Contemporary Clinical Trials Communications 17 (2020) 100491

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: http://www.elsevier.com/locate/conctc

Trauma Management Therapy and Prolonged Exposure Therapy for PTSD in an active duty sample: Design and methodology of a randomized clinical trial

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ARTICLE INFO

Keywords:
Posttraumatic stress disorder
Exposure therapy
Active duty military
Massed treatment
Trauma Management Therapy

ABSTRACT

Posttraumatic stress disorder (PTSD) resulting from military service is a common, yet often chronic condition. Treatment outcome often is attenuated by programs that are (a) lengthy in nature and (b) constricted in their target outcomes. These limitations leave much of the emotional and behavioral impairment that accompanies PTSD unaddressed and/or unassessed. Typical PTSD treatment programs are 3–4 months in length, which is challenging for the pace of the nation's military. In this investigation, we will compare two treatments, Trauma Management Therapy (TMT) and Prolonged Exposure (PE), both redesigned to address the needs of active duty personnel (300 participants at 3 military installations). Specifically, we will compare the TMT Intensive Outpatient Program (IOP; 3 weeks) to PE's compressed (2 week) format. Both interventions will be compared to a standard course of PE (12 weeks). In addition to PTSD symptomatology, outcome measurement includes other aspects of psychopathology as well as changes in social, occupational, and familial impairment. Potential negative outcomes of massed treatment, such as increased suicidal ideation or increased alcohol use, will be assessed, as will genetic predictors of PTSD subtype and treatment outcome. This study will inform the delivery of care for military-related PTSD and particularly the use of intensive or compressed treatments for active duty personnel.

1. Introduction

Posttraumatic Stress Disorder (PTSD) is one of the most common mental health disorders resulting from military service. Military personnel are exposed to many traumatic events, such as combat, sexual assault, or other events that occur within the context of service (e.g., motor vehicle accidents, training accidents, or witnessing civilian mistreatment). It has been reported that between 8% and 18% of military troops returning from the Iraq and Afghanistan conflicts manifest high levels of deployment-related PTSD symptoms [1–3]. Additionally, rates of Military Sexual Trauma (MST) range from 20% to 40% among female military personnel [4,5]. PTSD is often a chronic condition that is associated with significant social, familial, and occupational impairment.

Treatment programs for military PTSD include Prolonged Exposure Therapy [6] and Trauma Management Therapy [7,8]. The standard delivery of PE involves 10–15 sessions of imaginal exposure conducted weekly. TMT was developed because exposure therapy alone was ineffective in addressing the chronic functional impairment found among Vietnam veterans [9,10]. Initially, TMT involved 29 individual and group treatment sessions conducted over 17 weeks and included individual exposure therapy and a group component designed to address anger, social isolation, and depression. Although both interventions have demonstrated efficacy for military PTSD [10,11], these treatment programs, as well as others, face issues of high treatment attrition (averaging 28%; although some studies report up to 40%) and a

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https://doi.org/10.1016/j.conctc.2019.100491
Received 4 February 2019; Received in revised form 4 November 2019; Accepted 9 November 2019
Available online 15 November 2019

substantial number of patients who retain their PTSD diagnosis after a full course of treatment. As noted by Hoge and colleagues, there is still considerable room for improvement, "particularly interventions that enhance treatment engagement or retention" [12].

Intensive or massed treatment programs for PTSD may address engagement and attrition issues by delivering treatment rapidly. Rather than treatment once per week, these programs deliver therapy daily. Initial results from a civilian sample indicate that shorter time between treatment sessions results in improved treatment outcome [13]. Intensive outpatient or massed treatment programs are relatively new and untested. However, two recent trials [7,14] have demonstrated efficacious outcomes in veterans and active duty personnel; additionally, both programs evidenced low attrition, with rates of 2% and 13.6%, respectively. If these rates can be replicated in additional trials, intensive or massed treatment could be a solution to the challenge of providing interventions that enhance treatment engagement and retention. These delivery models could be particularly advantageous for active duty personnel who may not be able to complete extended outpatient programs because of deployment, unit training requirements and/or duty station change [e.g., 15].

Another barrier to care for military PTSD is the stigma associated with admitting the need for treatment [16]. Compressed treatment programs may begin to address the issue of stigma by placing treatment for PTSD on the same conceptual level and schedule as treatment for physical injuries. If PTSD was consistently conceptualized as a stress injury (or *operational* stress injury, as it is currently regarded by the Navy), the stigma of reporting for several weeks of PTSD treatment/rehabilitation could be reduced. This may well increase the likelihood that individuals who need treatment will seek it.

