

ORIGINAL ARTICLES

Authors alone are responsible for opinions expressed in the contribution and for its clearance through their federal health agency, if required.

MILITARY MEDICINE, 177, 6:635, 2012

Development and Testing of Virtual Reality Exposure Therapy for Post-Traumatic Stress Disorder in Active Duty Service Members Who Served in Iraq and Afghanistan

*CDR Robert N. McLay, MC USNR**; *Kenneth Graap, M.Ed.†*; *James Spira, PhD‡*; *Karen Perlman, PhD§*; *CAPT Scott Johnston, MSC USN||*; *Barbara O. Rothbaum, PhD¶*; *JoAnn Difede, PhD***; *William Deal, PhD**; *CDR David Oliver, MC USN**; *Alicia Baird, PhD**; *Patrick S. Bordnick, PhD††*; *Josh Spitalnick, PhD‡‡*; *Jeffrey M. Pyne, MD§§*; *Albert Rizzo, PhD|||*

ABSTRACT This study was an open-label, single-group, treatment-development project aimed at developing and testing a method for applying virtual reality exposure therapy (VRET) to active duty service members diagnosed with combat post-traumatic stress disorder (PTSD). Forty-two service members with PTSD were enrolled, and 20 participants completed treatment. The PTSD Checklist-Military version, Patient Health Questionnaire-9 for depression, and the Beck Anxiety Inventory were used as outcome measures. Of those who completed post-treatment assessment, 75% had experienced at least a 50% reduction in PTSD symptoms and no longer met DSM-IV criteria for PTSD at post treatment. Average PTSD scores decreased by 50.4%, depression scores by 46.6%, and anxiety scores by 36%. Intention-to-treat analyses showed that statistically significant improvements in PTSD, depression, and anxiety occurred over the course of treatment and were maintained at follow up. There were no adverse events associated with VRET treatment. This study provides preliminary support for the use of VRET in combat-related PTSD. Further study will be needed to determine the wider utility of the method and to determine if it offers advantages over other established PTSD treatment modalities.

*Naval Medical Center San Diego, 34800 Bob Wilson Drive, San Diego, CA 92134.

†CNS Response, Inc., 85 Enterprise, Suite 410, Aliso Viejo, CA 92656.

‡National Center for PTSD, Pacific Islands Division Veterans Health Administration, U.S. Department of Veterans Affairs, 3375 Koapaka street, Suite I-560; Honolulu, HI 96819.

§Private Practice, P.O. Box 633063, San Diego, CA 92163-3063.

||Naval Center for Combat and Operational Stress Control, 34800 Bob Wilson Drive, San Diego, CA 92134.

¶Trauma and Anxiety Recovery Program, Department of Psychiatry, Emory University School of Medicine, 1256 Briarcliff Road, Atlanta, GA 30306.

**Department of Psychiatry, Weill Cornell Medical College, 525 E. 68th St Box 200, NY 10021.

††Child and Family Center for Innovative Research, Graduate College of Social Work, University of Houston, 110HA Social Work Building Room 320 Houston, TX 77204-4013.

‡‡Virtually Better Corporation, Lawrenceville Highway, Suite 200 Decatur, GA 30033 404-634.

§§Central Arkansas Veterans Healthcare System, Center for Mental Health Outcomes Research, Little Rock, AR 72205.

|||Institute for Creative Technologies, University of Southern California, 13274 Fiji Way, Office 327, Marina del Rey, CA 90292-4019.

The opinions expressed are those of the authors and do not necessarily represent those of the U.S. Navy or of any other government organization.

INTRODUCTION

Once chronic, post-traumatic stress disorder (PTSD) is unlikely to resolve without active and effective treatment.¹ Therefore, there has been a great deal of interest in developing and testing treatments for this disorder.

Multiple reviewing agencies agree that exposure therapy has adequate evidence supporting its efficacy.²⁻⁵ Although it is widely agreed that exposure therapy works, the response rate is still less than ideal. A meta-analysis of PTSD treatments⁶ reported that an average of 52% (95% CI 42.37 to 62.82) of individuals who completed treatment in trials of prolonged exposure (PE) demonstrated clinically significant improvements.

Exposure therapy is based on the idea that facing fears allows a patient to overcome them. Various ideas have been put forth for why the treatment may sometimes fail. These may include inability to emotionally engage with the treatment and an unwillingness or inability to face traumatic events. Virtual reality (VR) may offer a means to address

some of these difficulties by allowing patients to face their fears in a more controlled environment.

In VR exposure therapy (VRET), the therapist presents computer-generated trauma cues to the patient through a computer simulator. The computer simulation is manipulated to approximate the patient's traumatic experience(s). VRET allows the traumatic experience to be confronted in a way that is easily controlled and replicated in a therapeutic manner.

VRET has amassed an evidence base as an efficacious treatment for anxiety disorders.⁷ For example, VRET has been shown to be equivalent to in vivo therapy within actual airplanes for the fear of flying⁸ and resulted in greater improvements in anxiety-symptom severity than treatments with imaginal exposure alone.⁹ VRET was first adapted for the treatment of PTSD in Vietnam veterans who had not responded to other treatments.¹⁰ Further preliminary evidence has shown a good treatment outcome in car-accident victims,¹¹ September 11 survivors,¹² and service members who served in Iraq and Afghanistan.¹³ Case reports have indicated that there are individuals who failed to respond to traditional PE who then improve when treated with VRET.¹⁴ The aggregate of these preliminary studies suggests that VR-based therapy holds promise for the current generation of service members with combat-related PTSD.

