
Virtual Reality for Treating Mental Health Disorders and Prevention of Suicide

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and well-being; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the US. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the [ESP website](#). Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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DISCLOSURES

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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. The final research questions, methodology, and/or conclusions may not necessarily represent the views of contributing operational and content experts. No investigators have affiliations or financial involvement (eg, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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ABBREVIATIONS TABLE

Abbreviation	Definition
2D	2-dimensional
3D	3-dimensional
AAAT	Alcohol Approach-Avoidance Training
ABM	Attentional Bias Modification
ADIS-IV	Anxiety Disorders Interview Schedule for DSM-IV
AUD	Alcohol use disorder
AUQ	Alcohol Use Questionnaire
AVH	Audiovisual hallucination
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BSS	Beck Scale for Suicide Ideation
CAINS	Clinical Assessment Interview for Negative Symptoms
CAPS	Clinician-Administered PTSD Scale
CBT	Cognitive behavioral therapy
CBTp	Cognitive behavioral therapy for psychosis
CI	Confidence interval
COE	Certainty of evidence
CSQ-8	Client Satisfaction Questionnaire
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EMDR	Eye movement desensitization and reprocessing therapy
EQ-5D-5L	EuroQol 5 Dimension 5 Level
EUROHIS-QOL	Eurohis Quality of Life Scale
FAS	Flight Anxiety Situations Questionnaire
FFS	Fear of Flying Scale
FMS	Fast Motion Sickness Scale
FNE-B	Brief Fear of Negative Evaluation
GAD	General Anxiety Disorder 7-item Scale
GDS	Patient-Reported Geriatric Depression Scale
GPTS	Green Paranoid Thoughts Scale
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation

Abbreviation	Definition
HADS	Hospital Anxiety and Depression Scale
HAMD	Hamilton Depression Rating Scale
HMD	Head-mounted device
ICD-10	International Classification of Diseases, 10 th revision
ISRCTN	International Standard Randomized Controlled Trial Number
KQ	Key question
LSAS	Liebowitz Social Anxiety Scale
MACS	Multidimensional Craving Scale
MDD	Major depressive disorder
MEDLINE	Medical Literature Analysis and Retrieval System Online
NOS	Not otherwise specified
NR	Not reported
OIL	VA Office of Innovation and Learning
OIS	Optimal information size
OMH	VA Office of Mental Health
PANSS	Positive and Negative Syndrome Scale
PC	Personal computer
PCL	PTSD Checklist
PE	Prolonged exposure
PHQ	Patient Health Questionnaire
PHQ-9	Patient Health Questionnaire-9
PI	Prediction interval
PRCS	Personal Report of Confidence as a Speaker
PTSD	Posttraumatic stress disorder
QAF	Questionnaire on Attitudes toward Flying
RCT	Randomized controlled trial
RoB	Risk of bias
RR	Rate ratio
SAE	Serious adverse events
SCT	Social cognition training
SD	Standard deviation
SIAS	Social Interaction Anxiety Scale
SMD	Standardized mean difference
SPDQ	Social Phobia Diagnostic Questionnaire

Abbreviation	Definition
SPS	Social Phobia Scale
SSQ	Simulator Sickness Questionnaire
SUD	Substance use disorder
TAU	Treatment as usual
TEP	Technical Expert Panel
VA	Veterans Affairs
VAS	Visual Analogue Scale
VR	Virtual reality

BACKGROUND

Over one quarter of Veterans in VA care have a diagnosed mental health disorder.¹ Depressive disorders, posttraumatic stress disorder (PTSD), and substance use disorders (SUD) are most prevalent, and co-occurrence of diagnoses is common. Along with serious mental illnesses such as schizophrenia, all of these mental health disorders are associated with increased risks of hospitalization, premature death and suicide among Veterans.^{1,2} Suicide prevention remains a high priority for VA; current estimates indicate 20 Veterans die by suicide each day and suicide prevention will likely require multi-level efforts, including in health care settings.³ Evidence-based psychotherapies for mental health conditions, such as prolonged exposure therapy for PTSD, are effective yet remain underutilized in VHA clinical settings, prompting multiple VA initiatives to implement evidence-based psychotherapies for mental health conditions.⁴⁻⁷ Interest in delivering psychotherapies through virtual reality technology is rising, and systematic assessment is necessary to determine the evidence base for rollout of these interventions in VA.

Virtual reality (VR) provides a technological means of delivering a range of health interventions by situating a participant in a computer-generated virtual environment. A key aspect of VR is immersion: its capacity to make a participant feel present in the created virtual environment rather than in their physical environment.⁸⁻¹⁰ VR properties that can contribute to a person's sense of being present in that immersive environment include interactivity (participants' ability to take actions that have impact on the virtual experience) and multisensory stimulation (such as olfactory or tactile effects). In recent years, VR technology has become more affordable and more capable of producing realistic environments, and clinical applications are proliferating. The use of immersive VR technology in VA has expanded from 5 clinical sites in 2017 to 160 sites across all 50 states, Guam, Puerto Rico, and American Samoa as of 2023, with a focus on use for mental health conditions including PTSD, SUD, and depression.¹¹ Expansion of VR in clinical settings is partially driven by the perception of patient enthusiasm for the technology.

The conceptual basis for VR's therapeutic effects depends on the interventions' core elements and proposed mechanisms of action. For example, VR environments can create exposure scenarios within exposure therapy for PTSD or for specific phobias. VR characteristics such as multisensory stimulation and therapist control of stimuli distinguish VR exposure from imaginal exposure, while elements of both therapist and participant control within pre-programmed scenarios distinguish VR exposure from *in vivo* exposure. Whether VR exposure scenarios differ in benefits and harms from non-VR exposure approaches is an empirical question specific to the therapeutic approach, the comparison groups, the mental health conditions being treated, and the population involved. Use of VR may also have important implications for participant engagement. Finally, consideration of broad VR application requires consideration of harms and adverse events.

The VA Office of Mental Health, Office of Innovation and Learning, and Digital Health Office requested this review of available evidence on VR interventions for mental health conditions and suicide prevention. The goal of this review is to inform VR implementation efforts in VA mental health care and identify evidence gaps to inform future research efforts.

In this systematic review, we synthesize evidence on the benefits and harms of fully immersive VR interventions for treating mental health disorders and for suicide prevention. We present findings by mental health disorder, beginning with PTSD. Within each condition, we provide results by VR intervention type, then by comparator type.

METHODS

TOPIC DEVELOPMENT

Collaborating with representatives from the VA Digital Health Office, VA Office of Mental Health, VA National Center for PTSD, and our technical expert panel (TEP), we defined the scope, formulated key questions (KQs), and determined eligibility criteria. We defined the list of eligible mental health disorders through discussions with partners and the TEP, and we focused on VR technologies that are fully immersive (virtual environments that visually seal off the user from their local physical environment).

REGISTRATION AND REVIEW

A preregistered protocol for this review can be found on the Open Science Framework Registries (<https://doi.org/10.17605/OSF.IO/RXWBH>). A draft version of this report was reviewed by external peer reviewers; their comments and author responses are provided in the Supplementary Materials.

KEY QUESTIONS AND ELIGIBILITY CRITERIA

The following key questions were the focus of this review:

- *Key Question 1 (KQ1):* What are the benefits and harms of VR interventions for treating mental health disorders?
- *Key Question 2 (KQ2):* What are the benefits and harms of VR interventions for suicide prevention?

Study eligibility criteria are shown in the table below.

Domain	Inclusion Criteria	Exclusion Criteria
Population	<p>KQ1:</p> <p>Adults with:</p> <p><u>Prioritized</u></p> <p>Posttraumatic stress disorder</p> <p>Social anxiety disorder (social phobia)</p> <p>Specific phobia of flying</p> <p>Alcohol use disorder</p> <p>Substance use disorder</p> <p>Depressive disorders</p> <p>Schizophrenia</p> <p>Schizoaffective disorder</p> <p>Other schizophrenia spectrum and psychotic disorders</p> <p><u>Non-prioritized^a</u></p> <p>Agoraphobia</p> <p>Bipolar disorder</p> <p>Dissociative disorders</p> <p>Generalized anxiety disorder</p> <p>Obsessive compulsive disorder</p> <p>Panic disorder</p> <p>Persistent depressive disorder (Dysthymia)</p> <p>Premenstrual dysphoric disorder</p> <p>KQ2: Adults</p>	—
Intervention	Fully immersive VR interventions (<i>ie</i> , virtual environments that visually seal off the user from their local physical environment) to treat mental health disorders (KQ1) or prevent suicide (KQ2)	—
Comparator	Any	—
Outcomes	<p><u>Primary outcomes^b</u></p> <p>Symptom severity</p> <p>Treatment response</p> <p>Recovery</p> <p>Suicidal ideation and/or behaviors</p> <p>Adverse events</p> <p><u>Secondary outcomes</u></p> <p>Quality of life</p> <p>Treatment engagement (<i>eg</i>, attendance of sessions, adherence to practice)</p>	—
Setting	Any	—
Study Design	RCTs with ≥ 10 participants per arm; observational studies ≥ 100 participants, if reporting adverse events or suicidal ideation and/or behaviors	Systematic reviews, study protocols, case reports, letters, conference abstracts, editorials, non-English studies (of any type), pre-clinical studies (in vitro or animal studies)

Notes. ^a Non-prioritized studies were included but did not undergo full data abstraction; ^b To be eligible, study had to address at least 1 primary outcome.

Abbreviations. VR=virtual reality.

SEARCHING AND SELECTION

To identify articles relevant to the key questions, a medical research librarian searched MEDLINE, Embase, CENTRAL, and PsycINFO databases from inception to December 2024, using key words and subject headings for *virtual reality* and eligible *mental health disorders*. See [Appendix](#) for complete search strategies. Additional citations were identified from hand-searching reference lists and consultation with content experts. Clinical trial registries (Clinical Trials, Australian and New Zealand Trials Registry, and ISRCTN) were also searched for recently completed and ongoing trials. For relevant completed trials found in those registries, we searched for associated publications using the protocol title, investigator names, and locations. Ongoing trials (without identified publications) are noted in the Supplementary Materials.

After removing duplicate search results, titles and abstracts were screened using DistillerSR version 2.35 (Evidence Partners, Ottawa, Canada).¹² Two independent reviewers were required to exclude abstracts. Included abstracts then underwent full-text review by 2 reviewers, with inclusion of papers requiring consensus of both reviewers. Consensus was reached after discussion and/or with the involvement of a third reviewer. Pilot rounds were completed at both abstract screening and full-text review to clarify operationalization of the eligibility criteria. Studies had eligible populations for KQ1 if they included individuals diagnosed with the disorder (*eg*, being treated in a mental health clinic), used clinician-assessed measures to determine the diagnosis, or used participant-reported measures that had been validated for diagnostic accuracy (see the Supplementary Materials for information on these measures).

DATA ABSTRACTION AND RISK OF BIAS ASSESSMENT

For all eligible studies, we abstracted the following information: study design, population, setting, intervention, comparator, and reported outcomes. With additional input from partners and TEP, we further prioritized the following disorders for detailed data abstraction and synthesis of KQ1 findings: PTSD, social anxiety, specific phobia of flying, alcohol use disorder, stimulant use disorder, depressive disorders, and schizophrenia spectrum disorders. The prioritization process involved a discussion of preliminary evidence map describing summary characteristics of eligible studies across all eligible mental health disorders, followed by individual surveys of partners and TEP members to elicit ratings for the top 3 highest priority disorders. As the partners and TEP members had diverse perspectives and interests, we mainly sought consensus by selecting the disorders with the highest ratings overall across all respondents. From these prioritized studies, we abstracted detailed characteristics of interventions and comparators, and findings for eligible outcomes (*eg*, effect measures, interview quotes). If findings were only reported in figures, we used PlotDigitizer (<https://plotdigitizer.com/app>) to derive numbers from figure images, per recommended practices.¹³ All data abstraction was completed by 1 reviewer and then checked by another.

The internal validity (risk of bias [RoB]) of each prioritized RCT was rated by 2 independent reviewers using Cochrane Risk of Bias 2.0.¹⁴ Disagreements (for domains and overall) were resolved by discussion and/or with input of a third reviewer (see the Supplementary Materials for detailed RoB ratings). We did not assess risk of bias for the 1 observational study that did not have concurrent comparators.

Demographics including sex or gender were abstracted using the terminology provided by authors (*eg*, woman or female). VR interventions were described using features from Persky 2023.¹⁵ Included

features of VR were embodiment, interactivity, and multisensory stimulation. Embodiment is defined as “the ability for [VR] to make users feel as if they are existing within a digital body other than their own (eg, an avatar) enacting behaviors in the virtual environment.” Interactivity is defined as “response of [VR] environments to user input including physical movements and input from hand controllers.” Multisensory stimulation is originally defined as “[VR] can engage multiple senses such as visual (3D and stereoscopic), aural, olfactory, haptic, as well as senses not typically engaged by media (eg, proprioception);” due to the prevalence of visual and aural stimulation in included VR interventions, we defined interventions that stimulated senses beyond sight and sound as having multisensory stimulation.

SYNTHESIS

We first grouped eligible studies for KQ1 by mental health disorder or category (eg, PTSD, Social Anxiety Disorder). We then further categorized studies by intervention and comparator components, including components of the intervention in addition to the VR (eg, education) and method of therapy utilized using VR technology (eg, prolonged exposure). We further stratified by comparator (eg, waitlist, active comparator).

We conducted meta-analyses when ≥ 3 sufficiently similar studies (based on populations, interventions and comparators) reported the same eligible outcome (eg, comparable measures of symptom severity). When meta-analyses could not be conducted, we provided qualitative syntheses of study characteristics and findings. For meta-analyses, we used random-effects models (with Hartung-Knapp-Sidik-Jonkman estimator) due to the anticipated heterogeneity in effects arising from variation in patient populations, interventions, and other study characteristics. We evaluated statistical heterogeneity using forest plots, τ^2 , and 95% prediction intervals (PI). We also estimated fixed-effects models when studies included the same participant population and evaluated essentially the same VR intervention and comparator; this was also evidenced by little to no heterogeneity in the random effects models. We planned to assess publication bias using funnel plots if there were ≥ 10 sufficiently similar studies (according to considerations described previously). We used *meta* and *metafor* packages and R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria)¹⁶ to conduct meta-analyses and generate forest plots.

Strength of Evidence

We used Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria to rate the strength of evidence for the following outcomes: symptom severity, treatment response, suicidal ideation and/or behaviors, and adverse events.^{17,18} Overall COE was rated as high, moderate, low, or very low (Table 1).^{17,19} These outcomes were selected with input from the TEP and topic nominators. We separately rated outcomes assessed immediately post-intervention and at 2–3 months. We did not determine strength of evidence if there was only a single applicable study (evaluating a particular VR intervention vs comparator for that mental health disorder) that reported an eligible outcome. GRADE assessment included evaluation of the evidence base across 5 domains: study limitations (RoB), inconsistency (in direction and magnitude of effect across studies), indirectness (applicability of results as a consideration of both population studied and outcome measures used), imprecision (limitations in precision of effect estimates), and other considerations (including publication bias). To assess imprecision when we did not have meta-analyses, we set thresholds for optimal information size (OIS) separately for efficacy and adverse events outcomes.¹⁸ For efficacy outcomes, we downgraded 1 level when a study did not have sufficient sample size n (for 2-tailed $\alpha =$

0.05 and $\beta = 0.2$) to detect a standardized mean difference (SMD) of 0.6–0.7 (medium effect size) and 2 levels if not sufficient to detect 1 SMD (large effect size). For adverse events, we downgraded 1 level if a study did not have sufficient sample size in the VR intervention arm to detect events that occurred in $\geq 5\%$ ($N \sim 60$) and 2 levels if it was not sufficient to detect events in $\geq 10\%$ ($N \sim 30$).

Table 1. GRADE Certainty of Evidence Ratings: Definitions and Recommended Statements

Certainty of Evidence	Rating Definition	Recommended Statements (“What Happens”)
High	We are very confident that the true effect lies close to that of the estimate of the effect.	<i>Intervention reduces/increases/improves outcome.</i> <i>Intervention results in little to no difference in outcome.</i>
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	<i>Intervention probably reduces/increases/improves outcome.</i> <i>Intervention probably results in little to no difference in outcome.</i>
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	<i>Intervention may reduce/increase/improve outcome.</i> <i>Intervention may result in little to no difference in outcome.</i>
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	<i>The evidence is very uncertain about the effect of intervention on outcome.</i>

RESULTS

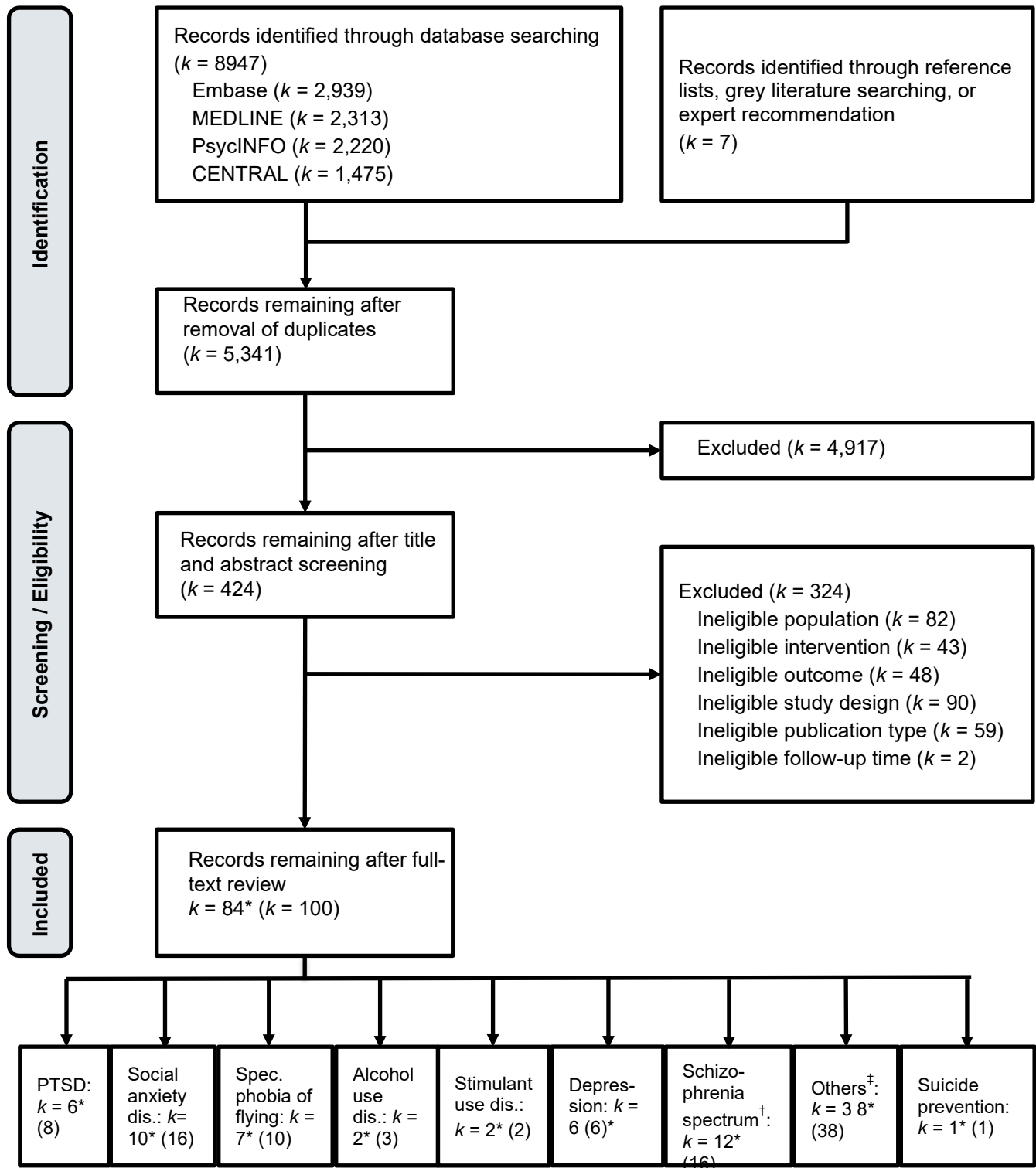
OVERVIEW OF INCLUDED STUDIES

We screened 5,341 unique citations and reviewed the full texts for 424 publications (Figure 1). Of these, we identified 100 eligible articles reporting 84 unique primary studies (83 RCTs, 1 observational study). A full list of excluded studies is provided in the Supplementary Materials. Eighty-four eligible studies addressed a variety of mental health disorders for KQ1, with about a fourth focusing on specific phobias ($k = 20$; Figure 1 and Table 2). Overall, 45 studies evaluated VR interventions for prioritized disorders: PTSD ($k = 6$),²⁰⁻²⁵ social anxiety disorder ($k = 10$),²⁶⁻³⁵ specific phobia of flying ($k = 7$),³⁶⁻⁴² alcohol use disorder (AUD, $k = 2$),⁴³⁻⁴⁵ stimulant use disorder ($k = 2$),^{46,47} depression ($k = 6$),⁴⁸⁻⁵³ and schizophrenia spectrum disorders ($k = 12$).⁵⁴⁻⁶⁶ The remaining studies focused on other disorders, including agoraphobia and/or panic disorder ($k = 10$),⁶⁷⁻⁷⁶ other specific phobias ($k = 12$),⁷⁷⁻⁸⁸ tobacco use disorder ($k = 8$),⁸⁹⁻⁹⁶ bipolar disorder ($k = 5$),⁹⁷⁻¹⁰¹ general anxiety disorder ($k = 2$),^{102,103} and obsessive compulsive disorder ($k = 1$).¹⁰⁴ KQ1 studies were generally small but some included more than 100 participants ($k = 11$). These were conducted in various countries around the world, with nearly half occurring in Europe ($k = 44$), a fourth in North America ($k = 20$), and fewer in Asia ($k = 16$), Australia/ New Zealand ($k = 2$), and South America ($k = 1$). The most commonly reported outcomes were symptom severity and treatment response or recovery, whereas quality of life and suicidal ideation and/or behaviors were rarely assessed.

Among studies addressing KQ1 prioritized disorders, the most frequently evaluated use of VR within an intervention was VR exposure therapy (with or without cognitive behavioral therapy [CBT]), including most studies for PTSD ($k = 6$), social anxiety disorder ($k = 9$), specific phobia of flying ($k = 7$), alcohol use disorder ($k = 2$), and stimulant use disorder ($k = 2$) (Figure 2). In contrast, studies addressing depressive symptoms or schizophrenia spectrum disorders evaluated a variety of VR interventions not necessarily based on evidence-based psychotherapies, with a focus on skills training in the majority of schizophrenia spectrum studies ($k = 8$). Characteristics of VR varied across studies, with embodiment, interactivity and multisensory stimulation most consistently present in VR exposure therapy for PTSD (Figure 3). Comparators varied across studies, including analogous non-VR therapies (*ie*, therapy content similar to that of the VR intervention) most common in phobia of flying interventions ($k = 8$) (Figure 4). Most studies were conducted in supervised health care or laboratory settings ($k = 35$). Detailed study characteristics and RoB ratings are provided in the Supplementary Materials.

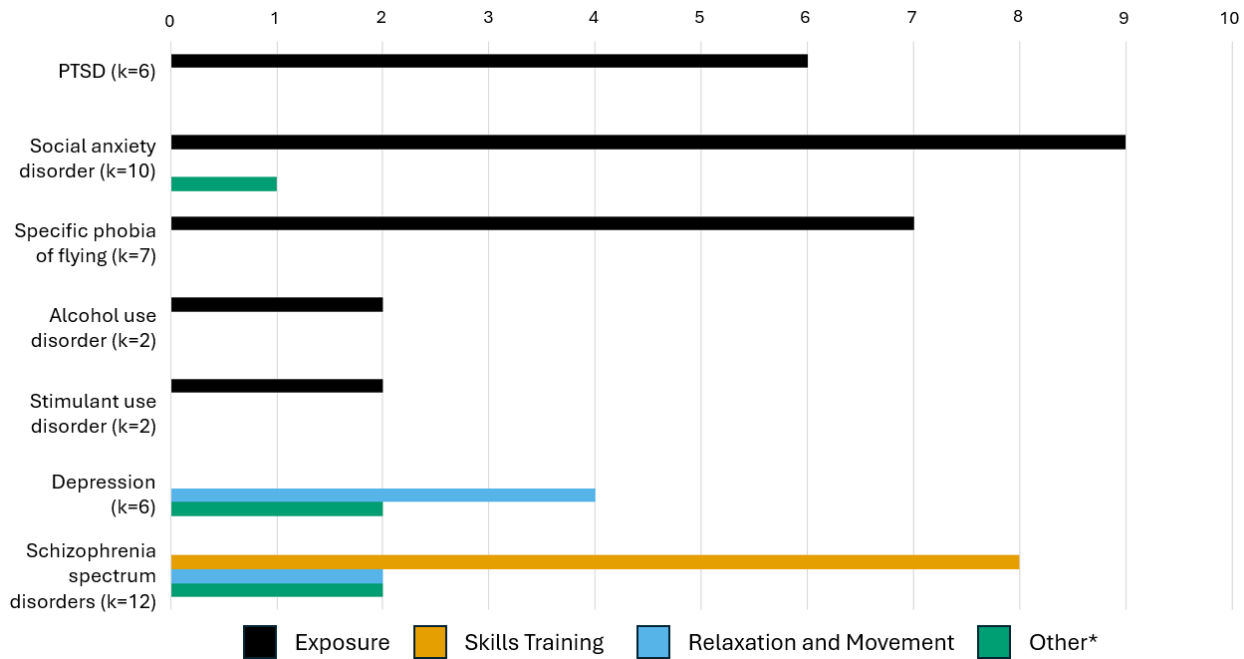
Below, we first present KQ1 findings for the prioritized mental health disorders, grouped by VR intervention and comparator characteristics within each disorder. We then describe results for the single study that evaluated a VR intervention for suicide prevention (KQ2).

Figure 1. Literature Flow Diagram



Notes. *Number of unique studies; †Schizophrenia, schizoaffective and schizophreniform disorders; ‡38 studies addressing non-prioritized disorders for KQ1: bipolar disorder, obsessive compulsive disorder, generalized anxiety disorder, agoraphobia and/or panic disorder, other specific phobias, and tobacco use disorder.

Figure 2. VR Intervention Content by Prioritized Mental Health Disorder (KQ 1)



Notes. *Including Attentional Bias Modification, behavioral activation, rehabilitation, and personified voices.