This paper describes the design, protocol, and methodology of a randomized controlled trial (RCT) examining whether the TMT Intensive Outpatient Program (TMT IOP) or the compressed PE protocol are efficacious therapies for the treatment of military-related PTSD in active duty service members. Specifically, this study will determine if a faster recovery period can be achieved by comparing the TMT IOP (3 weeks) and compressed PE (2 weeks) with the traditional 12-week PE treatment program. This study will also assess the impact of TMT IOP and compressed or standard PE on social, familial, and occupational impairment. Outcome will be determined based upon self-report and clinician ratings of PTSD symptomatology, other aspects of psychopathology, and social/emotional functioning. Additionally, this study will examine the PTSD biomarkers (predictors of response, biological subtypes of PTSD, and therapeutic markers) that may impact treatment outcome. Finally, this study will assess differences in attrition and the emergence of potential adverse events, such as increased suicidal ideation or increased alcohol use that may accompany intensive treatments.

1.1. Research objectives and hypotheses

The research objective is to determine whether compressed treatment formats for PTSD, TMT IOP and compressed PE, are as efficacious as a standard 12-week PE outpatient program. Furthermore, this project will determine whether the broader nature of the TMT IOP will produce significantly better effects for associated psychopathology (e.g., sleep, depression, anger, and guilt) and functional impairment (e.g., occupational, social, and familial functioning). The study will also document any instances of negative side effects (e.g., increased suicidal ideation, suicide attempts, or increased alcohol use) as a result of massed treatment. Finally, the study will attempt to identify PTSD biomarkers (e.g., predictors of response, biological subtypes of PTSD, and therapeutic markers).

The specific hypotheses are as follows:

Hypothesis 1. As assessed by clinician interview and self-report, TMT IOP and compressed PE will produce significantly greater decreases in PTSD symptomatology than PE delivered in a standard format, and differences will be maintained at follow-up.

Hypothesis 2. TMT IOP will increase socialization, quality of life, and overall functioning significantly more than PE delivered in compressed or standard formats, and differences will be maintained at follow-up.

Hypothesis 3. TMT IOP will produce significantly greater decreases in depression, anger, and guilt than PE delivered in a compressed or standard format, and differences will be maintained at follow-up.

Hypothesis 4. TMT IOP and compressed PE will result in significantly lower dropout rates than the standard 12-week PE program.

2. Materials and methods

2.1. Research design

Participants will be assessed and assigned to one of three treatment conditions, all of which have empirical support for the treatment of military-related PTSD. Participants will have a diagnosis of PTSD as a result of a traumatic event that occurred during their military service. The study design is illustrated below (see Fig. 1).

2.2. Participant recruitment

This study will be conducted at three military installations: Dwight D. Eisenhower Army Medical Center (DDEAMC), Naval Medical Center Portsmouth (NMCP), and Naval Medical Center Camp Lejeune (NMCCL). Recruitment from these three military installations will allow participation from all service branches as well as sufficient numbers to represent the various types of trauma (combat, MST, etc.).

Three hundred (300) active duty military personnel (100 per site) who have a history of military-related trauma and meet DSM-5 criteria for PTSD will be recruited for study participation. To be consistent with existing research, MST will be limited to cases of attempted or completed sexual assault while on active duty [17]. Our recruitment strategies will ensure that sex, ethnicity, and socioeconomic class distribution will be representative and generalizable to the military population and these demographics will not be dictated by sampling strategies. Recruitment of 300 participants will allow us to meet the requirements of our power analysis (71 per group), considering potential attrition across the groups.

2.3. Inclusion criteria

The inclusion criteria are as follows: (a) active duty service personnel seeking treatment for PTSD that occurred during their military service; (b) PTSD diagnosis as assessed by the Clinician Administered PTSD Scale for DSM-5 (CAPS-5); (c) ability to read and write English; (d) ability to participate in any of the 3 conditions (2 week, 3 week, 12 week); and (e) if taking an antidepressant medication, reached a stable dose, and expected to have no change in dosing throughout the study.

