. The institutional review boards of each site approved the study, and all participants signed a written informed consent form prior to any study procedures being performed.

Measures

Self-reported PTSD symptom severity was assessed using the PTSD Symptom Scale – Self-Report version (PSS-SR; (20), a 17-item questionnaire that reflects the DSM-IV PTSD symptoms, on a 0 to 3 scale. Clinician-rated PTSD symptom severity was assessed using the CAPS, a structured interview with established reliability and validity (21). The CAPS assesses the seventeen DSM-IV criterion symptoms for PTSD using a 5 point ratings scale from 0 (never) to 4 (daily) for both the frequency and intensity of each symptom. Total scores range from 0–136. Depression severity was measured using the Montgomery Asberg Depression Rating Scale (MADRS; 22), a clinician-rated scale consisting of 10 items. The Symptom Validity Index is a six-item measure designed to assess the validity and over-reporting of subject responses that was embedded in the version of the PSS-SR used in the trial (23). Each item of the Index is unrelated to PTSD symptoms as defined by the DSM-IV. The six items are rated on the same 0–3 scale as the PSS-SR.

Self-reported disability was examined with the Sheehan Disability Scale (SDS; 24), as assessment developed to measure disability in work, social relationships, and family life. The PSS-SR, CAPS, and MADRS were administered at time of screening, then visits V3-V6 and visits V9-V11. The SDS was administered at visits 3 and 9.

Performance-based assessments

Cognition was examined with a modified version of the MATRICS consensus cognitive battery (MCCB; (25, 26). The MCCB has nine different neurocognitive tests and examines 5

different domains of cognitive performance, including verbal memory, spatial memory, working memory, reasoning and problem solving, and processing speed. All of these cognitive domains have been examined in PTSD patients in the past (17), although meta-analyses of performance have implicated memory impairments as a primary deficit in PTSD. We calculated a composite score, an average of nine age-corrected T-scores based on the MCCB normative program, as our critical dependent variable. The norms program was developed with a comprehensive study of healthy individuals stratified across a wide range of age, sex, and ethnic characteristics.

The ability to perform everyday functional skills, known as functional capacity, was assessed using the Brief version of the UCSD Performance-based Skills Assessment (UPSA-B; (27)). The UPSA-B is a measure of functional capacity in which patients are asked to perform everyday tasks related to communication and finances. The UPSA-B raw scores are converted into a total score ranging from 0–100, with higher scores indicating better functioning. Testers administering the MCCB and UPSA-B across all sites were trained in person by one of the authors (PH).

Statistical Analysis

In these analyses, we first present a repeated-measures analysis of variance (ANOVA), wherein we examined the effects of treatment group (Active, Placebo) x time (Baseline, Endpoint) for each of the variables. We then examined the change scores within each treatment group with paired t-tests, in order to determine the effect sizes for time-related changes across self-report, clinician rated, and performance-based measures. Pearson-product moment correlations were computed between the change scores in order to determine if change scores within the same assessment modality were more highly intercorrelated than those correlations that crossed assessment modalities.

Results

For 6 of the 7 variables presented in Table II, the effect of time was statistically significant, all $F(1,92) > 53.02$, all $p < .001$. The only variable without a significant time effect was the UPSA-B, $F(1,92) = 0.67$, $p = .42$. However, the interaction of group x time was nonsignificant for all of the variables, all $F(1,92) < .71$, all $p > .40$. As shown in Table II, the changes from baseline to endpoint were significant using paired t-tests for all variables in both groups, other than for the UPSA-B. The effect sizes for changes in the placebo group were quite substantial, ranging from .63 to 1.70. Similarly large effect sizes were seen in the GSK561679 treatment group, ranging from .26 to 2.62. Consistent with our hypotheses, both self-reported and clinically rated symptoms had similarly large effect sizes for change and even the MCCB changed significantly, but considerably less, at retest.

