TITLE: Virtual Reality Exposure Therapy for Adults with Post-Traumatic Stress Disorder: A Review of the Clinical Effectiveness

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CONTEXT AND POLICY ISSUES

Post-traumatic stress disorder (PTSD) is a chronic psychiatric condition that develops following an exceptionally traumatic event.[1] Core symptoms of PTSD include re-experiencing the trauma (for example, through flashbacks and nightmares), avoidance of reminders of trauma, and hyperarousal (for example, feeling irritable or angry, startling easily, or experiencing difficulty sleeping or concentrating).[1] Lifetime prevalence rates of PTSD have been estimated as 9.2% in Canada[2] and ranging from 6.8% to 12.3% in the United States.[3] Certain groups of people, such as those exposed to military combat, are at a higher risk of developing PTSD;[3] lifetime prevalence of PTSD in Vietnam war veterans has been reported at 18.7%,[4] and up to 18% of Operation Iraqi Freedom veterans have experienced PTSD.[5]

Treatments for PTSD include pharmacotherapy and psychological therapy.[6] Selective serotonin reuptake inhibitors are the most common choice for PTSD pharmacotherapy.[7] Of the psychological therapies, cognitive behavioural therapy (CBT) is considered to be a first-line therapy for PTSD based on strong evidence of effectiveness from clinical trials.[6,8] CBT may involve multiple therapy approaches, including elements of cognitive therapy, development of coping skills, and exposure therapy.[6] Exposure therapy in particular refers to a method by which patients repeatedly confront memories or reminders of trauma in a safe and controlled environment in order to gradually reduce the distress associated with them.[6] Imaginal exposure therapy focuses on patients revisiting the event in their minds, in vivo exposure employs real-life trauma reminders, and prolonged exposure (PE) combines both types of exposure therapy.[5]

A recent expansion on traditional exposure therapy, virtual reality exposure therapy (VRET) creates an immersive and interactive virtual environment through the use of computer graphics and auditory cues to enhance a patient's imaginative capacities.[5,8] The virtual environment is often presented via a head-mounted display and can be manipulated by the therapist or patient as necessary.[5,8] Since engagement in imaginal exposure can be hindered by the avoidance behaviour that is characteristic of PTSD, VRET's use of multiple sensory prompts to assist recall of trauma and immersion has been suggested as an enhancement of conventional exposure

therapy.[5,8] However, VRET is a relatively recent development in the field and uncertainty remains about its clinical effectiveness. The purpose of this report is to examine the clinical effectiveness of VRET for the treatment of PTSD.

RESEARCH QUESTION

What is the clinical effectiveness of virtual reality exposure therapy (VRET) for the treatment of adults with post-traumatic stress disorder (PTSD)?

KEY FINDINGS

Limited evidence from a systematic review and a randomized controlled trial suggest that virtual reality exposure therapy may be as effective as other types of exposure therapy for PTSD.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, PsycINFO via OVID, The Cochrane Library (2014, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between Jan 1, 2009 and Jul 30, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with PTSD
Intervention	Virtual reality exposure therapy
Comparator	Other active treatment (usual care, exposure therapy, pharmacotherapy, psychological interventions)
Outcomes	Reduction in symptoms (for example, as measured by a validated scale, normalized brain function), quality of life
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications or included in a selected systematic review, or were published prior to 2009.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[9] The quality of RCTs was evaluated using the Downs and Black instrument.[10] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 552 citations were identified in the literature search. Following screening of titles and abstracts, 522 citations were excluded and 30 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 31 publications were excluded for various reasons: irrelevant population (3), irrelevant intervention (2), irrelevant comparator (6), irrelevant outcomes (1), duplicate publication or already included in at least one of the selected systematic reviews (9), review article (10). Two publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Characteristics of the included studies are summarized in Appendix 2.

Study Design

One systematic review published in 2012[11] that was identified for this report included 10 studies (four randomized controlled trials, two non-randomized controlled trials, four uncontrolled trials), five of which met inclusion criteria for this report. The literature search for this review was completed in May 2011; the exact search date range was not specified. One RCT published in 2014[12] was included in this report. The duration of the treatment phase as well as the length of the follow-up period was unclear.