2.4. Exclusion criteria

The exclusion criteria are as follows: (a) Due to the possibility of increased blood pressure and heart rate during exposure, patients with acute cardiac difficulties (angina, myocardial infarction, and severe hypertension) will be excluded unless medically cleared to participate; (b) patients with severe comorbid substance use disorders will be eligible once their substance use is under control for 2 weeks (c) a diagnosis of schizophrenia, other psychotic disorders, or antisocial personality disorder; (d) a diagnosis of moderate or severe traumatic brain injury (TBI); (e) patients who are pregnant and have not been medically cleared to participate; and (f) patients who are taking benzodiazepines and do not wish to discontinue use. This last exclusion is based on the empirical evidence suggesting that the efficacy of exposure

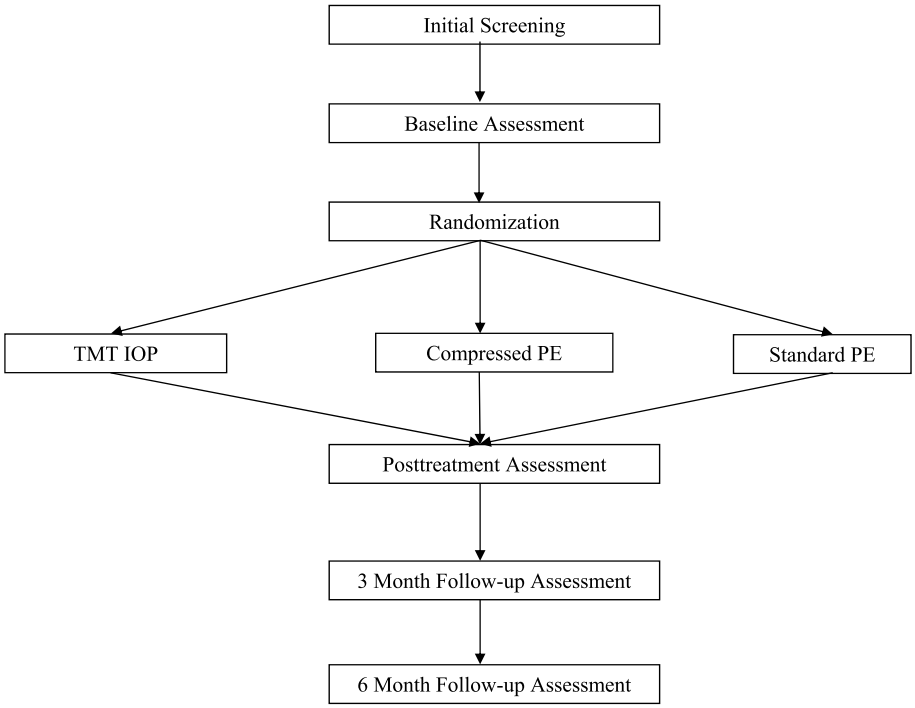


Fig. 1. Study Design.

therapy for other anxiety disorders may be attenuated by benzodiazepine use [18,19].

2.5. Treatment

2.5.1. Trauma Management Therapy

Trauma Management Therapy [20] is a multicomponent behavioral treatment program designed to target various aspects of chronic PTSD – reducing emotional and physiological reactivity to traumatic cues, reducing intrusive symptoms and avoidance behavior, improving interpersonal skills and emotion modulation (anger control, depression), and increasing the range of enjoyable social activities. In the initial investigations with Vietnam veterans, individual imaginal exposure therapy occurred first and occurred 3 times per week, resulting in a statistically significant decrease in PTSD symptoms. Upon its completion, patients began group therapy, designed to address anger, social isolation, and communication with non-veterans [10]. In comparison to a psychoeducation group, only the TMT group reported a statistically significant increase in both frequency of social activities and time spent in social activities. These changes occurred from mid-treatment (after completion of exposure therapy) to post-treatment (after completion of the social emotional rehabilitation component), supporting the hypothesis that exposure therapy alone did not result in improved social functioning.

Based on the initial outcome, TMT was revised to address the needs of Iraq and Afghanistan veterans and active duty personnel. In this investigation and in line with our previous publications [7,8], TMT uses virtual-reality augmented individual exposure therapy sessions and group therapy to address sleep, anger, depression, and social isolation. The program also includes in vivo exposure therapy to address behavioral avoidance.

In the TMT IOP, each participant receives virtual-reality assisted exposure therapy in the morning (5 days per week, Monday through Friday, for 3 weeks). Presentation of the traumatic event involves the therapist or the patient recounting the scene, incorporating the BraveMind VR program (Institute for Creative Technologies, University of Southern California) to present the sights, sounds, and odors that were present during the traumatic event. Unlike the exposure sessions in PE (see below), TMT IOP exposure sessions are not time-based, but continue until the patient's distress while imagining the traumatic scene dissipates and the patient achieves within session habituation. This means that initially, exposure therapy sessions may last 90–120 minutes. As treatment continues and between session habituation to the traumatic scene and the traumatic reminders occurs, later exposure sessions are shorter in duration, in some cases just 20 minutes.

Beginning in the second week, in vivo exposure is therapist accompanied and occurs daily. Sessions are continued until within and between session habituation is achieved. Group treatment occurs each afternoon and will consist of 4–6 participants (depending on recruitment rate and randomization) and will be led by two group leaders. The IOP group therapy protocol is presented in Table 1.

