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When translational neuroscience fails in the clinic: Dexamethasone prior to virtual reality exposure therapy increases drop-out rates

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ABSTRACT

Posttraumatic stress disorder (PTSD) is characterized by exaggerated expression of fear responses to danger and safety cues. Translational research suggests that dexamethasone facilitates fear extinction in animal and human fear conditioning models. For this randomized, placebo-controlled trial (N = 27), we aimed to translate these findings to the clinic by using virtual reality exposure (VRE) therapy for OEF/OIF/OND veterans with PTSD to determine whether dexamethasone will increase the efficacy of exposure therapy for VRE relative to placebo. VRE sessions involved imaginal exposure to the most traumatic war memories while viewing a computer-generated view of virtual Iraq or Afghanistan with multisensory stimulus options used to match patient's description of the trauma. VRE was effective in reducing PTSD symptoms but there was no interaction with dexamethasone. Drop-out rate was significantly higher in the dexamethasone group, with 10 of 13 (76.9%) participants in this group discontinuing, compared to only 4 of 14 (28.5%) in the placebo group, $\chi^2 = 6.31$, $p = 0.02$. Results indicate that the dexamethasone group may have experienced an increase in PTSD symptoms, particularly re-experiencing, at session 2 following first drug administration. Contrary to study hypotheses, dexamethasone did not enhance exposure therapy outcomes and was associated with increased drop-out. This demonstrates potential pitfalls in translating neuroscience models to the clinic; future research carefully examining glucocorticoid mechanisms involved in therapy augmentation is warranted.

1. Introduction

Posttraumatic stress disorder (PTSD) is characterized by exaggerated fear responses, overgeneralization of fear towards trauma-related stimuli, and impaired inhibition and extinction of trauma-linked conditioned fear responses. PTSD etiology can be understood in a reductionist model using a Pavlovian fear conditioning model, in which a neutral stimulus (CS or conditioned stimulus) is repeatedly paired with an innately aversive unconditioned stimulus (US or unconditioned stimulus), resulting in a previously neutral stimulus (CS) eliciting a conditioned fear response (CR: thus becoming a conditioned stimulus, CS; Pavlov, 1927). Fear extinction *training* is the process through which conditioned fear responses decrease or are inhibited by presenting the CS without the US. After multiple presentations the conditioned fear response decreases, known as *extinction learning*.

This model has been used in translational animal and human research to investigate mechanisms of fear acquisition and extinction. Research with Vietnam and Gulf War veterans suggested that PTSD is characterized by enhanced fear conditioning (Grillon & Morgan, 1999; Grillon, Morgan, Davis, & Southwick, 1998; Orr et al., 2000). A meta-analysis of fear conditioning studies found that patients with anxiety disorders showed greater levels of fear responses compared to healthy controls (Duits et al., 2015). PTSD subjects with higher severity of symptoms demonstrate impaired inhibition of fear in the presence of safety cues (Jovanovic et al., 2009) and exaggerated fear potentiated startle compared to trauma controls during both fear conditioning as well as extinction testing (Jovanovic et al., 2010; Norrholm et al., 2011). PTSD patients demonstrate delayed extinction of conditioned fear stimuli (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007). This deficit of fear extinction in PTSD patients has been consistently identified (Wessa & Flor, 2007), suggesting the possibility of using pharmacological agents to augment extinction of conditioned fear

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within exposure based therapy for PTSD.

A potential pharmacological target for reducing fear is the glucocorticoid system, given that elevated corticotropin releasing hormone (CRH) levels are associated with increased fear responses (Kalin & Takahashi, 1990), including startle response (Keen-Rhinehart & Bartness, 2008; Lee & Davis, 1997; Liang et al., 1992) and enhanced fear conditioning (Roozendaal, Brunson, Holloway, McGaugh, & Baram, 2002; Swerdlow, Britton, & Koob, 1989). Further, PTSD patients show glucocorticoid receptor (GR) hypersensitivity (Yehuda et al., 2015). Dexamethasone is a cortisol analogue that engages GR and suppresses cortisol release via negative feedback, and exaggerated suppression of hypothalamic-pituitary-adrenal (HPA) axis activity following administration of dexamethasone has been a consistent finding in PTSD (Yehuda, Golier, Halligan, Meaney, & Bierer, 2004; Yehuda, Halligan, Golier, Grossman, & Bierer, 2004; Yehuda, Halligan, Grossman, Golier, & Wong, 2002). Polymorphisms of the *FKBP5* gene have been associated with PTSD symptoms (Binder et al., 2008; Xie et al., 2010). FKBP5 is involved in regulating the negative feedback action of cortisol on the HPA axis (Binder, 2009; Binder et al., 2008), which is frequently implicated in neurobiological alterations in PTSD (Baker et al., 1999; De Kloet et al., 2007; Yehuda, 2009; Yehuda, Giller, Southwick, Lowy, & Mason, 1991).

Recent translational animal and human studies have provided evidence that dexamethasone administration and resulting cortisol suppression leads to a decrease in the fear responses characteristic of PTSD. Dexamethasone facilitated fear extinction in mice with stressor-induced fear extinction deficits (Sawamura et al., 2016) and enhanced *fkbp5* mRNA expression in the amygdala, a potential mechanism of fear regulation via GR (Sawamura et al., 2016). In a highly traumatized civilian sample, dexamethasone reduced fear-potentiated startle for PTSD subjects but not in controls (Jovanovic, Ely et al., 2013; Jovanovic, Sakoman et al., 2013). A randomized, double-blind placebo-controlled, cross-over design study in civilians with PTSD (n = 25) and trauma controls (n = 37) found that extinction and safety discrimination deficits were significantly improved in PTSD patients who had taken dexamethasone the night before a fear conditioning paradigm (Michopoulos et al., 2017), thereby normalizing their fear responses. In a double-blind randomized, placebo-controlled trial of 54 male veterans who received either four weekly high dose dexamethasone or placebo administrations and a trauma memory reactivation task, the dexamethasone group demonstrated a greater reduction of PTSD symptoms compared to placebo at one month and three month follow-up (Surís, Holliday, Adinoff, Holder, & North, 2017), providing further evidence that dexamethasone may enhance fear extinction learning of trauma memories in PTSD patients.