Of note, symptom severity on both the MADRS and CAPS was considerable, with mean scores on the CAPS exceeding the minimum entry criteria by 25 points and MADRS scores on average in the range consistent with major depression. In contrast is the finding that, on average, the sample of PTSD patients did not manifest neuropsychological test performance consistent with impairment ($t < 40$). There were 21% of the cases whose scores were below 40, but these scores could be consistent with lifelong levels of performance.

We calculated correlations between the baseline and change scores in the entire sample, as there were no treatment effects (Table III). Baseline scores on the clinician-rated and self-report measures were all significantly intercorrelated, with shared variance ranging from 14 to 38%. MCCB and UPSA-B scores were significantly intercorrelated, but there was essentially no shared variance between the MCCB or UPSA scores and any of the clinician-rated or self-reported symptom or disability measures. Validity scores did not share variance with either of the performance-based measures, but shared variance with all self-reported and clinician-rated variables. The amount of variance shared with validity scores was notably less than the overlap among the clinician rated and self reported symptom measures.

Changes in the CAPS shared variance with changes in all other self-reported and clinically rated variables, with a 50% overlap with changes in the MADRS (Figure 1). Changes in the PSS-SR also shared 50% variance with changes in the MADRS and shared 13–17% with changes in the validity index and the SDS. There was essentially no overlapping variance between changes on the MCCB and any of the clinician-rated or self-reported symptom variables or the validity index (Figure 1).

We performed two final analyses. In the first, we examined the correlations of baseline scores on the validity index and change scores on the other variables and in the second we examined how many patients manifested a substantial improvement in their MCCB scores at the single retest assessment. The correlations between baseline scores on the validity index and changes on the other clinically rated, self-reported, and performance based assessments were non-significant, all $r < .18$, all $p > .12$, other than the correlation between baseline scores and changes on the validity index itself, $r = .47$, $p < .001$. When the distribution of change scores on the MCCB was examined, it was found that 25% of the participants manifested an improvement of 5 or more t-score points (0.5 SD based on normative standards) when they were retested. No participants worsened by 5 t-score points or more. In order to retest for regression to the mean, we correlated baseline and change scores on the MCCB composite score. The correlation was statistically significant and positive, $r = .33$, $p < .001$, suggesting that better baseline performers had more improvements. This result was confirmed by comparing performance of patients whose baseline score was above and below the median with a t-test, finding that patients whose median scores were above the mean had larger improvements, $t(76) = 2.48$, $p < .005$.

Discussion

There are several potentially important findings in this study. First is the finding of a substantial placebo effect across both self-reported and clinician-rated PTSD symptoms, everyday functioning, and depression rating scales. As one may have predicted based on MDD trials, clinician-ratings were similarly influenced by placebo effect when compared with self report measures. Second, we did not find that scores on the Symptom Validity Index, designed to identify exaggerated reporting of symptoms, could predict placebo response. Thus, high endorsement of symptoms unrelated to PTSD did not predict increased response to inactive treatment and does not provide a potential screening tool. Third, the placebo effect was also detectable on performance-based measures, although the magnitude of the effect was markedly less. Finally, consistent with our analysis of the baseline data in

the study, there was no association between changes in self-reported disability and changes in direct measures of cognitive and functional skills. Thus, both baseline scores and changes in self-reported disability do not manifest any substantial relationship with objective indices of these elements of functioning.

The above findings largely replicate previous PTSD treatment trials, both positive and negative in their results. Numerous double-blind, placebo-controlled studies with agents including atypical antipsychotics and antidepressants have failed to find efficacy in treatment due to large placebo effect on CAPS assessments; however, there were several studies where the active and placebo treatment separated significantly, despite changes in the placebo group of over 1.0 SD (4, 15, 28). Thus, it is possible to identify a pharmacological treatment for PTSD that exceeds placebo responses, but a large response is clearly required. Notably, this trial was the first to use a CRF antagonist to treat PTSD. It may be that CRF antagonists are only useful in PTSD patients with certain genetic predisposition. Further, there is evidence in the literature that the CRH pathway is not associated with anxiety-related disorders. Future drug trials for PTSD must be constructed to minimize placebo responses as much as possible, but drug selection is also paramount.