2.5.2. Standard prolonged exposure

Standard prolonged exposure [6] consists of psychoeducation, imaginal exposure to the trauma memory, in vivo exposure to situations that are avoided due to their association with the trauma, and emotional processing. The standard protocol consists of 12 sessions (10 of which involve imaginal exposure), along with in vivo exposure/homework assignments, and listening to a recording of the imaginal sessions at home between sessions. Session 1 consists of presentation of the treatment rationale, gathering information about trauma history, and details on the most distressing trauma. Session 2 includes education about trauma-related symptoms, construction of the in-vivo hierarchy, and the assignment of homework that includes in vivo exposure activities. Individuals begin confronting items lower on the hierarchy and, as they are successful, they confront the more feared items. Imaginal exposure begins in session 3 and the patient recounts the trauma aloud for 45–60 min. The trauma narrative is audiotaped, and the patient is instructed to listen to it daily between sessions. Beginning with session 4 and continuing throughout the remaining sessions, the treatment includes review of homework, imaginal exposure for 30–45 min, a discussion of the imaginal exposure (i.e., emotional processing), and the assignment of homework to be completed between sessions.

Table 1
TMT group content.

Week	Monday	Tuesday	Wednesday	Thursday	Friday
Week 1	Behavioral Activation	Sleep Hygiene	Anger Management	Social Reintegration	Anger Management
Week 2	Behavioral Activation	Sleep Hygiene	Anger Management	Social Reintegration	Anger Management
Week 3	Behavioral Activation	Social Reintegration	Behavioral Activation	Relapse Prevention	

2.5.3. Compressed PE

Compressed PE consists of 10 standard PE sessions delivered on consecutive work days. The imaginal exposure sessions take place in the morning, with in vivo exposure activities assigned (not therapist accompanied) for the afternoons. Patients are instructed to listen to the recording of the imaginal exposure each night. Due to concerns about having enough time for in vivo practice, Session 1 does not start on a Monday, allowing for two full weekends in order to maximize in vivo exposures. If patients are not considered responders by session 10 (the termination session), the therapist assigns specific in vivo homework assignments and then follows up on their completion one week later.

2.5.4. Equality of treatment time for exposure therapy

The approximate number of hours of exposure therapy in each condition is depicted in Table 2.

The hours include clinician-assisted imaginal sessions as well as clinician-directed exposure therapy activities and homework assignments. Both forms of PE include instructions that the patient listen to a recording of the in-clinic imaginal exposure session as homework, something that is not done in TMT. Thus, although the number of hours is not identical, they are reasonably close. Our plan is to calculate the exact number of hours of exposure therapy for each patient in each condition, and if necessary, statistically control for the number of hours of exposure when completing the data analysis.

2.5.5. Therapist training and supervision

Licensed psychologists or licensed masters level clinicians will conduct treatment. Therapists will be trained and supervised in TMT under the supervision of the second and fourth authors (Neer and Newins). At a minimum, initial training for therapists will include 20 h of didactics and discussion (10 h) and videotaped practice sessions with play back to enable supervisors to provide feedback on performance (10 h). Therapists will be required to successfully treat one patient using TMT, under supervision, prior to admittance as a therapist in this project. Therapists will follow a session-by-session TMT manual developed by the PIs.

Training in compressed and standard PE will be conducted by the fifth author (Tuerk), who is a certified PE trainer. Training will consist of the gold-standard PE training, which is a 2 or 3-day intensive course, and then an additional day on how to deliver PE in a compressed fashion. As with TMT, therapists will be required to successfully treat one patient using PE, under supervision, prior to admittance as a therapist in this project. Therapists will follow PE manuals previously developed for the compressed and standard protocols.

2.5.6. Treatment integrity

Independent raters will assess treatment integrity by evaluating the content of periodic video-recorded therapy sessions. Raters will determine the presence of key therapeutic strategies via an inclusive checklist derived from key elements of each treatment condition. Therapists will be unaware of which sessions will be evaluated.

Table 2
Hours of exposure therapy across treatment conditions.

Hours of Exposure	TMT	Compressed PE	Standard PE
In Clinic	14.5	8.0	8.0
Out of Clinic	14.0	20.0	17.0
Total	28.5	28.0	25.0

Note. These times are estimated, as there is a range of possible duration for both TMT and PE exposure sessions.

2.5.7. Treatment credibility

To assess for differences in outcome expectancy, we will use the Credibility/Expectancy Questionnaire (CEQ) [21]. The CEQ includes questions regarding how logical the treatment seems, how confident participants are about treatment, their expectancy of success, and whether they would recommend the treatment to another person suffering from the same condition. If differences in treatment credibility exist, these data will be used as covariates in all treatment outcome analyses.