Figure 3. VR Characteristics by Prioritized Mental Health Disorder (KQ 1)

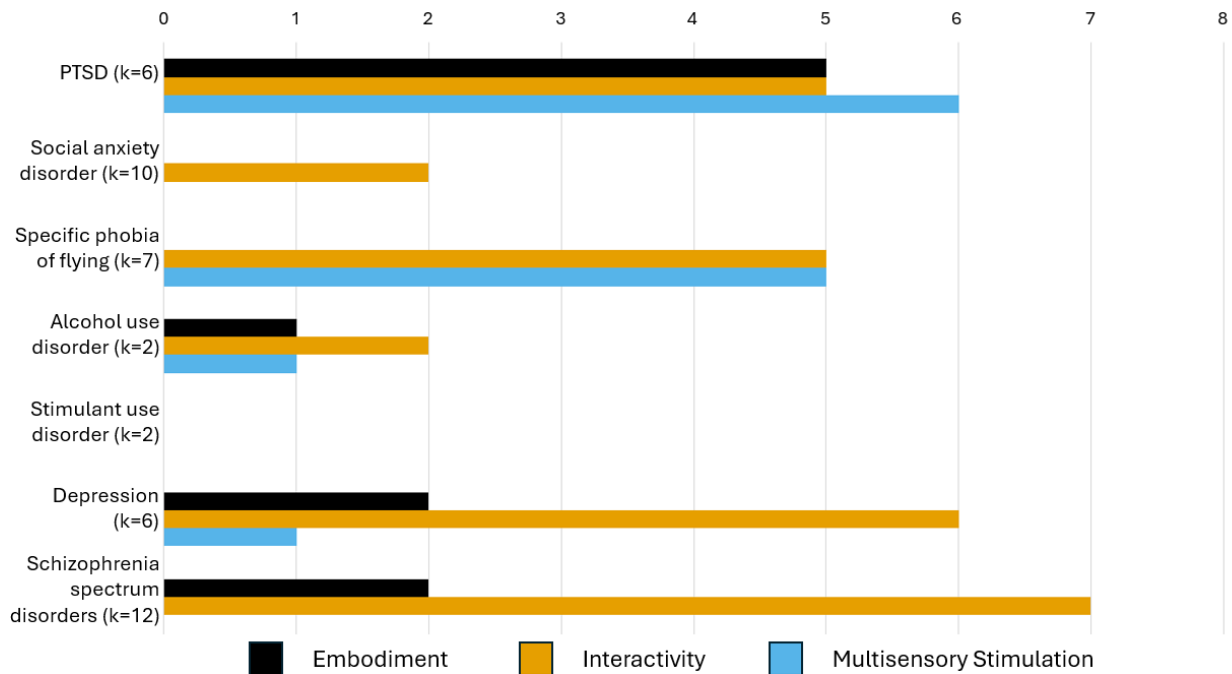
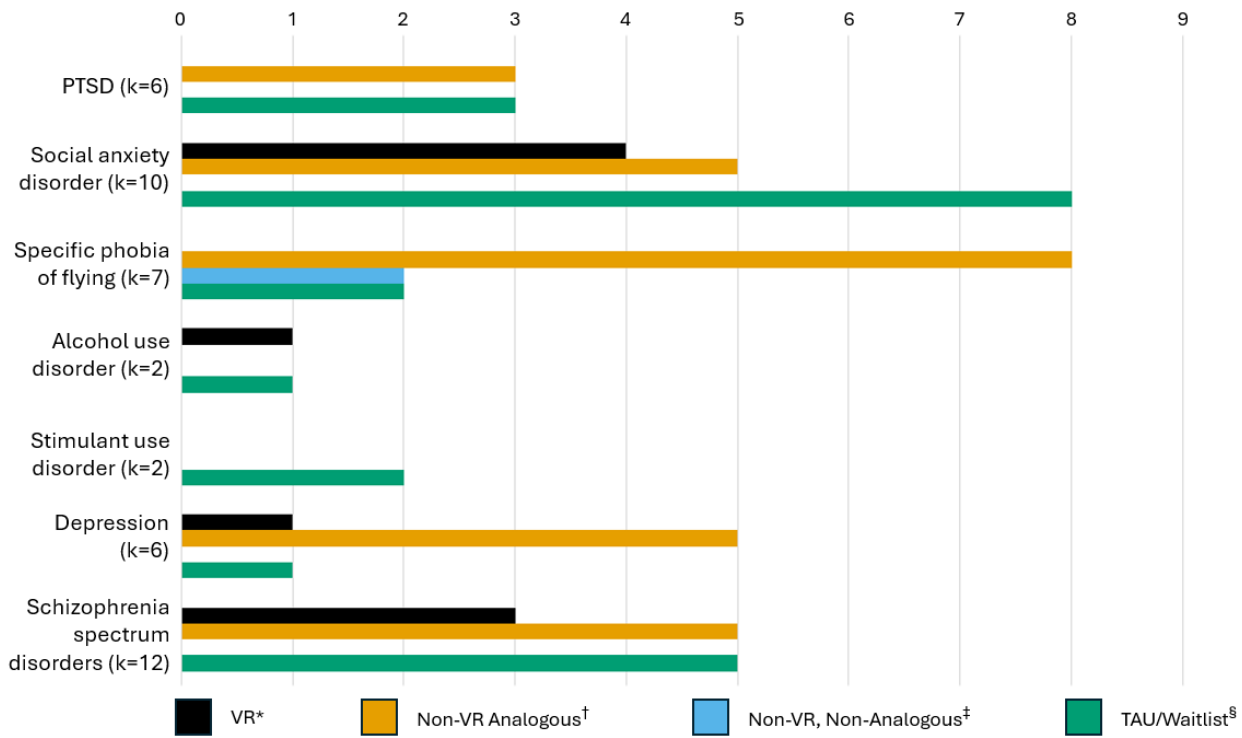


Figure 4. Comparator Arms for VR Interventions by Prioritized Mental Health Disorders (KQ 1)



Notes. Number of arms exceeds number of studies per condition due to trials evaluating more than 2 arms. *VR = VR-delivered intervention with different content from the VR intervention under investigation; †Non-VR Analogous = therapy content similar to that of the VR intervention, but delivered without VR; ‡Non-VR, Non-Analogous = therapy content different from that of the VR intervention, delivered without VR; §TAU/Waitlist = treatment as usual and/or waitlist for VR intervention under investigation.

Table 2: Overview of Characteristics of Eligible Studies for KQ1

Study Characteristic	Characteristic Category	PTSD (k = 6)	Social Anxiety Dis. (k = 10)	Specific Phobia of Flying (k = 7)	Alcohol Use Dis. (k = 2)	Stimulant Use Dis. (k = 2)	Depression (k = 6)	Schizophrenia Spectrum Dis. (k = 12)	Agoraphobia and/or Panic Dis. (k = 10)	Other Specific Phobia (k = 12)	Tobacco Use Dis. (k = 8)	Other Dis. ^a (k = 8)
Sample size	<50	2	3	3	1	—	3	3	4	8	—	2
	51-100	1	5	4	1	2	2	7	6	3	5	6
	>100	2	2	—	—	—	1	2	—	1	3	—
Location	Asia	—	2	—	1	2	2	5	2	1	—	1
	Australia/New Zealand	—	1	—	—	—	—	—	—	1	—	—
	Europe	—	3	3	1	—	3	6	8	8	5	7
	North America	6	4	4	—	—	1	1	—	2	2	—
	South America	—	—	—	—	—	—	—	—	—	1	—
Age (mean or median), y	<30	1	2	—	1	1	—	2	6	—	1	—
	30-64	4	5	7	1	1	3	10	2	5	—	7
	65+	—	—	—	—	—	3	—	—	6	8	—
	NR	1	3	—	0	—	—	—	2	1	—	1

Study Characteristic	Characteristic Category	PTSD (k = 6)	Social Anxiety Dis. (k = 10)	Specific Phobia of Flying (k = 7)	Alcohol Use Dis. (k = 2)	Stimulant Use Dis. (k = 2)	Depression (k = 6)	Schizophrenia Spectrum Dis. (k = 12)	Agoraphobia and/or Panic Dis. (k = 10)	Other Specific Phobia (k = 12)	Tobacco Use Dis. (k = 8)	Other Dis. ^a (k = 8)
Outcome Reported	Symptom severity	5	10	7	2	2	6	12	10	12	7	6
	Treatment response/ Recovery	4	2	5	1	—	1	—	3	8	5	4
	Quality of life	—	1	—	—	—	—	3	1	1	2	1
	Attendance	5	1	4	1	1	4	7	1	6	2	—
	Adherence	3	2	4	—	—	—	—	—	—	1	—
	Other engagement	2	4	4	—	—	1	4	3	3	2	1
	Adverse events	3	7	2	—	—	2	10	1	5	4	2
	Suicidal ideation and/or behaviors	1	—	—	—	—	—	2	—	—	—	—

Notes.^a Includes 5 studies addressing bipolar disorder, 2 on generalized anxiety disorder, and 1 on obsessive compulsive disorder.

Abbreviations. NR=not reported.

KQ1: PTSD (*k* = 6)

Overview

We identified 5 RCTs (reported in 7 articles) and 1 observational study evaluating the use of VR interventions in the treatment of PTSD (Table 3). In each of the trials, VR was used to deliver exposure therapy for combat-related trauma to active-duty service members or Veterans with PTSD in the United States. The VR exposure was part of formally designated prolonged exposure (PE) therapy (*k* = 2),^{20,23} a similarly structured exposure therapy protocol with essential elements of PE (*k* = 2),^{22,25} or an exposure therapy protocol with some elements of PE (*k* = 1).²⁴ The observational study evaluated VR exposure therapy for PTSD as part of an intensive outpatient program with no comparison group, and was included in this review due to reporting of adverse events.²¹

Below, we present findings from the 5 RCTs and 1 observational study evaluating VR exposure therapy. No studies reported quality of life outcomes. Below, we describe study characteristics and outcome findings for all included studies. Detailed study characteristics and outcome findings are located in the Supplementary Materials.

Table 3. Summary Characteristics of PTSD Studies (*k* = 6)

Author, Year; Study Design; Risk of Bias	Intervention Characteristics	Comparator Characteristics
Total N Key Participant Characteristics		
Difede, 2022 ²⁰ RCT Some concerns N = 192 Mean age: 34.3-35.0 years 88.4-90.7% male U.S. Service Members (of any duty status) and Veterans with combat-related PTSD	VR Prolonged Exposure Therapy <ul style="list-style-type: none"> • Prolonged exposure therapy using VR equipment to conduct in-session exposure. • Virtual combat scenarios customized by therapist during sessions • Beginning in session 3, D-cycloserine or placebo given before each session • No other medications with predominantly central nervous system activity • 9 x 90-minute sessions; 9 weeks Hardware: HMD (device NR) Embodiment: Yes Interactivity: Yes Multisensory stimulation: Yes	Non-VR Prolonged Exposure Therapy <ul style="list-style-type: none"> • Traditional imaginal exposure (imagine scenes of trauma) during sessions • Beginning in session 3, D-cycloserine or placebo given before each session • No other medications with predominantly central nervous system activity • 9 x 90-minute sessions; 9 weeks
Reger, 2016 ²³ RCT Some concerns N = 162 Mean age: 29.5-30.9 years 94-98% male Active Duty U.S. Service Members with deployment-related PTSD	VR Prolonged Exposure Therapy <ul style="list-style-type: none"> • Prolonged exposure therapy using VR equipment to conduct in-session exposure. • Virtual combat scenarios customized by therapist • No medication changes over 3 preceding months or during intervention; no other psychotherapy • 10 x 90-120-minute sessions; 5-10 weeks Hardware: eMagin z800 HMD Embodiment: Yes Interactivity: Yes Multisensory Stimulation: Yes	Non-VR Prolonged Exposure Therapy <ul style="list-style-type: none"> • Standard Prolonged Exposure protocol • Imaginal exposure in session and in vivo exposures between sessions • No medication changes over 3 preceding months or during intervention; no other psychotherapy • 10 x 90-120-minute sessions; 5-10 weeks Waitlist <ul style="list-style-type: none"> • 5-week waiting period with assessments • Began active treatment of choice after waiting period

Author, Year; Study Design; Risk of Bias Total N Key Participant Characteristics	Intervention Characteristics	Comparator Characteristics
McLay, 2017 ²² RCT Some concerns N = 81 Mean age: 32.5 years 90-93% male Active Duty U.S. Service Members with deployment-related PTSD	VR Prolonged Exposure Therapy <ul style="list-style-type: none"> • VR exposure therapy adherent to essential prolonged exposure elements • 2 sessions of assessment and psychoeducation • VR exposure customized to the Veteran's experience • In vivo exposures between sessions • No other individual psychotherapy; could continue group psychotherapy and/or medications • 8-12 x 90-minute sessions / 9 weeks Hardware: HMD (device NR) Embodiment: Yes Interactivity: Yes Multisensory Stimulation: Yes	Non-VR Prolonged Exposure Therapy <ul style="list-style-type: none"> • Same protocol as VR exposure therapy • In-session exposure involved looking at a 2D still image of the VR intervention (or real still image of Afghanistan or Iraq) chosen by participant from options provided • No other individual psychotherapy; could continue group psychotherapy and/or medications • 8-12 x 90-minute sessions; 9 weeks
McLay, 2011 ²⁵ RCT High N = 20 Mean age: 28.0-28.8 years 90-100% male Active Duty U.S. Service Members with combat-related PTSD	VR Exposure Therapy <ul style="list-style-type: none"> • VR exposure therapy adherent to essential prolonged exposure elements • 2 sessions of intake, treatment rationale, teaching relaxation and attentional control training • VR exposure to wartime situations with increasing intensity and realism • Cognitive restructuring after each exposure • No other individual psychotherapy; could continue group psychotherapy and/or medications • 4-20 sessions (duration NR); 10 weeks Hardware: HMD (device NR) Embodiment: Yes Interactivity: Yes Multisensory Stimulation: Yes	TAU <ul style="list-style-type: none"> • Any type of mental health treatment received at study hospitals • 3-38 sessions (duration NR); 10-46 weeks
Miyahira, 2012 ²⁴ RCT High N = 22 Mean age: NR % male NR Active Duty U.S. Service Members with PTSD symptoms who participated in military operations in Iraq or Afghanistan	VR Exposure Therapy <ul style="list-style-type: none"> • VR exposure therapy (with elements similar to prolonged exposure) • 1 session of orientation to treatment, review of traumatic memory, and breathing training • VR exposure to a combat environment customized by study therapist • No information on other treatments permitted during study • 10 sessions, NR; 5 weeks Hardware: HMD (device NR) Embodiment: NR Interactivity: No Multisensory Stimulation: Yes	Waitlist <ul style="list-style-type: none"> • 5-week waitlist with brief phone assessments every 2 weeks • Offered VR exposure treatment after waiting period

Author, Year; Study Design; Risk of Bias	Intervention Characteristics	Comparator Characteristics
Total N Key Participant Characteristics		
Beidel, 2017 ²¹ Observational N = 112 Mean age: 37.1 years 95% male U.S military Veterans and active duty personnel	Trauma Management Therapy Intensive Outpatient Program + VR Exposure Therapy <ul style="list-style-type: none"> • 3-week trauma management therapy IOP • VR exposure therapy • No benzodiazepines; any SSRI dose required to be stable 2 weeks prior to study; no medication changes during study • Other program components included: in vivo exposure practice; social and emotional rehabilitation, social reintegration, anger management, and brief behavioral activation Hardware: HMD (device NR) Embodiment: Yes Interactivity: Yes Multisensory Stimulation: Yes	No comparator

Abbreviations. HMD=head-mounted device; NR=not reported; TAU=treatment as usual; VR=virtual reality.

VR Exposure

Five RCTs evaluated VR exposure therapy for combat-related PTSD, all using versions of the Virtual Iraq/Afghanistan System.^{20,22-25,105} Sample size ranged from 20-192 and study participants were primarily male (88–100%) and in early to middle adulthood (mean age from 28.4 to 34.6 years). Interventions comprised 4–20 total sessions over a duration of 5–10 weeks. Three studies compared VR prolonged exposure to non-VR prolonged exposure ($N = 81-192$).^{20,22,23} Reger 2016 also included a minimal attention waitlist comparator.²³ All 3 studies were rated some concerns for RoB. The fourth RCT (McLay 2011) compared VR prolonged exposure to treatment as usual (TAU) ($N = 20$)²⁵ and was rated high for RoB due to study team and participant having knowledge of the group allocation (participants pulled slip of paper from an envelope to assign them to a group) and deviations from the intended interventions (participants in TAU group could seek other treatment and VR exposure group could participate in group but not individual treatment). The fifth RCT (Miyahira 2012) compared VR exposure to a minimal attention waitlist ($N = 22$) and was rated high RoB due to deviations from the intended interventions and missing outcome data (48% of randomized participants did not complete treatment).²⁴ One single-arm pre-post study of a VR exposure therapy was included for assessment of adverse events only.²¹

All VR exposure interventions included in the meta-analysis contained essential elements of prolonged exposure (PE) therapy. These 3 VR interventions incorporated embodiment, interactivity with the virtual environment, and multisensory stimulation (eg, tactile and olfactory stimuli). VR interventions and non-VR comparators varied with respect to customization of the VR environment and therapist/participant control.²³ The VR exposure groups in Reger 2016 and Difede 2022 observed a virtual environment selected as relevant to a participant's trauma and customized by the study therapist so that the scene and associated olfactory and tactile stimuli matched the participant's memory.^{20,23} McLay 2017 compared VR exposure to a 2D-image exposure protocol. VR exposure included customization of the VR environment, with some elements of participant control (eg, choosing to add

olfactory and tactile stimuli).²² The non-VR comparator involved observing a 2D image of the virtual environment or a still image of Iraq or Afghanistan while recounting a memory.

McLay 2011 evaluated a VR exposure intervention which they referred to as VR-graded exposure therapy.²⁵ The VR environment was customized to match a participant's traumatic memory, then adapted throughout treatment to increase intensity based on a participant's reactivity. The comparator was a TAU condition in which participants could receive any PTSD services offered at study hospitals (including evidence-based treatments such as PE, cognitive processing therapy, and psychiatric medication management). Unique to this study was the documented high variation in dosing, or number of treatment sessions attended in both arms (VR exposure therapy arm: VR sessions mean = 8.8, range = 4–20; other mental health sessions mean = 3.3, range = 1–8; TAU arm: mental health sessions mean = 13.8, range = 3–38).

Miyahira 2012 tested the effectiveness of VR exposure in active-duty service members compared to a minimal attention waitlist.²⁴ The intervention consisted of 10 sessions over 5 weeks. The first session consisted of information about the treatment, review of the traumatic event, and training in a breathing exercise. In sessions 2–10, participants took part in VR exposure to a virtual combat environment which could be customized by the study therapist to reflect aspects of the participant's trauma memory.

Beidel 2017 was a single arm study examining effectiveness of VR Exposure Trauma Management Therapy without a comparison group.²¹ This intervention was a 3-week intensive outpatient program incorporating daily individual sessions completing customized VR exposure (via the Virtual Iraq/Afghanistan System) with the assistance of a therapist, with daily group therapy covering topics like social skills, anger management, and behavioral activation, and in-vivo exposure assignments.

Symptom Severity

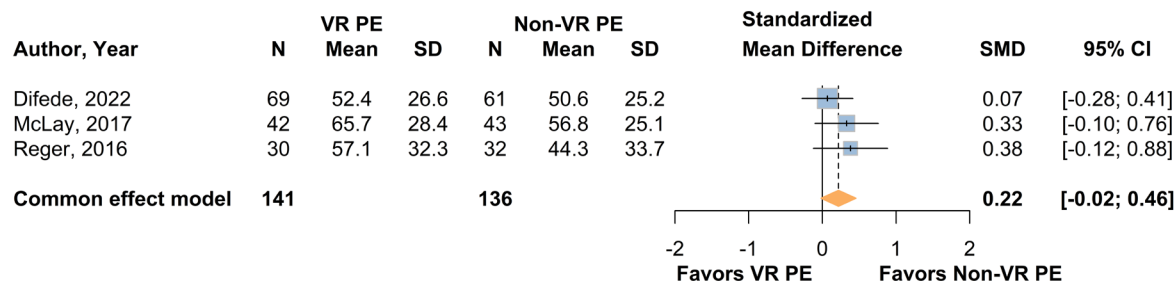
VR PE may improve symptom severity at post-intervention less than non-VR PE (low COE). VR PE compared to non-VR PE may result in little to no difference in symptom severity at 3-months follow-up (low COE). Three studies evaluated VR PE versus a non-VR PE and measured PTSD symptom severity using the Clinician-Administered PTSD Scale (CAPS).^{20,22,23} Due to studies' conceptual similarity and very low heterogeneity in random effects meta-analyses (see [Appendix Figure 1](#)), we estimated meta-analyses with fixed effects and referenced the fixed effects models for GRADE (Figure 5). Two of these studies also measured symptom severity using the patient-reported PTSD Checklist (PCL) and found no significant differences between arms at post-intervention and at 3-months follow-up.^{20,23} Difede et al²⁰ also stratified randomization by presence of major depressive disorder and found that VR PE was more effective among participants with depression (VR PE vs non-VR PE post-treatment mean CAPS difference = 3.51, 95% CI [1.17, 5.86], $p = 0.004$) while non-VR PE was more effective among participants without depression (mean difference = -8.87, 95% CI [-11.33, -6.40], $p < 0.001$).

Not included in the meta-analysis were McLay 2011 and Miyahira 2012, both of which had comparators that did not involve exposure. McLay 2011 compared a VR exposure therapy to TAU rather than to a non-VR exposure therapy arm.²⁵ While this study found no significant between-arm difference in mean CAPS scores post-intervention, the VR exposure arm had a significantly higher mean CAPS change score (35.4) than TAU (9.4) ($p < 0.05$). Miyahira 2012 found no significant difference in CAPS scores at post-intervention between VR exposure therapy and a minimal attention waitlist. Reger 2016 compared VR PE to non-VR PE (included in meta-analysis) and also to a waitlist.

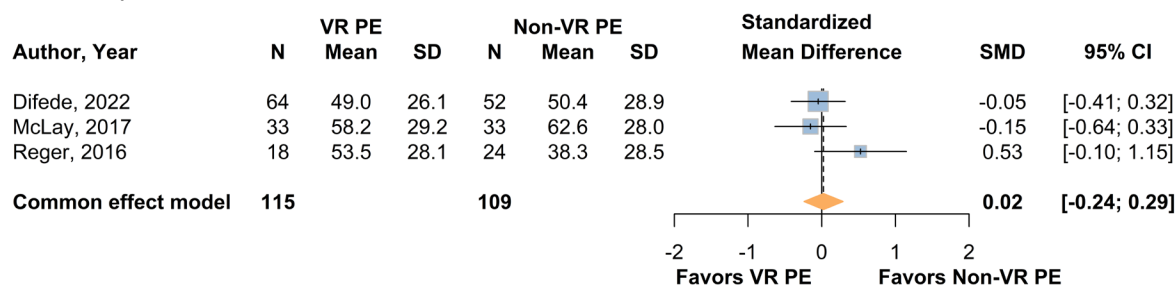
In comparison with the waitlist, Reger 2016 found the VR PE arm had significantly lower post-intervention scores on the CAPS and PCL.

Figure 5. Forest Plots Showing SMD in CAPS After VR Prolonged Exposure versus Non-VR Prolonged Exposure Therapy for PTSD

(a) Post-intervention



(b) 3 months post-intervention



Notes. Models estimated using fixed effects.

Treatment Response/Recovery

VR PE probably results in *less* treatment response immediately post-intervention, compared with non-VR PE (moderate COE; Table 4). Two trials used different criteria to define treatment response. Reger 2016 evaluated “reliable and clinically significant change” in PTSD symptoms as measured by the CAPS weekly (see Table 4 for definition).²³ McLay 2017 defined treatment response as $\geq 30\%$ improvement in CAPS.^{22,25} Both Reger 2016 and McLay 2017 reported lower proportions of improvement in the VR PE arm versus non-VR PE (eg, 50.0% vs 33.3% in Reger 2016) post-intervention, but did not test between-arm differences for statistical significance.^{22,23} McLay 2017 found no statistically significant difference in treatment response rates between the groups at 3 months follow-up (30% vs 36%).²² In an additional report derived from Reger 2016, authors reported that baseline dissociative symptoms did not impact between-group difference in treatment response.¹⁰⁶

McLay 2011 compared VR exposure therapy versus TAU and reported greater response (defined as $\geq 30\%$ improvement in CAPS) in the VR exposure arm than in the TAU arm (70.0% vs 12.5%).²⁵

Treatment Engagement

All studies reported on aspects of treatment engagement including session attendance and treatment discontinuation,^{20-24,106} treatment preference,²⁰ and treatment satisfaction.^{20,23} No homework was assigned and so treatment adherence was not relevant.

Attendance

Difede 2022 found no significant difference in proportion of participants discontinuing treatment between VR PE (27.8%) and non-VR PE (34.7%).²⁰ Reger 2016 also found no significant difference in the proportion of participants discontinuing treatment between VR PE (44.4%) and non-VR PE (40.7%), and no significant difference in session attendance (VR PE mean = 7.11, non-VR PE mean = 7.50).²³ A secondary analysis found no significant association between baseline dissociative symptoms and either treatment discontinuation or session attendance, but did not compare between treatment arms.¹⁰⁶ In McLay 2017, 7 VR PE participants (16%) discontinued treatment before completing a post-intervention assessment, while no non-VR PE participants discontinued. Study authors did not test for statistical difference.²² There was no significant difference between arms in the mean number of treatment sessions attended (VR exposure mean = 10.28, non-VR exposure mean = 9.24). McLay 2011 reported that all participants completed treatment.²⁵ In Miyahira 2012, 48% of participants (17 of 29 in the VR exposure arm and 3 of 12 on waitlist) did not complete treatment, and no information was available on reasons for discontinuation.²⁴ In Beidel 2017, 2 of 112 participants discontinued treatment, and 10 more participants were administratively removed from the study before receiving the intervention. Participants were reportedly removed due to protocol deviation ($n = 3$), malingering ($n = 4$), and primary diagnosis determined not to be PTSD ($n = 3$).²¹

Other Engagement Measures

Difede 2022 assessed treatment preference (using a form developed by the study team and administered prior to treatment) and found that most participants (76.7%) preferred VR PE to non-VR PE at baseline.²⁰ Treatment satisfaction was assessed post-intervention by the Client Satisfaction Questionnaire (CSQ-8) and did not significantly differ based on whether participants received their preferred treatment. Treatment satisfaction by arm was not reported or compared, but there was no significant difference in treatment satisfaction between participants who completed treatment (mean total score = 28.58) and those who discontinued (mean total score = 27.23). Neither treatment preference nor treatment satisfaction were associated with post-intervention symptom severity outcome (CAPS). Reger 2016 also assessed treatment satisfaction post-intervention using mean item score on the CSQ-8.²³ Both treatment arms reported high treatment satisfaction, with no significant difference between arms (VR PE mean item score = 3.47, non-VR PE mean item score = 3.52).

Adverse Events

VR PE compared to non-VR PE may have little to no difference in adverse events (low COE). Three of the 5 trials^{20,23,25} and 1 observational study²¹ reported on adverse events using different measures of different domains. Reger 2016²³ and Difede 2022²⁰ contributed to GRADE. Published results of the other 2 trials did not indicate presence or absence of adverse events.^{22,24}

In Reger 2016, simulator-related side effects were measured in both study arms. An adapted version of the Simulator Sickness Questionnaire (SSQ) was administered in each session of imaginal or virtual exposure.²³ A secondary data analysis of Reger 2016 reported the frequency of moderate or severe adverse symptoms (eg, dizziness, headache, “sickness in the stomach”).¹⁰⁷ There was no significant difference between arms in the prevalence of side effects before the first exposure session and side effects declined at a similar rate throughout treatment. Difede 2022 noted that no adverse events were reported, and did not define adverse events.²⁰

McLay 2011 reported no hospitalizations or emergency interventions and no study discontinuations due to adverse events (not otherwise defined) and noted that no participants had to stop VR sessions due to “discomfort caused by the equipment (cybersickness).”²⁵

Beidel 2017 reported no instances of adverse events (not defined) in the single arm during the 3-week intensive outpatient treatment or during the 6-month follow-up period.²¹

Suicidal Ideation and/or Behavior

Beidel 2017 reported no instances of suicide attempts in the single arm during the 3-week intensive outpatient treatment or during the 6-month follow-up period.²¹

Table 4. PTSD Certainty of Evidence: VR Prolonged Exposure versus Non-VR Prolonged Exposure

Outcome Measure	Follow-Up Total N (# of Studies)	SMD Pooled Estimate (95% CI)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up			Certainty	What Happens
			VR Prolonged Exposure	Non-VR Prolonged Exposure	Difference		
Symptom Severity CAPS	Post-intervention N = 277 (3 RCTs) <small>20,22,23</small>	SMD: 0.22 (-0.02, 0.46)	56.3 (50.1, 62.5)	50.6*	5.7 (-0.5, 11.9)	⊕⊕○○ Low ^{a,b}	VR prolonged exposure may result in less improvement in symptom severity post-intervention.
	3 months post-intervention N = 234 (3 RCTs) <small>20,22,23</small>	SMD: 0.02 (-0.24, 0.29)	50.9 (43.8, 58.3)	50.4*	0.5 (-6.6, 7.9)	⊕⊕○○ Low ^{a,c}	VR prolonged exposure may result in little to no difference in symptom severity at 3 months post-intervention.
Treatment Response/ Recovery	Post-intervention N = 194 (2 RCTs) <small>22,23</small> Varied threshold for change in CAPS score‡	—	33%	50% [†]	17%	⊕⊕⊕○ Moderate ^a	VR prolonged exposure probably results in less treatment response post-intervention.
Adverse Events	During intervention SSQ; NR N = 300 (2 RCTs) ^{20,23}	—	0	0 [§]	—	⊕⊕○○ Low ^{a,d}	VR prolonged exposure may result in little to no difference in adverse events.

Notes. *Values for mean follow-up scores for symptom severity for comparator arms from Difede 2022²⁰; †Values for mean follow-up scores for treatment response in intervention and comparator arms from Reger 2016²³; ‡McLay 2017²² calculated treatment response as ≥30% improvement in CAPS score. Reger 2016²³ calculated treatment response as above the threshold for reliable and clinically significant change. Clinically significant change was defined as at least the total baseline mean less twice the baseline standard deviation (SD). Reliability was defined as $(s_t^2 - S_E^2)/s_t^2$, where s_t equals the time or difference-specific SD, and S_E equals

the standard error of the mean derived from the baseline mean and internal consistency of the previous week's CAPS score among all study participants; §Difede 2022²⁰ selected as reference for adverse events. Study did not report how adverse events were operationalized or measured; ^aDowngraded 1 level for study limitations (1 or more studies rated some concerns for RoB); ^bDowngraded 1 level for imprecision (CI crosses the null); ^cDowngraded 1 level for imprecision (CI crosses thresholds for small effects in both directions); ^dDowngraded 1 level for indirectness (1 study did not describe how or which adverse events were assessed).

Abbreviations. CAPS=Clinician-Administered PTSD Scale; NR=not reported; RoB=risk of bias; SMD=standardized mean difference; SSQ=Simulator Sickness Questionnaire; VR=virtual reality.