Specific pharmacotherapeutic augmentation of psychotherapy is a novel area of research. Successful translational research in this area has significant clinical and public health implications via a relatively benign agent administered acutely prior to a psychotherapy session. Given that fear extinction training is a laboratory analogue to exposure therapy, the current RCT sought to translate the above findings from neuroscience to the clinic. Prolonged exposure therapy is an effective treatment for PTSD (Susskind, Ruzek, & Friedman, 2012) and is based on fear extinction principles, making it a prime candidate for direct translation of research suggesting that dexamethasone enhances fear extinction in laboratory paradigms.

Virtual reality exposure (VRE) was selected for the present study, as a VR-based approach provides experimental control, control of administering potent exposure stimuli, and the ability to conduct controlled and standardized assessments of treatment effects. VR involves an advanced technological communication interface in which the patient actively participates in a computer generated three-dimensional virtual world involving computer sensory input devices which simulate real-world interactive experiences. VRE is associated with a significant reduction in PTSD symptoms and performs comparably to standard exposure therapy (Botella, Serrano, Baños, & Garcia-Palacios, 2015; DiMauro, 2014; Reger et al., 2011; Rothbaum et al., 2014). The present randomized, placebo-controlled clinical trial used VRE for PTSD to determine whether dexamethasone, a cortisol suppressant, would increase the efficacy of exposure therapy for PTSD. Participants were randomized to placebo or dexamethasone administered the night before each of the VRE sessions, and it was hypothesized that those who received dexamethasone would demonstrate greater reduction in PTSD symptoms at post-treatment compared to placebo. We also hypothesized that dexamethasone and resulting reduced fear would make exposure therapy more tolerable for PTSD patients, resulting in decreased drop-out rates in the dexamethasone group compared to placebo.

2. Methods

This randomized double-blind placebo-controlled trial consisted of pre-treatment assessment and 6–11 weekly therapy sessions. Follow-up assessments were planned for post-treatment and 3, 6, and 12 months post-treatment. Participants were randomized in a 1:1 fashion using random block sizes of 4 to take 0.5 mg dexamethasone (n = 14) or placebo (n = 13) the night before their VRE therapy sessions. The study physician was responsible for randomization. The randomization schedule was not accessible to other study team members until after study completion and completion of all study related visits. Independent assessors were blind to treatment condition. Study medication was placed in pill bottles by the study physician; placebo and medication could not be visually distinguished and the study therapist provided a pill at each therapy visit. Research staff provided participants a text-message based reminder to take the pill the night prior to therapy at 11 pm. This timing is consistent with study procedures in a previous placebo-controlled double blind study which found that dexamethasone normalized fear extinction and enhanced fear discrimination in PTSD patients (Michopoulos et al., 2017). Participants provided informed consent and study procedures were approved by the Emory University Institutional Review Board (IRB). This study is registered through ClinicalTrials.gov (Identified NCT01965366).

2.1. Participants

The study participants were 27 patients who met DSM-5 criteria for PTSD resulting from military trauma while serving in Operation Iraqi Freedom and/or Operation Enduring Freedom-Afghanistan and Operation New Dawn. All participants self-identified as male with an average age of 35.42 (SD = 8.39, see Table 1 for demographic characteristics). Exclusion criteria included history of mania, schizophrenia, or psychoses, prominent suicidal ideation, current alcohol or drug dependence, current unstable medical illness that would represent a contraindication to taking low-dose dexamethasone such as osteoporosis, diabetes, narrow-angle glaucoma, immunosuppressed state (e.g. HIV infection), and current infection as assessed by a study

Table 1
Demographic characteristics of patients in the placebo versus DEX group.

Characteristic	Dexamethasone (N = 13)	Placebo (N = 14)	Total (N = 27)
Age, Categorical			
< = 18 years	0	0	0
Between 18 and 65 years	13	14	27
> = 65 years	0	0	0
Sex			
Female	0	0	0
Male	13	14	27
Race			
White	5	5	10
Black	5	7	12
Other	3	2	5

physician. Long-acting benzodiazepines were required to be stabilized for one month, 2 weeks for short-acting and as-needed benzodiazepines, and other psychotropic medications were required to be on a stable dose for at least 3 months prior to beginning the study and throughout the study.

2.2. Pre-treatment assessment

Participants were asked to provide a copy of their DD214 to verify military service. The Clinician Administered PTSD Scale (CAPS-5; Blake et al., 1995) was administered to assess for PTSD diagnostic status. The CAPS-5 is an interviewer-administered diagnostic instrument that provides a diagnostic measure of PTSD and a continuous measure of the severity, frequency, and intensity of PTSD symptoms. The MINI International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998) was administered to screen for psychiatric disorders and verify PTSD as primary diagnosis. The PTSD Symptom Scale (PSS-5; Foa & Capaldi, 2013) was administered and measured current symptom frequency and intensity for the past month. The Beck Depression Inventory-II (BDI; Beck, Steer, & Brown, 1996) is a 21-item measure of cognitive and vegetative symptoms of depression, is widely used in a variety of populations, including trauma victims, and is sensitive to treatment effects on depression. The Clinical Global Impressions Scale, Severity of Illness (CGI-Severity; Guy & Bonato, 1970) was rated by study therapist and is a measure of severity of illness ranging from 0 (not assessed) to 7 (among the most extremely ill patients).