In 2005, the Office of Naval Research funded projects to develop VR simulations and therapy approaches for the treatment of PTSD in service members who served in Iraq and Afghanistan. This report details the process by which VRET software and treatment protocols were developed and the results from one of these studies.

METHODS

Overview

This was an open label, treatment-development study in which a treatment protocol was initially developed and then modified

as the study progressed. Participants were assessed by research assistants using a validated self-report measure for PTSD-symptom severity before and after the VRET intervention.

Treatment Location, Approval, and Therapists

The study was conducted in Southern California at Naval Medical Center San Diego (NMCS) and Marine Corp Base Camp Pendleton (MCBCP) between 2004 and 2008. The facilities are about an hour apart by car and are covered by the same institutional review board, which approved all protocols with the review of a medical monitor. All participants gave written informed consent to take part in the study. All therapists on the project were licensed independent providers, either psychiatrists or psychologists, and were credentialed at the treating facility. All therapists (Robert N. McLay, William Deal, and Karen Perlman) underwent a 2-day training in VRET conducted by experts in the field (Barbara O. Rothbaum and JoAnn Difede), as well as training in PE. Supervision was conducted by leading VR treatment experts (JoAnn Difede and Barbara O. Rothbaum) Sessions were videotaped and reviewed with the supervisors.

Participants

Participants were active duty soldiers or marines with an existing diagnosis of chronic PTSD related to combat operations in Iraq or Afghanistan. They had to have an identifiable, traumatic event they could work on during the therapy. Initially, the study actively sought patients who were treatment resistant, defined as having failed treatment with at least 6 weeks of medication or talk-therapy intervention in the past. Over time, treatment resistance was dropped as an eligibility criterion for the study. Participants were excluded if they were actively suicidal or psychotic or had a diagnosis of substance dependence and use within 30 days. Participants

TABLE I. Demographics, Entry Scores, and Information on Treatment Received for Those Participants Who Eventually Completed Treatment (Completers), Those Who Left Treatment (Dropouts), and for the Total ITT Group

		Age	Male (%)	Years of Service	Number of Deployments	PCL-M Pretreatment	PHQ-9 Pretreatment	BAI Pretreatment	Number of Treatment Sessions
Completers <i>n</i> = 20	Mean	28.10	95.00	8.43	2.60	60.27	14.36	21.05	10.30
	SD	8.38		7.76	2.09	10.83	5.30	9.79	2.45
	Minimum	20		2	1	33.00	4.00	4.00	4
	Maximum	51		26	9	81.00	23.00	43.00	15
Dropouts <i>n</i> = 22	Mean	23.73	100.00	4.76	2.23	54.35	13.30	18.60	3.77
	SD	2.69		2.30	1.19	9.68	5.40	10.74	2.09
	Minimum	20		2	1	36.00	7.00	4.00	1
	Maximum	31		9.5	5	71.00	26.00	45.00	8
Total <i>n</i> = 42	Mean	25.81	97.62	6.50	2.40	57.45	13.86	19.88	6.88
	SD	6.41		5.83	1.67	10.60	5.31	10.20	3.99
	Minimum	20		2	1	33.00	4.00	4.00	1
	Maximum	51		26	9	81.00	26.00	45.00	15
Difference Between Completers and Dropout	<i>p</i> =	*0.04	NA	0.05	0.49	0.07	0.52	0.44	NA

had to be stable on their psychiatric medication, defined as having no changes within 6 weeks of starting the protocol. Participants were instructed not to use benzodiazepines or alcohol within 12 hours of treatment sessions. Participants were asked to forgo other therapy or psychiatric medication changes during the treatment protocol but were not discontinued if this occurred. Participants were recruited by referral from their mental health providers and by fliers posted and distributed directly to service members. Participants had to be able to travel to either NMCSO or MCBCP. Participants could leave the treatment protocol at any time and could have other services provided to them free of charge through the military. Participants were considered "intent-to-treat" if they met criteria and attended at least one treatment session. Demographics for those enrolled in the study are presented in Table I.

Participant Assessment

Participants were screened by research assistants to determine eligibility and provide informed consent for participation, and then met with a licensed therapist to determine safety for study entry. Baseline assessment included: review of existing medical records, structured psychiatric interview (Mini-international neuropsychiatric interview¹⁵), and self-report measures of symptom severity. Follow up assessments included all these measures, but demographic information and screen for comorbidity were not repeated. For an arbitrarily selected (based on when trained assessors were available) subset of participants, the clinician-administered PTSD scale (CAPS)¹⁶ was collected and correlated with the PTSD checklist military version (PCL-M), which was the primary outcome measure. Participants were assessed within 2 weeks before starting treatment, 1 week after completing treatment, and again 3 months after completing treatment. Assessments were conducted at military clinics, and participants were aware of the rules governing disclosure of records within the military. Participants who participated in both pretreatment and post-treatment assessments were considered completers in the study. For completers, all data used were taken from these assessments. Participants were administered the PCL-M, patient health questionnaire-9 (PHQ-9), and beck anxiety inventory (BAI) at the beginning of every other therapy session after session 4. Data from these measures were used to allow the therapist to monitor progress through the treatment. For participants who left treatment before completing a post assessment, data from these intra-session evaluations were used in last-observation-carried forward (LOCF) analysis.