KQ1: SOCIAL ANXIETY DISORDER ($k = 10$)

Overview

Ten eligible RCTs (reported in 16 articles) evaluated VR interventions for treating social anxiety disorder (Table 5).^{26-35,108-113} Four trials were conducted in North America,^{29,31,33,34} 3 in Europe,^{27,30,32} 2 in Asia,^{28,35} and 1 in New Zealand.²⁶ Six studies allowed participants to be on mental health medications if on stable doses (minimum of 6 weeks to 6 months),^{27,30-33,35} and one of these excluded individuals who were receiving other psychotherapy.³⁵ Two studies excluded participants receiving any other mental health treatments (psychotherapy or medications).^{29,31} Four studies compared VR exposure with waitlist,^{29,32,35,108} and one of these also included a non-VR exposure comparator arm.³² Five studies investigated CBT and VR exposure.^{26,27,31,33,34} Three of these were 3-arm trials comparing CBT + VR exposure versus CBT and non-VR exposure versus waitlist.^{31,33,34} The fourth was also a 3-arm trial but compared CBT and VR exposure versus CBT and non-VR exposure versus VR exposure only (no CBT arm).²⁷ The final study examining CBT and VR exposure only compared this treatment versus waitlist.²⁶ The tenth study examining VR treatment for social anxiety evaluated different versions of dot-probe tasks for Attentional Bias Modification (ABM).³⁰

Below, we present findings separately for various comparisons, beginning with VR exposure versus waitlist, and followed by CBT and VR exposure versus waitlist. We then focus on outcomes comparing VR treatments to active comparators, including CBT and VR exposure versus CBT and non-VR exposure, VR exposure versus non-VR exposure, and VR exposure versus CBT plus non-VR exposure. Lastly, we describe findings for the single study comparing various versions of VR dot-probe tasks for ABM. All eligible studies assessed symptom severity, and none reported findings regarding suicidal ideation and/or suicidal behavior. Detailed study characteristics and findings are provided in the Supplementary Materials.

Table 5. Summary Characteristics of Social Anxiety Disorder Studies (*k* = 10)

Author, Year; Study Design; Risk of Bias	Intervention Characteristics	Comparator Characteristics
Total N Key Participant Characteristics		
Kan 2024 ³⁵ High N = 61 Mean age: 22-23 86-88% female	VR Exposure <ul style="list-style-type: none"> • VR social situations presented, followed by instructions and a response from participants • Self-paced • NR sessions (length NR); duration NR Hardware: Thousand Wonders G04VR headset Embodiment: No Interactivity: NR Multisensory stimulation: No	Waitlist <ul style="list-style-type: none"> • 14 day waitlist then offered the VR Self-Training intervention
Kampmann, 2016 ³² Some concerns N = 60 Mean age: 37 years 63% women	VR Exposure <ul style="list-style-type: none"> • Virtual social scenarios customized by therapist during sessions • 2 sessions of therapy rationale and tailoring the virtual reality intervention to the participant • Therapist led • 10 x 65-minute sessions; 5 weeks Hardware: nVisor SX HMD Embodiment: No Interactivity: No Multisensory stimulation: No	Non-VR Exposure <ul style="list-style-type: none"> • Real world social scenarios (eg, shopping) • 2 sessions of therapy rationale and anxiety hierarchy creation • Therapist led • 10 60-minute sessions; 5 weeks <hr/> Waitlist <ul style="list-style-type: none"> • 5 week waitlist then rerandomized to one of the other arms
Kim, 2022 ^{28,108} High N = 41 Mean age: 24 years 62-65% female; 35-38% male	VR Exposure <ul style="list-style-type: none"> • Virtual social scenarios (eg, school or work) • Each scenario had four levels of difficulty • Self-paced • 8 sessions (length NR); 2 weeks Hardware: Samsung Galaxy S6 on Samsung Gear VR HMD powered by Oculus Embodiment: No Interactivity: No Multisensory stimulation: No	Waitlist <ul style="list-style-type: none"> • No treatment for 3 weeks
Zainal, 2021 ²⁹ Some concerns N = 44 Mean age: 23 years 77% female	VR Exposure <ul style="list-style-type: none"> • Virtual social scenarios (party or interview) • Increasingly more anxiety provoking • Self-paced • 4 x 50-60-minute sessions; 2 weeks Hardware: Pico Goblin VR HMD Embodiment: No Interactivity: Yes Multisensory stimulation: No	Waitlist <ul style="list-style-type: none"> • 4 week waitlist then received VR exposure therapy

Author, Year; Study Design; Risk of Bias Total N Key Participant Characteristics	Intervention Characteristics	Comparator Characteristics
Anderson, 2013 ^{33,110-113} Some concerns N = 97 Mean age: 39 years 62% female	CBT + VR Exposure <ul style="list-style-type: none"> • CBT with virtual social scenarios exposure (eg, conference room or classroom) • Virtual environments had increasingly larger audiences • Therapist led • 8 sessions (length NR); duration NR Hardware: NR Embodiment: NR Interactivity: NR Multisensory stimulation: NR	CBT + Non-VR Exposure <ul style="list-style-type: none"> • Participants gave speeches in front of a real life audience • Therapist led • 8 sessions (length NR); duration NR <hr/> Waitlist <ul style="list-style-type: none"> • 8 week waitlist then rerandomized to one of the other arms
Bouchard, 2017 ³¹ Some concerns N = 54 Mean age: 31-37 years 55-88% female	CBT + VR Exposure <ul style="list-style-type: none"> • CBT with virtual social scenarios exposures (eg, interviews or public speaking) • Therapist led • 14 x 1-hour long sessions; 14 weeks Hardware: eMagin z800 HMD and an InterSense Inertia Cube motion tracker Embodiment: NR Interactivity: Yes Multisensory stimulation: No	CBT + Non-VR Exposure <ul style="list-style-type: none"> • CBT with real world social scenarios (eg, making mistakes in public or giving a speech to staff members) • Therapist led • 14 1-hour long sessions; 14 weeks <hr/> Waitlist <ul style="list-style-type: none"> • 12 week waitlist then offered a combined treatment
Lacey, 2024 ²⁶ High N = 120 Mean age: 34-36 years 75-88% female	CBT + VR Exposure <ul style="list-style-type: none"> • CBT with virtual social scenarios • Modules 1-4 taught coping methods for social anxiety • Modules 5-6 involved creating a fear hierarchy, progressing through increasingly challenging social scenarios, and preventing relapse • Therapist led • 6 sessions (length NR); 6 weeks Hardware: oVRcome HMD Embodiment: No Interactivity: No Multisensory stimulation: No	Waitlist <ul style="list-style-type: none"> • No treatment
Robillard, 2010 ³⁴ High N = 45 Mean age: 35 years 71% female	CBT + VR Exposure <ul style="list-style-type: none"> • CBT with virtual social scenarios (not further described) • Therapist led • 16 sessions (length NR); 16 weeks Hardware: eMagin z800 3D Visor HMD Embodiment: NR Interactivity: NR Multisensory stimulation: NR	CBT + Non-VR Exposure <ul style="list-style-type: none"> • CBT with real world social scenarios (not further described) • Therapist led • 16 sessions (length NR); 16 weeks <hr/> Waitlist <ul style="list-style-type: none"> • 16 week waitlist then offered a treatment distinct from the other arms

Author, Year; Study Design; Risk of Bias	Intervention Characteristics	Comparator Characteristics
Total N Key Participant Characteristics		
Stefaniak, 2022 ²⁷ High N = 91 Mean age: 31-32 years 56-58% female	<p>CBT + VR Exposure</p> <ul style="list-style-type: none"> • CBT with virtual social scenarios (eg, interview, public speaking) • Therapist led • 12 x 45-minute sessions; 6 weeks <p>Hardware: HTC VIVE virtual helmet HMD Embodiment: NR Interactivity: NR Multisensory stimulation: NR</p> <p>VR Exposure</p> <ul style="list-style-type: none"> • Virtual social scenarios • Self-paced • 12 sessions (duration NR); 6 weeks <p>Hardware: HTC VIVE virtual helmet HMD Embodiment: NR Interactivity: NR Multisensory stimulation: NR</p>	<p>CBT + Non-VR Exposure</p> <ul style="list-style-type: none"> • CBT with real world social scenarios • Therapist led • 12 45-minute sessions; 6 weeks
Ma, 2019 ^{30,109} High N = 100 Mean age: 38-43 years 44-74% female	<p>ABM Training VR 3D Active Dot-Probe Task</p> <ul style="list-style-type: none"> • Dot-probe task using 3D image of a face with either a neutral or disgusted expression • 1 session (length NR); duration NR <p>Hardware: Oculus Rift HMD Embodiment: No Interactivity: No Multisensory stimulation: No</p>	<p>ABM Training VR 2D Active Dot-Probe Task</p> <ul style="list-style-type: none"> • Dot-probe task using 2D image of a face with either a neutral or disgusted expression • 1 session (length NR); duration NR <hr/> <p>ABM Training VR 2D Sham Dot-Probe Task</p> <ul style="list-style-type: none"> • Dot-probe task with a 2D sham stimulus • 1 session (length NR); duration NR <hr/> <p>ABM Training VR 3D Sham Dot-Probe Task</p> <ul style="list-style-type: none"> • Dot-probe task with a 2D sham stimulus • 1 session (length NR); duration NR

Abbreviations. 2D=2-dimensional; 3D=3-dimensional; ABM=Attentional Bias Modification; CBT=cognitive behavioral therapy; HMD=head-mounted device; NR=not reported; VR=virtual reality.

VR Exposure versus Waitlist

Four RCTs (reported in 5 articles) evaluated VR exposure compared with waitlist.^{28,29,32,108} Study characteristics are summarized in Table 5. Studies were small (total N = 40-61) and enrolled young and middle-aged adults (average age = 22.3–36.9 years, 57%–88% women). Interventions comprised 4–10 total sessions over a duration of 2–5 weeks. Two studies^{29,32} were appraised as some concerns for RoB and 2 studies^{28,35} were appraised high RoB, due to methodological concerns, including lack of information on if participants adhered to the intervention for the duration of the study and loss to follow-up that was not balanced between study arms.

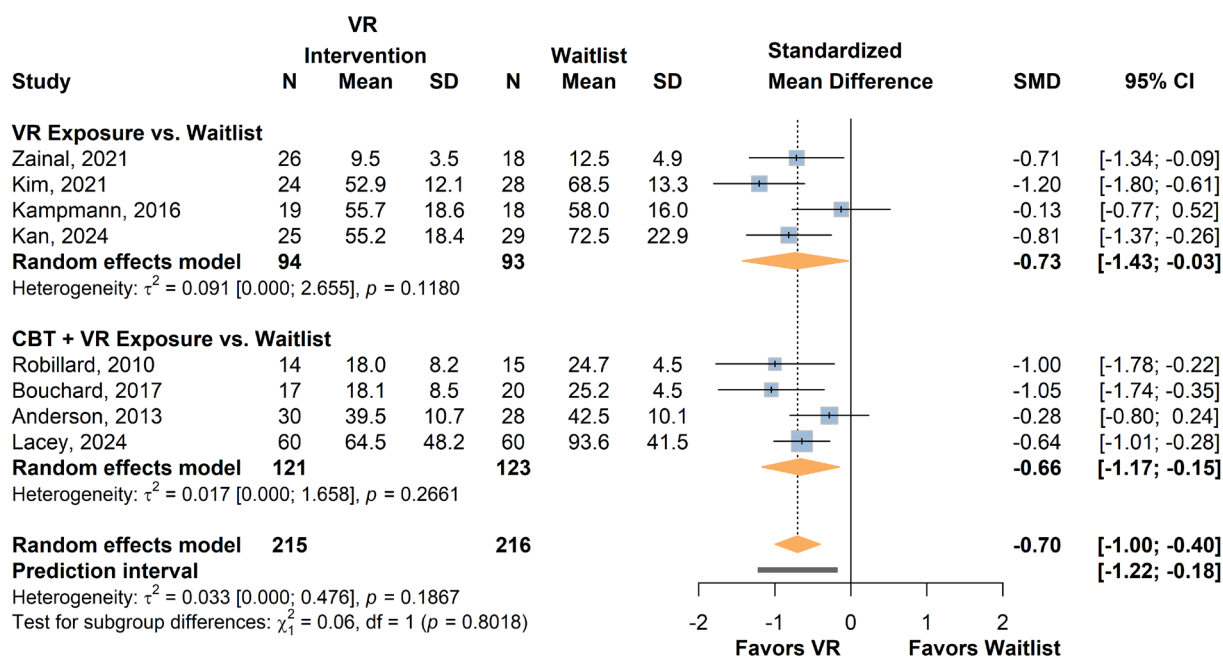
VR exposure intervention contained similar content across studies. Participants had to speak to a virtual audience in different virtual social settings (eg, interview or dinner party). Settings were designed to provoke varying degrees of anxiety, for example, by having more or fewer virtual audience members. Kampmann 2016 had therapists guiding VR exposure sessions,³² while Kan 2024, Kim

2022, and Zainal 2021 had participants pace themselves through the VR sessions.^{28,29,35} VR experiences did not provide a sense of embodiment or multisensory stimulation. Only Zainal 2021 had reported interactivity, with the VR program able to detect speech and provide prompts when the participant was not speaking.²⁹

Symptom Severity

The evidence is very uncertain on the effect of VR exposure on symptom severity, compared with waitlist, primarily due to concerns about methodological limitations and inconsistency (very low COE; Table 6). The meta-analysis included data from 4 studies^{28,29,32,35} and the pooled estimated favored VR exposure (SMD = -0.73 [-1.43, -0.03]; Figure 6). Studies measured symptom severity using either the Liebowitz Social Anxiety Scale (LSAS) or the Social Phobia Diagnostic Questionnaire (SPDQ).^{28,29,32,35} Studies also measured symptom severity using the Brief Fear of Negative Evaluation (FNE-B), Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire (PHQ), Penn State Worry Questionnaire, Social Interaction Anxiety Scale (SIAS), and Social Phobia Inventory (see Supplementary Materials for point estimates).^{28,29,32,108}

Figure 6. Social Anxiety Disorder: Effect of VR Exposure versus Waitlist on Symptom Severity Immediately Post-Intervention



Treatment Response/Recovery

Only Kampmann 2016 assessed treatment response as “reliable change” in LSAS from pre- to post-intervention (not further defined). There were no differences between arms (47% in the VR group vs 50% in the waitlist arm; $p = 0.873$).³²

Quality of Life

Only Kampmann 2016 evaluated quality of life, reporting participants in the VR arm had a larger increase in EUROHIS Quality of Life Scale scores over time (EUROHIS-QOL, follow-up mean = 25.74, SD = 6.85), compared with waitlist group (follow-up mean = 27.28, SD = 5.44) immediately post-intervention ($p = 0.018$).³²

Engagement

Three studies reported attendance,^{28,29,32} and one of these also assessed adherence and other measures of engagement.²⁹

Attendance

Participants in Zainal 2021 completed an average of 18 (SD = 14) VR scenes, with 58% ($n = 15$) reaching the highest difficulty level (not further defined) of the VR scenes.²⁹ All 3 studies reported discontinuation rates of each treatment with no statistical comparisons. Kampmann 2016 reported that 6 (20%) in the VR exposure arm and 2 (10%) in the waitlist arm discontinued treatment. Kim 2022 reported 3 (11%) participants discontinued treatment in the VR exposure arm, while 8 (33%) discontinued in the waitlist arm. Zainal 2021 reported 3 (12%) in the VR exposure arm and 2 (11%) in the waitlist arm discontinued.^{28,29,32}

Adherence and Other Engagement Measures

Participants in Zainal 2021 were assigned in vivo exposure therapy homework to complete between VR exposure therapy sessions, and 80% ($n = 21$) were noted to have completed at least 1 in vivo exposure between sessions (mean number of in vivo exposures between sessions = 3.96, SD = 4.27).²⁹ Zainal 2021 also assessed engagement in the VR arm using the iGroup Presence Questionnaire and found that participants' spatial presence in VR increased over time ($p = 0.019$). Additionally, 85% of participants would recommend VR exposure therapy to others with social anxiety disorder.²⁹

Adverse Events

The evidence is very uncertain on the effect of VR exposure on adverse events, compared with waitlist (very low COE; Table 6). Four RCTs reported adverse events only in the VR exposure arm, using different measures including the SSQ and undefined assessments.^{28,29,32,35} Kan 2024 stated that “no participants reported physical discomfort experienced after viewing virtual reality imagery.”³⁵ Kampmann reported 1 participant in the VR exposure therapy arm discontinued the intervention due to motion sickness.³² Kim 2022 reported no discontinuation of VR exposure therapy due to simulator sickness and a mean SSQ score of 27.7 (SD = 7.37).²⁸ Zainal 2021 stated that cybersickness decreased over time within the VR exposure therapy group, as assessed using the SSQ.²⁹

Table 6. Social Anxiety Disorder Certainty of Evidence: VR Exposure versus Waitlist

Outcome Measure	Follow-Up Total N (# of Studies)	SMD Pooled Estimate (95% CI)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up			Certainty	What Happens
			VR Exposure	Waitlist	Difference		
Symptom Severity	Post-intervention	SMD: -0.73 (-1.43, -0.03)	9.5 (6.6, 12.4)	12.5*	-3.0 (-5.9, -0.1)	⊕○○○ Very low ^{a,b}	The evidence is very uncertain on the effect of VR exposure on symptom severity post-intervention.
LSAS, SPDQ	N = 187 (4 RCTs) ^{28,29,32,35}						
Adverse Events	During intervention	—	16.39 (11.51) [†]	—	—	⊕○○○ Very low ^{a,c}	The evidence is very uncertain on the effect of VR exposure on adverse events.
SSQ, NR	N = 197 (4 RCTs) ^{28,29,32,35}						

Notes. *Values for mean follow-up scores for intervention and/or comparator arms from Zainal 2021.²⁹ Differences calculated by review team; [†]SSQ scores in VR Exposure Therapy group from Zainal 2021²⁹; ^aDowngraded 2 levels for study limitations (1 or more studies rated high RoB); ^bDowngraded 1 level for inconsistency (direction of effects inconsistent across studies); ^cDowngraded 1 level for indirectness (3 studies did not describe how or which adverse events were assessed, 1 study only assessed outcome for 1 arm).

Abbreviations. LSAS=Liebowitz Social Anxiety Scale; NR=not reported; RoB=risk of bias; SMD=standardized mean difference; SPDQ=Social Phobia Diagnostic Questionnaire; SSQ=Simulator Sickness Questionnaire; VR=virtual reality.

CBT + VR Exposure versus Waitlist

Four RCTs evaluated CBT + VR exposure compared with waitlist for social anxiety disorder.^{26,31,33,34} Study characteristics are summarized in Table 5. Study sample sizes ranged from 29–120, average age from 33.2–39.03 years, and 62%–81% were female.^{31,33,34} Interventions comprised 8–16 total sessions over a duration of 6–16 weeks. Two studies were appraised as some concerns RoB.^{31,33} Lacey 2024 and Robillard 2010 were appraised as high RoB due to methodological concerns, including the number of participants lost to follow-up.

Symptom Severity

The evidence is very uncertain on the effect of CBT + VR exposure on symptom severity, compared with waitlist (very low COE; Table 7). The meta-analysis used data from all 4 studies (either FNE-B or LSAS scores)^{31,33,34} and the pooled estimate indicated a moderate effect favoring CBT + VR exposure, when compared with waitlist (SMD = -0.66 [-1.17, -0.15]; Figure 6). Symptom severity was also measured using the SPS, SIAS, Personal Report of Confidence as a Speaker (PRCS), clinician ratings of global improvement, and Appraisal of Social Concerns (see Supplementary Materials for these findings).

Engagement

Three studies reported attendance data^{26,31,33} and 2 studies reported data on other engagement measures.^{26,31}

Attendance

Three studies reported on participant attendance. Anderson 2013 reported 1 (3%) in the CBT + VR exposure arm and 3 (11%) in the waitlist withdrew,³³ and Bouchard 2017 stated 2 (12%) and 4 (20%) dropped out in the CBT + VR exposure and waitlist arms, respectively.³¹ Lacey reported 25 (42%) in the CBT + VR exposure and 15 (25%) in the waitlist arm withdrew.²⁶

Other Engagement Measures

Bouchard 2017 reported engagement with the CBT + VR exposure intervention using the Presence Questionnaire, the Gatineau Presence Questionnaire, and treatment credibility.³¹ Lacey 2024 also used the Gatineau Presence Questionnaire to assess for degree of realism.²⁶ Neither provided comparisons within the VR arms across time points.

Adverse Events

The evidence is very uncertain on the effect of CBT + VR exposure on adverse events, compared to waitlist (very low COE; Table 7). Bouchard 2017 found no significant increase in SSQ scores over time ($p > 0.2$) in the VR arm, but did assess for adverse events in the waitlist arm.³¹ Lacey 2024 measured motion sickness using the Fast Motion Sickness Scale (FMS) and found that average FMS score was 8.1 at the last VR treatment (scale of 0–20, with 20 being “frank sickness”).²⁶ No participants withdrew due to motion sickness, and authors also stated “no adverse events were reported and no participant requested assistance from a clinical psychologist.”

Table 7. Social Anxiety Disorder Certainty of Evidence: CBT + VR Exposure versus Waitlist

Outcome Measure	Follow-Up Total N (# of Studies)	SMD Pooled Estimate (95% CI)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up			Certainty	What Happens
			CBT + VR Exposure	Waitlist	Difference		
Symptom Severity	Post-intervention	-0.66 (-1.17, -0.15)	35.6 (30.3, 40.9)	42.5*	-6.9 (-12.2, -1.6)	⊕○○○ Very low ^{a,b}	The evidence is very uncertain on the effect of CBT coupled with VR exposure on symptom severity post-intervention.
FNE-B	N = 244 (4 RCTs) ^{26,31,33,34}						
Adverse Events	During intervention	—	0.57 (0.79) [†]	—	—	⊕○○○ Very low ^{a,c}	The evidence is very uncertain on the effect of CBT coupled with VR exposure on adverse events.
FMS, SSQ, NR	N = 157 (2 RCTs) ^{26,31}						

Notes. *Values for mean follow-up scores for intervention and/or comparator arms from Anderson 2013.³³ Differences calculated by review team; [†]SSQ scores in VR Exposure Therapy group from Bouchard 2017³¹; ^aDowngraded 2 levels for study limitations (1 or more studies rated high RoB); ^bDowngraded 1 level for inconsistency (direction of effects inconsistent across studies); ^cDowngraded 1 level for indirectness (1 study did not describe how or which adverse events were assessed, 1 study only reported outcome for 1 arm).

Abbreviations. CBT=cognitive behavioral therapy; FNE-B=Brief Fear of Negative Evaluation; FMS=Fast Motion Sickness Scale; NR=not reported; RoB=risk of bias; SMD=Standardized Mean Difference; SSQ=Simulator Sickness Questionnaire; VR=virtual reality.

CBT + VR Exposure versus CBT + Non-VR Exposure

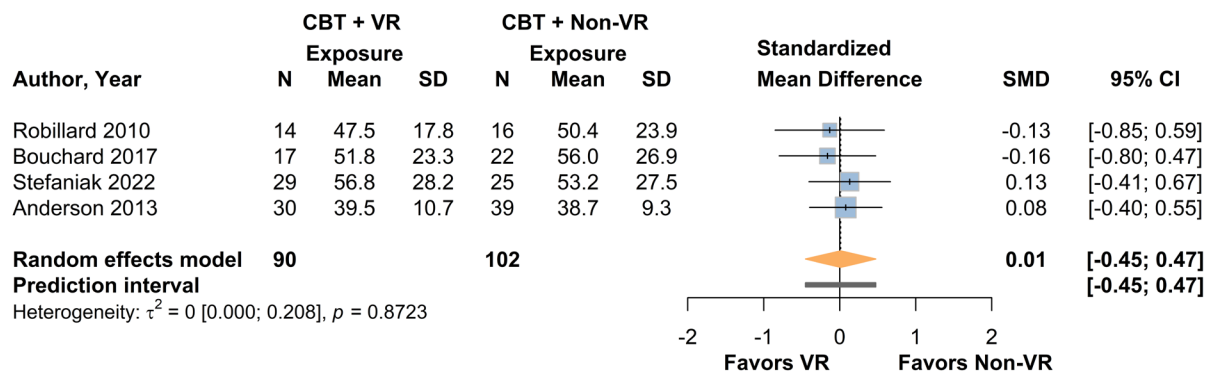
Four RCTs compared CBT + VR exposure with CBT + non-VR exposure for social anxiety disorder.^{27,31,33,34} Study characteristics are summarized in Table 5. Study sample sizes ranged from 30–69, average age from 31.7–36.5 years, and 57%–83% were women.^{27,31,34} Interventions comprised 8–16 total sessions over a duration of 6–16 weeks. Two studies^{31,33} were appraised as some concerns RoB and 2 studies^{27,34} were appraised as high RoB, in part due to a large number of participants who did not receive the intervention.

All 4 RCTs used the same CBT sessions in both the VR and non-VR exposure arms. VR characteristics, including embodiment, interactivity, and multisensory stimulation, of the intervention were infrequently reported or not included, though Bouchard 2017 did have a component of interactivity (participants could interact with objects in the virtual environment).³¹

Symptom Severity

The evidence is very uncertain on the effect of CBT + VR exposure on symptom severity, compared with CBT and non-VR exposure (very low COE; Table 8). The meta-analysis used data from all 4 studies (LSAS^{27,31,34} and FNE-B scores³³) and pooled estimates indicate no difference between arms (SMD 0.01[-0.45; 0.47]; Figure 7). Symptom severity was also measured using Appraisal of Social Concerns, Beck Depression Inventory (BDI), Clinician Global Impressions of Improvement, SIAS, PRCs, and Social Phobia Scale (SPS) (see Supplementary Materials for detailed findings).

Figure 7. Social Anxiety Disorder: Effect of CBT + VR Exposure versus CBT + Non-VR Exposure on Symptom Severity at Post-Intervention



Treatment Response/Recovery

Only Anderson 2013 evaluated treatment response, reporting no significant differences using a chi-square test between arms at 3 months for participants in full remission, partial remission, and those who still met diagnostic criteria.³³

Engagement

Two studies reported attendance data of participants,^{27,31} 1 study reported data on adherence,³³ and 2 studies on other engagement measures.^{31,33}

Attendance

Two studies reported on attendance of participants but did not report comparisons between arms. Bouchard 2017 reported 2 (12%) and 4 (18%) participants in the CBT + VR exposure arm and CBT arm + non-VR arm, respectively, discontinued treatment.³¹ Stefaniak 2022 reported 2 (6%) discontinuations in the CBT + VR exposure arm, while 5 (17%) in the CBT + non-VR arm discontinued.²⁷

Adherence

Anderson 2013 reported homework compliance at each treatment session (defined as participants completing half or more of homework). There was no statistically significant difference between groups at 7 of the 8 sessions.

Other Engagement Measures

Bouchard 2017 reported engagement in the CBT + VR exposure arm using the Presence Questionnaire, the Gatineau Presence Questionnaire, and treatment credibility. Participant's sense of presence in VR increased over time, while treatment credibility remained similar throughout the VR intervention, though statistical comparisons over time and between arms were not reported.³¹ Anderson 2013 reported no difference in treatment satisfaction between arms at post-intervention ($p = 0.2$) or 12-month follow-up ($p = 0.09$).³³

Adverse Events

The evidence is very uncertain on the effect of CBT + VR exposure on adverse events, compared to CBT + non-VR exposure (very low COE; Table 8). Two RCTs reported adverse events using the SSQ.^{27,31} Stefaniak 2022 reported 1 person in the CBT + VR exposure arm experienced simulator sickness symptoms and 4 people in the CBT + non-VR exposure arm experienced symptoms similar to simulator sickness.²⁷ Bouchard 2017 found no significant increase in SSQ scores after each VR session ($p > 0.2$) in the CBT + VR exposure arm, but did not assess for adverse events in the CBT + non-VR exposure arm.³¹

Table 8. Social Anxiety Disorder Certainty of Evidence: CBT + VR Exposure versus CBT + Non-VR Exposure

Outcome Measure	Follow-Up Total N (# of Studies)	SMD Pooled Estimate (95% CI)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up			Certainty	What Happens
			CBT + VR Exposure	CBT + non-VR Exposure	Difference		
Symptom Severity	Post-intervention	0.01 (-0.45, 0.47)	56.3 (44.6, 67.9)	56.0*	0.3 (-11.4, 11.9)	⊕○○○ Very low ^{a,b}	The evidence is very uncertain on the effect of CBT coupled with VR exposure therapy on symptom severity post-intervention.
LSAS	N = 192 (4 RCTs) ^{27,31,34,113}						
Adverse Events	During intervention	—	0.57 (0.79) [†]	—	—	⊕○○○ Very low ^{a,c}	The evidence is very uncertain on the effect of CBT coupled with VR exposure on adverse events.
SSQ	N = 95 (2 RCTs) ^{27,31}						

Notes. *Values for mean follow-up scores for intervention and/or comparator arms from Bouchard 2017.³¹ Differences calculated by review team; [†]SSQ scores in VR Exposure Therapy group from Bouchard 2017³¹; ^aDowngraded 2 levels for study limitations (1 or more studies rated high RoB); ^bDowngraded 1 level for imprecision (CI crosses thresholds for small effects in both directions); ^cDowngraded 1 level for indirectness (outcome not measured for all arms).

Abbreviations. CBT=cognitive behavioral therapy; LSAS=Liebowitz Social Anxiety Scale; RoB=risk of bias; SMD=standardized mean difference; SSQ=Simulator Sickness Questionnaire; VR=virtual reality.