2.6. Outcome measures

Because this study addresses aspects of social and emotional functioning not typically addressed/assessed in studies of PE, this assessment battery is extensive, assessing the following dimensions: (a) PTSD symptoms, trauma, and trauma-related symptoms; (b) symptoms of other psychiatric conditions; (c) social and occupational functioning; (d) sleep (as assessed by sleep actigraphy); and (e) biomarkers of PTSD. We will also assess heart rate and skin conductance during each imaginal session to further explicate the role of fear arousal and habituation during imaginal and VR-assisted exposure therapy sessions. Furthermore, we will assess differences in drop-out rates as well as potential "side-effects" of intensive treatment such as worsening depression or increased suicidal ideation. As depicted in Table 3 major assessment points occur at pretreatment, mid treatment, posttreatment, 3-month follow-up, and 6-month follow-up.

The primary outcome measures are the CAPS-5 [22], the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5; 23), and the World Health Organization Disability Assessment Schedule 2.0 (WHO-DAS 2.0; 35). Each of these is described below.

The CAPS-5 is a semi-structured interview designed to assess frequency and intensity of each symptom of PTSD and provide a composite rating for each item. As indicated above, clinicians on site will administer this measure at pretreatment to determine current diagnosis, initial eligibility, and initial clinician-rated severity of PTSD symptoms. Because the treatment protocols run for various lengths (potentially easily breaking the blind), an independent evaluator who is not at the site where the pretreatment assessment or treatment occurred will complete the CAPS-5 at posttreatment and follow-up. A recent study examining the use of the CAPS-5 in military veterans found high inter-rater reliability for both PTSD diagnosis ($\kappa = 0.78$ to 1.00) and total severity score (ICC = 0.91), good test-retest reliability for both PTSD diagnostic status ($\kappa = 0.83$) and severity score (ICC = 0.78), and good internal consistency for the severity items ($\alpha = 0.88$; [22]). This study also demonstrated convergent and discriminant validity of scores from the CAPS-5 [22].

The PCL-5 is a self-report measure assessing the 20 PTSD symptoms as outlined in the DSM-5. Participants rate how much they are bothered by each symptom using a 5-point scale. A total symptom severity score (range 0–80) can be obtained by summing the scores for each of the 20 items. This measure will be used during all assessments (pre, post, and follow-up) as well as weekly during all three treatments. Initial psychometric studies demonstrated that PCL-5 scores are reliable and valid measures of PTSD symptoms in college students who had experienced

Table 3
Assessment strategy.

Measure	Pre-Tx	Each Tx Session	Weekly During Tx	Mid-Tx	Post-Tx	3 Mo F/Up	6 Mo F/Up
Demographics	X						
PTSD Symptoms, Trauma, and Trauma-Related Symptoms							
CAPS-5 [22]	X				X	X	X
PCL-5 [23]	X		X		X	X	X
Traumatic Life Events Questionnaire [24]	X						
Combat Exposure Scale [25]	X						
Trauma-Related Guilt Inventory [26]	X			X	X	X	X
Posttraumatic Cognitions Inventory [27]	X			X	X	X	X
Moral Injury Event Scale [28]	X			X	X	X	X
Symptoms of Other Psychiatric Conditions							
Structured Clinical Interview for DSM-5, Clinician Version [29]	X						
Structured Clinical Interview for DSM-5, Personality Disorders [30]	X						
Dimensions of Anger Reactions-5 [31]	X		X		X	X	X
Patient Health Questionnaire-9 [32]	X		X		X	X	X
Generalized Anxiety Disorder-7 [33]	X		X		X	X	X
Clinical Global Impressions Scales [34]	X				X	X	X
Social and Occupational Functioning							
World Health Organization Disability Assessment Schedule 2.0 [35]	X				X	X	X
The Quality of Life Scale [36]	X				X	X	X
Inventory of Psychosocial Functioning [37]	X				X	X	X
Connor-Davidson Resilience Scale [38]	X				X	X	X
Therapy "Side Effects"							
Clinician Checklist	X	X			X	X	X
Medication Log	X	X			X	X	X
Sleep Actigraphy	X	X			X	X	X
Biomarkers of PTSD	X				X	X	X
Physiological Reactivity (heart rate and skin conductance) during exposure therapy sessions		X					
Treatment Credibility		Session 3					

trauma [39]. In a recent study with veterans, PCL-5 scores were shown to have excellent internal consistency ($\alpha = 0.96$) and good test-retest reliability ($r = 0.84$); convergent and discriminant validity were also demonstrated [40].