Enrollment

Seventy-two participants agreed to initial assessment. Four participants declined to give informed consent for evaluation, thus, baseline data were kept on a total of 68 participants. Eighteen participants did not meet inclusion and exclusion criteria, and were deemed ineligible for treatment, but provide baseline data. Eight participants declined to enter treatment

after completing their initial assessment. This left 42 participants who entered treatment and who were counted as intent-to-treat. Information on the flow of participants through the study is given in Figure 1.

Primary Outcome Measure

The PCL-M was used as the primary measure of PTSD symptom severity. This is a self-report scale in which a patient rates the severity of the 17 DSM-IV symptoms of PTSD on a scale from 1 (no symptoms) to 5 (extreme problems) over the past month. Scores on the PCL-M range from 17 to 85. To meet "clinical" criteria for PTSD according to the PCL-M, a respondent must rate as moderate (3) at least one criteria B symptom, three criteria-C symptoms, and at least two criteria D symptoms corresponding with a DSM diagnosis of PTSD. A respondent is considered to meet "strict" criteria for PTSD if clinical criteria are met and total severity score is 50 or higher.¹⁷ Previous studies have found that the PCL-M has a high correlation with the CAPS and is an accurate reflection of PTSD symptom severity.¹⁸ In this study, the PCL-M and CAPS showed a correlation of 0.88 in 59 assessments (data not shown).

Secondary Outcome Measures

In addition to PTSD symptoms, severity of depression and anxiety were assessed at the same time as PTSD. The PHQ-9 was used as the measure of depressive symptoms. The PHQ-9 is a self-report measure asking frequency of symptoms corresponding to the nine DSM-IV symptoms for major depressive disorder over the past 2 weeks.¹⁹ The BAI was used as the measure of anxiety. The BAI was used to quantify anxiety symptoms. The BAI is a well-validated, self-report measure developed to assess anxiety symptoms as separate from those of depression.²⁰

VR Apparatus

The VR hardware and software developed for this protocol are described in detail elsewhere.²¹ Briefly, the hardware consisted of two networked computers, one rendered the virtual environment and the other allowed the therapist to control and individualize stimuli presented. In the virtual environment (virtual Iraq), one could drive a Humvee down a desert highway either alone or in a convoy or navigate through Iraq-like city scenes. Visual, auditory, tactile, and olfactory cues could be introduced via the VR simulator.

VRET Treatment

An initial treatment protocol was developed building upon methods previously developed by Rothbaum et al,¹⁰ Difede et al,^{12,22} and Foa et al.²³ Participants selected their most traumatic combat incident that was the most closely related to their disabling symptoms of PTSD. In the VR environment, the therapist employed multiple sensory modalities to create the most immersive, realistic experience for the

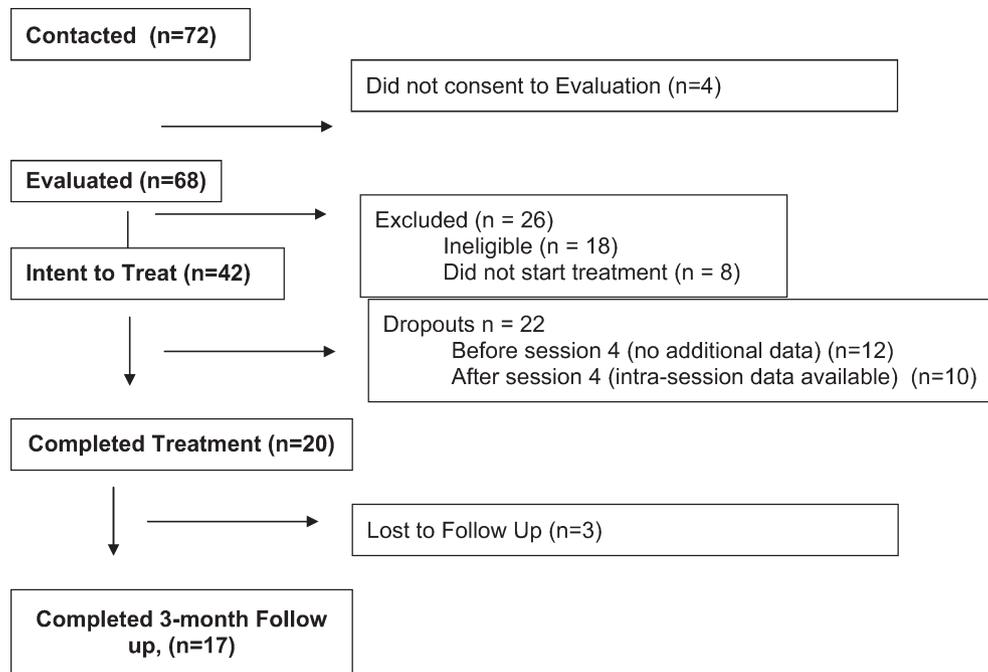


FIGURE 1. The entry and exit of participants through the study.