VR Exposure versus Non-VR Exposure

One study, Kampmann 2016, compared VR exposure with non-VR exposure. The sample size was 40, with a mean age of 38.6, and 70% of participants were female. The intervention comprised 10 total sessions over a duration of 5 weeks. The study was appraised as some concerns RoB due to loss to follow-up being imbalanced across arms. Non-VR and VR exposure sessions were 60 and 65 minutes long, respectively, for 10 sessions over a period of 5 weeks. Both exposure therapies were led by a therapist. Non-VR exposure consisted of participants engaging in social situations in the real world (eg, a supermarket or a café), while the VR exposure had similar social situations occur in a virtual environment.³²

Symptom severity was assessed at 5 weeks and 3 months using the LSAS and the FNE-B. Non-VR exposure was found to have a statistically significant decrease versus VR exposure at both 5 weeks and 4 months on both the LSAS ($p = 0.006$ and $p = 0.001$) and the FNE-B ($p = 0.008$ and $p = 0.007$).³² Kampmann 2016 found “reliable change” in treatment response from pre- to post-intervention using the LSAS. While VR and non-VR exposure achieved reliable change in 47% and 78% of participants, respectively, the difference was not statistically significant ($p = 0.057$). For quality of life, Kampmann 2016 found significant difference in the change from pre-intervention at post-intervention between VR exposure (mean = 25.74, SD = 6.85) and non-VR exposure (mean = 29.78, SD = 4.47) as measured by EUROHIS-QOL ($p = 0.004$). There was no statistically significant difference between VR exposure (mean = 25.00, SD = 9.12) and non-VR exposure (mean = 28.92, SD = 6.46) at 3 months ($p = 0.253$). For attendance, Kampmann 2016 reported 6 (20%) in the VR exposure and 4 (14%) in the non-VR

exposure arm discontinued treatment. Kampmann 2016 also reported adverse events; 1 participant in the VR exposure group discontinued the intervention due to motion sickness.³²

VR Exposure versus CBT Plus Non-VR Exposure

One study, Stefaniak 2022, also compared VR exposure with CBT plus non-VR exposure (as 2 of the 3 included arms).²⁷ In the VR exposure arm, participants experienced 9 virtual scenarios (eg, speaking at a meeting or buying a train ticket) with varying levels of difficulty. The CBT plus non-VR exposure arm has been described above.

Symptom severity was assessed at 7 weeks using the LSAS, BDI, and Clinician Global Impressions of Improvement. There was a statistically significant change in LSAS ($p = 0.008$) and BDI scores ($p = 0.002$) when comparing VR exposure and CBT plus non-VR exposure at 7 weeks from baseline, but there was no statistically significant change in Clinician Global Impressions of Improvement (p-value not reported). For adverse events, 3 participants in the VR arm experienced simulator sickness symptoms and 4 in the CBT plus non-VR exposure arm experienced symptoms similar to simulator sickness.

VR Attentional Bias Modification (ABM) Dot Probe Task

Ma 2019 compared 4 arms of ABM using a dot-probe task against each other (3D active, 3D sham, 2D active, 2D sham).^{30,109} The study enrolled 100 participants, 58.3% were female, and the average age was 40.8. All treatments were a single session each and were intended to reduce preferential focus on threatening faces and increase attention towards neutral faces. All arms used a VR head-mounted device. Two of the arms showed 3D rendered faces and 2 showed 2D rendered faces; 1 arm within each pair (3D or 2D) was considered active because it attempted to direct attention towards the neutral face using dots. The study was appraised as high ROB due to concerns about randomization, assignment to the intervention, missing outcome data, measurement of the outcome, and selection of reported results.

Symptom severity was assessed using LSAS and GAD. On the LSAS, mean (SD) scores at 3-month follow-up were as follows: 59.48 (23.18) (3D active), 43.76 (24.77) (3D sham), 56.65 (21.67) (2D active), and 49.48 (20.51) (2D sham). A mixed effects model found no significant differences between 2D/3D or active/sham in LSAS. No analyses were reported for GAD. All participants completed the intervention.

KQ1: SPECIFIC PHOBIA OF FLYING ($k = 7$)

Overview

Seven eligible RCTs (reported in 10 publications) evaluated VR interventions for specific phobia of flying (Table 9).³⁶⁻⁴² All of these used VR exposure therapies, with half also including CBT. Four studies were conducted in the US^{39-42,114-116} and 3 were conducted in Europe (Spain,³⁷ Italy,³⁶ and the Netherlands³⁸). Two studies permitted continuation of antidepressants or other medications (at stable doses),^{36,38,41} and 1 excluded individuals who had any other ongoing psychological or medication treatments for mental health disorders.³⁷

We next present findings from the 6 RCTs comparing VR exposure therapy versus non-VR exposure, first focusing on the 2 trials evaluating only VR exposure therapy,^{37,42} then followed by the 4 studies using CBT plus VR exposure.^{36,38,39,41} Lastly, we describe the single study comparing VR exposure

therapy with supportive group therapy.⁴⁰ No studies reported findings on quality of life or suicidal ideation and/or suicidal behavior. Detailed study characteristics and findings may be found in the Supplementary Materials.

Table 9. Summary Characteristics of Specific Phobia of Flying Studies (k = 7)

Author, Year; Study Design; Risk of Bias Total N Key Participant Characteristics	Intervention Characteristics	Comparator Characteristics
Tortella-Feliu, 2011 ³⁷ Some concerns N = 60 Mean age: 36-38 years 52-75% female	<p>VR Exposure</p> <ul style="list-style-type: none"> VR scenarios preparing for flying, in airport, and during flight, with progression from easiest to most difficult Therapists guided sessions, use of cognitive strategies 6 x 60-minute sessions; 3 weeks <p>Hardware: 5DT HDM 800 HMD Embodiment: No Interactivity: Yes Multisensory stimulation: No</p>	<p>Non-VR Exposure (with therapist)</p> <ul style="list-style-type: none"> 2-dimensional photos (on computer screen) and sounds for same types of scenarios as VR arm, provided additional exposures based on participant fear ratings Therapists present but did not guide treatment 6 x 60-minute sessions; 3 weeks <hr/> <p>Non-VR Exposure (self-administered)</p> <ul style="list-style-type: none"> 2-dimensional computer-based program, same as comparator above, but therapist not present except during first and last sessions 6 x 60-minute sessions; 3 weeks
Wiederhold, 2001 ⁴² High N = 36 Mean age: 36-44 years 30-60% male; 40-70% female*	<p>VR Exposure (no physiologic feedback)</p> <ul style="list-style-type: none"> VR graded exposure therapy, initial training in relaxation techniques 8 x 30-minute sessions; 8 weeks <p>Hardware: MRG4 (Liquid Image Inc.) HMD Embodiment: No Interactivity: Yes Multisensory stimulation: Yes</p> <hr/> <p>VR Exposure (with physiologic feedback)</p> <ul style="list-style-type: none"> VR graded exposure therapy (with physiologic data displayed in virtual settings), initial training in relaxation techniques 8 x 30-minute sessions; 8 weeks <p>Hardware: MRG4 (Liquid Image Inc.) HMD Embodiment: No Interactivity: Yes Multisensory stimulation: Yes</p>	<p>Non-VR Exposure</p> <ul style="list-style-type: none"> Graded imaginal exposure therapy, initial training in relaxation techniques 8 x 30-minute sessions; 8 weeks
Krijn, 2007 ³⁸ High N = 86 Mean age: 39 years 39% men; 61% women*	<p>CBT + VR Exposure</p> <ul style="list-style-type: none"> VR scenarios in airport and on airplanes CBT group sessions 4 x 60-minute sessions; 4 weeks <p>Hardware: Cybermind Visette Pro HMD Embodiment: No Interactivity: Yes Multisensory stimulation: Yes</p>	<p>CBT + Non-VR Exposure</p> <ul style="list-style-type: none"> Individual sessions using imaginal exposure (and sitting on aircraft seat in office setting) CBT group sessions 4 x 60-minute sessions; 4 weeks <hr/> <p>Bibliotherapy</p> <ul style="list-style-type: none"> Encouraged to read book to help address phobia of flying (also provided to participants in other 2 arms)

Author, Year; Study Design; Risk of Bias	Intervention Characteristics	Comparator Characteristics
Total N Key Participant Characteristics		
Rothbaum, 2000 ⁴¹ High N = 49 Mean age: 41 years 71% female	CBT + VR Exposure <ul style="list-style-type: none"> Individual sessions on cognitive restructuring, coping skills VR scenarios in airplane and during flights, therapist provided feedback and encouragement 8 x 60-90 minute sessions; 6 weeks <p>Hardware: Virtual Research VR6 HMD Embodiment: No Interactivity: No Multisensory stimulation: Yes</p>	CBT + non-VR Exposure <ul style="list-style-type: none"> Individual sessions on cognitive restructuring, coping skills In vivo exposure in airport and airplane (not in flight) 8 x 60-90 minute sessions; 6 weeks <hr/> Waitlist <ul style="list-style-type: none"> No active treatment
Rothbaum, 2006 ³⁹ High N = 83 Mean age: 37-45 years 76-84% female	CBT + VR Exposure <ul style="list-style-type: none"> Individual sessions on cognitive restructuring, coping skills VR scenarios in airplane and during flights, therapist guided exposures, provided feedback and encouragement 8 x 60-90 minute sessions; 6 weeks <p>Hardware: IISVR-VFX3D HMD Embodiment: No Interactivity: No Multisensory stimulation: Yes</p>	CBT + non-VR Exposure <ul style="list-style-type: none"> Individual sessions on cognitive restructuring, coping skills In vivo and imaginao exposure in airport 8 x 60-90 minute sessions; 6 weeks <hr/> Waitlist <ul style="list-style-type: none"> No active treatment
Triscari, 2015 ³⁶ Some concerns N = 65 Mean age: 42-46 years 24-36% men; 64-76% women	CBT + VR Exposure <ul style="list-style-type: none"> Individual sessions on cognitive restructuring, coping skills, in vivo and imaginal exposures VR scenarios NR 10 x 120-minute sessions; 10 weeks <p>Hardware: NR Embodiment: NR Interactivity: NR Multisensory stimulation: NR</p>	CBT + non-VR Exposure <ul style="list-style-type: none"> Individual sessions on cognitive restructuring, coping skills, in vivo and imaginal exposures Systematic desensitization (details NR) 10 x 120-minute sessions; 10 weeks <hr/> CBT + Eye Movement Desensitization and Reprocessing Therapy <ul style="list-style-type: none"> Individual sessions on cognitive restructuring, coping skills, in vivo and imaginal exposures EMDR (details NR) 10 x 120-minute sessions; 10 weeks
Maltby, 2002 ⁴⁰ High N = 45 Mean age: 45 years 79% women	VR Exposure <ul style="list-style-type: none"> VR graded exposure therapy Therapist adjusted exposure intensity (eg, smooth versus turbulent flight) 5 x 50-90 minute sessions; 3 weeks <p>Hardware: Virtual Research V6 HMD Embodiment: No Interactivity: Yes Multisensory stimulation: No</p>	Supportive Group Therapy <ul style="list-style-type: none"> Education about flight mechanics and safety, group sharing of flying experiences and fears 5 x 50-90 minute sessions; 3 weeks

Abbreviations. CBT=cognitive behavioral therapy; HMD=head-mounted display; NR=not reported; VR=virtual reality.

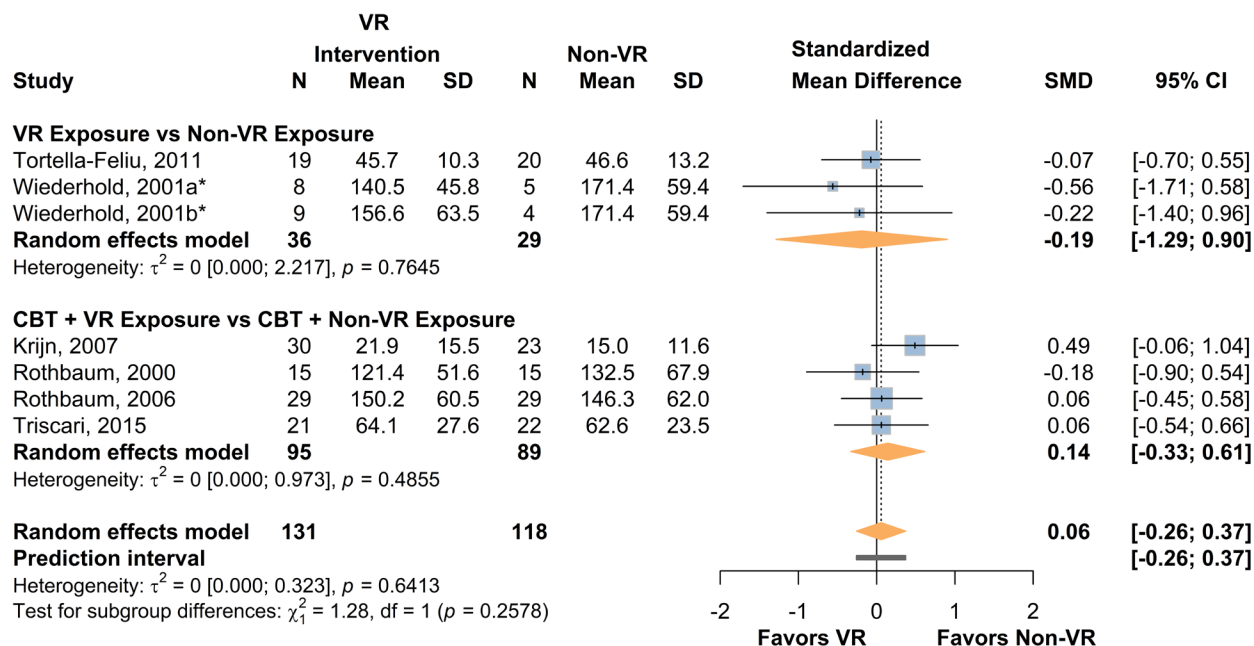
VR Exposure versus Non-VR Exposure

Two RCTs compared VR exposure with non-VR exposure,^{37,42} with 1 of these including 2 VR treatment arms (with or without biofeedback).⁴² Both assessed symptom severity, treatment response or recovery, and participant engagement. Both were small (total $N = 36-60$) and enrolled young and middle aged adults (mean age = 36–44 years, 40%–75% women).^{37,42} Treatments comprised 6–8 total sessions over a duration of 3–8 weeks, and 1 specified therapist involvement.³⁷ Tortella-Feliu 2011³⁷ was rated some concerns for RoB, while Wiederhold 2001⁴² had high RoB due to a number of methodological concerns including allocation concealment, balance in non-protocol interventions, and adherence to assigned treatment.

Symptom Severity

The evidence is very uncertain on the effect of VR exposure on symptom severity immediately post-intervention, as compared with non-VR exposure therapy (very low COE; Table 10). Tortella-Feliu 2013 assessed symptom severity using the Fear of Flying Scale (FFS),³⁷ and Wiederhold 2001 employed the Questionnaire on Attitudes toward Flying (QAF).⁴² The pooled estimate (using data from both VR exposure arms in Wiederhold 2001) indicated potentially small effect favoring VR exposure, but with 95% CI extending to very large effects in both directions (SMD = -0.19 [-1.29, 0.90]; Figure 8). Both studies reported improvement in all groups over time and no significant between-group differences immediately post-intervention. Tortella-Feliu 2013 also assessed symptom severity at 1 year, finding that all groups maintained improvements in symptoms and no between-group differences at longer term follow-up.³⁷

Figure 8. Specific Phobia of Flying: Effect of VR Exposure versus Non-VR Exposure on Symptom Severity Immediately Post-Intervention

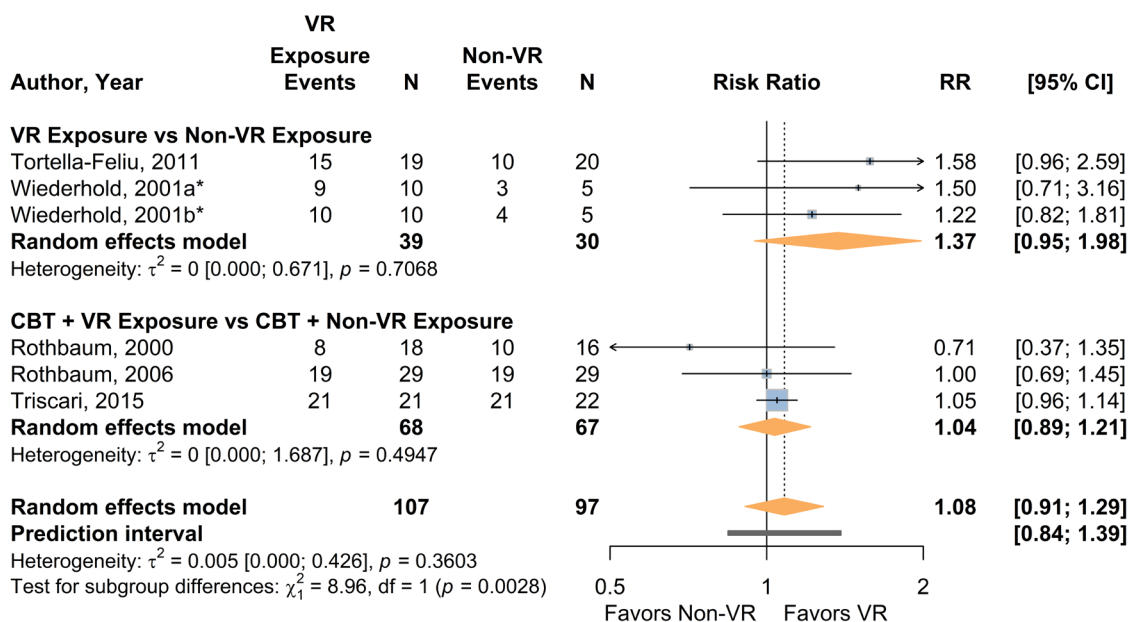


Notes. *VR exposure arms without biofeedback (Wiederhold, 2001a) or with biofeedback (Wiederhold, 2001b). Same mean and SD from non-VR exposure arm was used for each comparison, with N split between the 2 comparisons.

Treatment Response/Recovery

The evidence is very uncertain on the effect of VR exposure on treatment response, compared with non-VR exposure therapy (very low COE; Table 10). Both studies assessed the proportion of participants who completed flights after treatment, finding higher rates of flight completion in the VR arms (Figure 9). Tortella-Feliu 2013 encouraged participants to take a flight on their own within 15 days post-intervention, and then assessed who had done so.³⁷ Wiederhold 2001 also evaluated self-reported flight completion post-intervention, but did not specify the time period.⁴² The pooled estimate potentially indicated higher completion in the VR group but the 95% CI extended into effects favoring non-VR treatment (pooled RR = 1.37, 95% CI [0.95, 1.98]; Figure 9).

Figure 9. Specific Phobia of Flying: Effect of VR Exposure versus Non-VR Exposure on Flight Completion Post-Intervention



Notes. *VR exposure arms without biofeedback (Wiederhold, 2001a) or with biofeedback (Wiederhold, 2001b). Total of 7 events in non-VR group; events were divided and N split between the 2 comparisons.

Using the Anxiety Disorders Interview Schedule for Diagnostic and Standards Manual-IV (ADIS-IV), Tortella-Feliu 2013 also assessed proportion of participants who no longer met criteria for flying phobia immediately post-intervention and at 1 year.³⁷ There were no between-group differences either immediately post-intervention or at 1 year (eg, 68% in VR group vs 52%–60% non-VR post-intervention, $p = 0.59$).

Engagement

Both studies reported on discontinuation or completion of treatments, and 1 study also evaluated treatment satisfaction. Tortella-Feliu 2013 reported similar discontinuation across arms (1 participant in the VR exposure group, and 1 and 2 in each of the 2 non-VR exposure arms); reasons given were scheduling conflicts and illness unrelated to the study.³⁷ Wiederhold 2001 found that drop-out was substantial in the non-VR exposure group (4 out of 10), whereas no one in the VR arms did so.⁴²

Tortella-Feliu 2013 also assessed satisfaction, reporting this was greater for the VR exposure arm; satisfaction was assessed with an adapted Borkovec and Nan Credibility/Expectations Scale, but authors did not provide mean values.³⁷ None of the studies assessed other measures of engagement.

Table 10. Specific Phobia of Flying Certainty of Evidence: VR Exposure versus Non-VR Exposure

Outcome Measure	Follow-Up Total N (# of Studies)	Pooled Estimate (95% CI)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up			Certainty	What Happens
			VR Exposure	Non-VR Exposure	Difference		
Symptom Severity	Post-intervention	SMD: -0.19 (-1.29, 0.90)	44.3 (31.3, 57.3)	46.6*	-2.3 (-15.3, 10.7)	⊕○○○ Very low ^{a,b}	The evidence is very uncertain on the effect of VR exposure on symptom severity immediately post-intervention.
FFS; QAF	N = 65 (2 RCTs) ^{37,42}						
Treatment Response	N = 65 (2 RCTs) ^{37,42}	RR: 1.37 (0.95, 1.98)	77% (53%, 100%)	56%*	21% (-3%, 44%)	⊕○○○ Very low ^{a,c}	The evidence is very uncertain on the effect of VR exposure on flight completion post-intervention.
Flight completion							

Notes. *Mean FFS score for comparator arm and proportion who completed flights are both from Tortella-Feliu 2011³⁷; ^aDowngraded 2 levels for study limitations (1 or more studies rated high RoB); ^bDowngraded 2 levels for imprecision (CI crosses threshold for small effects in opposing direction); ^cDowngraded 1 level for imprecision (CI crosses into effect in opposing direction).

Abbreviations. FFS=Fear of Flying Scale; QAF=Questionnaire on Attitudes toward Flying; RoB=risk of bias; RR=rate ratio; SMD=standardized mean difference; VR=virtual reality.

CBT and VR Exposure versus CBT and Non-VR Exposure

Four RCTs compared CBT and VR exposure with CBT and non-VR exposure.^{36,38,39,41} Study characteristics and interventions are summarized in Table 9. Studies were small (total N = 34–86), and enrolled young and middle-aged adults (mean age = 37–46 years, 61%–84% women). VR interventions comprised 4–10 sessions over a duration of 4–10 weeks. Triscari 2015³⁶ had some concerns for RoB, while the other 3 studies all had high RoB due to substantial methodological concerns, including allocation concealment and loss to follow-up.^{38,39,41}

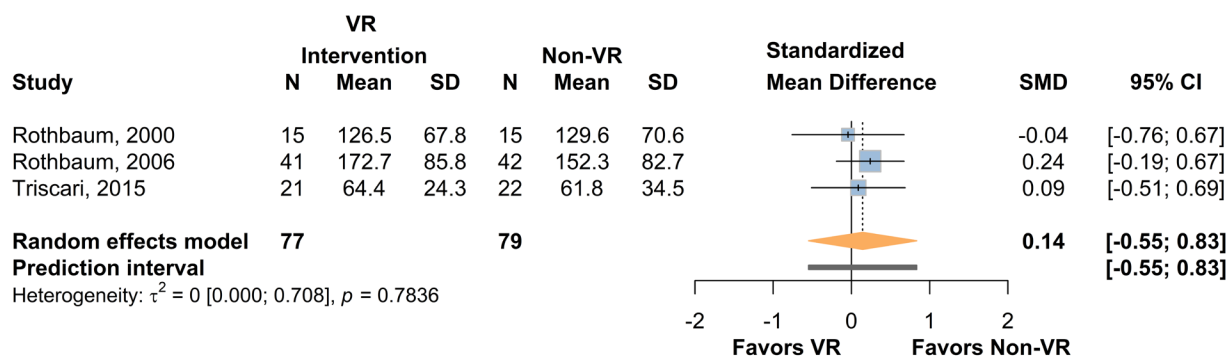
Rothbaum 2000 and Rothbaum 2006 were conducted by the same research group, and both studies involved similar treatment protocols with 4 sessions of CBT that preceded exposure sessions (VR vs imaginal and in vivo exposures).^{39,41} Both of these trials also included a third waitlist arm; findings for comparisons between VR and waitlist arms will be described in the next section. Krijn 2007 evaluated treatment with VR exposure sessions that preceded final group CBT sessions; the comparator group had individual CBT sessions (incorporating imaginal exposures), followed by the same group CBT sessions.³⁸ The fourth RCT, Triscari 2015, compared CBT plus VR exposure versus CBT plus non-VR exposure versus CBT plus eye movement desensitization and reprocessing therapy (EMDR); CBT sessions were the same in all 3 arms.³⁶

Symptom Severity

The evidence is very uncertain on the effect of CBT plus VR exposure on symptom severity immediately post-intervention, compared with CBT plus non-VR exposure (very low COE; Table 11). All 4 studies assessed symptom severity using the Flight Anxiety Situations Questionnaire (FAS)^{36,38} or QAF.^{39,41} The pooled estimate showed no significant between-group effects, with the 95% CI extending from small effects favoring VR to moderate effects favoring non-VR exposure (SMD = 0.14 [-0.33, 0.61]; see Figure 8 above). The COE was reduced due to study methodological limitations and wide confidence interval (crossing small to moderate effects in both directions). Triscari 2015 also compared CBT plus VR exposure with CBT plus EMDR, reporting no significant between-group differences.³⁶

The evidence is very uncertain on the effect of CBT plus VR exposure versus CBT plus non-VR exposure on symptom severity at 6 and 12 months post-intervention (very low COE; Table 11). Three studies reported longer-term findings on symptom severity at 12 months.^{36,39,41} The pooled estimate showed no significant between-group effects (SMD = 0.14 [-0.55, 0.83]; Figure 10). The COE was reduced due to study methodological limitations and wide confidence interval (crossing small to moderate effects in both directions). Two of these studies also assessed outcomes at 6 months, both reporting no between-group differences.^{39,41} Additionally, Triscari 2015 reported no significant between-group differences between CBT plus VR exposure and CBT plus EMDR groups at 12 months.³⁶

Figure 10. Specific Phobia of Flying: Effect of CBT with VR Exposure versus CBT with Non-VR Exposure on Symptom Severity 12 Months Post-Intervention



Treatment Response/Recovery

The evidence is very uncertain on the effect of CBT plus VR exposure on treatment response, compared with CBT plus non-VR exposure (very low COE; Table 11). Pooled effect estimate using data from 3 studies^{36,39,41} showed no differences between groups but 95% CI extended into potentially important differences in both directions (RR = 1.04 [0.89, 1.21]; Figure 9). Treatment response was assessed as flight completion in all 3 studies, with both Rothbaum 2000 and Rothbaum 2006 including the flights (1.5–2 hours) as part of the study assessment protocol.^{39,41} Triscari 2015 asked participants to report on flights they had completed on their own (outside of the study protocol), and also indicated there were no between-group differences between CBT plus VR exposure and CBT plus EMDR arms.³⁶ Rothbaum 2000 also reported flight completion at 6 and 12 months post-intervention, finding no between-group differences at these later time points.^{41,114} Finally, Rothbaum 2006 found that similar proportions of individuals no longer met full criteria for flying phobia at 6 months, assessed

using the Structured Clinical Interview for the DSM-IV (71% for VR group vs 76% for non-VR arm, p-value not reported).

Table 11. Specific Phobia of Flying Certainty of Evidence: CBT + VR Exposure versus CBT + Non-VR Exposure

Outcome Measure	Follow-Up Total N (# of Studies)	Pooled Estimate (95% CI)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up			Certainty	What Happens
			CBT + VR Exposure	CBT + Non-VR Exposure	Difference		
Symptom Severity	Post-intervention	SMD: 0.14 (-0.33, 0.61)	154.9 (126.1, 183.7)	146.3*	8.6 (-20.2, 37.4)	⊕○○○ Very low ^{a,b}	The evidence is very uncertain on the effect of VR exposure on symptom severity immediately post-intervention.
FAS QAF	N = 184 (4 RCTs) 36,38,39,41						
	6 months post-intervention	—	161.3*	136.8*	24.5	⊕○○○ Very low ^{a,c}	The evidence is very uncertain on the effect of VR exposure on symptom severity at 6 months post-intervention.
	N = 96 (2 RCTs) ^{39,41}						
	12 months post-intervention	SMD: 0.14 (-0.55, 0.83)	164.1 (106.0, 222.2)	152.3*	11.8 (-46.3, 69.9)	⊕○○○ Very low ^{a,b,d}	The evidence is very uncertain on the effect of VR exposure on symptom severity at 12 months post-intervention.
	N = 127 (3 RCTs) ^{37,39,114}						
Treatment Response	Post-intervention	RR: 1.04 (0.89, 1.21)	68% (58%, 79%)	66%*	2% (-8%, 13%)	⊕○○○ Very low ^{a,e}	The evidence is very uncertain on the effect of VR exposure on flight completion post-intervention.
Flight completion	N = 135 (3 RCTs) ^{36,39,41}						

Notes. *Values for mean QAF scores and flight completion rates from Rothbaum 2006³⁹; ^aDowngraded 2 levels for study limitations (1 or more studies rated high RoB); ^bDowngraded 2 levels for imprecision (CI crosses thresholds for small effects in opposing direction); ^cDowngraded 1 level for imprecision (using OIS, studies were not powered to detect minimum SMD of 0.6; see Methods for more information); ^dDowngraded 1 level for inconsistency (direction of effects inconsistent across studies); ^eDowngraded 1 level for imprecision (CI includes potentially important effects in both directions).

Abbreviations. CBT=cognitive behavioral therapy; FAS=Flight Anxiety Situations Questionnaire; OIS=optimal information size; QAF=Questionnaire on Attitudes toward Flying; RoB=risk of bias; RR=rate ratio; SMD=standardized mean difference; VR=virtual reality.

Engagement

Three studies assessed treatment discontinuation, with both Rothbaum 2000⁴¹ and Rothbaum 2006³⁹ reporting similar rates for CBT plus VR exposure and CBT plus non-VR exposure arms (eg, 12% for both VR exposure and non-VR exposure arms).³⁹ Krijn 2007 found higher discontinuation in the CBT plus VR exposure arm (34%) compared with CBT plus non-VR exposure (11%); 1 discontinuation in the VR arm was due to simulation sickness.³⁸ Both Rothbaum 2000 and Rothbaum 2006 also assessed

treatment satisfaction using the CSQ-8, finding no differences between groups and generally high levels of satisfaction.^{39,41} None of the studies assessed other measures of engagement.