The World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0; [35]) is a 36-item measure; participants rate each item from "none" to "extreme or cannot do." The WHODAS 2.0 assesses impairment in six domains: cognition, mobility, self-care, getting along with people, life activities (at home and work), and participation in society. Good internal consistency has been demonstrated for all subscales, test-retest reliability is also moderate to good at the item level and excellent at the domain level, and concurrent validity was demonstrated [35]. This measure will be administered at pre, post, and follow-up assessments.

Self-report of sleep is often not reliable owing to apparent sleep misperception, with only moderate correlations with sleep actigraphy in veteran populations [e.g., 41]. Indeed, veterans with PTSD are likely to underreport sleep duration. To collect an objective measure of sleep, we will use sleep actigraphy to assess changes in sleep as a result of treatment. Sleep actigraphy has been validated against polysomnography (PSG), with greater than 90% agreement for minute-by-minute sleep/-wake identification [42–44]. Variables derived from actigraphy include total sleep time (TST), sleep-onset latency (SOL), sleep efficiency (SE), and wake minutes after sleep onset (WASO). Information on bedtimes and sleep schedules is also collected.

Although not a primary outcome measure, and we have made no specific hypotheses, we will collect blood samples from participants in order to correlate biomarkers, including differentially expressed molecules in blood sampled before and after treatment that may predict successful resolution of PTSD. Blood samples will be collected from participants at baseline, posttreatment, and 3- and 6-month follow-up in order to identify PTSD biomarkers (e.g., predictors of response, biological subtypes of PTSD) and therapeutic markers.

Given the different lengths of treatment, the mid-treatment, post-treatment and follow-up assessments will not occur at the exact same time chronologically for each of the three groups. There was consideration as to whether the assessments should be timed so that all occurred at the same calendar time (one month after the initiation of treatment) or at the same phase of treatment (after half of the sessions were completed). There are merits to both approaches. However, we came down on the side of phase of treatment because understanding the impact of more rapid treatments requires the ability to assess improvement and perhaps relapse. Tying assessments for all groups to one specific calendar time, such as one month after treatment initiation, means that one group would still be only halfway through treatment whereas the other two groups would have finished treatment 1–2 weeks earlier when they were compared. Comparisons across groups would not be possible. Furthermore, in the latter two cases, it would be difficult to tell if no clinical change occurred as a result of treatment or if there had been clinical change, but then there had been rapid relapse. We believe that this is a critically important point and must be addressed. Given that (a) military PTSD remains very difficult to treat and (b) these rapid treatments are so new and potentially so efficacious, we believe that, at this time, the stronger arguments can be made for assessing clinical change pegged to treatment phase rather than other assessment schedules.

2.7. Power analysis

Participants will be randomized into one of three treatment conditions: Trauma Management Therapy IOP (TMT), standard PE, and compressed PE. To account for multiple pairwise tests among the treatment groups and to adjust for a parallel gatekeeping approach, we will apply Bonferroni correction to the chosen α value: $\alpha/m = 0.05/4 = 0.0125$. The formula for target sample size is:

$$n = \frac{2\sigma^2\left[z_{(1-0.05/4)} + z_{(1-0.20)}\right]^2}{(0.3\mu_c)^2} = \frac{2*0.252^2\left[z_{(0.9875)} + z_{(0.80)}\right]^2}{(0.3*0.434)^2} = 71.08$$

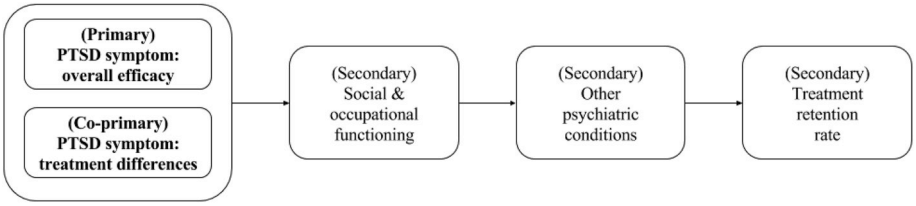
In our previous IOP study, the dropout rate for TMT IOP was 2% [7]. Conservatively, we assumed a 5% dropout rate for the TMT IOP group in this study. Dropout rates for Standard PE and Compressed PE are anticipated as 40% and 10%, respectively, based on the existing

literature. Subsequently, to achieve the statistical power discussed above, we proposed recruiting 75 (71.08/0.95) participants for TMT, 119 (71.08/0.60) participants for Standard PE, and 79 (71.08/0.90) participants for Compressed PE, resulting in a total of 273 participants. On the advice of the funding agency statisticians, we were encouraged to "round up" to a total of 300 participants by recruiting an additional 9 participants per group. Thus, we will recruit 84 participants for TMT, 128 participants for Standard PE, and 88 participants for Compressed PE, to achieve at least 71 completed participants for each group.