patient. VR exposure was conducted for approximately 45 minutes per session. Following the VR exposure, the patient and therapist processed²³ the material that emerged in the exposure. Processing involved discussing themes and stuck points such as guilt, responsibility, and safety issues in a format similar to cognitive restructuring. Participants were treated twice weekly in sessions that lasted 90 to 120 minutes each. Sessions were recorded on audio tape and given to participants to review as homework. The first session consisted of a trauma interview, psychoeducation on PTSD, and training in breathing techniques. The second session consisted of introduction to the concept of subjective units of distress, construction of in vivo hierarchy items related to the index trauma, and the patient's first experience of imaginal exposure, where the patients verbally narrated their index trauma (without VR). In the third session, the patient was introduced to, and explored, the VR environment. The patient was encouraged to describe the feelings, thoughts, sensations, or memories emerged while being immersed in the VR environment. In the fourth session, VR and PE were combined so that the patient narrated his or her trauma while in the VR environment. In future sessions, the intensity of VR experiences was progressively increased to make the simulation more realistic. The patient continued to verbally recount the trauma experience, focusing on areas of particular stress (i.e., "hot spots") in the trauma by session 6. For participants with multiple traumas, the therapist and patient could decide together when to move on to other traumas, always starting with the worst remaining trauma.

In early participants ($n = 26$, including 14 of those who completed the protocol) clinical flexibility was allowed

in assigning the number of therapy sessions. The target was 10 sessions. However, participants could leave treatment early and participate in post assessment if both the participant and therapist agreed that the participant had reached clinical remission. Conversely, the number of treatment sessions could be increased up to 15 sessions if the therapist and patient felt that additional sessions would be helpful. The experience with these early participants helped to determine a fixed protocol, which called for 12 to 15 sessions over a maximum of 10 weeks. A treatment manual was written at the end of the study documenting the final treatment protocol.²⁴

Statistical Methods

Results were analyzed in two ways. A set of comparisons was made, which included only those participants for whom complete evaluations were available. Also, a second set of comparisons was made using intention-to-treat (ITT) analysis with LOCF methods. LOCF has been criticized as a method of data imputation, based on the tendency of the method to bias outcomes toward one outcome or the other when two groups are compared.⁶ As there was no comparison group, the issue of biasing outcomes was felt to be less relevant here. For ITT analysis, the last observation used could be taken either from the initial evaluation, or, for those who completed at least four sessions of treatment, from intra-session administration of the measures. Student *t*-tests were used to compare changes from pretreatment to post-treatment and from pretreatment to 3-month follow up. Bonferroni corrections were applied to control for the running of multiple-*t*-tests. A corrected *p* value for significance was used ($p = 0.05/12$ tests =

new corrected p threshold of $p < 0.004$). Post-hoc comparisons were made by comparing the characteristics of those who completed treatment (as defined as having completed post-treatment assessment) and those who dropped out. Student t -tests, Welch correction, χ^2 , and Pearson correlations were used where appropriate.

RESULTS

Forty-two participants entered treatment and were counted as ITT. Of these, eight dropped out before ever experiencing the VR. Four dropped out immediately after session 3, the exploratory VR session. The remaining twelve dropouts occurred later in the course of treatment. Of 42 ITT participants, 20 patients finished treatment and participated in the post-treatment assessment (48%).

Demographics of those participants who entered treatment, dropped-out, and for the entire ITT group are given in Table I. Participants who dropped out were younger than those who completed treatment, but no other significant differences were seen between baseline scores for completers and dropouts (Table I). There was no statistically significant

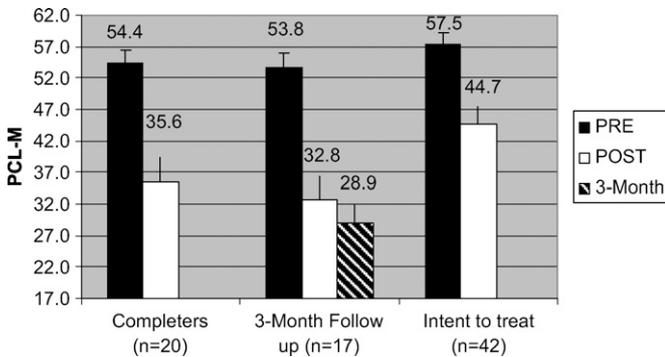


FIGURE 2. PCL-M scores before and after treatment. Data are shown for those who completed treatment (completers), those who were assessed at 3-month follow up, and for all ITT participants. For ITT participants, results shown in post assessment were determined by LOCF methods. Mean scores are illustrated with standard errors. Note that for the PCL-M a score of 17 indicates no PTSD symptoms.