CBT and VR Exposure versus Waitlist

As noted above, both Rothbaum 2000 and Rothbaum 2006 included a waitlist arm with no active treatments described.^{39,41} The evidence is very uncertain on the effect of CBT plus VR exposure on symptom severity post-intervention, compared with waitlist (very low COE; Table 12). As noted above, symptom severity was assessed with the QAF; both studies reported lower scores for CBT plus VR exposure compared with waitlist (eg, mean = 150.3 [SD = 60.6] for VR compared with mean = 205.9 [72.0] in the waitlist arm, pairwise p-value not reported).^{39,41} The COE was reduced due to study methodological limitations and insufficient power of studies to detect a minimum SMD of 0.6 (see OIS criteria described in Methods).

CBT plus VR exposure may lead to higher flight completion post-intervention, compared with waitlist (low COE; Table 12). Both studies reported higher flight completion rates in the CBT plus VR arm (eg, 66% versus 20% in the waitlist group).³⁹

Table 12. Specific Phobia of Flying Certainty of Evidence: CBT + VR Exposure versus Waitlist

Outcome Measure	Follow-Up Total N (# of Studies)	SMD Pooled Estimate (95% CI)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up			Certainty	What Happens
			VR Exposure	Waitlist	Difference		
Symptom Severity QAF	Post-intervention N = 87 (2 RCTs) ^{39,41}	—	150.3 (60.6)*	204.9 (72.0)*	-54.6*	⊕○○○ Very low ^{a,b}	The evidence is very uncertain on the effect of CBT and VR exposure on symptom severity post-intervention.
Treatment Response Flight completion	Post-intervention N = 80 (2 RCTs) ^{39,41}	—	76% (19/25)*	20% (5/25)*	56%*	⊕⊕○○ Low ^a	CBT and VR exposure may lead to higher flight completion post-intervention.

*Mean QAF scores (SD) and proportion with flight completion for both arms from Rothbaum 2006.³⁹ Differences calculated by review team; ^aDowngraded 2 levels for study limitations (1 or more studies rated high RoB); ^bDowngraded 1 level for imprecision (using OIS, studies were not powered to detect minimum SMD of 0.6; see Methods for more information).

Abbreviations. CBT=cognitive behavioral therapy; OIS=optimal information size; QAF=Questionnaire on Attitudes toward Flying; RoB=risk of bias; SMD=standardized mean difference; VR=virtual reality.

VR Exposure versus Supportive Group Therapy

Maltby 2002 compared VR exposure with supportive group therapy, randomizing 45 adults with mean age of 45 years, 79% being women.⁴⁰ The intervention comprised 5 sessions over 3 weeks. This study was rated high RoB due to a number of concerns, including lack of information about allocation concealment and imbalance in number of drop-outs across groups.

Immediately post-intervention, the VR group had lower mean FAS scores for both in-flight and anticipatory domains, compared with the supportive therapy group (eg, in-flight 20.5 [SD = 9.1] for VR vs 28.9 [12.0] for supportive therapy, $p < 0.01$). However, there were no between-group differences in FAS scores at 6 months post-intervention. For treatment response, there were no between-group differences in the study proportion of participants who were able to complete a 10–15 minute flight (59% VR vs 57% supportive therapy, p-value not reported). Regarding engagement, 2 participants dropped out of the VR group and none from the supportive therapy group. No other aspect of engagement was reported. For adverse events, authors reported that 1 of the participants who withdrew from the study did so due to motion sickness during VR exposure treatment, but they did not describe whether other participants may have experienced any symptoms during treatment sessions. This study did not assess any other eligible outcomes.

KQ1: ALCOHOL USE DISORDER ($k = 2$)

Overview

We identified 2 studies (reported in 3 articles) evaluating the use of VR interventions in the treatment of patients with alcohol use disorder (AUD; Table 13). One trial in Spain combined a VR version of cue exposure therapy with TAU.^{43,45} The other trial in Korea combined VR exposure with alcohol approach-avoidance training.⁴⁴ Neither study reported quality of life, adherence, other engagement, adverse events, or suicidal ideation and/or behaviors outcomes. Below, we describe study characteristics and outcomes for both studies for VR exposure. Detailed study characteristics and detailed findings are presented in the Supplementary Materials.

Table 13. Summary Characteristics of AUD Studies ($k = 3$)

Author, Year; Study Design; Risk of Bias	Intervention Characteristics	Comparator Characteristics
Total N Key Participant Characteristics Hernandez-Serrano, 2020 ⁴³ ; Figueras-Puigderrajols, 2020 ⁴⁵ High N = 79 Mean age: 54.6 years 50% women Patients in substance use clinic	VR Cue Exposure Therapy + TAU <ul style="list-style-type: none"> Virtual cue exposure therapy in environments (eg, restaurant, bar) that elicit cravings Olfactory stimuli included smells corresponding to alcohol types Progression through levels of increasing difficulty by craving ratings Individual + group psychotherapy, pharmacotherapy as per TAU No use of anti-craving medication (eg, naltrexone) 6 x 50-minute VR sessions; 3 weeks Hardware: Oculus Rift S HMD Embodiment: Yes Interactivity: Yes Multisensory stimulation: Yes	TAU <ul style="list-style-type: none"> Pharmacotherapy (disulfiram, anxiolytics and/or antidepressants) Individual + group psychotherapy Individual psychotherapy session dose not reported No use of anti-craving medication (eg, naltrexone) 3–6 1.5-hour group sessions; 3 weeks

Author, Year; Study Design; Risk of Bias	Intervention Characteristics	Comparator Characteristics
Total N Key Participant Characteristics Kim, 2019 ⁴⁴ High N = 28 Mean age: 22-23 years 39% female College undergraduates; heavy social drinkers	VR Approach Avoidance Exposure Therapy <ul style="list-style-type: none"> • Virtual social situations with and without alcohol, training in approach and avoidance cues to reduce automatic action tendencies toward alcohol • Color signals instructed participants to use a joystick to approach alcohol-unrelated situations and avoid alcohol-related situations • 3 1-hour sessions; 2–3 weeks Hardware: NR Embodiment: NR Interactivity: Yes Multisensory stimulation: No	VR Sham Approach Avoidance Exposure Therapy <ul style="list-style-type: none"> • Sham training in which no association was assumed between alcohol-related situations and participant actions • 3 1 hour sessions; 2–3 weeks Hardware: NR Embodiment: NR Interactivity: Yes Multisensory stimulation: No

Abbreviations. AUD=alcohol use disorder; HMD=head-mounted display; NR=not reported; TAU=treatment as usual; VR=virtual reality.

VR Exposure

Two RCTs evaluated VR exposure therapy for AUD.⁴³⁻⁴⁵ Study characteristics and findings for VR interventions are summarized in Table 13. Both studies were small (total $N = 28-79$) and included young and middle-aged adults (mean ages = 22–57 years, 39%–50% women). However, while Hernandez-Serrano 2020 enrolled patients from addiction clinics in Spain,⁴³ Kim 2019 recruited Korean college undergraduates who were “heavy social drinkers” (defined as >22 on Alcohol Use Disorders Identification Test [AUDIT]).⁴⁴ VR interventions involved 3–5 sessions, each lasting about an hour long and delivered over 2–3 weeks. Both studies were rated high for RoB due to substantial loss to follow-up.

Hernandez-Serrano 2020 evaluated VR cue exposure therapy to desensitize participants to alcohol-related scenarios in the virtual environment as well as to olfactory inputs provided by the attending clinical staff, progressing through stages of increasing difficulty based on subjective cravings ratings.⁴³ Participants also received debriefings intended to reduce levels of craving and anxiety, immediately following the exposure session. The VR group also received TAU, which consisted of pharmacotherapy, individual and group psychotherapy (based on CBT), and motivational interviewing; the comparator group received only TAU. Figueras-Puigderrajols 2020 reported an earlier pilot’s results (for 28 participants) that appeared to be part of this same study,⁴⁵ although it was unclear whether the same participants may have been included in both reports. Therefore, we present findings mainly from Hernandez-Serrano 2020,⁴³ as it was larger and had better described study outcomes.

Kim 2019 used VR to re-condition alcohol-related behaviors while the patient remained present in the virtual environment.⁴⁴ Participants encountered virtual scenarios that did or did not have the presence of alcohol, and were trained with color signals to activate an approach or avoidance response depending on the presence or non-presence of alcohol. Patients in the comparator arm received a sham training modality, which operated on a similar approach/avoidance basis but was programmed to impart only a neutral association of avoidance with alcohol.⁴⁴

Symptom Severity

Both trials assessed AUD symptoms in terms of craving for alcohol, but were not combined to assess CoE due to substantial differences in populations, VR interventions, and comparators.⁴³⁻⁴⁵ Hernandez-Serrano 2020 assessed craving for alcohol with a modified version of the Multidimensional Craving Scale (MACS).⁴³ MACS scores by study arm at baseline and follow-up were not presented, and no between-group statistical analyses were reported; however, authors stated that there were significant reductions only in the VR arm.⁴³ Kim 2019 assessed participants' cravings using the Alcohol Use Questionnaire (AUQ), and post-intervention AUQ scores did not differ significantly between arms.⁴⁴

Treatment Response

Hernandez-Serrano 2020 also evaluated treatment response, defined as post-intervention improvement in craving category. MACS scores were categorized as nonexistent, mild, moderate, or intense at baseline, and improvement post-intervention was defined as improvement (by at least 1 level).⁴³ Cravings improved for 87% (13/15) of completers in the VR group, compared with 33% (9/27) in control group.

Engagement

Only Hernandez-Serrano 2020 evaluated engagement, reporting that 57% (20/35) of participants in the VR group and 39% (17/44) of the TAU group failed to complete the assigned intervention.⁴³ No reasons for discontinuation were noted.

KQ1: STIMULANT USE DISORDER ($k = 2$)

Overview

We identified 2 RCTs evaluating the use of VR interventions in the treatment of patients with stimulant use disorder (Table 14). In both trials, VR was used to deliver exposure therapy to patients with methamphetamine dependence. Both trials were conducted in Asia. We describe these 2 VR exposure studies together. No studies reported treatment response/recovery, quality of life, adherence, other engagement, adverse events, or suicidal ideation and/or behaviors outcomes. Below, we describe study characteristics and outcome findings for the included VR exposure studies. Detailed study characteristics and detailed results are provided in the Supplementary Materials.

Table 14. Summary Characteristics of Stimulant Use Disorder Studies (k = 2)

Author, Year; Study Design; Risk of Bias Total N Key Participant Characteristics	Intervention Characteristics	Comparator Characteristics
Wang, 2019 ⁴⁷ Some concerns N = 61 Mean age: 33–35 years 100% men Patients in substance addiction clinic	VR Exposure Therapy + TAU <ul style="list-style-type: none"> • Virtual scenarios of methamphetamine use followed by scenarios showing adverse consequences, designed to create an aversive response to methamphetamine use through counterconditioning • TAU: conventional psychotherapy plus physical exercises • 6 sessions (duration NR); 3 weeks Hardware: HMD version 2.0, Hangzhou Seventh Science and Technology Co., Ltd Embodiment: No Interactivity: No Multisensory stimulation: No	TAU <ul style="list-style-type: none"> • Conventional psychotherapy plus physical exercises
Ji, 2023 ⁴⁶ Some concerns N = 60 Mean age: 23 years 100% women Enrolled in compulsory drug rehabilitation center	VR Exposure Therapy + Motivational Reinforcement <ul style="list-style-type: none"> • Motivational reinforcement initial phase to establish intent to cease methamphetamine use (3 sessions: 2 individual + 1 group) • Virtual methamphetamine cue scenarios designed to activate addiction memories and desensitize participants, followed by group relaxation skills training • 6 x 60-minute VR sessions; 4 weeks Hardware: PICO G2 HMD Embodiment: No Interactivity: NR Multisensory stimulation: NR	TAU <ul style="list-style-type: none"> • Regular detoxification management • 8 sessions (duration NR); 4 weeks

Abbreviations. HMD=head-mounted display; NR=not reported; TAU=treatment as usual; VR=virtual reality.

VR Exposure

Both studies evaluated VR exposure therapies for stimulant use disorder.^{46,47} Study characteristics and findings for VR interventions are summarized in Table 14. Both studies were conducted in China and included participants with diagnoses of amphetamine dependence who were receiving care through detoxification or drug rehabilitation centers. Inpatient versus outpatient status was unclear for both studies. Sample sizes were 60 and 61. One study recruited only women in early adulthood (mean age 23)⁴⁶ and the other recruited only men (mean age 35).⁴⁷ Interventions comprised 6 sessions over 3–4 weeks. Both studies compared a VR exposure intervention with TAU, and both were rated some concerns for RoB. Both studies reported symptom severity outcomes and 1 reported on engagement though only presented data for attendance.

Though both studies cite cue exposure therapy as fundamental to their approach, strategies used to produce a therapeutic effect through VR exposure differed. Ji 2023 focused primarily on the mechanism of desensitization through VR, after an initial motivational reinforcement phase. Patients were exposed to virtual cue scenarios which were then followed by group relaxation skills training intended to reduce psychological cravings for methamphetamine. Participants in the comparator arm received TAU, described as regular detoxification and drug rehabilitation management.⁴⁶ Wang 2019

evaluated a counterconditioning VR exposure therapy intervention intended to instill an aversive response to methamphetamine use. Through interviews conducted with patients with methamphetamine dependence, authors identified common negative themes (*eg*, encounters with police, death) which were then incorporated in immersive methamphetamine-related VR videos intended to recondition patients to develop methamphetamine-aversive behaviors. Both the intervention and the comparator arm received TAU (*ie*, psychotherapy, physical exercise).⁴⁷

Symptom Severity

VR exposure therapy to treat methamphetamine dependence may result in improved symptom severity post-intervention when compared to TAU (low COE; Table 15). Both studies compared a VR exposure intervention with TAU for a duration of 3–4 weeks and reported subjective craving for methamphetamine using visual analogue scale (VAS) scores asking patients to indicate their levels of craving (*eg*, “how much do you crave METH/ice right now?”).⁴⁷ Wang 2019⁴⁷ and Ji 2023⁴⁶ both assessed craving immediately post-intervention. In Wang 2019, the VR exposure therapy arm had significantly lower mean craving post-intervention than the TAU arm (mean levels NR, $p < 0.001$). In Ji 2023, the VR exposure therapy arm also had significantly lower mean craving immediately post-intervention and at 1 month, compared with the TAU arm (*eg*, mean VAS craving 10.17 VR vs 27.67 control at 1 month, $p < 0.0001$).

Engagement

Only Ji 2023 evaluated engagement, reporting that 1 participant missed 4 treatment sessions due to work; authors excluded this patient from analyses.⁴⁶

Table 15. Stimulant Use Disorder Certainty of Evidence: VR Exposure Therapy versus TAU

Outcome Measure	Follow-Up	Anticipated Absolute Effects (SD)			Certainty	What Happens
		VR Exposure Therapy	TAU	Difference		
Symptom Severity	Post-intervention	7.59 (1.65)*	27.67 (3.99)*	-20.08*	⊕⊕○○ Low ^{a,b}	VR exposure therapy may result in lower craving post-intervention.
VAS Craving	$N = 119$ (2 RCTs) ^{46,47}					

Notes. *Mean (SD) for intervention and comparator arms taken from Ji 2023,⁴⁶ and difference calculated by review team; ^aDowngraded 1 levels for study limitations (study rated some concerns for RoB); ^bDowngraded 1 level for imprecision (using OIS, studies were not powered to detect minimum SMD of 0.6; see Methods for more information).

Abbreviations. SD=standard deviation; TAU=treatment as usual; VAS=Visual Analogue Scale; VR=virtual reality.

KQ1: DEPRESSION ($k = 6$)

Overview

Six eligible RCTs evaluated VR interventions to address depression, with 4 focusing on treatment of depressive symptoms in older adults (Table 16).^{48,50,52,53} These trials all used the Geriatric Depression

Scale (GDS) to assess presence of substantial depressive symptoms, defined as $GDS \geq 10$.^{48,50,52,53} Three of these studies compared combined VR relaxation and exercise versus non-VR relaxation and exercise, and were conducted in Europe by the same group of investigators^{50,52,53}; 1 of these focused exclusively on post-stroke depression.⁵² The fourth trial was conducted in China and compared VR Tai Chi versus non-VR Tai Chi for treatment-naïve older adults with depression.⁴⁸ Below, we first present findings from this group of 4 studies. Then, we separately describe results from the 2 remaining studies; 1 compared VR behavioral activation versus non-VR behavioral activation for adults with major depressive disorder (MDD),⁴⁹ and the other evaluated a VR rehabilitation program for post-stroke depression.⁵¹ No studies reported quality of life, adherence, or suicidal ideation and/or behaviors. Detailed study characteristics and outcome findings are located in the Supplementary Materials.

Table 16. Summary Characteristics of Studies Evaluating VR Interventions for Depression ($k = 6$)

Author, Year; Study Design; Risk of Bias Total N Key Participant Characteristics	Intervention Characteristics	Comparator Characteristics
Cieslik, 2023 ⁵⁰ Some concerns N = 60 Mean age: 68 years 100% women Members of community center for older women	Exercise + VR Relaxation <ul style="list-style-type: none"> • VR garden with music, mandala coloring task • Group-based low-intensity exercises • 16 x 20-minute sessions; 8 weeks Hardware: VRTierOne device, VR HTC VIVE goggles and controllers Embodiment: No Interactivity: Yes Multisensory stimulation: No	Exercise + Non-VR Relaxation <ul style="list-style-type: none"> • Group-based relaxation, psychoeducation • Group-based low-intensity exercises • 16 x 20-minute sessions; 8 weeks
Kiper, 2022 ⁵² High N = 60 Mean age: 66 years 43-57% female, 43-57% male Post-stroke patients, academic medical rehabilitation center	Exercise + VR Relaxation <ul style="list-style-type: none"> • VR garden with music, mandala coloring task; focus on breathing • Personalized exercise and rehabilitation • 10 x 20-minute sessions; 3 weeks for VR Hardware: VR TierOne device, HTC VIVE PRO goggles and a controller Embodiment: No Interactivity: Yes Multisensory stimulation: NR	Exercise + Non-VR Relaxation <ul style="list-style-type: none"> • Relaxation through Schultz’s Autogenic Training (via audio recording) • Personalized exercise and rehabilitation • 10 x 20-minute sessions; 3 weeks
Szczepanska-Gieracha, 2021 ⁵³ Some concerns N = 25 Mean age: 71 years 100% women Non-responders to therapeutic group program for depression at community center for older women	Exercise + VR Relaxation <ul style="list-style-type: none"> • VR garden with music, mandala coloring task; focus on breathing • Group-based fitness program, relaxation exercises, and psychoeducation • 8 x 80-minute sessions; 4 weeks Hardware: VRTierOne device, VR HTC VIVE goggles and two controllers plugged into a PC Embodiment: No Interactivity: Yes Multisensory stimulation: Yes	Exercise + Non-VR Relaxation <ul style="list-style-type: none"> • Group-based fitness program, relaxation exercises, and psychoeducation • 8 x 60-minute sessions; 4 weeks

Author, Year; Study Design; Risk of Bias Total N Key Participant Characteristics	Intervention Characteristics	Comparator Characteristics
Qiu, 2024 ⁴⁸ High N = 300 Mean age: 62 years 50% male, 50% female Treatment-naïve patients of private medical center	VR Tai Chi <ul style="list-style-type: none"> Tai Chi in VR environment 24 sessions (duration NR); 6 months Hardware: Oculus Quest 2 headset Embodiment: Yes Interactivity: Yes Multisensory stimulation: No	Non-VR Tai Chi <ul style="list-style-type: none"> Tai Chi with in-person instructor, video clips 24 sessions (duration NR); 6 weeks <hr/> Waitlist <ul style="list-style-type: none"> No intervention
Paul, 2024 ⁴⁹ High N = 26 Mean age: 50 years 23% male, 73% female, 4% nonbinary/ other Community members	Behavioral Activation with VR Activities <ul style="list-style-type: none"> Self-selected pleasant activities from commercially available catalogue (standard for VR system), complete ≥ 4 activities per week in home setting Weekly therapist sessions 4 x 30-50-minute sessions; 4 weeks Hardware: VR Meta Quest 2 headset Embodiment: Yes Interactivity: Yes Multisensory stimulation: No	Non-VR Behavioral Activation <ul style="list-style-type: none"> Self-selected pleasant activities in real life, complete ≥ 4 activities per week Weekly therapist sessions 4 x 30-50-minute sessions; 4 weeks
Wu, 2022 ⁵¹ Some concerns N = 44 Mean age: 51 years 36-41% female, 59-64% male Post-stroke patients, academic medical rehabilitation center	VR Rehabilitation <ul style="list-style-type: none"> Fruit selection task in 3D virtual living room Difficulty of task personalized prior to each session 20 x 20-minute sessions; 4 weeks Hardware: Unity 3D engine run on a PC (CPU Intel I7 9700K) with VR VIVE Pro headset Embodiment: No Interactivity: Yes Multisensory stimulation: No	2D Rehabilitation <ul style="list-style-type: none"> Fruit selection task on computer screen 20 x 20-minute sessions; 4 weeks Hardware: Fourier M2 rehabilitation system Embodiment: No Interactivity: Yes Multisensory stimulation: No

Abbreviations. 2D=2-dimensional; 3D=3-dimensional; NR=not reported; PC=personal computer; VR=virtual reality.

VR Relaxation and Exercise versus Non-VR Relaxation and Exercise

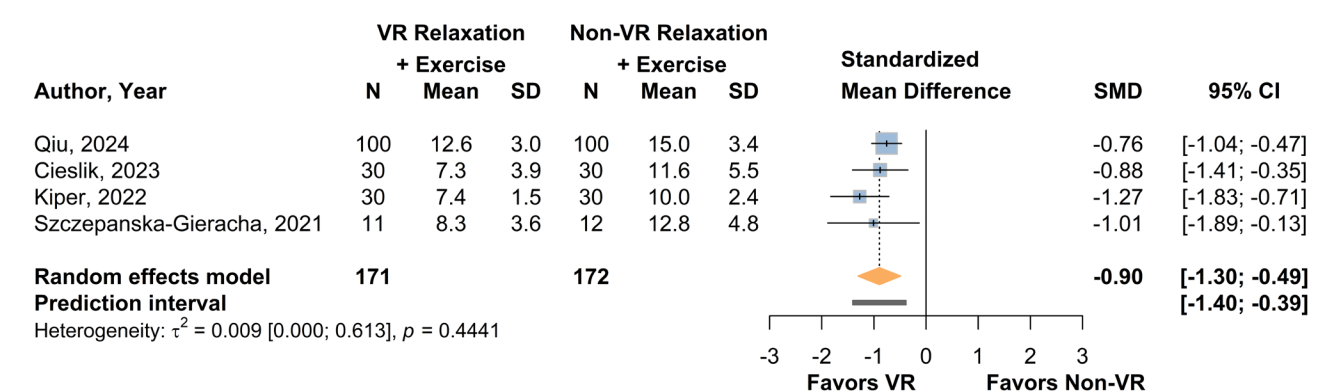
Three small Polish RCTs (total $N = 25-60$) were conducted by the same team of investigators and compared a similar VR relaxation and exercise program versus non-VR relaxation and exercise over 1–2 months.^{50,52,53} In the VR group, participants were immersed in a black and gray virtual garden scene (that saturated in color as sessions progressed) and asked to color in a mandala presented to them within the garden space. Two of these studies focused solely on older women (mean ages = 68–71 years) with depressive symptoms and excluded those who had any ongoing mental health treatment.^{50,53} The third study included both older women and men (50% each, mean age = 66 years) with post-stroke depressive symptoms, and did not specify exposure to other mental health treatment (in eligibility or baseline characteristics).⁵² The fourth study, Qiu 2024, was a 3-arm RCT conducted in China that enrolled 300 older women and men (50% each) with depressive symptoms and no previous or ongoing treatments; authors compared VR versus non-VR tai chi versus waitlist.⁴⁸ In the non-VR tai chi group, participants were supervised by an instructor in person “in a designated space.”⁴⁸

Interventions comprised 8–24 total sessions over a duration of 3–24 weeks. Three studies^{48,50,53} had some concerns for RoB, while Kiper 2022 was rated high RoB primarily due to very substantial loss to follow-up (overall 35%) that was furthermore unbalanced between groups.⁵²

Symptom Severity

The evidence is very uncertain about the effect of VR relaxation and exercise on depressive symptom severity (very low COE; Table 17). All 4 studies assessed depressive symptoms with GDS and 3 of use also used the HADS.^{50,52,53} The pooled estimate for symptoms immediately post-intervention indicates that VR relaxation and exercise led to lower symptom severity (SMD = -0.90 [-1.30, -0.49], using GDS data) (Figure 11). Sensitivity analysis using HADS-depression subscale scores from the 3 available studies also showed similar results (SMD = -0.64 [-1.42, 0.13]) (see [Appendix Figure 2](#)). The COE is very low due to study methodological concerns (1 trial was rated high RoB)⁵² and limited applicability given these specific study populations (2 focused exclusively on older women,^{50,53} and 1 on post-stroke depressive symptoms in older adults⁵²).

Figure 11. Depression: Effect of VR Relaxation and Exercise versus Non-VR Relaxation and Exercise on Symptom Severity Immediately Post-Intervention



Treatment Response and Recovery

Only Kiper 2022 reported on treatment response, assessed as proportion of participants with GDS <10 post-intervention; the VR group had 73% ($N = 22$) below this threshold, compared with 43% ($N = 13$) in the non-VR arm.⁵²

Table 17. Depression Certainty of Evidence: VR Relaxation + Exercise versus Non-VR Relaxation + Exercise

Outcome Measure	Follow-Up Total N (# of Studies)	SMD (95% CI)	Anticipated Absolute Effects on Mean Score at Follow-Up			Certainty	What Happens
			VR Relaxation and Exercise	Non-VR Relaxation and Exercise	Mean Difference		
Symptom Severity	Post-intervention	SMD: -0.90 (-1.3, -0.49)	7.3 (5.4, 9.3)*	11.6*	-4.3 (-6.2, -2.3)	⊕○○○ Very low ^{a,b}	The evidence is very uncertain on the effect of VR relaxation and exercise on symptom severity post-intervention.
GDS	N = 343 (4 RCTs) 48,50,52,53						

Notes. *Values for mean follow-up scores for intervention and/or comparator arms from Cieslik 2023⁵⁰; ^aDowngraded 2 levels for study limitations (1 or more studies rated high RoB); ^bDowngraded 1 level for indirectness (2 studies only included older women, 1 study included only those with post-stroke depressive symptoms).

Abbreviations. GDS=Geriatric Depression Score; RoB=risk of bias; SMD=Standardized Mean Difference; VR=virtual reality.

Engagement

Two studies reported that 100% of participants completed the assigned treatment in both arms.^{50,53} As noted above, Kiper 2022 reported high drop-outs in both arms (26% in VR group).⁵² The fourth study did not report on attendance or discontinuation rates.⁴⁸ None of the studies assessed other measures of engagement.

Adverse Events

Only Kiper 2022 reported on adverse events, stating “no adverse events were reported...and no negative emotional effects were recorded, such as anxiety, discomfort or inconvenience associated with using the device...”⁵²

Other VR Interventions

VR Behavioral Activation versus Non-VR Behavioral Activation

Paul 2024 compared behavioral activation using VR pleasant activities at home versus non-VR activities (in real life) for 26 middle-aged adults with MDD.⁴⁹ Participants were predominantly women (73%), with 23% men and 4% nonbinary or third gender. Treatment in both arms also had weekly sessions with a clinical psychologist over 4 weeks and were asked to complete ≥ 4 activities between sessions. Most participants were middle-aged women (73%, mean age = 50.3 years), and the majority (65%) had other ongoing mental health treatments. This trial was rated high RoB for concerns including substantial loss to follow-up and imbalance in important co-interventions (including other mental health treatments).

Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9) at baseline and immediately post-intervention, and there were no between-group differences in changes in PHQ-9 ($p = 0.78$). However, authors did not directly compare mean scores at follow-up time points (VR = 8.4 [SD = 3.7] vs non-VR = 10.7 [4.6]). There was a higher discontinuation rate in the VR arm (23% vs 15% in

non-VR arm) and adherence was only assessed for participants in the VR group (number of headset uses per participant). The VR arm was assessed using the SSQ, with eyestrain being the most commonly reported symptom (exact proportion or number was not reported). Authors also reported there were no “serious adverse events” in either group but did not specify which events this would include.

VR Rehabilitation versus 2-Dimensional Rehabilitation

Wu 2022 compared VR program involving fruit selection tasks ($N = 22$) with a 2D version of the same tasks on a computer screen ($N = 22$) to treat middle-aged adults (mean age = 51–52 years, 36%–41% women) with depressive symptoms post-stroke.⁵¹ Depression was assessed as Hamilton Depression Rating Scale (HAMD) ≥ 17 , there was no specified requirement for upper extremity weakness or paresis, and use of mental health treatment was not described (either in eligibility or baseline characteristics). The VR setting was a living room and participants were prompted to “select” a piece of fruit. The intervention comprised 20 sessions over 4 weeks. This study was rated some concerns for RoB.