2.3. Within-session assessment

Participants completed the PSS at the beginning of each treatment session. During each VRE session, therapist queried participants on their Subjective Units of Distress (SUDS: ranging from 0 to 100) before the VRE ("pre SUDS"), the highest level of distress during VRE ("peak SUDS"), and immediately following VRE ("post SUDS"). The therapist documented the number of imaginal exposure repetitions within VRE and the total number of minutes in VRE.

2.4. Treatment

Medication was not administered prior to the first session which involved information gathering, reviewing treatment rationale, and treatment planning. The first dose was administered the night before the second session (i.e., first VRE exposure). The VRE sessions were 90 min and involved implementing a VR based exposure to the index trauma. The session included administration of symptom measures, a brief check in, VRE for approximately 30–45 minutes, and approximately 20 min of processing the exposure experience (i.e., discussion of material that emerged during exposure). During VRE, patients wore a head-mounted display with stereo earphones that provided visual and audio cues consistent with Iraq or Afghan military scenarios. VRE was limited to a minimum of 6 sessions and a maximum of 11 sessions, in addition to the first psychoeducational session, based upon reaching a criterion of 70% symptom improvement as indicated on the PSS. All sessions were individual and occurred weekly. During VRE sessions, participants were encouraged to emotionally engage with traumatic memories consistent with traditional prolonged exposure therapy (Foa, Hembree, & Rothbaum, 2007). The therapist viewed the VR scene on a video monitor and attempted to match stimuli to trauma details as the patient described them, consistent with previous studies (Rothbaum et al., 2014). VRE was followed by approximately 20 min of processing the exposure experience.

2.5. VR apparatus

During VRE sessions, participants wore an eMagin Z800 head-mounted display (eMagin Corp., Bellevue, Wash.) with integrated eye tracking and stereo earphones and separate screens for each eye. The participant viewed a computer-generated view of virtual Iraq or Afghanistan, and participants held a handheld controller that allowed the participant to navigate within the environment (e.g., Humvee driving down desert highway, foot patrol in middle eastern city). Stimulus options were auditory (e.g., weapons fire, explosions), visual (e.g., night vision, civilians, burned vehicles), olfactory (e.g., diesel fuel, Middle Eastern spices, burning rubber), and tactile (i.e., vibrations delivered through a raised platform with a subwoofer and audio amplifier). The therapist controlled stimuli throughout the session matching what the patient described and viewed the patient's VR scene on a monitor.

2.6. Psychophysiology: Skin conductance and heart rate

Given the translational research conducted on dexamethasone and associations with physiological markers (e.g., Jovanovic, Ely et al., 2013; Jovanovic, Sakoman et al., 2013), psychophysiological indices of fear responding were collected at pre-treatment and post-treatment. Specifically, skin conductance and heart rate were assessed during a viewing of three VR scenes. Methods for psychophysiological data collection were consistent with previous studies (Rothbaum et al., 2014). Each VR scene was presented through a head-mounted display for a duration of two minutes. The sequence was presented twice, with neutral blue squares in between each VR scene, for a total duration of 15 min. Psychophysiological data, including heart rate and skin conductance response, was acquired at a sample rate of 1 kHz and was amplified and digitized using the GSR and ECG modules of the Biopac MP150 for Windows (Bipac Systems, Inc., Aero Camino, CA). Two 5 mm Ag/AgCl disposable electrodes filled with isotonic paste were attached to middle phalanges of the second and fourth finger of the non-dominant hand while participants viewed VR scenes to measure skin conductance. Five mm Ag/AgCl electrodes were also placed on the chest above the right clavicle and on the chest under the side of the ribcage to measure heart rate.

2.7. Statistical analysis

Paired t-tests were used in the combined sample to investigate treatment outcome of VRE, including clinician and self-reported PTSD symptoms, depression symptoms, and global improvement. The study planned to enroll 100 participants (50 per group), however, 51.9% of participants discontinued therapy early (14 of 27) so enrollment was paused and the blind was broken early to investigate potential associations with dexamethasone. Chi square analysis were used to investigate if drop-out differed across dexamethasone and placebo group. One way ANOVA was used to investigate potential baseline differences between the two groups across symptom measures and psychophysiology (i.e., skin conductance and heart rate). Differences between completers and drop-out across these measures was investigated. Finally, identified differences in drop-out between groups underwent additional exploratory analyses to investigate potential PTSD symptom differences at session 2, the first session that participants had been administered medication.

3. Results

3.1. VRE treatment outcome

Demographic data for each group individually and in the combined sample are presented in Table 1. Across the entire sample, there was a significant reduction from pre-treatment to post-treatment on PTSD symptoms across clinician assessed PTSD symptoms (CAPS severity: $t(12) = 4.22$; $p = .001$) and self-reported PTSD (PSS: $t(11) = 3.90$; $p = .003$) symptoms (Table 2). There was a significant reduction in depression symptoms (BDI: $t(11) = 3.93$; $p = .003$) and clinician-rated

Table 2
Treatment effectiveness in combined sample across self and clinician-rated PTSD symptoms, self-rated depression symptoms, and global clinical severity.