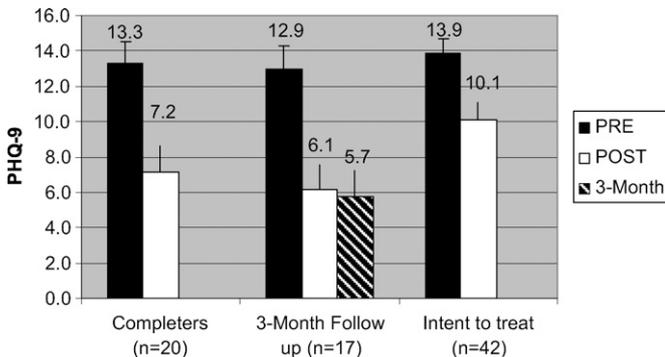


FIGURE 3. PHQ-9 scores before and after treatment. Data are shown for those who completed treatment (completers), those who were assessed at 3-month follow up, and for all ITT participants. For ITT participants, results shown in post assessment were determined by LOCF methods. Mean scores are illustrated with standard errors.

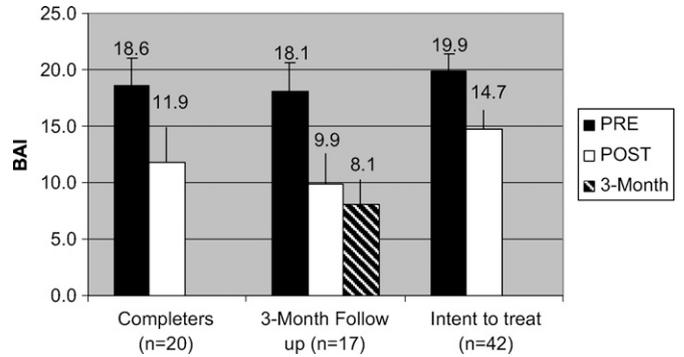


FIGURE 4. BAI scores before and after treatment. Data are shown for those who completed treatment (completers), those who were assessed at 3-month follow up, and for all ITT participants. For ITT participants, results shown in post assessment were determined by LOCF methods. Mean scores are illustrated with standard errors.

difference in the chance of dropping out in the first and second half of the study ($p = 0.46$), or according to which therapist treated the patient ($p = 0.87$). There was no significant correlation ($R = 0.137$, $p = 0.39$) between the number of participants that a therapist had previously treated using VRET and the number of sessions a subject completed before dropout.

Of the 20 participants who completed treatment, 15 (75%) no longer met diagnostic criteria for PTSD on the PCL-M at the post assessment. The same 15 participants had improved at least 50% on the PCL-M. Of the 17 participants who could be followed up at 3-month assessment, 13 (76%) no longer met criteria for PTSD on the PCL-M, and these 13 maintained at least a 50% improvement in their PCL-M score.

Changes in symptoms for those who went on to 3-month assessment, and for all ITT participants, expressed as LOCF, as assessed by the PCL-M, PHQ-9, and BAI are given in Figures 2, 3, and 4, respectively.

Of all the participants who entered the study, only one had a significant adverse event, and this was not considered study related. He was psychiatrically hospitalized after the initial assessment but before session 1.

COMPLETER ANALYSIS (n = 20)

PTSD Checklist Military Version

PCL-M scores were compared using separate, paired t -tests. For the participants ($n = 20$) who completed post-treatment assessment, average PCL-M scores (standard deviation [SD]) were 54.4 (9.7) for pretreatment and 35.6 (17.4) for post-treatment (effect size Cohen's $d = 1.34$, 95%CI 0.86 to 1.81). Because a score of 17 on the PCL-M indicates an absence of symptoms, 17 was subtracted from both the pre- and post-treatment scores in order to calculate percent improvement. Thus, participants averaged a $((54.4 - 17) - (35.6 - 17)) / (54.4 - 17) = 50.3\%$ improvement. For the participants ($n = 17$) who went on to complete a 3-month follow up evaluation,

average PCL-M scores (SD) were 53.8 (9.6) pretreatment and 28.9 (13.0) for 3-month follow-up (Cohen's $d = 2.17$, 95%CI 1.51 to 2.83). There was a significant difference in PCL-M scores between pre- and post-treatment, $t(19) = 5.92$, $p < 0.001$, and between pre-treatment and 3-month follow-up, $t(16) = 6.97$, $p < 0.001$. There was not a statistically significant difference between post-treatment and 3-month follow-up, $t(16) = 2.13$, $p = 0.048$, indicating that participants maintained their post-treatment gains.

Patient Health Questionnaire-9

PHQ-9 scores were compared using separate, paired t -tests. For the participants ($n = 20$) who completed post-treatment assessment, average PHQ-9 scores (SD) were 13.3 (5.4) for pretreatment and 7.1 (6.7) for post-treatment (effect size Cohen's $d = 1.01$, 95%CI 0.44 to 1.58). For the participants ($n = 17$) who went on to complete a 3-month follow up evaluation, average PHQ-9 scores (SD) were 12.9 (5.4) for pretreatment and 5.7 (6.1) for 3-month follow-up (Cohen's $d = 1.25$, 95%CI 0.60 to 1.91). There was a significant difference in PHQ-9 scores between pre- and post-treatment ($t(19) = 3.69$, $p = 0.002$ and between pretreatment and 3-month follow-up ($t(16) = 4.05$, $p < 0.001$). There was not a statistically significant difference between post-treatment and 3-month follow-up ($t(16) = 0.51$, $p = 0.620$).