Wu 2022 only reported symptom severity, assessed using HAMD scores immediately post-intervention. The VR group had lower scores (mean = 18.3 [SD = 3.3]) than the 2D arm (mean = 21.1 [1.9], $p < 0.001$).

KQ1: SCHIZOPHRENIA SPECTRUM AND PSYCHOTIC DISORDERS ($k=12$)

Overview

We identified 12 RCTs (reported in 16 articles) evaluating the use of VR interventions in the treatment of schizophrenia spectrum disorders or disorders with psychotic episodes. The most common ($k = 12$) diagnoses were schizophrenia spectrum disorders (*ie*, schizophrenia, schizophreniform, and schizoaffective disorder), followed by other psychotic disorders ($k = 4$) including delusional disorder, brief psychotic disorder, and psychotic disorder not otherwise specified (NOS) or unspecified. Study characteristics are summarized in Table 18. A third of the studies evaluated VR social cognition training (VR SCT; $k = 4$). Two studies examined VR CBT, one of which aimed to reduce the impact of negative symptoms, while the other addressed avoidance behaviors due to paranoia. Two studies evaluated a VR intervention personifying a participant’s auditory hallucinations in the virtual environment. The remaining 5 trials addressed cognition training ($k = 3$) and relaxation/mindfulness ($k = 2$). Nearly all participants also received TAU, with TAU protocols varying slightly across studies.

Below, we first describe study characteristics and results for the 5 studies evaluating VR SCT, followed by studies of VR CBT, VR personified voices therapy, and lastly the other interventions (including VR cognition training + TAU, VR relaxation, and VR mindfulness therapy). No studies reported treatment response/recovery, quality of life, or adherence. Detailed study characteristics and outcome findings are located in the Supplementary Materials.

Table 18. Summary Characteristics of Schizophrenia Spectrum and Other Psychotic Disorders Studies ($k = 12$)

Author, Year; Study Design; Risk of Bias Total <i>N</i> Randomized Age Sex/Gender Key Participant Characteristics	Intervention	Comparator(s)
<p>Nijman, 2023⁵⁵</p> <p>High</p> <p><i>N</i> = 83</p> <p>Mean age: 36-40 years</p> <p>65-73% male; 27-35% female</p> <p>Schizophrenia spectrum disorder, brief psychotic disorder, delusional disorder, or other psychotic disorder; inpatient and outpatient</p>	<p>VR Social Cognition Training + TAU</p> <ul style="list-style-type: none"> Practiced with social stimuli and developed social strategies Role played with a therapist-controlled virtual entity Also received psychoeducation about social cognition 16 x 45-60-minute sessions; 8 weeks <p>Hardware: Oculus Rift HMD. Therapists controlled the environment and virtual entities through a tablet interface and viewed participants' field of vision using a second monitor.</p> <p>Embodiment: No</p> <p>Interactivity: Yes</p> <p>Multisensory stimulation: No</p>	<p>VR Relaxation + TAU</p> <ul style="list-style-type: none"> Engaged in relaxation exercises (eg, breathing exercises, progressive relaxation) with audio guidance while looking at relaxing nature scenes Participants controlled the environment with their gaze Also received psychoeducation about stress and coping 16 45-60-minute sessions; 8 weeks <p>Hardware: Samsung Gear VR headset with a Samsung Galaxy S7 smartphone</p> <p>Embodiment: No</p> <p>Interactivity: Yes</p> <p>Multisensory Stimulation: No</p>
<p>Park, 2011⁶⁵</p> <p>High</p> <p><i>N</i> = 91</p> <p>Mean age: 28-31 years</p> <p>42-52% female</p> <p>Schizophrenia; inpatient</p>	<p>VR Social Cognition Training</p> <ul style="list-style-type: none"> Developed conversation, assertion, and emotional expression skills First, therapist modeled then participant role played followed by feedback from the therapists Repeated role play of the same scene and feedback Each session included 3 role plays with different scenes per participant Role plays occurred in virtual environments with therapist-controlled virtual entities Intensive psychiatric care for 2-4 weeks prior to SCT 10 x 90-minute sessions; 5 weeks <p>Hardware: Eye Trek FMD 250W, OLYMPUS head mounted display and a position tracker (InterTrax2, InterSense)</p> <p>Embodiment: No</p> <p>Interactivity: Yes</p> <p>Multisensory stimulation: No</p>	<p>Non-VR Social Cognition Training</p> <ul style="list-style-type: none"> Same session structure as VR SCT Role plays occurred in physical environments with therapist actors Intensive psychiatric care for 2-4 weeks prior to SCT 10 90-minute sessions; 5 weeks

Author, Year; Study Design; Risk of Bias Total N Randomized Age Sex/Gender Key Participant Characteristics	Intervention	Comparator(s)
<p>Shen, 2022⁵⁶ Some concerns N = 87 Mean age: 31 years 65-67% male; 33-35% female Schizophrenia; inpatient</p>	<p>VR Social Cognition Training + TAU</p> <ul style="list-style-type: none"> • Three phases, all in VR: (1) emotion-perception training, (2) theory of mind deficits and attributional bias, and (3) applying social cognitive skills to choose reactions in role playing game • Continued usual medical treatment; only atypical antipsychotics • 10 sessions (duration NR); 3 weeks <p>Hardware: Pico Goblin2 All-In-One Embodiment: No Interactivity: Yes Multisensory stimulation: No</p>	<p>Non-VR Social Cognition Training + TAU</p> <ul style="list-style-type: none"> • Three phases: (1) introduction and emotions, (2) figuring out situations, and (3) checking it out • Received psychoeducation about social cognition and emotion • Learned about attributional bias and developed strategies to avoid jumping to conclusions • Practiced applying learned skills to cope with daily interpersonal problems • Each session involved 6 inpatient participants • Continued usual medical treatment; only atypical antipsychotics • 10 sessions (duration NR); 5 weeks <hr/> <p>Waitlist + TAU</p> <ul style="list-style-type: none"> • Continued usual medical treatment • 3 weeks
<p>Vass, 2022⁵⁹ High N = 43 Mean age: 37-42 years 48-57% male; 43-52% female Schizophrenia or schizoaffective disorder; outpatient</p>	<p>VR Social Cognition Training + TAU</p> <ul style="list-style-type: none"> • Interacted with a therapist-controlled virtual entity, which played pre-recorded audio and had facial expressions • Afterward, used visual display to change the virtual entity's facial expressions based on its perceived emotional state • Discussed experience and its challenges with therapist • Continued outpatient treatment • 9 x 60-minute sessions; 9 weeks <p>Hardware: Samsung Gear Head Mounted Displays with a Samsung S7 or S8 smartphone and a Samsung Simple Controller Embodiment: Yes Interactivity: No Multisensory stimulation: No</p>	<p>VR Sham + TAU</p> <ul style="list-style-type: none"> • Explored virtual environments in which they could build virtual entities and change locations. • Participants were unable to interact with other users or with therapist in virtual environment • Continued outpatient treatment • 9 60-minute sessions; 9 weeks <p>Hardware: Samsung Gear Head Mounted Displays with a Samsung S7 or S8 smartphone and a Samsung Simple Controller Embodiment: Yes Interactivity: No Multisensory stimulation: No</p>
<p>Cella, 2022⁶⁰ RCT High N = 30 Mean age: 37 years 70% male; 30% female Schizophrenia or psychotic episode; outpatient</p>	<p>VR CBT + TAU</p> <ul style="list-style-type: none"> • Principles based on CBT and cognitive remediation therapy • Performed tasks in preset virtual environments at differing levels of motivational challenge • Also received TAU • 12 sessions (duration NR); 12 weeks <p>Hardware: Oculus Rift-S with ear covering headphones for sound Embodiment: Yes Interactivity: Yes Multisensory stimulation: No</p>	<p>TAU</p> <ul style="list-style-type: none"> • Regular contact with a care coordinator and medication management by a psychiatrist • Session amount and treatment duration NR

Author, Year; Study Design; Risk of Bias Total N Randomized Age Sex/Gender Key Participant Characteristics	Intervention	Comparator(s)
Pot-Kolder, 2018 ⁶⁴ Some concerns N = 116 Mean age: 37-40 years 69-72% male; 28-31% female Schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorder NOS; outpatient	VR CBT + TAU <ul style="list-style-type: none"> Communicated with therapist during personalized VR sessions to explore and challenge suspicious thoughts while engaging with 4 virtual social environments VR exercises comprised 2/3 of each session; reflection and planning with therapist comprised remaining 1/3 Continued existing medication regimen 16 x 60-minute sessions; 8-12 weeks Hardware: Sony HMZ-T1/T2/T3 Head Mounted Display with Logitech F310 Gamepad and a 3DOF tracker for head rotation Embodiment: No Interactivity: Yes Multisensory stimulation: No	TAU <ul style="list-style-type: none"> Regular contact with a psychiatrist and a psychiatric nurse to improve self-care, daytime activities, and social and community functioning Continued existing medication regimen Session amount and treatment duration NR
Dellazizzo, 2021 ⁶³ High N = 74 Mean age: 41-44 years 73-78% male; 22-27% female Schizophrenia or schizoaffective disorder; outpatient	VR Personified Voices Therapy + TAU <ul style="list-style-type: none"> Engaged in dialogue with a therapist-controlled virtual entity, which was meant to personify the abusive, critical, and hostile nature of AVHs Participant-virtual entity interactions became less abusive and more supportive as the sessions progressed Continued existing medication regimen 9 x 60-minute sessions; 9 weeks Hardware: Samsung Gear VR HMD or Oculus Rift HMD Embodiment: No Interactivity: No Multisensory stimulation: No	Non-VR CBT for Psychosis + TAU <ul style="list-style-type: none"> Learning modules and task assignments aimed to identify and develop new means to navigate hallucination experiences Continued existing medication regimen 9 60-minute sessions; 9 weeks
Liang, 2022 ⁶¹ High N = 65 Mean age: 25-27 years 44-52% male; 48-56% female Schizophrenia; setting unclear	VR Personified Voices Therapy + TAU <ul style="list-style-type: none"> Spoke to a virtual entity meant to resemble the source of their AVHs Each session included 3 parts, during which the participant and therapist agreed on the focus of the dialogue, engaged in dialogue (with the therapist controlling the virtual entity) for 10-15 minutes, and shared feedback Continued existing medication regimen 7-9 x 60-minute sessions; 7-9 weeks Hardware: HTC VIVE HMD. Unity 3D game engine and Blendshape were used to create virtual entities. Embodiment: No Interactivity: No Multisensory stimulation: No	Non-VR CBT for Psychosis + TAU <ul style="list-style-type: none"> Completed daily log about AVHs Identified current strategies for coping with AVHs and explored new ways to manage them Re-evaluated negative beliefs based on disconfirming evidence Engaged in mindfulness exercises and practiced daily at home Developed plans to prevent relapse and maintain gains Continued existing medication regimen 7-9 60-minute sessions; 7-9 weeks

Author, Year; Study Design; Risk of Bias Total N Randomized Age Sex/Gender Key Participant Characteristics	Intervention	Comparator(s)
<p>Freeman, 2022⁶² Some concerns N = 346 Mean age: 37-38 years 67% men; 31-33% women; 0-1% other gender; 0-1% prefer not to say; 0-1% missing gender Schizophrenia spectrum disorder, delusional disorder, schizotypal disorder, brief psychotic disorder, unspecified psychosis, or affective diagnosis with psychotic symptoms; outpatient</p>	<p>VR Cognition Training + TAU</p> <ul style="list-style-type: none"> Guided by a pre-programmed virtual coach through automated situational behavioral experiments Chose from 6 virtual social scenarios, each with 5 levels of difficulty Focused on treating agoraphobic-type fears impacting everyday interactions Also received usual care 6 x 30-minute sessions; 6 weeks <p>Hardware: HTC Vive Pro headset and Dell G5 15 5590 laptop Embodiment: No Interactivity: Yes Multisensory stimulation: No</p>	<p>TAU</p> <p>6 weeks of prescription medication, visits from a mental health worker, and outpatient appointments with a psychiatrist</p>
<p>Li, 2022⁵⁷ Some concerns N = 68 Mean age: 46-47.5 years 60-67% male; 33-40% female Schizophrenia; inpatient</p>	<p>VR Cognition Training + TAU</p> <ul style="list-style-type: none"> Completed different shopping tasks in a virtual supermarket Aimed to improve cognitive function Also received antipsychotic treatment 10 sessions (duration NR); 2 weeks <p>Hardware: NR Embodiment: No Interactivity: Yes Multisensory stimulation: No</p>	<p>TAU</p> <p>2 weeks of antipsychotic treatment</p>
<p>Fusco, 2018⁶⁶ High N = 22 Mean age: 48 years 60% male; 40% female Schizophrenia spectrum disorder or other psychotic disorder; all participants recruited from a psychiatric rehabilitation program</p>	<p>VR Relaxation</p> <ul style="list-style-type: none"> Learned about the effects of triggering psychosocial situations and progressive muscle relaxation techniques Immersed in a relaxing scenario on a beach by the ocean, accompanied by music and a voice guiding a progressive muscle relaxation exercise 10 x 10-minute sessions (duration NR); 2 months <p>Hardware: HMD and a pair of headphones Embodiment: NR Interactivity: NR Multisensory stimulation: No</p>	<p>Non-VR Relaxation</p> <ul style="list-style-type: none"> Learned about the effects of triggering psychosocial situations and progressive muscle relaxation techniques Entered a "classic relaxation setting" (not further specified) to apply techniques 10 10-minute sessions; 2 months

Author, Year; Study Design; Risk of Bias Total <i>N</i> Randomized Age Sex/Gender Key Participant Characteristics	Intervention	Comparator(s)
Lee, 2023 ⁵⁴ Some concerns <i>N</i> = 64 Mean age: 31-33 years 45-46% male; 54-55% female Schizophrenia spectrum disorder, psychotic disorder NOS, or delusional disorder; outpatient	VR Mindfulness Training + TAU <ul style="list-style-type: none"> • Watched educational videos about mindfulness and self-awareness • Engaged with therapeutic videos that guided meditation (eg, sense awareness, awareness, looking back at self, loving-kindness) • Received intermittent instructions during therapeutic meditation sessions • Also received psychotherapy, psychoeducation, and pharmacotherapy • 8 30-minute sessions; 8 weeks Hardware: Oculus Rift CV1 Embodiment: No Interactivity: No Multisensory stimulation: No	VR Sham + TAU <ul style="list-style-type: none"> • Watched 3D, virtual nature scenes • Also received psychotherapy, psychoeducation, and pharmacotherapy • 8 30-minute sessions; 8 weeks Hardware: Oculus Rift CV1 Embodiment: No Interactivity: No Multisensory stimulation: No

Abbreviations. 3D=three-dimensional; AVH=audiovisual hallucination; CBT=cognitive behavioral therapy; HMD=head-mounted display; NOS=not otherwise specified; NR=not reported; SCT=social cognition training; TAU=treatment as usual; VR=virtual reality.

VR Social Cognition Training

Four RCTs^{55,56,59,65} evaluated VR SCT for patients who had a diagnosis of schizophrenia or other disorders involving psychosis. Study characteristics including study population diagnoses are summarized in Table 18. Two studies enrolled only inpatients,^{56,65} while 1 study focused on outpatients,⁵⁹ and another study included both inpatient and outpatient participants.⁵⁵ Sample size ranged from 42–81, and study participants were primarily young to middle-aged men (mean age = 33 years, 48%–73% male). Comparators varied, with the most common being non-VR SCT (*k* = 2).^{57,59} Three trials⁵⁵⁻⁵⁷ were rated some concerns for RoB, while the other trials^{59,65} were rated high RoB.

All the studies evaluated similar VR SCT that utilized role play of social situations with a therapist to foster development of social skills (eg, conversing, expressing/recognizing emotion, and interpreting behavior).^{55,56,59,65} In Nijman 2023, the therapists spoke to the participants using a virtual entity whose appearance, voice, and behavior the therapist could control, along with environment.⁵⁵ Therapists in Vass 2022⁵⁹ could control the virtual entity's movements and the timing of pre-recorded verbal responses.⁵⁹ Park 2011⁶⁵ and Shen 2022⁵⁶ did not detail the therapist-controlled versus preset aspects of virtual entity behavior in the role plays.

Symptom Severity

Two studies^{56,65} evaluated VR SCT versus non-VR SCT in 10 sessions delivered over 3–5 weeks and measured symptom severity. Due to heterogeneity of outcome domains measured, these studies were not combined to assess certainty of evidence. Using the Positive and Negative Syndrome Scale (PANSS), Park 2011⁶⁵ reported no between-arm differences in positive, negative, and general symptoms of psychosis immediately post-intervention.⁶⁵ Using the Personal and Social Performance

(PSP) scale, Shen 2022 found that both VR SCT (mean = 73.08, $p = 0.001$) and non-VR SCT (mean = 66.30, $p = 0.005$) had significantly higher social functioning than the waiting list arm (mean = 66.67) post-intervention, but no significant difference was reported between VR SCT and non-VR SCT.^{56?}

The other 2 studies used 2 different comparators and were thus not combined to assess certainty of evidence.^{55,59} Nijman 2023 compared VR SCT with VR relaxation therapy, which aimed to reduce stress and improve coping through a combination of virtual relaxation and psychoeducation.⁵⁵ None of the time by treatment interactions were statistically significant for outcomes including general psychotic symptoms, social cognition, social functioning, anxiety, and depression immediately post-intervention and at 3 months post-intervention. Vass 2022 used a VR sham comparator. Using the PANSS, Vass 2022 reported significantly better results for VR SCT than for VR sham in PANSS total score (mean = 42.76 vs 55.00, $p \leq 0.0001$), PANSS negative symptoms (mean = 12.28 vs 16.14, $p = 0.005$) and PANSS cognitive symptoms (mean = 11.66 vs 14.90, $p = 0.003$) immediately post-intervention. At 3 months post-intervention, VR SCT continued to have significantly better results than VR sham in PANSS total score (mean = 42.57 vs 52.00, $p \leq 0.0001$), negative symptoms (mean = 12.47 vs 16.15, $p = 0.0005$) and cognitive symptoms (mean = 11.52 vs 14.15, $p \leq 0.0001$).⁵⁹ There were no significant results for positive or affective symptoms at either time point.

Engagement

Four studies reported aspects of treatment engagement including attendance^{55,56,59,65} and participant VR experience.^{59,65}

Attendance

Shen 2022 reported no significant difference in the overall treatment discontinuation proportions between the VR SCT and non-VR SCT groups at 3 weeks (2/28 VR participants vs 6/30 non-VR participants, $p = 0.299$) and 5 weeks (2/28 vs 7/30, $p = 0.181$), although this is difficult to compare between arms given the 3-week duration of VR SCT and the 5-week duration of non-VR SCT.⁵⁶ Park 2011⁶⁵ reported no difference in discontinuation proportions between VR and non-VR SCT groups, though they observed higher attendance in the VR SCT group compared with the non-VR SCT group (mean 95.3% vs 91.0%, $p = 0.019$).⁶⁵

Nijman 2023 reported no significant difference in discontinuation proportions between VR SCT and VR relaxation.⁵⁵ Vass 2022 reported that across the VR SCT and VR sham arms, only 1 VR SCT participant did not complete the allocated intervention due to an adverse event deemed unrelated to treatment.⁵⁹

Other Engagement Measures

Park 2011 assessed participant SCT-related motivation and skills knowledge in the VR and non-VR arms at the end of each treatment session using study-developed measures, and found that the VR arm scored higher than the non-VR arm on average post-session interest in participation (mean = 81.5 vs 75.5, $p = 0.09$) and average post-session social cognition skills knowledge (mean = 88.0 vs 82.9, $p = 0.033$).⁶⁵ Vass 2022 solicited feedback on the VR SCT experience and reported that most respondents found the intervention interesting (100%), entertaining (93.3%), realistic (86.7%), and important to their rehabilitation (78%).⁵⁹ Most respondents felt safe using the VR devices (93.3%) and considered the virtual entity interactions pleasant (80%). Some participants found the Temporal Disc Controller

aspect of VR SCT cumbersome (13.4%) and difficult (26.7%), while others reported anxiety related to treatment (20%).

Adverse Events

Three studies reported adverse events.^{55,59,65} Park 2011 assessed for simulator sickness in the VR SCT arm after each session, using a study-developed questionnaire which did not apply to the non-VR arm.⁶⁵ They reported no symptoms related to the use of an immersive HMD (eg, nausea, sweating, and dizziness). Vass 2022 used the SSQ to monitor possible side effects, but did not report quantitative results.⁵⁹ Authors stated that only mild symptoms were reported (eg, difficulty focusing, sweating, and blurred vision), and that all symptoms resolved within a few minutes. Nijman 2022⁵⁵ also used the SSQ at the end of session 3. Nausea was reported significantly more often by VR SCT participants compared with VR relaxation participants (mean = 3.1 vs 2.0, $p = 0.036$), while there was no significant difference between groups in the oculomotor score (mean = 3.2 vs 4.26, $p = 0.262$).⁵⁵ Furthermore, 2 serious adverse events (SAE) were reported in the VR SCT arm compared with 1 SAE in the VR relaxation arm, though all were deemed unrelated to study participation.⁵⁵

VR CBT + TAU

Two RCTs evaluated VR CBT + TAU for patients who had a diagnosis of a schizophrenia spectrum disorder or psychotic disorder or who had experienced a psychotic episode.^{60,64} Study characteristics are summarized in Table 18. Sample size ranged from 30–116 and study participants were primarily male (69%–72%) in early to middle adulthood (mean age = 37.7 years). Both studies compared VR CBT plus TAU versus TAU alone. Cella 2022⁶⁰ was rated high RoB and Pot-Kolder 2018⁶⁴ was rated some concerns for RoB.

The interventions varied with respect to therapist/participant control. Cella 2022⁶⁰ evaluated a CBT approach they called VR negative symptom therapy (and abbreviated as V-NeST) involving therapist-supported activities including psychoeducation, behavioral activation, and activity appraisal. This therapy was designed to help participants achieve personal recovery goals and improve negative symptoms. The intervention offered 5 preset VR environments (designed by study authors) with motivational challenges of varying difficulty. The authors described TAU as a multi-modal treatment approach including regular contact with a care coordinator and medication management by a psychiatrist. In Pot-Kolder 2018, VR CBT consisted of 4 VR social environments which participants could navigate using a gamepad.⁶⁴ The intervention was designed to address paranoid thoughts during social encounters in an effort to improve social participation. Individualized case formulation guided the selection of social environmental cues to elicit fear, paranoid thoughts, and safety behaviors. Therapists could customize the experience by adjusting the number of human virtual entities present, their characteristics, their engagement with the participant, and their use of pre-recorded sentences. The authors described TAU as consisting of antipsychotic medication and regular contact with a psychiatric nurse to improve activities of daily living and quality of life.

Symptom Severity

The evidence is very uncertain on the effect of VR CBT + TAU on psychotic symptom severity compared with TAU alone (very low COE; Table 19). Both studies^{60,64} evaluated VR CBT + TAU versus TAU alone lasting 8–12 weeks (12–16 sessions) and measured psychotic symptom severity. Cella 2022⁶⁰ monitored negative symptoms (Clinical Assessment Interview for Negative Symptoms (CAINS)), while Pot-Kolder 2018⁶⁴ assessed changes in paranoia symptoms (GPTS). Both studies

reported treatment by time interactions that favored the VR CBT + TAU arms for all outcomes. Cella 2022 reported that pairwise comparisons between VR CBT + TAU and TAU, post-intervention and controlling for baseline scores, favored VR CBT+TAU for improving negative symptoms.⁶⁰ Pot-Kolder 2018 found a significant treatment by time interaction favoring VR CBT+TAU in ideas of persecution (GPTS).⁶⁴ By additional measures, Pot-Kolder 2018 also reported a significant reduction in momentary paranoia based on the Experience Sampling Method (ESM) in the VR CBT + TAU arm and a slight increase in the TAU arm, and found significant treatment arm by time interactions favoring VR CBT + TAU over TAU in momentary paranoia (ESM) and paranoid ideation (ESM) post-intervention and at 3 months follow-up.

Engagement

Both studies^{60,64} reported aspects of treatment engagement including attendance,^{60,64} adherence,⁶⁴ and participant VR experience.⁶⁴

Attendance

Cella 2022⁶⁰ reported that 2 participants allocated to VR CBT did not receive the intervention due to moving ($n = 1$) or competing demands ($n = 1$). All participants in the TAU control group received treatment. Pot-Kolder 2018⁶⁴ reported that 11 participants (19%) in the VR CBT group did not complete treatment, including 4 participants who did not start treatment. The other 7 participants discontinued for various reasons, including being too afraid ($n = 1$), not having enough time ($n = 1$), not willing to travel ($n = 1$), nausea ($n = 1$), unable to attend sober ($n = 1$), and finding the HMD too uncomfortable ($n = 2$).

Adherence

A secondary report of Pot-Kolder 2018¹¹⁷ reported that on average, participants completed 47.4 out of 70 diary entries. Participants completed more diary entries on average before treatment than after treatment (mean = 49.9 vs 45.4, no statistical comparison).

Other Measures of Engagement

Pot-Kolder 2018⁶⁴ used the Igroup Presence Questionnaire to assess participants' experience in the VR environments. Results show that participants felt satisfied with spatial presence (mean = 3.79), involvement (mean = 3.16), and realness (mean = 2.96).

Adverse Events

Both studies^{60,64} reported adverse events. The evidence is very uncertain on the effect of VR CBT + TAU on adverse events compared with TAU alone (very low COE; Table 19). In Cella 2022,⁶⁰ 2 participants in the TAU control arm reported serious adverse events. There were 11 adverse events (7 in the VR CBT group and 4 in the TAU group), none of which authors deemed associated with study participation. Pot-Kolder 2018⁶⁴ used the SSQ to assess cybersickness symptoms in the VR CBT group after sessions 4 and 8. One participant dropped out because of nausea, and authors stated that no other adverse events related to either VR CBT or TAU were reported.

Table 19. Schizophrenia Spectrum and Other Psychotic Disorders Certainty of Evidence: VR CBT + TAU versus TAU Alone

Outcome Measure	Follow-Up Total N (# of Studies)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up			Certainty	What Happens
		VR Exposure	Waitlist	Difference		
Symptom Severity	Post-intervention					
CAINS; ⁶⁰ GPTS Ideas of persecution ⁶⁴	N = 125 (2 RCTs) ^{60,64}	33.4*	38.2*	-4.8*	⊕○○○ Very low ^{a,b}	The evidence is very uncertain on the effect of VR CBT + TAU on psychotic symptom severity post-intervention.
Adverse events	During intervention					
NR	N = 125 (2 RCTs) ^{60,64}	7 AEs [†]	4 AEs [†]	—	⊕○○○ Very low ^{a,c}	The evidence is very uncertain on the effect of VR CBT + TAU on adverse events post-intervention.

Notes. *Values for mean follow-up scores for intervention and comparator arms taken from Pot-Kolder 2018.⁶⁴ Differences calculated by review team; [†]Values for adverse events for intervention and comparator arms from Cella, 2022.⁶⁰ ^aDowngraded 2 levels for study limitations (one or more studies rated high RoB); ^bDowngraded 1 level for imprecision (study measurement tool does not comprehensively assess psychotic or other schizophrenic symptoms); ^cDowngraded 1 level for indirectness (outcome not measured consistently).

Abbreviations. AE=adverse event; CAINS=Clinical Assessment Interview for Negative Symptoms; CBT=cognitive behavioral therapy; GPTS=Green Paranoid Thoughts Scale; NR=not reported; RoB=risk of bias; TAU=treatment as usual; VR=virtual reality.

VR Personified Voices Therapy

Two RCTs evaluated a VR intervention comprising role plays designed to teach participants to manage their paranoid hallucinations. Patients in these studies were diagnosed with schizophrenia or schizoaffective disorder.^{61,63} Study characteristics are summarized in Table 18. Sample size ranged from 58–62. In 1 study,⁶¹ the sample was half female and primarily young adults (mean age = 25.9 years). The other study⁶³ enrolled primarily men (76%) in early to middle adulthood (mean age = 42.5 years). Both studies evaluated a VR intervention in which a therapist-controlled virtual entity was used for role playing participant responses to hallucinations, compared with non-VR CBT for psychosis (CBTp). Both trials were rated high RoB.

The VR intervention in these studies¹¹⁸⁻¹²¹ used a visual depiction of the participants' audiovisual hallucinations (AVHs) in the form of a virtual entity visible and audible in the virtual environment, which the therapists controlled to engage in dialogue with the participants. The intervention was designed to help patients develop new strategies for interacting with the content of their AVHs, improved their emotional regulation, and modified their negative self-perceptions. Liang 2022⁶¹ described a collaborative process in which the therapist developed the virtual entity with the participant to ensure it resembled the most distressing aspects of their AVHs. The therapist controlled the virtual entity's face and body during dialogue with the participant and used either the virtual entity's voice or their own to offer guidance and feedback. Dellazizzo 2021⁶³ did not describe the development of the virtual entity, though there was a similarly high degree of therapist control of the entity during

dialogue therapy. Both studies used CBTp as the comparator, which was delivered in an individual format by a licensed psychologist or psychiatrist.