Country of Origin

The systematic review[11] was performed by a group in Brazil and included studies from multiple different countries. The included RCT[12] was conducted in the United States.

Patient Population

The systematic review[11] included 10 studies that assessed patients of an unspecified age range with PTSD, including active military personnel and war veterans. The data from the included studies were not pooled due to small sample sizes, which ranged from 10 to 40 participants per study. The RCT[12] involved 37 combat veterans, 19 with PTSD and 18 without PTSD; patient demographics were not described.

Interventions and Comparators

The main intervention of interest in all included studies was VRET for the treatment of PTSD.[11,12] The RCT[12] compared VRET with prolonged exposure (PE) therapy. There was another control group in the RCT comprised of patients who did not have PTSD and did not receive either VRET or PE treatment, but were evaluated for the outcomes of interest at baseline and at three to four months. A comparator group was not specified for the systematic review, which included six comparative and four non-comparative primary studies.[11] One of the six primary studies compared VRET with a wait-list control group. The remaining five comparative studies had active therapy comparators, including present-centred therapy (non-specific psychotherapy without discussion of the traumatic event), CBT, exposure therapy (including "traditional", PE, and imaginal exposure), and a combination of psychological and/or pharmacological therapies described as treatment as usual.[11]

Outcomes

The systematic review focused on outcome measures of PTSD symptoms, including a number of different self or clinician-administered questionnaires and scales.[11] The RCT reported patient scores on the self-administered PTSD Checklist – Military Version (PCL-M) and the Clinician-Administered PTSD Scale (CAPS) as well as functional MRI (fMRI) results for a subset of patients with PTSD and controls without PTSD.[12]

Summary of Critical Appraisal

The methodological quality of the included studies was generally low. The strengths and limitations of the included studies are summarized in Appendix 3.

The systematic review[11] employed a comprehensive literature search based on pre-defined criteria, but it was unclear whether grey literature was included in the search strategy. Two independent reviewers selected articles and collected data, but a list of excluded studies was not provided. The likelihood of publication bias was not addressed. No formal statistical analyses were performed but the scientific quality of the RCTs (four of 10 included studies) was assessed. In the discussion, the authors acknowledged that the methodological conduct of the included RCTs was not sufficiently rigorous, as they each had study design limitations that introduced a high risk of bias: none of the four studies employed an intention-to-treat analysis, the outcome assessment was not blinded in two studies, the relevant comorbidities were not described in one study, and the concurrent treatment was not described in one study. The RCTs were also limited by small sample sizes, ranging from 10 to 20 patients each. Furthermore, the authors reported that critical information for the proper evaluation of VRET efficacy was missing from all 10 trials included in the systematic review. However, the limitations in scientific quality of the reviewed studies did not temper the authors' conclusion that VRET was as effective as exposure therapy for the treatment of PTSD, but rather were only presented as a rationale for future research.

Several critical pieces of information regarding the conduct of the RCT[12] were not described in the publication. The source of the patients, baseline characteristics of each group, and potential confounders were not provided. The intervention and outcomes of interest were described; however, the method of randomization was not discussed and the length of the treatment phase and follow-up period for the VRET group were not specified. It was unclear whether an attempt was made to blind the researchers to a patient's group assignment when administering the

CAPS or PCL-M or interpreting the results of the fMRI. Due to the small sample size, fMRI results for VRET and PE subjects were combined, and they were not clearly, numerically presented. A power calculation to determine a sufficient sample size to detect differences between groups was not provided. Specific *P* values for reported statistically significant results were not defined.

Summary of Findings

The study findings and author's conclusions are summarized in Appendix 4.

The systematic review[11] evaluated and narratively summarized the results of 10 studies, five of which included an active control group. Comparator therapies in the primary studies included present-centred therapy, CBT, exposure therapy (including "traditional", PE, and imaginal exposure), and treatment as usual. Of the five studies that compared VRET with a control therapy group, three studies reported a statistically significant decrease in PTSD symptoms as measured by a validated scale following treatment. However, there were no significant differences in the PTSD symptom scores between the VRET and control therapy groups.