		M	SD	T	p
CAPS	Pre	35.58	11.90	4.22**	.001
	Post	21.42	13.41		
PSS	Pre	33.90	11.52	3.90**	.003
	Post	18.73	15.71		
BDI	Pre	17.90	9.58	3.94**	.003
	Post	10.72	6.92		
CGI	Pre	3.44	1.23	2.49*	.038
	Post	2.00	1.22		

Note. CAPS = Clinician Administered PTSD Scale; PSS = PTSD Symptom Scale; BDI = Beck Depression Inventory; CGI = Clinical Global Impression Scale; *$p \leq$ .05; **$p \leq$ .01.

global severity (CGI: $t(9) = 2.49$; $p = .038$). Overall, VRE was effective in reducing PTSD symptoms across three measures and in reducing depression symptoms and overall clinical global impressions, but there was no interaction with dexamethasone.

3.2. Timing of medication administration

The average time of medication self-administration, average time of start of therapy session, and duration of medication action at the start of therapy session are presented in Table 3. On average across sessions, medication was taken 772.52 min or approximately 12 h and 52 min prior to the start of therapy sessions.

3.3. Drop-out across groups

Of the 27 participants entered, 14 (51.9%) discontinued therapy early. Chi-square analysis indicate that the drop-out rate was significantly higher in the dexamethasone group, with 10 of 13 (77%) participants in this group discontinuing, compared to only 4 of 14 (28.5%) in the placebo group, $\chi^2 = 6.31$, p = 0.02 (Fig. 1). The timing of participant drop-out is presented in Table 4. Participants who terminated treatment early dropped out on average around the third session.

3.4. Baseline differences across groups

Given the elevated drop-out rates in the dexamethasone group, baseline differences across medication groups were investigated. One-way ANOVAs did not identify significant differences across dexamethasone and placebo groups with regard to baseline self-reported PTSD symptoms (PSS: F = 1.96, p = 0.18; M = 46.60/SD = 12.97 and M = 38.69/SD = 13.73, respectively), clinician-rated PTSD symptoms (F = .85, p = 0.37; M = 42.27/SD = 8.02 and M = 36.25/SD = 10.55, respectively), depression symptoms (BDI: F = 1.83, p = 0.19; M = 26.00/SD = 10.52 and M = 20.08/SD = 10.88, respectively), or clinician-rated global severity (CGI: F = 2.40, p = .14; M = 4.33/SD = 1.00 and M = 3.58/SD = 1.16, respectively). T-tests were conducted to investigate if dexamethasone and placebo groups differed on heart rate and skin conductance when viewing trauma-relevant stimuli at baseline. No significant differences were identified across skin conductance ($t(22) = -.31$; $p = .76$) or heart rate ($t(22) = -.21$; $p = .83$) when viewing trauma-relevant VR stimuli.

3.5. Differences across completers and drop-outs

Baseline difference in those who discontinued compared to those who completed treatment were investigated. The drop-out group significantly differed from completers in that they demonstrated higher baseline severity of self-reported PTSD symptoms (PSS: F = 11.05, p

Table 3
Timing of medication administration.

	Session 2	Session 3	Session 4	Session 5	Session 6	Session 7	Session 8	Session 9
Average time: medication administration	11:52 pm (156.43)	12:35 pm (190.61)	12:50 am (209.46)	1:35 am (245.79)	1:27 am (225.94)	11:43 pm (164.43)	1:37 am (377.39)	10:00 pm (51.96)
Average time: session start	12:19 pm (152.58)	1:18 pm (114.78)	1:55 pm (96.53)	1:39 pm (114.50)	1:22 pm (129.53)	1:51 pm (120.83)	1:22 pm (168.23)	1:36 pm (136.64)
Duration of medication action at start of session	763.67 (153.51)	795.63 (202.20)	733.33 (192.38)	713.38 (220.90)	707.38 (204.07)	829.50 (177.99)	707.25 (357.36)	930.00 (106.67)

Note. Standard deviation in minutes provided in parentheses.

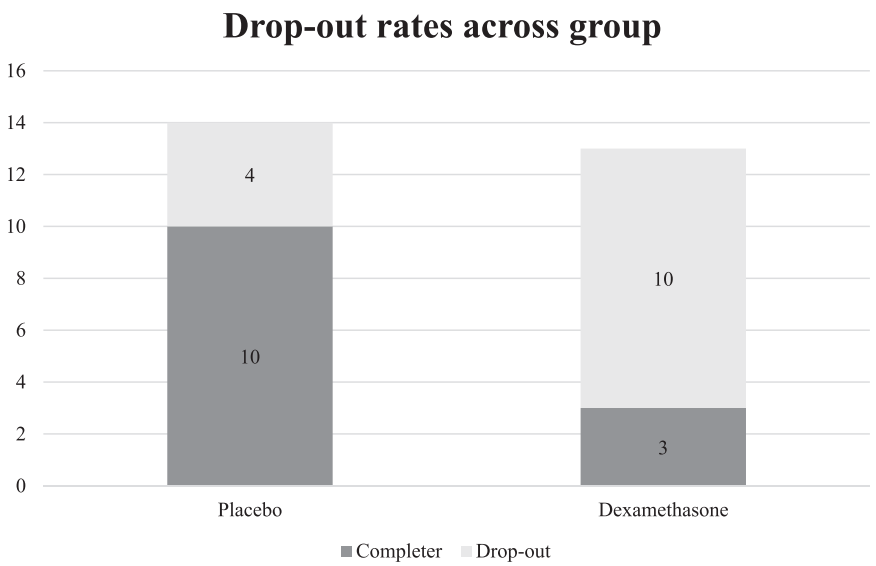

Fig. 1. Treatment completion and drop-out rates across group.

Table 4
Timing of drop-out.