2.8. Data analytic plan

One of the primary reasons for conducting this study is to determine if the group intervention that is part of TMT IOP produces outcomes for social and emotional functioning that are superior to standard or compressed PE. Thus, one very possible outcome is that both TMT and PE produce identical reductions on the CAPS-5, but that TMT produces superior outcomes on other measures, suggesting a greater impact in overall functioning. The approach we have chosen will control for multiplicity but still allows examination of the efficacy of the TMT IOP vis-à-vis compressed and standard PE.

The efficacy outcome variable for the primary hypothesis (#1) is the change as a percentage of pretreatment CAPS-5 and the PCL-5 scores. We will use pairwise or independent samples testing procedures (i.e., *t*-test or Wilcoxon rank sum test, as appropriate) to evaluate overall treatment efficacy and to compare treatment groups on the primary outcome variable. Under a parallel gatekeeping setup, we will require statistically significant change on the CAPS-5 or PCL-5 (at an adjusted alpha level) before proceeding to the secondary objectives. Our three remaining hypotheses constitute three domains of secondary analysis that we will investigate sequentially also using a parallel gatekeeping approach. The truncated Holm procedure will be applied to adjust for multiplicity at each stage; any amount of alpha unused in a stage is passed onto the next stage. The first secondary domain involves social and occupational functioning, which will be measured by WHODAS. The second domain encompasses mental health symptoms other than PTSD, which include guilt (measured by TRGI), anger (by DAR-5), and depression (by PHQ-9). The last domain deals with treatment retention rate. We will compare treatment groups using *t*-tests or Wilcoxon tests for continuous variables and chi-square or Fisher's exact tests for categorical variables.



To further comprehensively evaluate the relationships between efficacy and treatment groups (TMT, standard PE, compressed PE), we will use a generalized linear mixed models (GLMM) approach [45] or equivalent hierarchical linear models [HLM], random regression models [RRM], or mixed effects models [MEM]), with treatment group as the primary independent variable and individual measures of efficacy used separately as the dependent variable. This approach accommodates a wide range of distributional assumptions for continuous and categorical outcome variables, including ordinal measures (e.g., patient ratings, CGI), count, and binary outcomes (e.g., response/nonresponse, relapse status), as well as multilevel data such as longitudinal measurements on subjects and possible cluster effects within site, therapist, or group through inclusion of random effects in the model [46]. For longitudinal outcomes, time and time × treatment group will be considered random effects and treatment group will be considered a fixed effect. Additional variables will be added to the multivariable GLMM model as adjustment covariables, if indicated. Putative covariables include initial PTSD severity, psychiatric comorbidity, time since trauma exposure, presence/absence of comorbid diagnoses, presence/absence of mild TBI, and level of combat exposure. Cluster effects will be accounted for through inclusion of random effects in the model. Using this modeling approach, we will assess the active phase results and the naturalistic follow-up phase results in separate analyses. The magnitude of intervention effect sizes (e.g., difference in treatment means for continuous outcomes, differences in proportions, and odds ratios for categorical outcomes) will be estimated using 95% confidence intervals (CIs). Effect size estimates allow evaluation of the clinical significance/relevance of the study findings.

Analysis of genetic markers will utilize the Core Module Biomarker Identification with Network Exploration [COMBINER; 47], to look for novel functional groupings of genes across PTSD sub-populations and cohorts. All two-way comparisons will be made using *t*-tests with *Benjamini–Hochberg FDR correction* for multiple comparisons, unless otherwise noted. Interaction analysis (e.g., covariate analysis) will employ ANOVA and multiple regressions for categorical and ordinal data, respectively. All identified biomarkers will be subjected to permutation-based statistical validation and further feature selection (random forest) where necessary. The selected biomarkers will be evaluated using receiver operator curves (ROCs) and associated performance values (sensitivity, specificity, positive and negative predictive value, and area under the curve), generated using several different classification methods including Random Forest, Support Vector Machines, Partial Least Squares - Linear Discriminant Analysis, and Penalized Logistic Regression using 1000 iterations of five-fold cross--validation as implemented in the CMA R package.