The RCT[12] examined the comparative effectiveness of VRET and PE for the treatment of PTSD. A second component of the study evaluated the effect of exposure therapy (VRET or PE) on brain activity on fMRI. The authors reported a significant reduction in CAPS scores relative to baseline in the VRET group but not the PE group; however, PCL-M scores significantly decreased after therapy in both treatment groups. They concluded that because CAPS is a preferred screening tool for PTSD, their findings suggest that VRET may be more effective than PE for resolving combat-related PTSD. Due to the small number of patients with PTSD who underwent fMRI scanning at baseline and post-treatment (n = 10; 4 VRET and 6 PE), fMRI results for these patients were combined and no comparison between the effect of VRET and PE on brain function was conducted.

Limitations

As the included studies were generally of poor methodological quality, results should be interpreted with caution. The literature regarding the clinical effectiveness of VRET for PTSD is limited; of the 10 studies listed in the systematic review,[11] four lacked a comparator group. Four of the remaining six included studies were RCTs, and the authors reported that they were unable to perform a meta-analysis of the results due to the small sample sizes of these studies (n = 10 to 20). The single more recent RCT[12] that was identified for this report also had a small sample size (n =19; 9 VRET and 10 PE), which may limit the validity of the study conclusions. Since patient demographics were not presented, it is unclear whether there were other factors in this group that may have affected their response to treatment. Notably, the VRET group had a higher baseline mean CAPS score than the PE group, introducing the possibility that the significant reduction in CAPS scores after VRET reported in the RCT[12] was influenced by the greater initial severity of the condition in this group (as measured by CAPS) rather than the effectiveness of the treatment. Furthermore, the majority of studies included in the systematic review[11] as well as the RCT[12] evaluated American military patients with PTSD, which may limit the generalizability of results to other patient populations, including military service members from other countries and those with non–combat-related PTSD. Stronger evidence, supported by large RCTs, is needed to confirm the clinical effectiveness of VRET for PTSD.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There is limited evidence to suggest that VRET may be as effective as other types of exposure therapy for the treatment of PTSD. Findings presented in the publications included in this report[11,12] are consistent with the results of a broader meta-analysis[13] that assessed the clinical effectiveness of several PTSD treatments and found no difference in effect size between simulator-based exposure therapy and control groups. However, multiple control conditions were acceptable for study inclusion in this meta-analysis (including non-active, wait-list controls) and individual study characteristics were not elucidated further. Therefore, it is unclear whether the lack of an observed difference in effect size was driven by active treatment comparisons or non-active control comparisons. Since the use of VRET for the treatment of PTSD has only recently been studied in clinical trials, there is little available literature. The strength of the conclusions made in these studies is also limited by the small study sample sizes. Further rigorous trials are required to provide sufficient high quality evidence regarding the clinical effectiveness of VRET for PTSD.