Beck Anxiety Inventory

BAI scores were compared using separate, paired t -tests. For the participants ($n = 20$) who completed post-treatment assessment, average BAI scores (SD) were 18.6 (10.7) for pretreatment and 11.9 (13.3) for post-treatment (effect size Cohen's $d = 0.56$, 95%CI 0.60 to 1.91). This is a 36.0% improvement. For the participants ($n = 17$) who completed a 3-month follow up evaluation, average BAI scores (SD) were 18.1 (10.6) for pretreatment and 8.12 (9.0) for 3-month follow-up (Cohen's $d = 1.01$, 95%CI 0.61 to 1.41). There was a significant difference in BAI scores between pre- and post-treatment ($t(19) = 3.67$, $p = 0.003$) and between pretreatment and 3-month follow-up ($t(16) = 5.36$, $p < 0.001$). There was not a statistically significant difference between post-treatment and 3-month follow-up ($t(16) = 1.63$, $p = 0.123$).

INTENT TO TREAT ANALYSIS ($n = 42$)

PTSD Checklist Military Version

PCL-M scores were compared using a separate, paired t -test. PCL-M scores (SD) were 57.5 (10.6) for pretreatment and 44.7 (17.3) for post-treatment. There was a significant difference in PCL-M scores between pre- and post-treatment ($t(41) = 5.92$, $p < 0.001$). Of the 42 patients in the ITT analysis, 20 (47%) had shown a PCL-M score that was at least 30% lower than at baseline, and 19 (45%) did not meet criteria for PTSD on the PCL-M at the last observation.

Patient Health Questionnaire-9

PHQ-9 scores were compared using a separate, paired t -test. PHQ-9 scores (SD) were 13.9 (5.3) for pretreatment and 10.1 (6.5) for post-treatment. There was a significant difference in PHQ-9 scores between pre- and post-treatment ($t(41) = 3.99$, $p < 0.001$). Excluding subjects where changes for both depression and PTSD were assumed to be zero because of LOCF, changes on the PHQ-9 were positively correlated with the changes on the PCL-M, with $R = 0.694$.

Beck Anxiety Inventory

BAI scores were compared using a separate, paired t -test. BAI scores (SD) were 19.9 (10.2) for pretreatment and 14.7 (11.0) for post-treatment. There was a significant difference in BAI scores between pre- and post-treatment ($t(41) = 4.06$, $p < 0.001$). Excluding subjects where changes for both depression and PTSD were assumed to be zero because of LOCF, changes on the BAI were positively correlated with the changes on the PCL-M, with $R = 0.715$.

DISCUSSION

This study provided a first step in the development of treatment protocols for active duty military personnel diagnosed with combat-related PTSD. Previously, all aspects of the protocol, from recruitment to the treatment itself, were untested in this population and context. The project shows that it is possible to recruit research participants from among previously deployed active duty military personnel diagnosed with PTSD and suggests the relevance of the VRET treatment to this population. It joins a handful of studies to have published treatment results in active duty patients with PTSD related to service in Iraq or Afghanistan.²⁵⁻²⁷

Our results provide preliminary evidence for the effectiveness of VRET for active duty service members diagnosed with PTSD. As many of the participants had failed previous treatments or had comorbid TBI, little, spontaneous improvement would have been expected.¹ Participants showed significant improvements in their PTSD severity scores over the course of treatment (Figure 2). These improvements were maintained 3 months after treatment. Similarly, significant reductions were seen in depression (Figure 3) and anxiety (Figure 4), with changes in both being highly correlated to the changes in PTSD. In this study, 75% of those completing VRET treatment had greater than 50% reduction on the PCL-M and no longer met DSM-IV criteria for PTSD. That is, for the majority of subjects, the results were impressive, but the remaining 25% saw little to no change.

By design, this study was not randomized and did not include a control group; so, it is impossible to say if the VRET resulted in greater improvement than other forms of treatment. However, compared to other published results, the improvements seen here were impressive. A 2005 meta-analysis⁶ of PTSD treatments concluded that active treatment for PTSD averages a 54% response rate in those who

complete treatment (95% CI 47.3 to 61.13%), compared to 12.43% (95% CI, -0.12 to 24.97%) of those in wait-list controls. Clinically significant response is defined differently in different studies. However, a greater than 30% improvement in symptoms was generally considered clinically meaningful.⁶ Thus, the response rate seen here in those who completed treatment (75%) was above the 95% confidence interval for most effective treatments.

We were pleased to see that depression and general anxiety symptoms also improved along with PTSD. Similarly to PTSD symptoms, the improvement was maintained even after the active phase of treatment was complete. This observation supports earlier findings that exposure therapies may result in an overall change in cognitive processing and thus allow more wide spread improvements across multiple domains.²⁸

Although the VRET resulted in greater symptom improvement than has been commonly reported in most studies of PTSD, dropout rate was high. Over half of participants left treatment before completing a post-treatment assessment. The typical rate of dropout for PTSD treatment is generally closer to 25%.⁶ The only study, of which we are aware, that published dropout rates in active duty members reported a 30% dropout rate,²⁵ and trials of an alternate method for treating PTSD using VR that was conducted at the same time as this trial had overall dropout rates of 33%.²⁹

It is unclear why there was such a high dropout rate here. Those who dropped out of treatment were younger than those who completed, but no other demographic factor was significantly different between dropouts and completers. Likewise, no significant effect on dropout was seen for symptom severity, therapist experience, or in comparing the first half versus second half of patients enrolled in the study. We were unable to obtain detailed information from the participants who left the study. We did discover that some participants who dropped had physically left the Southern California area, but we did not have access to detailed statistics on how often this occurred. Service members often move, deploy, or have other commitments that could limit their abilities to come in for

regular appointments. Also, service members have other treatment options and so may have elected for other treatments that were more convenient or preferable. We are unaware of any adverse events related to dropout.