Our study is unique in that a significant improvement in cognition while on a placebo was detected. Modest improvements in performance-based measures during a clinical trial are not unusual, but these improvements tend to average 0.1–0.2 SD per retest assessment. In this trial, the average retest effect of 0.6 SD was detected. Further, a substantial proportion (25%) of participants in the current trial demonstrated an increase in MCCB score equivalent to 8 IQ points, considered a “clinically meaningful” level of improvement. This level of improvement exceeds typical standards for retest effects in either neuropsychiatric conditions or healthy controls (25). One possibility for these substantial improvements with reassessment may be that study participants had minimal previous experience with performance-based psychological assessments. Completing a neuropsychological test can lead to an increase in familiarity and comfort with the assessment process at the time of the second assessment, which may result in score improvements. Consequently, using performance-based assessments does not obviate placebo effects.

Placebo effects are not unique to PTSD. A meta-analysis done by Khin and colleagues in 2011 (29) evaluated 25 years of MDD placebo-controlled trials and found only 53% of trials were successful, largely due to significant and increasing placebo effects. Little research has been done comparing the size of placebo effects in PTSD compared to MDD, however this would be an interesting area of future research.

The women participating in the study were not receiving any psychotherapy or pharmacologic therapy at the time of entry into the trial, so the process of entering into the treatment structure of a clinical trial may have elicited strong placebo effects. The psychoeducational effects patients receive through trial participation may provide meaningful therapeutic benefits that contribute to placebo-associated symptom reduction. Furthermore, the unexpected improvements in cognition as detected by the MCCB suggest that patients may have performed particularly poorly at the pre-randomization testing timepoint. PTSD is characterized by high sensitivity to stress. The initial phases of a clinical

trial with an investigational medication expose study participants to several uncertainties and stressors, including discussing trauma histories with new people (trial staff), potential medication side effects, potential randomization to the inactive placebo arm, repeated phlebotomy, and, in the current study, psychophysiological and cognitive testing. The stress sensitivity of PTSD patients might contribute to elevated symptom scores and reduced testing performance at study baseline, thereby contributing to apparent placebo response as stress declines as they become more comfortable with the processes of the trial. Conceptualizing placebo effects in PTSD patients in this way warrant consideration of using single-blind placebo lead-in phases for medication PTSD trials. Although placebo lead-in designs have not proven to enhance drug-placebo signal detection in MDD trials (28), the particularly pronounced stress sensitivity in PTSD patients suggest that incorporating placebo lead-in periods for PTSD trials may improve signal detection.

When discussing the ‘placebo effect’ in this particular study we must consider that the nature of the assessments performed in the clinical trial, particularly in reference to PTSD symptoms. In this study participants may have actually received treatment for PTSD symptoms in the form of exposure-related therapy, through the repeated CAPS evaluations. It is not clear to what extent the women participating in the trial had ever discussed their PTSD symptoms with others. The CAPS involves systematic discussions of current PTSD symptoms, as relevant to the proximal trauma associated with current PTSD symptoms. This patient population is extremely unlikely to have received a systematic course of prolonged exposure therapy, thus the assessments included in the repeated CAPS assessment may have had an unintended therapeutic effect.

These findings may call for a reevaluation of psychiatric trial protocols to control for trauma re-exposure effects, which may lead to unwanted treatment effects in placebo groups. Modest improvements in performance-based measures are not unusual, although a substantial proportion (25%) of participants demonstrated an increase in cognitive performance equivalent to 8 IQ points on the MCCB. Thus, using performance-based assessments does not obviate placebo effects. One possibility for these substantial improvements with reassessment may be that study participants had minimal previous experience with performance-based psychological assessments. Taking neuropsychological tests can lead to an increase in familiarity and comfort with cognitive assessments at the time of the second assessment.