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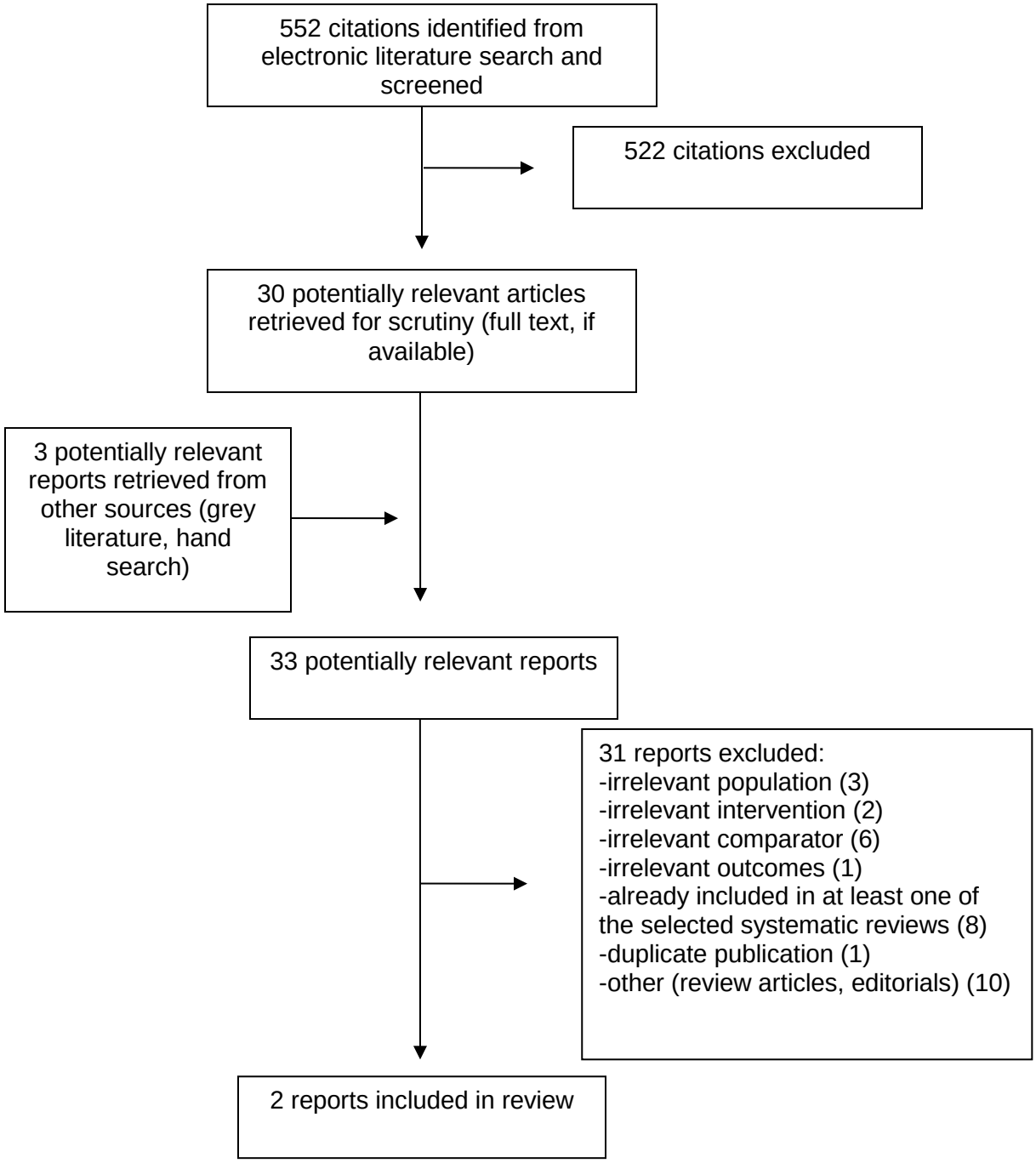
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

Objectives, Scope	Types of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Gonçalves, 2012[11]					
To conduct a systematic review of studies that have used VR in the treatment of PTSD	RCT, parallel case series, non-randomized controlled trial 10 studies included in analysis	Patients diagnosed with PTSD according to DSM-IV	VRET ± other CBT inverventions (e.g., psychoeducation, anxiety management techniques, IE, in vivo exposure)	Baseline PTSD scores, wait-list control, treatment as usual, PCT, traditional exposure therapy, PE, IE, CBT	PTSD symptoms as measured by validated scales 3-6 month follow-up for five studies Follow-up not reported for five studies

CBT = cognitive behavioural therapy; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; IE = imaginal exposure; PCT = present-centred therapy; PE = prolonged exposure; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; VR = virtual reality; VRET = virtual reality exposure therapy

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Roy, 2014[12] USA	RCT	19 combat veterans with PTSD	VRET: n = 9; 12-20 sessions of 90 minutes each	PE: n = 10; 12-20 sessions of 90 minutes each	PCL-M and CAPS scores, brain function as measured by fMRI
		18 combat veterans without PTSD	N/A	N/A	

CAPS = Clinician-Administered PTSD Scale; fMRI = functional magnetic resonance imaging; N/A = not applicable; PCL-M = PTSD Checklist – Military Version; PE = prolonged exposure; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[9]