3. Discussion

Although empirically supported treatments for military-related PTSD are available, their utilization and overall effectiveness remain questionable. Despite the adoption of Cognitive Processing Therapy (CPT) and PE by the US Department of Veterans Affairs (VA), the application of these treatment programs for military-related PTSD, particularly combat-related PTSD, still faces issues of treatment attrition averaging 28% per RCT (but up to 40% in more recent RCTs). Furthermore, even when a full course of treatment results in symptom reduction, a substantial number of patients retain their PTSD diagnosis. As noted by Hoge and colleagues [12], there is a particular need for "interventions that enhance treatment engagement or retention" ([12], p. E2). Other barriers to care include difficulty getting time off to attend appointments, perceived stigma, and a preference for treatment of issues such as sleep disruption, anger, and stress [12,16,48].

With this list of potential barriers to successful treatment outcomes, some investigators and policy-makers have suggested the need for different treatments. Our approach has been to suggest that current

effective treatments may need to be delivered *differently*. Using an IOP model [7], we demonstrated enhanced treatment outcomes using a schedule of daily exposure therapy sessions, coupled with group treatment. At posttreatment, 67% no longer met criteria for PTSD and the attrition rate was 2%. Compressed PE treatment also resulted in a lower attrition rate than standard PE with no difference in treatment outcome between the two methods of delivery [14]. If these initial positive outcomes are replicated in this study, intensive or compressed treatments may become the treatment of choice for military PTSD, particularly among active duty personnel.

In the same manner, these compressed or intensive programs may help to reduce the stigma associated with treatment for PTSD. Effective treatments that do not require an extended period may help strengthen the notion that PTSD (or PTS) is a stress injury that should be treated in the same manner as physical injuries that occur during military service. Demonstrating that individuals benefit from treatment and can return to full duty status would reinforce the conceptualization that PTS is not a chronic condition and treatment is effective and short-term.

Using rigorous RCT methodology, this study will also, for the first time, assess the impact of PE and TMT on a broader range of psychopathology (e.g., depression, anger, sleep, social isolation) than has been previously reported. TMT was developed as a result of dissatisfaction with the impact of exposure therapy to address these variables in Vietnam veterans, for whom treatment was provided 20–30 years after the war had ended. However, the less chronic nature of PTSD among military service members who served in the Iraq and Afghanistan conflicts may mean that providing treatment earlier may negate the disorder's impact on some of these other areas of functioning. Thus, a major thrust of this investigation is to assess the importance of adding a group intervention in order to achieve optimal treatment outcomes. Given that veterans have specifically indicated a need for treatment for sleep, depression, and stress [48], TMT may have more face validity for participants, which may enhance reported treatment outcome. This investigation will provide a clearer answer on whether a component specifically designed to address these issues is needed.

Finally, although not listed among the specific hypotheses, the data collected through this investigation will provide information that will further clarify issues with respect to the treatment of PTSD. For example, it will provide information on the utility of VR augmentation for exposure therapy sessions. Although most individuals can clearly recall their imaginal events, it is unclear if augmentation of sounds and smells (which may be harder to imagine than visual stimuli) may enhance behavioral treatment by providing direct exposure to these traumatic cues/reminders. Because we will be utilizing two different approaches, data from this investigation will directly address this issue. Similarly, the need for within and between session habituation for exposure therapy to be efficacious has been the subject of much discussion and some controversy. Although several studies suggest that within session habituation is not necessary for positive treatment outcome [e.g., 49,50], these conclusions were drawn from treatment for specific phobias or discrete traumatic events such as car accidents. It is unclear whether such conclusions apply to the multiple and reoccurring types of trauma that occur in war zones. Furthermore, those studies were retrospective in the sense that conclusions were drawn based on the outcome of positive patient change even when within session habituation was not evident. This study will use a prospective approach by randomizing patients to conditions that differ in the need for within session habituation. Finally, the collection of genetic samples may provide information on biomarkers that lead to better understanding of treatment response, PTSD subtypes, and how to construct more personalized treatments.

In summary, military-related PTSD continues to challenge mental health providers and military readiness. Standard treatment delivery paradigms are effective but plagued by high drop-out rates and stigma, such that many who need treatment do not receive it. Compressed treatment programs (e.g., compressed PE) and IOPs (e.g., TMT) have shown initial treatment efficacy but have yet to be tested rigorously with an all active duty sample. Should they be effective, treatment may be available and accessible to more individuals who need them. Additionally, recovery from PTSD requires more than simply a reduction in PTSD symptoms; it means remediating associated behavioral and emotional dysfunction (e.g., anger, depression, sleep problems, social isolation), thus restoring optimal functioning. Addressing all aspects of impairment means a greater likelihood of recovery, benefitting not only the individual but the family, the military community, and society.

Author note

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Funding

This study is funded by contract #W81XWH18C0331, Joint Warfighters Medical Research Program (JWMRP), Congressionally Directed Medical Research programs (CDMRP).

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