	Intake	S1	S2	S3	S4	S5
Dexamethasone	2	0	3	2	0	3
Placebo	1	1	1	0	1	0

Note. S = session.

= 0.003; M = 49.67/SD = 11.20 and M = 33.90/SD = 11.51, respectively) and depression symptoms (BDI: F = 5.36, p = .03; M = 27.38/SD = 10.32 and M = 17.90/SD = 9.58, respectively). Drop-out and completer groups did not differ significantly on clinician-rated PTSD symptoms however there was a trend towards the drop-out group demonstrating elevated symptoms (CAPS: F = 3.77, p = .066, M = 43.00/SD = 4.94 and M = 35.58/SD = 11.90, respectively). Drop-out and completer groups did not differ significantly on clinician-rated global severity at baseline (CGI: F = 2.82, p = .11). No significant differences in drop-out and completer group were identified across skin conductance (F = .285, p = .60) or heart rate (F = .40, p = 0.54) when viewing trauma-relevant VR stimuli.

3.6. Exploratory investigation of treatment session 2 across medication groups

Individual PSS scores across sessions one through five visually represented indicate an increase in PTSD symptoms in dexamethasone participants at session two compared to plateau or slight downward trend in placebo participants (see Fig. 2). Difference scores for total PTSD symptoms and symptom clusters from session 1 to session 2 across dexamethasone and placebo groups were computed (Table 5). Independent samples t-tests were conducted to compare differences in symptoms from session 1 to session 2 across dexamethasone and placebo groups. A significant difference was identified (t = 2.76, p = .015) across groups, such that the dexamethasone group demonstrated an increase in symptoms (M = 2.00, SD = 5.96) and the placebo group demonstrated a decreased in symptoms (M = -4.35, SD = 4.59). Differences in PTSD symptom clusters were investigated; a significant difference was identified in re-experiencing symptoms (t = -2.80, p = .017) such that the dexamethasone group demonstrated an increase in symptoms (M = 1.00, SD = 3.23) and the placebo group demonstrated a decrease (M = -2.09, SD = 1.64).

Treatment session two was the first therapy session for which patients had taken the study medication the night prior to VRE; consequently, we focused analyses on this session to investigate potential differences in dexamethasone versus placebo group that may help elucidate factors that contributed to elevated drop-out in the dexamethasone group (Table 6). T-tests were used to compare dexamethasone and placebo group on overall PTSD symptom severity and PTSD symptom clusters over the last month reported at the beginning of session 2 after taking study medication but prior to exposure. A significant difference was not identified for overall PTSD symptom severity (t(20) = -1.61; p = .12), however it is notable that the sample size is likely underpowered to detect a difference and approximately a 10 point difference was identified in the dexamethasone group (M = 46.40/SD = 13.53) compared to the placebo group (M = 36.50/SD = 14.99). Groups were not significantly different across avoidance, cognition and mood, or hyperarousal and reactivity symptoms; a trend was identified (t(20) = -1.85; p = .08)) towards elevated re-experiencing symptoms in the dexamethasone group (M = 11.10/SD = 5.54) compared to the placebo group (M = 7.58/SD = 3.26).

Subsequent analyses were conducted on the individual re-experiencing symptom items at start of session two. Significant differences were not identified for cued psychological or physical distress, or for distressing dreams though the study may have been underpowered to identify this difference (t(20) = -1.66; p = .11). Results suggest potentially higher distressing dreams in dexamethasone group (M = 2.00/SD = 1.41) compared to placebo group (M = 1.25/SD = .62). Significant differences were identified for intrusive memories (t(20) = -2.23; p = .04)) and dissociative reactions (t(20) = -2.06; p = .05) indicating higher scores in the dexamethasone group compared to placebo group (Table 5).

Session two details regarding the imaginal exposure were investigated, including the pre, peak, and post SUDS, number of imaginal exposure repetitions, and minutes in imaginal exposure in dexamethasone compared to placebo group. No significant differences were identified; however, on average the dexamethasone group pre, peak, and post SUDS were lower than the placebo group, suggesting that they were not reporting greater subjective distress.

3.7. Exploratory investigation of treatment session 2 across drop-out and completers

Treatment session 2 data was analyzed comparing drop-out and treatment completers in the entire sample (Table 7). Participants who dropped out of treatment demonstrated higher PTSD symptoms at session two compared to treatment completers (t(20) = 4.30; p <