The importance of the high dropout rate seen here should not be minimized. It is important to note, however, that clinical measures taken during treatment in participants who dropped out were not worsening (Table II). ITT analyses indicated that the effect of VRET treatment was significant even when using the LOCF method. This method assumes that any individual who drops out early will show no additional improvement beyond the point of their previous assessment. This method is sometimes criticized in PTSD research³ because, in a disorder in which spontaneous improvement may occur, LOCF will make any treatment that discourages dropout appear superior to the control condition. In this study, however, LOCF is a conservative assumption. Complex imputation models might have predicted that some of the patients who dropped out would actually have continued to improve. It was felt, however, that given the small amount of data and the high dropout rate seen here, that such a model could not be properly constructed. In this case, the assumption that patients who dropped out simply stopped improving was felt to be more conservative.

Given this assumption, at least a 47% of participants who entered VRET showed a clinically significant (30% or greater) improvement on the PCL-M. Meta-analysis of ITT analysis for response rates in PTSD⁶ indicate that 44% of patients who enter active treatments for PTSD improve (95% CI 37-51%). Thus, taking into account the dropout rate, the response rate observed here would be fairly typical for active treatments of PTSD.

Overall, the high improvement rates and the absence of negative events associated with the treatment all indicate that VRET is a safe and effective treatment for PTSD in service members diagnosed with PTSD related to deployment in Iraq or Afghanistan. Several important questions still remain and will need further investigation. Probably the most important of these is the need to determine if VRET is superior to other

TABLE II. Scores on the PCL-M, PHQ-9, and BAI from all Available Data in ITT Participants

		N	Mean	SD	Minimum	Maximum
PCL-M	Pretreatment	42	57.45	10.60	33	81
	Post-treatment	20	35.55	17.39	18	79
	3-month follow up	17	28.94	13.02	18	56
	Clinical Observation in Dropouts	10	49.60	13.48	32	68
PHQ-9	Pretreatment	42	13.86	5.31	4	26
	Post-treatment	20	7.15	6.71	1	21
	3-month follow up	17	5.71	6.08	0	20
	Clinical Observation in Dropouts	10	11.20	5.14	4	19
BAI	Pretreatment	42	19.88	10.20	4	45
	Post-treatment	20	11.85	13.31	0	46
	3-month follow up	17	8.12	8.98	1	30
	Clinical Observation in Dropouts	10	17.00	9.36	3	31

Data were gathered initially on 42 ITT participants. Twenty of these completed treatment and provided data at post assessment. Seventeen went on to complete a 3-month follow up. No additional data was available for 12 of the dropout participants. However, 10 of the participants who dropped out had completed the PCL-M, PHQ-9, and BAI within clinical sessions. These data (clinical observation in dropouts) were used to provider LOCF data in the ITT analysis.

existing treatments, particularly PE therapy. Also, VRET is not the only VR-based approach to PTSD treatment that has been developed. Alternative methods based on physiologic monitoring and skill development in VR have been used for the treatment of PTSD.¹³ It will be necessary to examine factors that predict who might most benefit from VRE, what is the cost-effectiveness of VRE, and what aspect (if any) in the VR enhances results. This may extend beyond just the overall efficacy of the treatment and may include the desirability of the treatment, and the overall effectiveness of therapy in the context of stigma and potential dropout. The VR might also help serve not just as a treatment, but, if properly developed, as a means of assessing who is ready to return to active duty. In short, there is more work to be done, but these initial findings suggest that VRET is a promising avenue for treatment in active duty Operation Iraqi Freedom service members with PTSD.

ACKNOWLEDGMENTS

The authors wish to thank Waine MacAllister for editorial assistance and Robert Riffenberg, PhD for advice on statistical analysis.

This study was funded by a grant from the Office of Naval Research, grant number DOD-N0384.