Symptom Severity

The evidence is very uncertain on the effect of VR personified voices therapy on psychotic symptom severity compared with non-VR CBTp, immediately post-intervention and at 3 months post-intervention (very low COE; Table 20). Both studies reported treatment by time interactions. In Liang 2022,⁶¹ there were no statistically significant differences between arms over time for auditory hallucination, positive, or negative symptoms. There were also no interaction effects for anxiety or depressive symptoms. Dellazizzo 2021⁶³ measured PANSS, Psychotic Symptom Rating Scales (PSYRATS) and BDI at baseline, post-intervention, and 3 month follow-up, but did not test between-arm differences in means at any time point. Time by treatment effects across all 3 time points, however, were assessed for these measures and several subscales. Only PANSS anxio-depressive subscale was statistically significant, in favor of the VR personified voices therapy arm ($p = 0.025$).

Engagement

Both studies^{60,63} reported aspects of treatment engagement including discontinuation^{61,63} and participant experience.⁶³

Attendance

In Liang 2022,⁶¹ 94% percent of VR personified voices therapy participants completed all treatment sessions, compared with 85% of CBTp participants. Two participants did not complete the VR personified voices intervention, compared with 5 CBTp participants. Authors cited reasons including failure to attend, adjustment to antipsychotic medication, or no desire to continue treatment. Dellazizzo 2021⁶³ reported that 9 participants in the VR personified voices arm did not attend sessions or discontinued treatment, compared with 3 participants in the CBTp arm. Reasons for discontinuation included lack of motivation, not wanting to reduce their AVH voices, and moving away.

Other Measures of Engagement

Dellazizzo 2021⁶³ used semi-structured interviews to assess the acceptance and feasibility of both interventions in a subsample of participants ($n = 15$). The questions asked about factors including content, sequence, dose, setting, mode of delivery, and materials used. Most participants rated the intervention aspects as adequate, though one-third found the dose to be too short or described the intervention as stressful, particularly related to VR personified voices therapy. Almost half the CBTp participants reported that the homework was uninteresting or unhelpful.

Adverse Events

Liang 2022⁶¹ stated that no adverse events attributed to either intervention occurred during the course of the study, and did not define adverse events. Dellazizzo 2021⁶³ reported that no patients were re-hospitalized during the trial.

Table 20. Schizophrenia Spectrum and Other Psychotic Disorders Certainty of Evidence: VR Personified Voices Therapy versus Non-VR CBTp

Outcome Measure	Follow-Up	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-up			Certainty	What Happens
		VR Personified Voices Therapy	Non-VR CBTp	Difference		
Symptom Severity	Post-intervention N = 120 (2 RCTs) ^{61,63}	70.3*	73.4*	-3.1*	⊕○○○ Very low ^{a,b}	The evidence is very uncertain on the effect of VR personified voices therapy on psychotic symptom severity post-intervention.
	PANSS total 3 months post-intervention N = 120 (2 RCTs) ^{61,63}	67.5*	71.4*	-3.9*	⊕○○○ Very low ^{a,b}	The evidence is very uncertain on the effect of VR personified voices therapy on psychotic symptom severity at 3 months post-intervention.

Notes. *Values for mean follow-up scores for intervention and comparator arms taken from Liang 2022.⁶¹ Differences calculated by review team; ^aDowngraded 2 levels for study limitations (1 or more studies rated high risk of bias); ^bDowngraded 1 level for imprecision (sample size did not meet OIS).

Abbreviations. CBTp=Cognitive Behavioral Therapy for psychosis; OIS=optimal information size; PANSS=Positive and Negative Syndrome Scale; VR=virtual reality.

Other Interventions

VR Cognition Training Plus TAU versus TAU Alone

Three studies investigated VR cognition training plus TAU compared with TAU alone. Two studies included inpatients with a schizophrenia diagnosis,^{57,58} while the third study recruited outpatients with a diagnosis of a schizophrenia spectrum disorder or an affective disorder with psychotic symptoms.⁶² Study characteristics are summarized in Table 18. Sample size ranged from 64–346. In the study with N = 346,⁶² the average age of participants was 37.2 years, and 32% were female. The average age in the other 2 studies was 25–46 years and 33%–52% were female. Interventions comprised 7 to at least 20 sessions over a duration of 2–6 weeks. One study was rated as low RoB.⁵⁸ The other 2 studies were appraised as some concerns RoB.^{57,62} All the studies investigated novel cognitive training interventions with the goal of improving cognitive function. Studies were not combined to assess certainty of evidence due to differences in intervention content and outcome measures (Table 18).

Freeman 2022⁶² assessed paranoia using the Green Paranoid Thoughts Scale (GPTS) and depressive symptoms using the PHQ-9, post-intervention and at 20 weeks post-intervention. They reported no significant between-arm differences in either outcome at either time point. Li 2022 found no significant treatment by time interactions for psychotic symptoms (PANSS) or social functioning (PSP) post-intervention.⁵⁷ There was a significant interaction between time and treatment for cognitive function ($p < 0.001$).

Freeman 2022⁶² found no significant between-arm differences in suicidal ideation by the Columbia Suicide Severity Rating Scale (C-SSRS) post-intervention or at 20-week follow-up, and found no significant differences between groups in quality of life based on the EuroQol 5 Dimension 5 Level (EQ-5D-5L).⁶²

Freeman 2022⁶² cited ISO14155:2011 guidelines for medical device trials as guidance in their SAE definition.¹²² Authors defined an adverse event as serious if it led to any of the following: death; life-threatening illness or injury; hospitalization or prolongation of existing hospitalization; persistent or clinically significant disability or incapacity; medical or surgical intervention to prevent any of the aforementioned outcomes; fetal distress or death, or congenital anomaly or birth defect; or “otherwise considered medically significant by the investigator.” Authors noted that an independent data monitoring and ethics committee chair rated whether any SAE was related to trial procedures. Freeman 2022 reported 12 SAEs (in 9 participants) in the VR cognition training + TAU group and 8 SAEs (in 7 participants) in the TAU alone group (no significant between-group difference). Authors stated that “we also checked medical notes for adverse events that were not serious,” without further definition of non-serious adverse events. Freeman 2022 reported 25 adverse events (in 21 participants) in the VR cognition training + TAU group and 29 adverse events (in 19 participants) in the TAU alone group (no significant between-group difference). In Li 2022, 1 participant in the VR cognition training + TAU arm reported feeling dizzy during treatment, but this did not impact their treatment completion.⁵⁷ Authors stated that no other “uncomfortable feelings” or SAE were reported (without further definition).

Li 2022⁵⁷ reported 2 participants in the TAU group did not receive the intervention (1 due to adjusting drug dosage, 1 due to being over the age of 55), and 4 in the VR cognition training + TAU did not start the intervention due to being unable to complete the initial cognitive battery.

VR Relaxation

One study, Fusco 2018,⁶⁶ investigated VR relaxation (which they entitled progressive muscle relaxation) compared with non-VR relaxation in a sample of participants with a diagnosis of a schizophrenia spectrum or other psychotic disorder. Study characteristics are summarized in Table 18. The intervention arm received 10 sessions of VR relaxation over 2 months, while the control arm followed similar non-VR procedures. The average age of participants was 48 years and 41% were female. The study was appraised as some concerns RoB.

Fusco 2018⁶⁶ did not report eligible psychotic symptom severity outcomes, but did assess anxiety using the Beck Anxiety Inventory (BAI), finding significantly lower mean anxiety scores in the VR relaxation arm than in the non-VR relaxation arm (17.54 vs 23.45, $p < 0.01$).

VR Mindfulness Therapy

One study, Lee 2023,⁵⁴ investigated VR mindfulness + TAU compared with VR sham + TAU in a sample of participants with a diagnosis of a schizophrenia spectrum disorder or other psychotic disorder not otherwise specified. Study characteristics are summarized in Table 18. The intervention arm received 8 sessions of educational and therapeutic experiences over 8 weeks, while the control arm engaged with virtual nature scenes. Usual treatment including supportive psychotherapy, psychoeducation, and pharmacotherapy was provided to all participants during the trial. The average age of participants was 32 years and 54% were female. The study was appraised as some concerns RoB due to assignment to the intervention and measurement of the outcome.

Lee 2023⁵⁴ found no significant between-arm differences in post-intervention means and no significant treatment arm by time interactions for measures assessing positive and negative symptoms (PANSS), delusions and auditory hallucinations (PSYRATS), and depressive symptoms (BDI). Authors also measured the motivation and pleasure domain of negative symptoms using the Motivation and Pleasure Scale-Self Report (MAP-SR), finding no significant between-arm differences in post-intervention means, and a significant treatment arm by time interaction only for the subscale assessing feelings and motivation about close, caring relationships ($p = 0.027$). There were no significant between-arm differences in suicidal ideation based on the C-SSRS post-intervention.

Lee 2023⁵⁴ used the SSQ to assess cybersickness symptoms in both study arms (VR mindfulness and VR sham) after the first and eighth (final) session of treatment. In the VR mindfulness group ($n = 33$), the most common symptoms were difficulty with visual focus (77%), blurred vision (69%), and eye fatigue (69%). In the VR sham group ($n = 28$), the most common symptoms were blurred vision (67%), general discomfort (90%), and difficulty with visual focus (53%). There were no significant between-arm differences in incidence of cybersickness symptoms at either time point, and severity of symptoms was usually less than moderate in both groups.

KQ2: BENEFITS AND HARMS OF VR INTERVENTIONS FOR SUICIDE PREVENTION

The single study evaluating an VR intervention for suicide prevention was a 3-arm RCT conducted in Iran that enrolled 189 young and middle-aged men and women (95% \leq age 50 years, 59% women) who had at least 1 suicide attempt in the past year.¹²³ Ronaghi 2024 compared 2 months of VR-based education and counselling with non-VR-based education and counseling, and no intervention.¹²³ Duration of interventions, length of sessions, and further description of education or counseling content were not provided. Ronaghi 2024 also did not report any additional evaluation of participants for specific mental health disorders or whether participants may have been receiving other treatments. This study was rated high RoB due to substantial concerns regarding lack of reported information on intervention completion and loss to follow-up, and whether analytic methods accounted for these issues.

Ronaghi 2024 reported using the Beck Scale for Suicide Ideation (BSS) to assess participants at baseline and post-intervention, but did not report summary scores for any time point.¹²³ Rather, scores were provided for “suicidal intent,” “suicidal ideation,” and “contemplated attempt” at baseline and follow-up, but authors did not describe how these were derived from BSS items. Although authors reported that there were greater reductions in these scores for the VR group (compared with both non-VR education and counseling, and the no treatment arms), it is unclear that this indicates any meaningful change in suicide ideation given the lack of information regarding assessment and scoring. No other eligible outcomes were reported.

DISCUSSION

SUMMARY OF KEY FINDINGS

Characteristics of Evidence Base for KQ1 Prioritized Disorders

- Most VR interventions were conducted in supervised health care or laboratory settings ($k = 42$); only 2 studies evaluated a VR intervention for home use (1 for social anxiety disorder, 1 for depression). There was substantial variation in VR session number and the total duration of interventions.
- Young and middle-aged adults (mean age <65) comprised the main study population across various disorders, except for depression studies.
- Studies evaluating VR exposure therapy interventions dominated the evidence base, comprising all studies for PTSD, specific phobia of flying, alcohol use disorder, and stimulant use disorder.
- VR interventions to treat depression primarily involved relaxation and exercise for older adults.
- For schizophrenia spectrum disorders, VR interventions varied in content, including social cognition training ($k = 6$), CBT ($k = 2$), personified voices therapy ($k = 2$), and others.
- No study evaluated whether VR characteristics (embodiment, interactivity, or multisensory stimulation) impacted VR intervention effects or engagement.

Effects of VR Interventions for KQ1 Prioritized Disorders

- Compared with non-VR PE therapy, VR PE therapy for PTSD may result in less symptom severity improvement immediately post-intervention, and little to no difference at 3 months post-intervention (both low COE). VR PE therapy probably results in less treatment response immediately post-intervention (moderate COE).
- For social anxiety disorder, the evidence is very uncertain on the effects of VR exposure therapy alone, or of CBT plus VR exposure therapy, on symptom severity (all very low COE) as compared to waitlist or to CBT plus non-VR exposure therapy.
- For specific phobia of flying, the evidence is very uncertain on the effect of VR exposure on symptom severity or flight completion, compared with either non-VR exposure or waitlist (very low COE).
- For alcohol use disorder, the 2 studies were too heterogeneous and COE was not assessed.
- For stimulant use disorder, VR exposure therapy may result in less craving immediately post-intervention (low COE) as compared to treatment as usual.
- The evidence is very uncertain on the effect of VR relaxation and exercise on depressive symptoms immediately post-intervention, compared with exercise and non-VR relaxation (very low COE).
- For schizophrenia spectrum disorders, the evidence is very uncertain on the effect of VR CBT on psychotic symptom severity immediately post-intervention, as compared to treatment as usual (very low COE). The evidence is also very uncertain on the effect of VR personified

voices therapy on psychotic symptom severity, immediately post-intervention and at 3 months post-intervention, as compared to non-VR CBT (both very low COE).

- Adverse events were often not assessed, and when reported, not systematically assessed for all arms. This contributed to the uncertainty in adverse effects of VR interventions across mental health disorders.

VR Interventions for Suicide Prevention (KQ2)

- One eligible RCT evaluated a VR intervention for suicide prevention; this Iranian study was rated high RoB due to substantial methodological concerns and only reported limited findings on suicide ideation (assessed by unclear measures)

EVIDENCE GAPS AND FUTURE RESEARCH

For PTSD, specific phobia of flying, alcohol use disorder, and stimulant use disorder, all VR interventions involved exposure therapy. The earliest studies were of specific phobia of flying, with VR exposure therapy expanding in recent years into other mental health disorders. Despite sharing the same underlying conceptual basis for effectiveness, unanswered questions remain about effects and mechanisms of VR exposure therapy across the varying target populations. For example, all studies of VR PE for PTSD included exposure to combat trauma, and found that VR exposure may have effects similar to standard imaginal exposure at long-term follow-up. In these interventions, VR exposure involved virtual combat scenarios meant to emulate combat service in Iraq and/or Afghanistan. While therapists controlled the delivery of many features of stimuli within scenarios, some fundamental elements of scenarios (such as specific combat environment visuals and sounds) were preset and unchangeable at point of care. Findings from a bespoke combat-exposure VR setup may not generalize to other combat scenarios, and arguably cannot generalize to PTSD caused by non-combat traumas. For example, studies evaluating PTSD treatment effectiveness of bespoke VR exposure scenarios related to sexual violence are ongoing (without results in time for this report).^{124,125} Similarly, evaluated alcohol and stimulant use VR interventions were designed to be specific both to the substances used and the sociocultural context of use, and it is not clear that findings would generalize to other substances and settings.¹²⁶

VR exposure scenarios require substantial tailoring to address specific clinical situations, including the type of mental health disorder (*eg*, PTSD vs social anxiety disorder). The development and testing of VR interventions to treat mental health disorders has required the dedication and committed efforts of multidisciplinary teams with both expertise in rapidly evolving VR technologies and clinical experience with mental health disorders. Thus, in all the studies included here, VR scenarios were largely preset with limited customization at the time a therapist is considering how exposure therapy should be applied for individual participants. In the future, advancements in VR technology may increase the level of flexibility and customization that can be accomplished by clinics or mental health professionals at the time they would be initiating treatments, thus leading to greater efficiencies and usability (by avoiding the need to acquire and learn entirely new VR systems for specific disorders and clinical situations). However, to understand whether these potential improvements in VR technology actually lead to better outcomes (or greater access) for patients, future research will be needed to compare these treatments to other forms of therapy, particularly non-VR exposure (*eg*, imaginal or in vivo exposure).

Additionally, mechanistic research to clarify the underlying key contributions of *virtual* exposure remains key for determining the added value of VR interventions. It remains unclear when VR exposure may replace either imaginal or in vivo exposure across multiple disorders, or when and how VR exposure may lead to greater efficacy by functioning in ways different from both imaginal and in vivo exposure. For example, while it has been proposed that VR exposure adds value to real-world exposure therapy by allowing finer therapist control of stimuli delivery and processing,¹²⁶⁻¹³⁰ included studies did not specifically address how this would be the potential mechanism (as distinct from other treatment differences) between VR and non-VR arms, or indicate under what circumstances (or for which patients) this element of therapist control would have been most beneficial.

VR technology has advanced quickly in recent years, and one could question whether findings from studies employing earlier technologies may generalize to state-of-the-art VR interventions. The ability of technology to improve efficacy depends on the mechanistic role of the VR characteristics that future technological progress can offer. Within exposure therapies, VR characteristics such as interactivity (a measure of participant control) and multisensory stimulation varied, but we found no studies comparing VR exposure therapies that differed regarding these key elements. Studies evaluating effects in relation to such mechanistically relevant VR characteristics could clarify when and how VR can add value to specific types of exposure therapy.

Beyond exposure therapy for above disorders, VR relaxation and exercise interventions were evaluated for depression in older adults, and demonstrated some potential for greater improvement of symptoms, compared with non-VR analogous interventions. However, the COE was very low due to concerns with study methodology and the applicability of findings from these specific populations to the greater diversity of adults with depression. Future work is needed to demonstrate whether these VR interventions may work well for young and middle-aged adults, and to investigate comparative efficacy against other treatments, both pharmacological and psychological.

The schizophrenia spectrum disorder studies, in contrast, comprised a wide array of VR-delivered therapy types, most in early phases of development, for participants with psychoses. The majority of studies leveraged VR environments to build participants' social and/or cognition skills, with elements of therapist control and/or participant control that are infeasible in the real world (such as therapists determining virtual entities' appearance or behaviors to allow participants to build social interaction skills, or participants expressing emotion perception by choosing a virtual entity's facial expression in response to communication). VR personified voices therapy, in contrast, stands out as an example of a therapy in which VR enables a therapeutic approach—creating a naturalistic, therapist-controlled entity that personifies a patient's audiovisual hallucinations—whose fundamentals cannot be achieved in the real world. This use of VR is distinct from approaches that seek to leverage VR as a means of delivery for therapies that are evidence based in the physical world,¹³¹ and was unique among VR therapies identified in this review. As this new therapeutic concept remains actively under development for a population with severe mental illness refractory to evidence-based psychotherapies, benefits and harms remain in question and are still under study. For such new approaches that leverage elements available only in VR space, studies evaluating the impact of presence versus absence of key VR characteristics (such as elements of therapist control, or levels of interactivity and/or multisensory stimulation) could be key both to understanding effects and maximizing feasibility of implementation.

Most included studies did not use clear and systematic methods to evaluate adverse events for VR interventions and comparator groups. This is an important gap for future research to address because this information will inform clinician decision-making, promote shared decision-making with well-

informed patients, and potentially impact prioritization of limited medical resources. Trials should assess adverse events for each treatment arm using open-ended questions and/or checklists administered to all participants on a regular basis.¹³² Additionally, studies should clearly define the severity of adverse events (*eg*, serious events can be defined as life threatening, requiring hospitalization, or resulting in persistent disability) and rates of events that led to discontinuation of the treatment. Evaluation of adverse events will likely also require larger studies that are adequately powered to detect differences in adverse event rates across groups.

Research on heterogeneity of treatment effects may be key to understanding when and how VR delivery can improve either therapy effectiveness or participant engagement, and when and how it may have additional risks. We did not identify consistent trends with respect to VR's impact on therapy attendance in included studies, and most studies did not evaluate any other measures of patient engagement with VR. Few included studies evaluated relationships between participant characteristics and clinical outcomes of VR interventions. One notable example²⁰ found that VR PE therapy was more effective for PTSD symptom severity among participants with depression, while non-VR PE was more effective among participants without depression, prompting further research questions about how VR may enhance exposure therapy for people with comorbid PTSD and depression, who tend to have worse PTSD outcomes in current care contexts.¹³³ Findings suggest that heterogeneity of VR intervention effects, in terms of both clinical outcomes and treatment engagement, is an area broadly in need of study. This requires studies designed and powered to assess outcomes in prespecified subgroups with variation in key characteristics relevant to the potential mechanisms of effect; the most rigorous study design would be randomized trials with sufficient power and stratified sampling to detect potential differences in efficacy.

The severity of the mental health condition, which is often associated with the intensity of therapy and the need for clinician oversight, also informs the types of studies needed to build the VR evidence base. With respect to clinician-intensive therapies for mental health conditions with high acuity, it is essential to establish benefits and harms of VR approaches, and to determine whether VR adds value given the need for clinician presence regardless of technological approach. With respect to low-touch therapies (for appropriate conditions and symptom severity, such as low-intensity depressive symptoms, fear of public speaking, or phobia of flying), it is theoretically possible that VR interventions could enable immersive therapies—potentially with therapist control of key elements—to be delivered in home settings, which is arguably a potential benefit. Strikingly, our review identified only 2 studies of VR interventions for home use (VR pleasant activities to treat depressive disorder and VR exposure to treat social anxiety disorder). If an important goal is to increase reach of psychotherapies by using VR as a means of enhancing treatments delivered via telehealth or independent home use, then effectiveness and safety of home use must be evaluated for these future VR interventions.

Finally, there is a profound evidence gap regarding VR interventions for suicide prevention. We identified only a single, poor-quality study that reported findings that were challenging to understand and interpret. Future work is needed to understand whether VR interventions can reduce suicide risk, and where these may be useful in the context of adequate evaluation and treatment for specific mental health disorders.

IMPLICATIONS FOR POLICY AND PRACTICE

For PTSD, social anxiety disorder, specific phobia of flying, alcohol use disorder, and stimulant use disorder, the reviewed comparative effectiveness evidence indicated that VR exposure therapy interventions performed similarly to non-VR evidence-based psychotherapies. As studied, these therapies also require substantial therapist involvement, and involve preset content with limited customizability at point of care. The rationale for implementing VR exposure therapy interventions in widespread clinical contexts remains unclear, pending identification of subpopulations or contexts in which VR may add value in terms of effectiveness and/or patient engagement in therapy.

VR interventions for depressive symptoms were mostly targeting community populations of older adults with depressive symptoms, and may be useful for improving access to self-management treatments (such as relaxation and exercise) for these populations. Before focusing resources on implementing these, it may be best to evaluate how they compare with other low-touch interventions that address mental health for older adults.

For schizophrenia spectrum disorders, novel VR interventions are in early phases of development, and benefits and harms require more definitive study before clinical implementation.

LIMITATIONS

We limited eligibility to VR interventions that were fully immersive (*ie*, virtual environments that visually separated participants entirely from the physical environment), and therefore cannot comment on augmented reality approaches that visually incorporate virtual elements into the physical environment. We limited eligibility to English-language studies, and thus relevant studies published in other languages may have been missed. However, we note that included studies were conducted in a great variety of locations and non-English speaking countries.

CONCLUSIONS

VR exposure therapy for PTSD may be less effective, or had little to no difference in effect, when compared with non-VR exposure therapy. For stimulant use disorder, VR exposure therapy may result in less craving, compared to treatment as usual. The evidence is uncertain regarding the effects of VR therapies for social anxiety disorder, flying phobia, depression, and schizophrenia spectrum disorders. The evidence is also very uncertain regarding adverse events of VR interventions across prioritized disorders, and there is a lack of evidence on VR interventions for suicide prevention. In addition to the need for higher quality studies addressing the areas lacking evidence, future research should focus on clarifying the impacts of key VR characteristics on treatment effects, and how population characteristics may be important for both effectiveness and engagement.

REFERENCES

1. Trivedi RB, Post EP, Sun H, et al. Prevalence, comorbidity, and prognosis of mental health among US veterans. *American journal of public health*. 2015;105(12):2564-2569.
2. Trivedi RB, Post EP, Piegari R, et al. Mortality among veterans with major mental illnesses seen in primary care: results of a national study of veteran deaths. *Journal of general internal medicine*. 2020;35(1):112-118.
3. National strategy for preventing veteran suicide 2018-2028. U.S. Department of Veterans Affairs, Office of Mental Health and Suicide Prevention. https://www.mentalhealth.va.gov/suicide_prevention/docs/Office-of-Mental-Health-and-Suicide-Prevention-National-Strategy-for-Preventing-Veterans-Suicide.pdf
4. Karlin BE, Cross G. From the laboratory to the therapy room: National dissemination and implementation of evidence-based psychotherapies in the U.S. Department of Veterans Affairs Health Care System. *Am Psychol*. Jan 2014;69(1):19-33. doi:10.1037/a0033888
5. Valenstein-Mah H, Greer N, McKenzie L, et al. Effectiveness of training methods for delivery of evidence-based psychotherapies: a systematic review. *Implement Sci*. May 27 2020;15(1):40. doi:10.1186/s13012-020-00998-w
6. Goldsmith ES, Koffel E, Ackland PE, et al. Evaluation of Implementation Strategies for Cognitive Behavioral Therapy (CBT), Acceptance and Commitment Therapy (ACT), and Mindfulness-Based Stress Reduction (MBSR): a Systematic Review. *J Gen Intern Med*. Sep 2023;38(12):2782-2791. doi:10.1007/s11606-023-08140-4
7. VA/DOD Clinical Practice Guidelines. U.S. Department of Veterans Affairs. Accessed 8/21/2025, 2025. <https://www.healthquality.va.gov/guidelines/MH/>
8. Steuer J. Defining virtual reality: Dimensions determining telepresence. *Journal of communication*. 1992;42(4):73-93.
9. Mütterlein J. The three pillars of virtual reality? Investigating the roles of immersion, presence, and interactivity. 2018;
10. Rauschnabel PA, Felix R, Hinsch C, Shahab H, Alt F. What is XR? Towards a framework for augmented and virtual reality. *Computers in human behavior*. 2022;133:107289.
11. Bailey AL, Haywood T. VA Immersive Executive Roundtable 2023. US Department of Veterans Affairs. <https://innovation.va.gov/hil/assets/documents/va-immersive-executive-roundtable-final.pdf>
12. DistillerSR. DistillerSR Inc. <https://www.distillersr.com/>
13. Cochrane Handbook for Systematic Reviews of Interventions. Updated August 22, 2023. <https://training.cochrane.org/handbook>
14. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. Aug 28 2019;366:l4898. doi:10.1136/bmj.l4898
15. Persky S, Colloca L. Medical Extended Reality Trials: Building Robust Comparators, Controls, and Sham. *J Med Internet Res*. Nov 22 2023;25:e45821. doi:10.2196/45821
16. metafor: Meta-Analysis Package for R. <https://cran.r-project.org/web/packages/metafor/index.html>
17. GRADEpro GDT. <https://www.gradepro.org/>
18. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol*. Dec 2011;64(12):1283-93. doi:10.1016/j.jclinepi.2011.01.012
19. Santesso N, Glenton C, Dahm P, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *J Clin Epidemiol*. Mar 2020;119:126-135. doi:10.1016/j.jclinepi.2019.10.014

20. Difede J, Rothbaum BO, Rizzo AA, et al. Enhancing exposure therapy for posttraumatic stress disorder (PTSD): a randomized clinical trial of virtual reality and imaginal exposure with a cognitive enhancer. *Transl Psychiatry*. Jul 27 2022;12(1):299. doi:10.1038/s41398-022-02066-x
21. Beidel DC, Frueh BC, Neer SM, Lejuez CW. The efficacy of Trauma Management Therapy: A controlled pilot investigation of a three-week intensive outpatient program for combat-related PTSD. *J Anxiety Disord*. Aug 2017;50:23-32. doi:10.1016/j.janxdis.2017.05.001
22. McLay RN, Baird A, Webb-Murphy J, et al. A Randomized, Head-to-Head Study of Virtual Reality Exposure Therapy for Posttraumatic Stress Disorder. *Cyberpsychol Behav Soc Netw*. Apr 2017;20(4):218-224. doi:10.1089/cyber.2016.0554
23. Reger GM, Koenen-Woods P, Zetocha K, et al. Randomized controlled trial of prolonged exposure using imaginal exposure vs. virtual reality exposure in active duty soldiers with deployment-related posttraumatic stress disorder (PTSD). *J Consult Clin Psychol*. Nov 2016;84(11):946-959. doi:10.1037/ccp0000134
24. Miyahira SD, Folen RA, Hoffman HG, Garcia-Palacios A, Spira JL, Kawasaki M. The effectiveness of VR exposure therapy for PTSD in returning warfighters. *Stud Health Technol Inform*. 2012;181:128-32.
25. McLay RN, Wood DP, Webb-Murphy JA, et al. A randomized, controlled trial of virtual reality-graded exposure therapy for post-traumatic stress disorder in active duty service members with combat-related post-traumatic stress disorder. *Cyberpsychol Behav Soc Netw*. Apr 2011;14(4):223-9. doi:10.1089/cyber.2011.0003
26. Lacey C, Frampton C, Beaglehole B. A self-guided virtual reality solution for social anxiety: Results from a randomized controlled study. *J Psychiatr Res*. Dec 2024;180:333-339. doi:10.1016/j.jpsychires.2024.10.032
27. Stefaniak I, Hanusz K, Mierzejewski P, Bienkowski P, Parnowski T, Murawiec S. Preliminary Study of Efficacy and Safety of Self-Administered Virtual Exposure Therapy for Social Anxiety Disorder vs. Cognitive-Behavioral Therapy. *Brain Sci*. Sep 13 2022;12(9)doi:10.3390/brainsci12091236
28. Kim MK, Eom H, Kwon JH, Kyeong S, Kim JJ. Neural effects of a short-term virtual reality self-training program to reduce social anxiety. *Psychol Med*. May 2022;52(7):1296-1305. doi:10.1017/S0033291720003098
29. Zainal NH, Chan WW, Saxena AP, Taylor CB, Newman MG. Pilot randomized trial of self-guided virtual reality exposure therapy for social anxiety disorder. *Behav Res Ther*. Dec 2021;147:103984. doi:10.1016/j.brat.2021.103984
30. Ma L, Kruijt AW, Nojd S, Zetterlund E, Andersson G, Carlbring P. Attentional Bias Modification in Virtual Reality - A VR-Based Dot-Probe Task With 2D and 3D Stimuli. *Front Psychol*. 2019;10:2526. doi:10.3389/fpsyg.2019.02526
31. Bouchard S, Dumoulin S, Robillard G, et al. Virtual reality compared with in vivo exposure in the treatment of social anxiety disorder: a three-arm randomised controlled trial. *Br J Psychiatry*. Apr 2017;210(4):276-283. Comment in: *Br J Psychiatry*. 2018 Oct;213(4):617<ovid:br/> PMID: 30247117 [<https://www.ncbi.nlm.nih.gov/pubmed/30247117>]<ovid:br/> <ovid:br/>Comment in: *Br J Psychiatry*. 2018 Oct;213(4):617<ovid:br/> PMID: 30741144 [<https://www.ncbi.nlm.nih.gov/pubmed/30741144>]. doi:10.1192/bjp.bp.116.184234
32. Kampmann IL, Emmelkamp PM, Hartanto D, Brinkman WP, Zijlstra BJ, Morina N. Exposure to virtual social interactions in the treatment of social anxiety disorder: A randomized controlled trial. *Behav Res Ther*. Feb 2016;77:147-56. doi:10.1016/j.brat.2015.12.016
33. Anderson PL, Price M, Edwards SM, et al. Virtual reality exposure therapy for social anxiety disorder: a randomized controlled trial. *J Consult Clin Psychol*. Oct 2013;81(5):751-60. doi:10.1037/a0033559