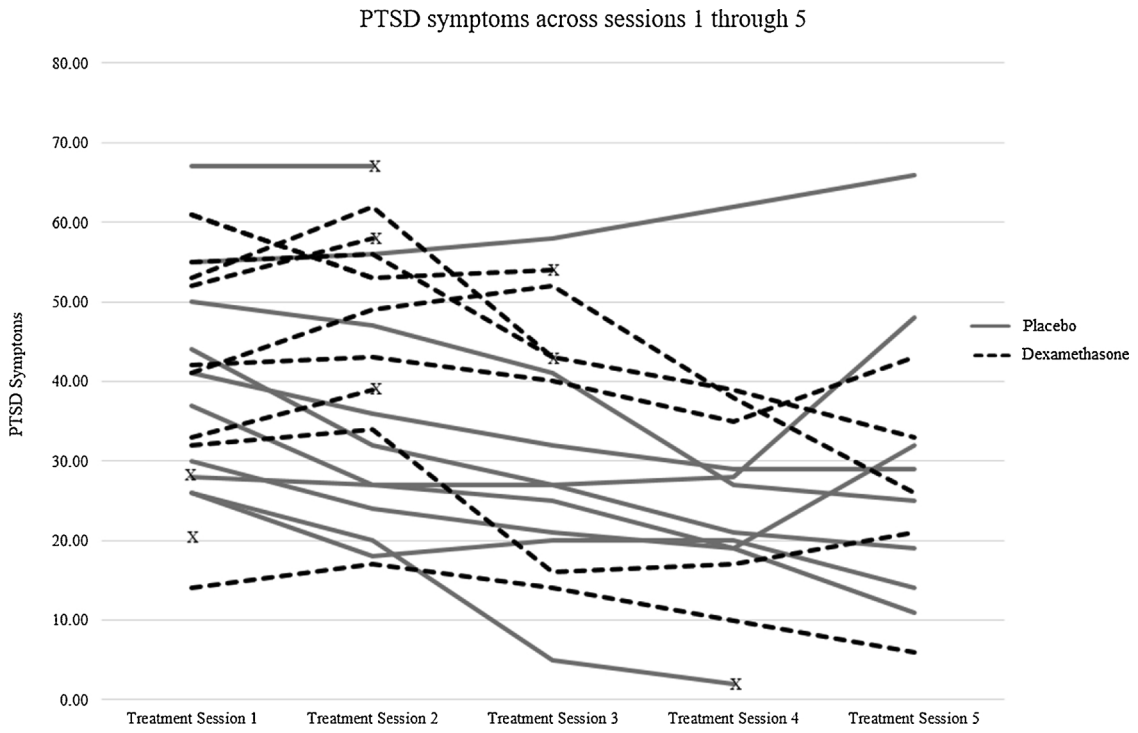

Fig. 2. PTSD symptoms reported at treatment sessions 1 through 5.

Table 5
Comparison of session 1 and 2 difference scores between placebo and dexamethasone groups.

		Mean Difference (Session 2 – 1)	SD	t	*p*
PTSD Symptom Severity					
	Placebo	−4.36	4.59	−2.76*	.013
	Dexamethasone	2.00	5.96		
PTSD Symptom Clusters					
Re-experiencing	Placebo	−2.09	1.64	−2.80*	.011
	Dexamethasone	1.00	3.23		
Avoidance	Placebo	−0.54	1.44	−1.12	.287
	Dexamethasone	0.30	2.00		
Cognitions and mood	Placebo	−0.81	2.56	−1.10	.286
	Dexamethasone	0.60	3.34		
Arousal and reactivity	Placebo	−0.91	2.26	−0.98	.340
	Dexamethasone	0.10	2.47		

Note. *$p \leq .05$; **$p \leq .01$.

.001) as well as lower SUDS reported prior to beginning imaginal exposure ($t(20) = -3.54$; $p = .002$). Drop-out and treatment completer groups did not differ on peak SUDS, post imaginal SUDS, number of exposure repetitions, or minutes in exposure.

4. Discussion

Evidence from preliminary studies in animal models and non-treatment human samples suggests that dexamethasone, a cortisol suppressor, facilitates fear extinction, reduces fear responding, and reduces startle response (Jovanovic, Ely et al., 2013; Jovanovic, Ely et al., 2013; Michopoulos et al., 2017; Sawaruma et al., 2016). As such, the present study aimed to determine whether dexamethasone would enhance the efficacy of exposure therapy, a psychotherapy based on extinction learning principles, in a double-blinded, randomized, placebo-controlled study. Contrary to study hypothesis, dexamethasone did not enhance VRE outcomes compared to placebo. Consistent with previous literature, VRE was effective overall in the sample in decreasing PTSD symptoms (Maples-Keller, Yasinski, Manjin, & Rothbaum, 2017;

Table 6
Session two comparison between placebo and dexamethasone groups.

		Mean	SD	t	*p*
PTSD symptom severity					
PTSD symptoms	Placebo	36.50	14.99	−1.61	.12
	Dexamethasone	46.40	13.53		
PTSD Symptom Clusters					
Re-experiencing	Placebo	7.58	3.26	−1.85	.08
	Dexamethasone	11.10	5.54		
Avoidance	Placebo	4.41	2.35	−1.06	.30
	Dexamethasone	5.40	1.90		
Cognitions and mood	Placebo	12.67	6.54	−.89	.39
	Dexamethasone	15.00	5.66		
Arousal and reactivity	Placebo	11.83	4.86	−1.48	.15
	Dexamethasone	14.90	4.79		
Re-experiencing items					
Intrusive memories	Placebo	1.67	.49	−2.23*	.04
	Dexamethasone	2.60	1.35		
Distressing dreams	Placebo	1.25	.62	−1.66	.11
	Dexamethasone	2.00	1.41		
Dissociative reactions	Placebo	1.00	.85	−2.06*	.05
	Dexamethasone	1.90	1.20		
Cued psychological distress	Placebo	2.08	1.16	−.61	.54
	Dexamethasone	2.40	1.26		
Cued physiological distress	Placebo	1.58	1.08	−1.30	.21
	Dexamethasone	2.20	1.14		
Imaginal exposure					
SUDS-pre	Placebo	36.36	27.76	1.35	.19
	Dexamethasone	21.91	22.40		
SUDS-peak	Placebo	76.50	25.93	.70	.49
	Dexamethasone	69.09	22.67		
SUDS-post	Placebo	66.00	24.24	.77	.45
	Dexamethasone	57.73	24.73		
Exposure repetitions	Placebo	3.27	1.62	−.84	.41
	Dexamethasone	3.91	1.92		
Minutes in exposure	Placebo	34.20	5.43	.36	.72
	Dexamethasone	33.00	9.18		

Note. *$p \leq .05$; **$p \leq .01$; SUDS = subjective units of distress; SD = standard deviation.