Strengths	Limitations
Gonçalves, 2012[11]	
• Used an *a priori* review design • Comprehensive literature search • Two reviewers independently extracted data • Characteristics of included studies narratively described • Scientific quality of the included studies was assessed and documented	• Unclear whether grey literature was searched • List of excluded studies was not provided • Study findings not combined using statistical methods due to small sample sizes within primary studies • Unclear whether likelihood of publication bias was assessed • Conflict of interest declarations not provided for the primary studies • Methodological limitations of included studies not sufficiently addressed in review conclusions

Table A4: Strengths and Limitations of Randomized Controlled Trials using Downs and Black[10]

Strengths	Limitations
Roy, 2014[12]	
• Clearly described hypothesis • Interventions and main outcomes clearly described • All patients in the treatment groups completed the intervention	• Unclear source of study participants • Patient characteristics and potential confounders not provided • Method of randomization not described • Unclear whether investigator blinding occurred • Main findings not clearly described • Unclear probability values for statistically significant results (only reported as $P < 0.05$) • Unclear whether treatment and control groups were reassessed at the same length of time post-baseline • No power calculation to determine adequate sample size to detect differences

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Gonçalves, 2012[11]	
5/10 studies included in this systematic review, contained an active control group. The data were not pooled but individual study findings were summarized and presented narratively. 3/5 studies reported that, following treatment, PTSD symptoms as measured by validated scales (including PCL-M, BAI, PHQ-9, CAPS, DTS, PTCI, BDI, SCL-90-R) significantly decreased, but there was no significant difference in these scores between the VRET and active control groups.	• "The results of this systematic review suggest the potential efficacy of VRET in the treatment of PTSD for different types of trauma. VRET proved to be as efficacious as exposure therapy. VRET can be particularly useful in the treatment of PTSD that is resistant to traditional exposure because it allows for greater engagement by the patient and, consequently, greater activation of the traumatic memory, which is necessary for the extinction of the conditioned fear." p. 7
Roy, 2014[12]	
VRET: n = 9; PE: n = 10; non-PTSD controls: n = 18 **CAPS Scores** VRET group baseline = 80.44 (SD 13.31) post-VRET = 64.5 (23.07) *P* < 0.05 PE group baseline = 72.7 (13.01) post-PE = 75.9 (11.79) *P* = 0.27 Control group baseline = 21.67 (12.53) At 3-4 month follow-up = 12.39 (11.06) *P* < 0.05 **PCL-M Scores** VRET group baseline = 60.44 (13.65) post-VRET = 47.67 (13.73) *P* < 0.05 PE group baseline = 64.9 (10.39) post-PE = 49.9 (11.51) *P* < 0.05 Control group baseline = 27.11 (7.48) At 3-4 month follow-up = 23.44 (5.5) *P* < 0.05 **fMRI** PTSD group (n = 10; combined 4 VRET and 6 PE patients) Significantly reduced activity in the	• "…with the CAPS considered the gold standard for assessment of PTSD, our results suggest that VRET may have even greater efficacy than PE for combat-related PTSD" p. 65 • "PTSD is associated with alterations in regional brain function" and "Overall, our findings imply that exposure therapy promotes recovery, or return to baseline, in brain regions that are associated with emotion regulation and management of stress" p. 65

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
ventromedial prefrontal cortex and anterior cingulate cortex as well as significantly increased amygdala activity in response to negative but not neutral images were initially detected. These abnormal brain activity patterns were significantly improved with treatment. <u>non-PTSD control group (n = 18)</u> There was no significant change in brain activity at baseline compared with follow-up at 3-4 months. Numeric results not provided.	

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CAPS = Clinician Administered PTSD Scale; DTS = Davidson Trauma Scale; PCL-M = PTSD Checklist – Military Version; PE = prolonged exposure; PHQ-9 = Patient Health Questionnaire; PTCI = Posttraumatic Cognitions Inventory; PTSD = post-traumatic stress disorder; SCL-90-R = Symptom Checklist-90-Revised; SD = standard deviation; VRET = virtual reality exposure therapy