Further, these findings have implications for future studies using completely novel performance-based assessment paradigms, such as would be expected in the rDOCS initiative. Considerations to decrease this placebo response would include maintaining a strict script for researchers when communicating with patients to minimize therapeutic discussion with patients. Decreasing eye contact and unspoken positive gestures may help to mitigate comfort and familiarity of the patient with the researchers. Further, testing effects may be minimized with multiple tests being given before starting the medication to ensure an accurate baseline score and decrease re-testing phenomena across the drug trial itself.

Conclusion

Placebo effects are a significant challenge in the conduct of clinical trials for mood and anxiety disorder, and are particularly relevant in studies of PTSD, where stress sensitivity may drive high baseline scores that can result in large placebo effect sizes by trial's end. Objective performance based measures are also susceptible to placebo effects, though to a lesser degree than symptom report indices or rater indices. Modifications to clinical trial designs are necessary to minimize the effects of placebo treatments. These findings have implications for future studies using novel performance-based assessment paradigms, such as those that may find use in studies applying the National Institute of Mental Health Research Domain Criteria (RDoC) initiative.

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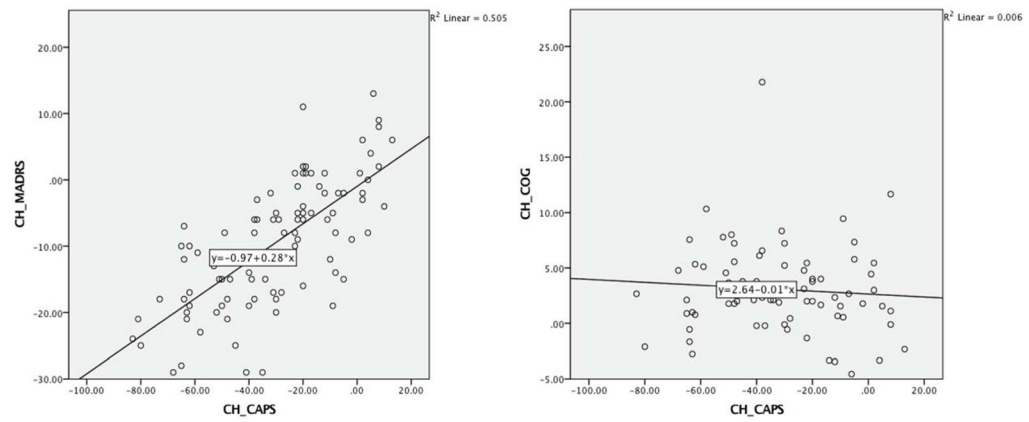


Figure 1. Changes in the CAPS compared to Changes in the MADRS and Neuropsychological performance

CH_CAPS: Change in score at baseline and after trial on the CAPS assessment of clinician-rated PTSD symptomatology

CH_MADRS: Change in score at baseline and after trial on the MADRS assessment of depression severity

CH_COG: Change in score at baseline and after trial on the MCCB cognitive assessment

Table I

Demographic and clinical variables at baseline

Variable	Placebo n=65 n (%)	GSK561679 n=63 n (%)
Race		
White/Caucasian	32 (49)	40 (64)
African American	28 (43)	18 (29)
Other	5 (8)	5 (8)
Hispanic	5 (8)	8 (13)
Current Major Depression	43 (66)	41 (65)
Education (n=125)		
<High School	4 (6)	7 (11)
High School degree/Some college	29 (45)	24 (38)
College degree	15 (23)	19 (30)
Graduate degree	16 (25)	11 (18)
Current Smoker	17 (26)	12 (19)
Time since primary trauma (n=125)		
6 months	5 (8)	6 (10)
6 months – 3 years	15 (24)	11 (18)
3–5 years	11 (18)	5 (8)
5 years	32 (51)	39 (64)
	Mean (SD)	Mean (SD)
Age (yrs)	40.4 (12.3)	40.6 (11.8)
Traumatic events, lifetime	3.7 (2.2)	3.5 (1.6)
CAPS Past Month Total	79.8 (15.6)	82.0 (12.5)
CAPS Past Week Total	74.8 (17.6)	77.5 (14.3)
PSS-SR Total	30.0 (9.3)	31.1 (7.1)
MADRS	25.1 (8.3)	26.5 (7.0)
SDS	16.3 (7.1)	15.5 (7.1)