Table 7
Session two comparison between drop-out and completer groups.

		Mean	SD	t	*p*
PTSD symptoms	Dropout	53.11	10.46	4.30**	< .001
	Completer	32.61	11.34		
SUDS-pre	Dropout	12.10	9.93	−3.54**	.002
	Completer	43.33	26.31		
SUDS-peak	Dropout	67.78	25.01	−.79	.44
	Completer	76.25	23.56		
SUDS-post	Dropout	53.55	24.88	−1.40	.18
	Completer	67.92	22.81		
Exposure repetitions	Dropout	4.10	1.91	1.25	.23
	Completer	3.17	1.59		
Minutes in exposure	Dropout	31.40	7.65	−1.29	.21
	Completer	35.55	7.08		

Note. *$p \leq .05$; **$p \leq .01$; SUDS = subjective units of distress.

Goncalves et al., 2012; DiMauro, 2014; Rothbaum et al., 2014). Similar null results have been found with other medications used to enhance exposure therapy previously. For instance, yohimbine, a noradrenaline agonist, has been found to facilitate fear extinction (Cain, Blouin, & Barad, 2004) but some clinical trials have failed to identify a significant augmentation effect in exposure therapy compared to placebo (e.g., Meyerbroeker, Powers, van Stegeren, & Emmelkamp, 2012), highlighting the importance of consideration of potential pitfalls when translating neuroscience findings to the clinic.

A secondary hypothesis of this study was that dexamethasone and an associated reduction in fear would make exposure therapy more tolerable for PTSD patients, resulting in decreased drop-out rates compared to placebo, consistent with Yehuda et al. (2015). The initial study goal was to enroll 100 participants, however, after enrolling 27 participants the overall study drop-out rate was elevated compared to previous trials (Van Etten & Taylor, 1998; Van Minnen, Arntz, & Keijsers, 2002), with 14 of 27 (51.9%) discontinuing therapy early. Given this elevated drop-out rate, a decision was made to pause enrollment and break the blind early to investigate potential associations between dexamethasone and drop-out. Contrary to study hypothesis, drop-out was significantly higher in the dexamethasone group, with 10 of 13 (77%) participants in this group discontinuing, compared to only 4 of 14 (28.5%) in the placebo group. As a result of this finding, recruitment of new participants into the trial ended and the remaining participants progressed through study protocol.

Given the premature study termination, the sample size (N = 27) limits the statistical power for analyses and thus results are of a preliminary nature and should be interpreted with caution. While no significant differences across groups at baseline were identified, it is notable that the dexamethasone group was on average 7.91 points higher on the PSS and 5.92 higher on the BDI, suggesting the possibility of a failure of randomization. Exploratory analyses were conducted to attempt to elucidate why dexamethasone was associated with increased drop-out, contrary to hypotheses. A comparison of PTSD symptom difference scores across groups from session 1 to 2 identified a significant difference such that dexamethasone group increased on PTSD and re-experiencing symptoms, whereas the placebo group decreased. An investigation of specific symptoms identified a significant difference such that the dexamethasone group reported elevated levels of distressing dreams and intrusive memories compared to the placebo group. Dexamethasone's suppression of cortisol may have led to less available cortisol to bind to GR in the brain, resulting in decreased suppression of trauma memories and increased re-experiencing symptoms at session 2.

Given the animal data showing increased *fkbp5* mRNA expression in the amygdala after dexamethasone administration, it is possible that the increased re-experiencing symptoms observed the morning after dexamethasone were related to higher amygdala activity. Neuroimaging studies in PTSD participants have found that amygdala activity is highly associated with re-experiencing symptoms (Stevens et al., 2018). A single glucocorticoid injection has been shown to increase anxiety in rats, but did not affect conditioned fear or locomotor activity (Mitra & Sapolsky, 2008). Corticosteroid treatment's side effect profile includes acute anxiety, sleep disturbances including insomnia, and mood disturbances, (Kenna, Poon, de los Angeles, & Koran, 2011), providing some evidence across translational studies indicating a potential for an increase in anxiety related distress. As such, it is possible that side effect related to dexamethasone administration, particularly acute increases in anxiety or sleep disturbances, led to decreased tolerability of treatment.

Session two involved conducting the first VR exposure, therefore differences in imaginal exposure were compared across medication groups. Interestingly, dexamethasone and placebo groups did not differ with regard to distress during session 2 VRE, including SUDS prior to exposure, highest SUDS reported during exposure, SUDS immediately following exposure, number of exposure repetitions, and minutes in imaginal exposure. This suggests that dexamethasone did not appear to affect the subjective experience in session VRE but may have led to an increase in PTSD symptoms prior to the treatment session, specifically re-experiencing symptoms, which decreased tolerability of treatment and led to elevated drop-out rates.

Emotional processing theory suggests pathological fear responses are characterized by inaccurate associations with stimuli, responses, and meaning related to exaggerated probability of threat or danger. Exposure therapy involves activating this "fear network" via exposure to feared stimuli resulting in patients learning that conditioned fear responses will decrease and feared outcomes do not occur (Foa & Kozak, 1986). As such, fear activation and emotional engagement during exposure therapy for PTSD are a crucial aspect of the therapeutic process (Foa & Kozak, 1986). This has been demonstrated empirically in several clinical trials in which emotional engagement was associated with improved outcome in exposure therapy for PTSD (Foa, Riggs, & Gershuny, 1995; Jaycox, Foa, & Morral, 1998). In the present study, participants who terminated treatment early on average dropped out around the third session, consistent with previous research finding that most patients who terminate exposure treatment drop out early (Van Minnen, Arntz, & Jeijsers, 2002). The results suggest that dexamethasone may have increased PTSD re-experiencing symptoms and negatively impacted treatment tolerability during a crucial phase for continued engagement in treatment. In comparing drop-out and treatment completers across both groups, the drop-out group did demonstrate higher PTSD symptoms at baseline, higher PTSD symptoms at session two, and lower SUDS prior to beginning imaginal exposure compared to treatment completers. While this combines both medication groups within drop-out, it is notable that only 4 of 14 participants dropped out in the placebo group, making comparison of drop-out across medication groups difficult and indicating that the drop-out group is primarily composed of participants who received dexamethasone.