REFERENCES

- Rothbaum BO, Foa EB: Subtypes of posttraumatic stress disorder and duration of symptoms. In: *Posttraumatic Stress Disorder: DSM-IV and Beyond*, pp. 23–36. Edited by J. R. T. Davidson, E. B. Foa. Washington, DC, American Psychiatric Press, 1992.
- Ursano RJ, Bell C, Eth S, et al: Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. *Am J Psychiatry* 2004; 161(Suppl 11): 3–31.
- Institute of Medicine Committee On Treatment Of Posttraumatic Stress Disorder: *Treatment Of Posttraumatic Stress Disorder, An Assessment Of The Evidence*. Washington, DC, The National Academies Press, 2008.
- Foa E, Keane T, Friedman M (editors): *Effective Treatments for PTSD: practice guidelines from the International Society for Traumatic Stress Studies*. New York, Guilford Press, 2000.
- National Institute for Clinical Excellence: *Post-traumatic Stress Disorder (PTSD): The Management of PTSD in Adults and Children in Primary and Secondary Care*. London, National Institute for Clinical Excellence, 2005.
- Bradley R, Greene J, Russ E, Dutra L, Westen D: A multidimensional meta-analysis of psychotherapy for PTSD. *Am J Psychiatry* 2005; 162(2): 214–27.
- Powers MB, Emmelkamp PMG: Virtual reality exposure therapy for anxiety disorders: a meta-analysis. *J Anxiety Disord* 2008; 22: 561–9.
- Rothbaum BO, Anderson P, Zimand E, Hodges L, Lang D, Wilson J: Virtual reality exposure therapy and standard (in vivo) exposure therapy in the treatment of fear of flying. *Behav Ther* 2006;37(1): 80–90.
- Wiederhold BK, Jang DP, Gevirtz RG, Kim SI, Kim IY, Wiederhold MD: The treatment of fear of flying: a controlled study of imaginal and virtual reality graded exposure therapy. *IEEE Trans Inf Technol Biomed* 2002; 6(3): 218–23.
- Rothbaum BO, Hodges LF, Ready D, Graap K, Alarcon RD: Virtual reality exposure therapy for Vietnam veterans with posttraumatic stress disorder. *J Clin Psychiatry* 2001; 62(8): 617–22.
- Beck JG, Palyo SA, Winer EH, Schwagler BE, Ang EJ: Virtual Reality Exposure Therapy for PTSD symptoms after a road accident: an uncontrolled case series. *Behav Ther* 2007; 38(1): 39–48.
- Difede J, Cukor J, Jayasinghe N, et al: Virtual reality exposure therapy for the treatment of posttraumatic stress disorder following September 11, 2001. *J Clin Psychiatry* 2007; 68: 1639–47.
- Wood DP, Murphy JA, Center KB, et al: Combat related post traumatic stress disorder: a multiple case report using virtual reality graded exposure therapy with physiological monitoring. *Stud Health Technol Inform* 2008; 132: 556–61.
- Difede J, Hoffman HG: Virtual reality exposure therapy for World Trade Center Post-traumatic Stress Disorder: a case report. *Cyberpsychol Behav* 2002; 5(6): 529–35.
- Sheehan DV, Lecrubier Y, Sheehan KH, et al: The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; 59(Suppl 20): 22–33.
- Blake DD, Weathers FW, Nagy LM, et al: The development of a Clinician-Administered PTSD Scale. *J Trauma Stress* 1995; 8(1): 75–90.
- Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA: Psychometric properties of the PTSD Checklist (PCL). *Behav Res Ther* 1996; 34(8): 669–73.
- Monson CM, Gradus JL, Young-Xu Y, Schnurr PP, Price JL, Schumm JA: Change in posttraumatic stress disorder symptoms: do clinicians and patients agree? *Psychol Assess* 2008; 20(2): 131–8.
- Spitzer RL, Kroenke K, Williams JB: Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA* 1999; 282(18): 1737–44.
- Beck AT, Epstein N, Brown G, Steer RA: An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988; 56(6): 893–7.
- Rizzo A, Pair J, McNerney PJ, et al: Development of a VR therapy application for Iraq war military personnel with PTSD. *Stud Health Technol Inform* 2005; 111: 407–13.
- Difede J, Malta LS, Best S, et al: A randomized controlled clinical treatment trial for World Trade Center attack-related PTSD in disaster workers. *J Nerv Ment Dis* 2007; 195(10): 861–5.
- Foa E, Hembree E, Rothbaum BO: *Prolonged Exposure Therapy for PTSD: Emotional Processing of Traumatic Experiences: Therapist Guide*. Oxford University Press, 2007.
- Rothbaum BO, Difede J, Rizzo A: (2008). *Therapist Treatment Manual for Virtual Reality Exposure Therapy: Posttraumatic Stress Disorder in Iraq Combat Veterans*. Tacoma, Washington, Geneva Foundation, 2008.
- Litz BT, Engel CC, Bryant RA, Papa A: A randomized, controlled proof-of-concept trial of an Internet-based, therapist-assisted self-management treatment for posttraumatic stress disorder. *Am J Psychiatry* 2007; 164(11): 1676–83.
- Schnurr PP, Friedman MJ, Engel CC, et al: Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. *JAMA* 2007; 297(8): 820–30.
- McGhee LL, Maani CV, Garza TH, Desocio PA, Gaylord KM, Black IH: The effect of propranolol on posttraumatic stress disorder in burned service members. *J Burn Care Res* 2009; 30(1): 92–7.
- Hofmann SG: Cognitive processes during fear acquisition and extinction in animals and humans: implications for exposure therapy of anxiety disorders. *Clin Psychol Rev* 2008; 28(2): 199–210.
- McLay RN, Wood DP, Rizzo A, et al: Different Methods for Conducting Virtual Reality Therapy for Combat PTSD: What Studies Show, and Practical Application of VR Treatment in Iraq. *Frontiers in Neuro-engineering. Conference Abstract: Annual CyberTherapy and Cyber-Psychology 2009 conference*.