Note:

CAPS: Clinician-administered PTSD Scale; MADRS: Montgomery Asberg Depression Rating Scale; PSS-SR: PTSD Symptom Scale – Self-report; SDS: Sheehan Disability Scale.

Clinician Rated, Self Reported, and Performance-Based Measures: Baseline and Change Scores

Table II

	Baseline Active		Change		T	P	D	Baseline Placebo		Change		T	P	D
	M	SD	M	SD				M	SD	M	SD			
CAPS	76.4	14.1	30.0	25.3	7.73	0.001	1.80	72.4	17.9	30.4	23.1	9.00	0.001	1.70
MADRS	25.0	7.7	10.4	10.2	7.03	0.001	1.35	25.3	9.1	8.6	8.8	6.67	0.001	0.94
PSS-SR	32.3	5.6	14.8	9.4	10.98	0.001	2.62	29.9	9.8	13.1	12.9	6.82	0.001	1.34
SDS	15.2	7.1	5.1	7.8	4.40	0.001	0.72	16.0	7.2	5.9	7.7	5.78	0.001	0.82
Validity	5.3	3.0	2.8	3.0	6.10	0.001	0.93	5.2	3.4	2.2	3.5	4.34	0.001	0.65
MCCB	45.4	7.7	2.0	3.0	4.00	0.001	0.26	43.6	7.6	4.1	4.8	5.43	0.001	0.63
UPSA-B	77.5	20.7	0.5	22.0	0.01	0.99	0.00	81.5	11.2	3.0	11.3	1.76	0.09	0.27

Note:

CAPS: Clinician Administered PTSD Scale

MADRS: Montgomery Asberg Depression Rating Scale

PSS-SR: PTSD Symptom Scale- Self Report

SDS: Sheehan Disability Scale

MCCB: MATRICS Consensus Cognitive Battery

UPSA-B: UCSD Performance- Based Skills Assessment Brief Version

T: t-test

P: p-value

D: effect size

Table III

Shared Variance (R^2) for Baseline and Change Scores: Combined Sample

	CAPS	MADRS	PSS-SR	SDS	Validity	MCCB	UPSA-B
CAPS	--	0.26**	0.38**	0.14**	0.14**	0.02	0.00
MADRS	0.50**	--	0.35*	0.16*	0.10*	0.01	0.00
PSS-SR	0.41**	0.55**	--	0.12*	0.26**	0.02	0.00
SDS	0.09*	0.04	0.17	--	0.17	0.01	0.01
Validity	0.07*	0.04	0.13**	0.08	--	0.01	0.03
MCCB	0.01	0.01	0.11	0.02	0.02	--	0.13*
UPSA-B	0.00	0.01	0.04	0.03	0.04	0.01	--

Note:

** : $p < .001$;

* $p < .05$.

Baseline correlations are above the diagonal and correlations of change scores are below. Variance accounted for is Pearson r squared.

CAPS: Clinician Administered PTSD Scale

MADRS: Montgomery Asberg Depression Rating Scale

PSS-SR: PTSD Symptom Scale-Self Report

SDS: Sheehan Disability Scale

MCCB: MATRICS Consensus Cognitive Battery

UPSA-B: UCSD Performance-Based Skills Assessment Brief Version