Notably, the difference in SUDS prior to imaginal exposure indicated that the drop-out group reported significantly *lower* SUDS compared to those who completed treatment, and did not demonstrate differences in peak SUDS or SUDS immediately following exposure. Affective contrast theory suggests that the effect of an emotional experience is contingent on the level of contrast with a preceding emotion state (Bacon, Rood, & Washburn, 1914) and it has been theorized that anxious responding can be activated by perceiving a mismatch between expected and encountered stimuli (Gray, 1982); it is possible that the drop-out group may have experienced the VRE as more aversive given the low reported distressed/non-aversive mood state prior to beginning the exposure.

A recent randomized trial in veterans receiving PE for PTSD found that hydrocortisone administered twenty minutes prior to exposure therapy increased retention and that treatment responders had higher GR sensitivity pre-treatment compared to placebo (Yehuda et al.,

2015). Given that dexamethasone administered the night before treatment results in lower cortisol levels at the time of the session, our results are consistent with the above study suggesting that increased cortisol may be beneficial for retention in therapy. The hydrocortisone trial also found that participants with higher lifetime PTSD severity were most likely to respond positively to hydrocortisone augmentation (Yehuda et al., 2015), suggesting that specific subsets of PTSD patients may be optimally targeted by pharmacological interventions addressing glucocorticoid responsivity. It is possible that while lower cortisol levels facilitate experimental extinction, successful exposure therapy requires a responsive HPA axis. Dexamathasone suppresses endogenous cortisol concentrations and does not effectively cross the blood-brain barrier thus may reduce activation of central GR receptors. Overall, the results in the present study indicate the potential pitfalls of translating neuroscience findings to the clinic, and suggest that future research should include careful examination of glucocorticoid mechanisms involved. This is particularly relevant for HPA axis focused research, given the dynamic nature of cortisol levels and significant individual variability (Kellner, Yehuda, Arlt, & Wiedemann, 2002; Yehuda & Golier, 2009;). The present study procedures involved medication administration the night before treatment based on a previous study which found that dexamethasone normalized fear extinction and enhanced fear discrimination in PTSD patients (Michopoulos et al., 2017); future research could investigate specific aspects of timing and dosing to identify how these factors could be optimally targeted to improve extinction learning and harness effects on memory processes within exposure therapy.

One such study investigated glucocorticoid-related predictors of PTSD treatment response and found that the *BCLI* polymorphism of the glucocorticoid receptor gene, higher bedtime salivary cortisol, and 24-hour urinary cortisol excretion were predictive of treatment gains (Yehuda et al., 2014). Pre-treatment plasma dehydroepiandrosterone/cortisol ratio and neuropeptide Y were also predictors of PTSD symptom improvement, and glucocorticoid sensitivity changed along with PTSD symptom change (Nijdam, Van Amsterdam, Gersons, & Olff, 2015). Consistent with the current study, analyses within this sample found that a more suppressed cortisol curve after dexamethasone administration was associated with improved treatment outcome (Nijdam et al., 2015). Another study in a sample of veterans receiving psychotherapy for PTSD found that increased cortisol response during a trauma script task was associated with PTSD symptom reduction in exposure therapy (Rauch et al., 2015). In a sample of female rape victims with PTSD, a significant decrease in salivary cortisol levels over the course of treatment was observed in treatment responders (Gerardi, Rothbaum, Astin, & Kelley, 2010), and VRE has previously been shown to relate to an attenuation in cortisol reactivity to trauma-relevant cues and elevated cortisol at baseline was predictive of decreased treatment response (Rothbaum et al., 2014).

This is a promising line of research and additional longitudinal studies on glucocorticoid-based biomarkers within the context of psychotherapy will likely prove beneficial in informing how to optimally translate neuroscience findings into augmentation strategies within clinical treatment seeking samples, and can also inform our understanding of the role of biomarkers in therapy response and symptom maintenance. As noted in a recent review of the literature on glucocorticoid and inflammatory dysregulation and PTSD, longitudinal/prospective studies that include HPA axis biomarkers, inflammatory, and other neurobiological factors are needed, and treatment focused research will benefit from identifying optimal timing of hormone administration and personalized targeting of individuals who may benefit (Olff & van Zuiden, 2017).

5. Limitations, conclusions and future directions

The results from the current study are based on a small sample and underpowered for some analyses. Additionally, the sample is composed of male veterans suggesting potential limits to the generalizability of these findings. Additionally, future research should consider incorporating data collection procedures following participant drop-out to collect qualitative information regarding the participant's experience of the medication, including potential side effects, and reasons for dropping out.

The present results were contrary to study hypotheses, as dexamethasone was not associated with improved treatment outcome but rather elevated drop-out compared to placebo. Results indicate that the dexamethasone group may have experienced an increase in PTSD symptoms, particularly re-experiencing symptoms, following first drug administration which may have impacted treatment tolerability. These findings demonstrate the need for continued research clarifying the role of glucocorticoid mechanisms within the context of exposure therapy for PTSD when considering potential augmentation strategies.

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