34. Robillard G, Bouchard S, Dumoulin S, Guitard T, Klinger E. Using virtual humans to alleviate social anxiety: preliminary report from a comparative outcome study. *Stud Health Technol Inform.* 2010;154:57-60.
35. Kan C, Wang Y, Hu R, Chen K, Zhang Y. Convenient virtual reality exposure self-training for social anxiety: a randomized controlled study. 2024;
36. Triscari MT, Faraci P, Catalisano D, D'Angelo V, Urso V. Effectiveness of cognitive behavioral therapy integrated with systematic desensitization, cognitive behavioral therapy combined with eye movement desensitization and reprocessing therapy, and cognitive behavioral therapy combined with virtual reality exposure therapy methods in the treatment of flight anxiety: a randomized trial. *Neuropsychiatr Dis Treat.* 2015;11:2591-8. doi:10.2147/NDT.S93401
37. Tortella-Feliu M, Botella C, Llabres J, et al. Virtual reality versus computer-aided exposure treatments for fear of flying. *Behav Modif.* Jan 2011;35(1):3-30. doi:10.1177/0145445510390801
38. Krijn M, Emmelkamp PM, Olafsson RP, et al. Fear of flying treatment methods: virtual reality exposure vs. cognitive behavioral therapy. *Aviat Space Environ Med.* Feb 2007;78(2):121-8.
39. 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.* Mar 2006;37(1):80-90. doi:10.1016/j.beth.2005.04.004
40. Maltby N, Kirsch I, Mayers M, Allen GJ. Virtual reality exposure therapy for the treatment of fear of flying: a controlled investigation. *J Consult Clin Psychol.* Oct 2002;70(5):1112-8. doi:10.1037//0022-006x.70.5.1112
41. Rothbaum BO, Hodges L, Smith S, Lee JH, Price L. A controlled study of virtual reality exposure therapy for the fear of flying. *J Consult Clin Psychol.* Dec 2000;68(6):1020-6. doi:10.1037//0022-006x.68.6.1020
42. Wiederhold BK, Gevirtz RN, Spira JL. Virtual reality exposure therapy vs. imagery desensitization therapy in the treatment of flying phobia. *Towards cyberpsychology: Mind, cognition and society in the internet age.* 2001:253-272.
43. Hernandez-Serrano O, Ghita A, Figueras-Puigderrajols N, et al. Predictors of Changes in Alcohol Craving Levels during a Virtual Reality Cue Exposure Treatment among Patients with Alcohol Use Disorder. *J Clin Med.* Sep 18 2020;9(9)doi:10.3390/jcm9093018
44. Kim DY, Lee JH. The Effects of Training to Reduce Automatic Action Tendencies Toward Alcohol Using the Virtual Alcohol Approach-Avoidance Task in Heavy Social Drinkers. *Cyberpsychol Behav Soc Netw.* Dec 2019;22(12):794-798. doi:10.1089/cyber.2019.0121
45. Figueras-Puigderrajols N, Fernandez-Ruiz J, Ferrer-Garcia M, et al. Virtual reality-cue exposure therapy for the treatment of alcohol use disorder: Preliminary results. *Annual Review of CyberTherapy and Telemedicine.* 2020;18:261-264.
46. Ji X, Tang Y, Jing L, et al. Effects of a virtual reality-based motivational reinforcement + desensitization intervention program on psychological craving and addiction memory in female MA-dependent young adults. *Front Psychiatry.* 2023;14:1114878. doi:10.3389/fpsy.2023.1114878
47. Wang YG, Liu MH, Shen ZH. A virtual reality counterconditioning procedure to reduce methamphetamine cue-induced craving. *J Psychiatr Res.* Sep 2019;116:88-94. doi:10.1016/j.jpsychires.2019.06.007
48. Qiu T, Zhang G, Zhou F, Jiang H. Application of virtual reality to enhance therapeutic Tai Chi for depression in elderly people. *Acta Psychol (Amst).* Aug 2024;248:104316. doi:10.1016/j.actpsy.2024.104316
49. Paul M, Bullock K, Bailenson J, Burns D. Examining the Efficacy of Extended Reality-Enhanced Behavioral Activation for Adults With Major Depressive Disorder: Randomized Controlled Trial. *JMIR Ment Health.* Apr 15 2024;11:e52326. doi:10.2196/52326

50. Cieslik B, Juszko K, Kiper P, Szczepanska-Gieracha J. Immersive virtual reality as support for the mental health of elderly women: a randomized controlled trial. *Virtual Real.* May 7 2023;1-9. doi:10.1007/s10055-023-00797-w
51. Wu JJ, Zheng MX, Hua XY, et al. Altered effective connectivity in the emotional network induced by immersive virtual reality rehabilitation for post-stroke depression. *Front Hum Neurosci.* 2022;16:974393. doi:10.3389/fnhum.2022.974393
52. Kiper P, Przysieszna E, Cieslik B, et al. Effects of Immersive Virtual Therapy as a Method Supporting Recovery of Depressive Symptoms in Post-Stroke Rehabilitation: Randomized Controlled Trial. *Clin Interv Aging.* 2022;17:1673-1685. doi:10.2147/CIA.S375754
53. Szczepanska-Gieracha J, Cieslik B, Serweta A, Klajs K. Virtual Therapeutic Garden: A Promising Method Supporting the Treatment of Depressive Symptoms in Late-Life: A Randomized Pilot Study. *J Clin Med.* May 1 2021;10(9)doi:10.3390/jcm10091942
54. Lee BM, Kim SW, Lee BJ, et al. Effects and safety of virtual reality-based mindfulness in patients with psychosis: a randomized controlled pilot study. *Schizophrenia (Heidelb).* Sep 13 2023;9(1):57. doi:10.1038/s41537-023-00391-8
55. Nijman SA, Pijnenborg GHM, Vermeer RR, et al. Dynamic Interactive Social Cognition Training in Virtual Reality (DiSCoVR) versus Virtual Reality Relaxation (VRRelax) for People With a Psychotic Disorder: A Single-Blind Multicenter Randomized Controlled Trial. *Schizophr Bull.* Mar 15 2023;49(2):518-530. doi:10.1093/schbul/sbac166
56. Shen ZH, Liu MH, Wu Y, Lin QQ, Wang YG. Virtual-reality-based social cognition and interaction training for patients with schizophrenia: A preliminary efficacy study. *Front Psychiatry.* 2022;13:1022278. doi:10.3389/fpsy.2022.1022278
57. Li S, Liu R, Sun B, et al. Effect of Virtual Reality on Cognitive Impairment and Clinical Symptoms among Patients with Schizophrenia in the Remission Stage: A Randomized Controlled Trial. *Brain Sci.* Nov 18 2022;12(11)doi:10.3390/brainsci12111572
58. Wang X, Kou X, Meng X, Yu J. Effects of a virtual reality serious game training program on the cognitive function of people diagnosed with schizophrenia: A randomized controlled trial. *Front Psychiatry.* 2022;13:952828. doi:10.3389/fpsy.2022.952828
59. Vass E, Simon V, Csukly G, Fekete Z, Kis B, Simon L. Virtual reality-based theory of mind intervention in schizophrenia: Preliminary efficacy results. *Compr Psychiatry.* Nov 2022;119:152350. doi:10.1016/j.comppsy.2022.152350
60. Cella M, Tomlin P, Robotham D, et al. Virtual Reality Therapy for the Negative Symptoms of Schizophrenia (V-NeST): A pilot randomised feasibility trial. *Schizophr Res.* Oct 2022;248:50-57. doi:10.1016/j.schres.2022.07.013
61. Liang N, Li X, Guo X, et al. Visual P300 as a neurophysiological correlate of symptomatic improvement by a virtual reality-based computer AT system in patients with auditory verbal hallucinations: A Pilot study. *J Psychiatr Res.* Jul 2022;151:261-271. doi:10.1016/j.jpsychires.2022.04.027
62. Freeman D, Lambe S, Kabir T, et al. Automated virtual reality therapy to treat agoraphobic avoidance and distress in patients with psychosis (gameChange): a multicentre, parallel-group, single-blind, randomised, controlled trial in England with mediation and moderation analyses. *Lancet Psychiatry.* May 2022;9(5):375-388. doi:10.1016/S2215-0366(22)00060-8
63. Dellazizzo L, Potvin S, Phraxayavong K, Dumais A. One-year randomized trial comparing virtual reality-assisted therapy to cognitive-behavioral therapy for patients with treatment-resistant schizophrenia. *NPJ Schizophr.* Feb 12 2021;7(1):9. doi:10.1038/s41537-021-00139-2
64. Pot-Kolder R, Geraets CNW, Veling W, et al. Virtual-reality-based cognitive behavioural therapy versus waiting list control for paranoid ideation and social avoidance in patients with psychotic disorders: a single-blind randomised controlled trial. *Lancet Psychiatry.* Mar 2018;5(3):217-226.

- Comment in: *Lancet Psychiatry*. 2018 Mar;5(3):189-191<ovid:br/> PMID: 29429949
[<https://www.ncbi.nlm.nih.gov/pubmed/29429949>]. doi:10.1016/S2215-0366(18)30053-1
65. Park KM, Ku J, Choi SH, et al. A virtual reality application in role-plays of social skills training for schizophrenia: a randomized, controlled trial. *Psychiatry Res*. Sep 30 2011;189(2):166-72. doi:10.1016/j.psychres.2011.04.003
 66. Fusco C, Di Nunzio M, Moccia A. Progressive muscle relaxation training: classic technique and virtual reality for psychotic patients. *Minerva Psichiatrica*. 2018;59(4):177 EP - 180. doi:10.23736/s0391-1772.18.01987-8
 67. Shin B, Oh J, Kim BH, et al. Effectiveness of Self-Guided Virtual Reality-Based Cognitive Behavioral Therapy for Panic Disorder: Randomized Controlled Trial. *JMIR Ment Health*. Nov 22 2021;8(11):e30590. doi:10.2196/30590
 68. Perez-Ara MA, Quero S, Botella C, et al. Virtual reality interoceptive exposure for the treatment of panic disorder and agoraphobia. *Stud Health Technol Inform*. 2010;154:77-81.
 69. Botella C, García-Palacios A, Villa H, et al. Virtual reality exposure in the treatment of panic disorder and agoraphobia: A controlled study. *Clinical Psychology & Psychotherapy*. 2007;14(3):164-175. doi:10.1002/cpp.524
 70. Choi YH, Vincelli F, Riva G, Wiederhold BK, Lee JH, Park KH. Effects of group experiential cognitive therapy for the treatment of panic disorder with agoraphobia. *Cyberpsychol Behav*. Aug 2005;8(4):387-93. doi:10.1089/cpb.2005.8.387
 71. Pelissolo A, Zaoui M, Aguayo G, et al. Virtual reality exposure therapy versus cognitive behavior therapy for panic disorder with agoraphobia: a randomized comparison study. Journal article. *Journal of cyber therapy and rehabilitation*. 2012;5(1):35-43.
 72. Lorenzo Gonzalez M, Castro WP, Pitti Gonzalez CT, Bethencourt Perez JM, de la Fuente Portero JA, Marco RG. Efficacy of virtual reality exposure therapy combined with two pharmacotherapies in the treatment of agoraphobia. *Health & Mental Health Treatment & Prevention* 3300. *International Journal of Clinical and Health Psychology*. 2011;11(2):189-203.
 73. Pitti CT, Penate W, de la Fuente J, et al. The combined use of virtual reality exposure in the treatment of agoraphobia. *Actas Esp Psiquiatr*. Jul-Aug 2015;43(4):133-41.
 74. Quero S, Pérez-Ara MÁ, Bretón-López J, García-Palacios A, Baños RM, Botella C. Acceptability of virtual reality interoceptive exposure for the treatment of panic disorder with agoraphobia. *British Journal of Guidance & Counselling*. 2013;42(2):123-137. doi:10.1080/03069885.2013.852159
 75. Castro WP, Sanchez MJR, Gonzalez CTP, Bethencourt JM, de la Fuente Portero JA, Marco RG. Cognitive-behavioral treatment and antidepressants combined with virtual reality exposure for patients with chronic agoraphobia. *Health & Mental Health Treatment & Prevention* 3300. *International Journal of Clinical and Health Psychology*. 2014;14(1):9-17. doi:<https://dx.doi.org/10.1016/S1697-2600%2814%2970032-8>
 76. Meyerbroeker K, Morina N, Kerkhof GA, Emmelkamp PM. Virtual reality exposure therapy does not provide any additional value in agoraphobic patients: a randomized controlled trial. *Psychother Psychosom*. 2013;82(3):170-6. doi:10.1159/000342715
 77. Shibani Y, Schelhorn I, Pauli P, Muhlberger A. Effect of combined multiple contexts and multiple stimuli exposure in spider phobia: A randomized clinical trial in virtual reality. *Behav Res Ther*. Aug 2015;71:45-53. doi:10.1016/j.brat.2015.05.014
 78. Jiang MYW, Upton E, Newby JM. A randomised wait-list controlled pilot trial of one-session virtual reality exposure therapy for blood-injection-injury phobias. *J Affect Disord*. Nov 1 2020;276:636-645. doi:10.1016/j.jad.2020.07.076

79. Gujjar KR, van Wijk A, Kumar R, de Jongh A. Efficacy of virtual reality exposure therapy for the treatment of dental phobia in adults: A randomized controlled trial. *J Anxiety Disord*. Mar 2019;62:100-108. doi:10.1016/j.janxdis.2018.12.001
80. Michaliszyn D, Marchand A, Bouchard S, Martel MO, Poirier-Bisson J. A randomized, controlled clinical trial of in virtuo and in vivo exposure for spider phobia. *Cyberpsychol Behav Soc Netw*. Dec 2010;13(6):689-95. doi:10.1089/cyber.2009.0277
81. Garcia-Palacios A, Hoffman H, Carlin A, Furness TA, 3rd, Botella C. Virtual reality in the treatment of spider phobia: a controlled study. *Behav Res Ther*. Sep 2002;40(9):983-93. doi:10.1016/s0005-7967(01)00068-7
82. Shiban Y, Brutting J, Pauli P, Muhlberger A. Fear reactivation prior to exposure therapy: does it facilitate the effects of VR exposure in a randomized clinical sample? *J Behav Ther Exp Psychiatry*. Mar 2015;46:133-40. doi:10.1016/j.jbtep.2014.09.009
83. Alvarez-Perez Y, Rivero F, Herrero M, et al. Changes in Brain Activation through Cognitive-Behavioral Therapy with Exposure to Virtual Reality: A Neuroimaging Study of Specific Phobia. *J Clin Med*. Aug 9 2021;10(16)doi:10.3390/jcm10163505
84. Miloff A, Lindner P, Dalfgard P, et al. Automated virtual reality exposure therapy for spider phobia vs. in-vivo one-session treatment: A randomized non-inferiority trial. *Behav Res Ther*. Jul 2019;118:130-140. doi:10.1016/j.brat.2019.04.004
85. Emmelkamp PM, Krijn M, Hulsbosch AM, de Vries S, Schuemie MJ, van der Mast CA. Virtual reality treatment versus exposure in vivo: a comparative evaluation in acrophobia. *Behav Res Ther*. May 2002;40(5):509-16. doi:10.1016/s0005-7967(01)00023-7
86. Freeman D, Haselton P, Freeman J, et al. Automated psychological therapy using immersive virtual reality for treatment of fear of heights: a single-blind, parallel-group, randomised controlled trial. *Lancet Psychiatry*. Aug 2018;5(8):625-632. Comment in: *Lancet Psychiatry*. 2018 Aug;5(8):606-607<ovid:br/> PMID: 30007518 [<https://www.ncbi.nlm.nih.gov/pubmed/30007518>]. doi:10.1016/S2215-0366(18)30226-8
87. Krijn M, Emmelkamp PM, Biemond R, de Wilde de Ligny C, Schuemie MJ, van der Mast CA. Treatment of acrophobia in virtual reality: the role of immersion and presence. *Behav Res Ther*. Feb 2004;42(2):229-39. doi:10.1016/S0005-7967(03)00139-6
88. Hodges LF, Kooper R, Meyer TC, et al. Virtual environments for treating the fear of heights. *Computer*. 1995;28(7):27-34.
89. Pericot-Valverde I, Secades-Villa R, Gutierrez-Maldonado J. A randomized clinical trial of cue exposure treatment through virtual reality for smoking cessation. *J Subst Abuse Treat*. Jan 2019;96:26-32. doi:10.1016/j.jsat.2018.10.003
90. Goldenhersch E, Thrul J, Ungaretti J, Rosencovich N, Waitman C, Ceberio MR. Virtual Reality Smartphone-Based Intervention for Smoking Cessation: Pilot Randomized Controlled Trial on Initial Clinical Efficacy and Adherence. *J Med Internet Res*. Jul 29 2020;22(7):e17571. doi:10.2196/17571
91. Girard B, Turcotte V, Bouchard S, Girard B. Crushing virtual cigarettes reduces tobacco addiction and treatment discontinuation. *Cyberpsychol Behav*. Oct 2009;12(5):477-83. doi:10.1089/cpb.2009.0118
92. Schroder B, Kroczeck A, Kroczeck LOH, Ehliis AC, Batra A, Muhlberger A. Cigarette craving in virtual reality cue exposure in abstainers and relapsed smokers. *Sci Rep*. Mar 30 2024;14(1):7538. doi:10.1038/s41598-024-58168-7
93. Bordnick PS, Traylor AC, Carter BL, Graap KM. A Feasibility Study of Virtual Reality-Based Coping Skills Training for Nicotine Dependence. *Res Soc Work Pract*. May 2012;22(3):293-300. doi:10.1177/1049731511426880

94. Malbos E, Borwell B, Einig-Iscaim M, et al. Virtual reality cue exposure therapy for tobacco relapse prevention: a comparative study with standard intervention. *Psychol Med*. Aug 2023;53(11):5070-5080. doi:10.1017/S0033291722002070
95. Malbos E, Borwell B, Cantalupi R, Lancon C. Virtual reality cue exposure for smoking relapse prevention: A comparative trial. *Annual Review of CyberTherapy and Telemedicine*. 2018;2018(16):124-130.
96. Machulska A, Eiler TJ, Kleinke K, et al. Approach bias retraining through virtual reality in smokers willing to quit smoking: A randomized-controlled study. *Behav Res Ther*. Jun 2021;141:103858. doi:10.1016/j.brat.2021.103858
97. Sancassiani F, Perra A, Galetti A, et al. Alexithymia and Bipolar Disorder: Virtual Reality Could Be a Useful Tool for the Treatment and Prevention of These Conditions in People with a Physical Comorbidity. *J Clin Med*. Oct 18 2024;13(20)doi:10.3390/jcm13206206
98. Carta MG, Kurotschka PK, Machado S, et al. A Virtual Reality Cognitive Stimulation Program as an Effective Tool Against Residual/Prodromal Depressive Symptoms in Bipolar Disorders. *J Clin Med*. Aug 11 2024;13(16)doi:10.3390/jcm13164714
99. Primavera D, Urban A, Cantone E, et al. The Impact on Anxiety Symptoms of an Immersive Virtual Reality Remediation Program in Bipolar Disorders: A Randomized Clinical Trial. *J Clin Med*. Jul 18 2024;13(14)doi:10.3390/jcm13144203
100. Primavera D, Migliaccio GM, Garau V, et al. Improving Quality of Life in Bipolar Disorders with an Immersive Virtual Reality Remediation Training Randomized Controlled Trial (RCT). *J Clin Med*. Jul 2 2024;13(13)doi:10.3390/jcm13133886
101. Perra A, Galetti A, Zaccheddu R, et al. A Recovery-Oriented Program for People with Bipolar Disorder through Virtual Reality-Based Cognitive Remediation: Results of a Feasibility Randomized Clinical Trial. *J Clin Med*. Mar 9 2023;12(6)doi:10.3390/jcm12062142
102. Popa CO, Sava FA, Muresan S, et al. Standard CBT versus integrative and multimodal CBT assisted by virtual-reality for generalized anxiety disorder. *Front Psychol*. 2022;13:1008981. doi:10.3389/fpsyg.2022.1008981
103. Navarro-Haro MV, Modrego-Alarcon M, Hoffman HG, et al. Evaluation of a Mindfulness-Based Intervention With and Without Virtual Reality Dialectical Behavior Therapy((R)) Mindfulness Skills Training for the Treatment of Generalized Anxiety Disorder in Primary Care: A Pilot Study. *Front Psychol*. 2019;10:55. doi:10.3389/fpsyg.2019.00055
104. Javaherirenani R, Mortazavi SS, Shalbahfan M, Ashouri A, Farani AR. Virtual reality exposure and response prevention in the treatment of obsessive-compulsive disorder in patients with contamination subtype in comparison with in vivo exposure therapy: a randomized clinical controlled trial. *BMC Psychiatry*. Nov 28 2022;22(1):740. doi:10.1186/s12888-022-04402-3
105. Rizzo A, Reger G, Perlman K, et al. Virtual reality posttraumatic stress disorder (PTSD) exposure therapy results with active duty OIF/OEF service members. 2011;
106. Verdi EK, Katz AC, Gramlich MA, Rothbaum BO, Reger GM. Impact of dissociation on exposure therapy for PTSD outcomes and Adherence among U.S. Military service members. *J Psychiatr Res*. Oct 2023;166:86-91. doi:10.1016/j.jpsychires.2023.09.011
107. Reger GM, Smolenski D, Edwards-Stewart A, Skopp NA, Rizzo AS, Norr A. Does Virtual Reality Increase Simulator Sickness During Exposure Therapy for Post-Traumatic Stress Disorder? *Telemed J E Health*. Sep 2019;25(9):859-861. doi:10.1089/tmj.2018.0175
108. Kim H, Kim BH, Kim MK, Eom H, Kim JJ. Alteration of resting-state functional connectivity network properties in patients with social anxiety disorder after virtual reality-based self-training. *Front Psychiatry*. 2022;13:959696. doi:10.3389/fpsyg.2022.959696

109. Ma L, Kruijt AW, Ek AK, et al. Seeking neutral: A VR-based person-identity-matching task for attentional bias modification - A randomised controlled experiment. *Internet Interv.* Sep 2020;21:100334. doi:10.1016/j.invent.2020.100334
110. Ngai I, Tully EC, Anderson PL. The course of the working alliance during virtual reality and exposure group therapy for social anxiety disorder. *Behav Cogn Psychother.* Mar 2015;43(2):167-81. doi:10.1017/S135246581300088X
111. Price M, Anderson PL. Outcome expectancy as a predictor of treatment response in cognitive behavioral therapy for public speaking fears within social anxiety disorder. *Psychotherapy (Chic).* Jun 2012;49(2):173-9. doi:10.1037/a0024734
112. Price M, Anderson PL. The impact of cognitive behavioral therapy on post event processing among those with social anxiety disorder. *Behav Res Ther.* Feb 2011;49(2):132-7. doi:10.1016/j.brat.2010.11.006
113. Anderson PL, Edwards SM, Goodnight JR. Virtual Reality and Exposure Group Therapy for Social Anxiety Disorder: Results from a 4–6 Year Follow-Up. *Cognitive Therapy and Research.* 2016;41(2):230-236. doi:10.1007/s10608-016-9820-y
114. Klein H, Bartnicki J, Brown JE, et al. Consequences for Norway from a hypothetical accident at the Sellafield reprocessing plant: Atmospheric transport of radionuclides. *J Environ Radioact.* Oct 2021;237(2):106703. doi:10.1016/j.jenvrad.2021.106703
115. Anderson P, Jacobs CH, Lindner GK, et al. Cognitive behavior therapy for fear of flying: sustainability of treatment gains after September 11. *Behav Ther.* Mar 2006;37(1):91-7. doi:10.1016/j.beth.2005.05.001
116. Wiederhold BK, Wiederhold MD. Three-year follow-up for virtual reality exposure for fear of flying. *Cyberpsychol Behav.* Aug 2003;6(4):441-5. doi:10.1089/109493103322278844
117. van der Stouwe ECD, Booij SH, Geraets CNW, et al. Daily-life stress reactivity and recovery following virtual-reality-based cognitive behavioral therapy in patients with a psychotic disorder. *Front Psychiatry.* 2024;15:1360165. doi:10.3389/fpsy.2024.1360165
118. Leff J, Williams G, Huckvale M, Arbuthnot M, Leff AP. Avatar therapy for persecutory auditory hallucinations: What is it and how does it work? *Psychosis.* 2014;6(2):166-176.
119. Leff J, Williams G, Huckvale MA, Arbuthnot M, Leff AP. Computer-assisted therapy for medication-resistant auditory hallucinations: proof-of-concept study. *Br J Psychiatry.* Jun 2013;202(6):428-33. doi:10.1192/bjp.bp.112.124883
120. Du Sert OP, Potvin S, Lipp O, et al. Virtual reality therapy for refractory auditory verbal hallucinations in schizophrenia: a pilot clinical trial. *Schizophrenia research.* 2018;197:176-181.
121. Basant, Pradhan P, Pinninti N, Rathod S. *Chapter 4 AVATAR Therapy for Refractory Auditory Hallucinations.* Springer International Publishing; 2016.
122. Singh K. ISO 14155: clinical investigation of medical devices for human subjects. *Medical device guidelines and regulations handbook.* Springer; 2022:1-18.
123. Ronaghi MH, Ronaghi M. How Does Virtual Reality Technology Affect Suicidal Ideation in Society? *Int J Ment Health Nurs.* Feb 2025;34(1):e13443. doi:10.1111/inm.13443
124. Loucks L, Yasinski C, Norrholm SD, et al. You can do that?!: Feasibility of virtual reality exposure therapy in the treatment of PTSD due to military sexual trauma. *Journal of anxiety disorders.* 2019;61:55-63.
125. Loucks L, Rizzo A, Rothbaum BO. Virtual reality exposure for treating PTSD due to military sexual trauma. *Journal of Clinical Psychology.* 2025;81(2):81-92.
126. Emmelkamp PMG, Meyerbroeker K. Virtual Reality Therapy in Mental Health. *Annu Rev Clin Psychol.* May 7 2021;17(1):495-519. doi:10.1146/annurev-clinpsy-081219-115923
127. Rothbaum BO, Hodges L, Alarcon R, et al. Virtual reality exposure therapy for PTSD Vietnam Veterans: a case study. *J Trauma Stress.* Apr 1999;12(2):263-71. doi:10.1023/A:1024772308758

128. Hodges LF, Rothbaum BO, Kooper R, Opdyke D, Meyer T. Virtual environments for exposure therapy. *IEEE Computer Journal*, July. 1995:27-34.
129. Rizzo A, Koenig S, Lange B. Clinical virtual reality: The state of the science. 2023;doi:<https://doi.org/10.1037/0000308-023>
130. Rizzo A. CBITs Digital Mental Health Lecture Series featuring Skip Rizzo Title of Talk: Clinical Virtual Reality: A Brief Review of the Future! Accessed 8/21/2025. <https://www.youtube.com/watch?v=2CuwpVrB0XY>
131. Rizzo AS, Koenig ST. Is clinical virtual reality ready for primetime? *Neuropsychology*. Nov 2017;31(8):877-899. doi:10.1037/neu0000405
132. Allen EN, Chandler CI, Mandimika N, Leisegang C, Barnes K. Eliciting adverse effects data from participants in clinical trials. *Cochrane Database Syst Rev*. Jan 16 2018;1(1):MR000039. doi:10.1002/14651858.MR000039.pub2
133. Dewar M, Paradis A, Fortin CA. Identifying trajectories and predictors of response to psychotherapy for post-traumatic stress disorder in adults: A systematic review of literature. *The Canadian Journal of Psychiatry*. 2020;65(2):71-86.