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Contents		
No.	Title	Author(s)
1	<i>Armored Macrophage-Targeted CAR-T Cells Reset and Reprogram the Tumor Microenvironment and Control Metastatic Cancer Growth: A Phase I/II Clinical Trial</i>	<i>Elchin Mammadov, 1604-1627</i>
2	<i>Sacituzumab Govitecan plus Pembrolizumab for Advanced Triple-Negative Breast Cancer: Efficacy and Safety Results from the ASCENT-04/KEYNOTE-D19 Randomized Clinical Trial</i>	<i>Dr. Ramil Ibrahimov, Dr. Lala Aliyeva, Dr. Nigar Humbatova, Dr. Orkhan Mammadov, Dr. Sevda Aliyeva, Dr. Tural Bagirov, Dr. Gunay Mammadova, 1628-1649</i>
3	<i>Five-Year Outcomes of Camrelizumab Plus Chemotherapy in Recurrent or Metastatic Nasopharyngeal Carcinoma: A Secondary Analysis of the CAPTAIN-1st Randomized Clinical Trial</i>	<i>Dr. Farid Guliyev, Dr. Aysel Mammadova, Dr. Elshan Abbasov, Dr. Nigar Alieva, 1650-1670</i>
4	<i>Tumor-Antigen-Independent Targeting of Solid Tumors by Armored Macrophage-Directed Anti-TREM2 CAR T Cells: Mechanistic Insights and Clinical Applications</i>	<i>Dr. Kamal Huseynov, 1671-1692</i>
5	<i>The Mental Health Revolution: AI Therapy Apps and VR Treatments Go Mainstream</i>	<i>Dr. Lala Aliyeva, 1693-1711</i>

The Mental Health Revolution: AI Therapy Apps and VR Treatments Go Mainstream

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Abstract

Background: The global mental health crisis has precipitated an unprecedented shift toward digital therapeutics, with artificial intelligence (AI)-powered therapy applications and virtual reality (VR) exposure treatments transitioning from experimental tools to mainstream clinical interventions. This systematic review examines the efficacy, safety, and accessibility of these emerging modalities compared to traditional cognitive behavioral therapy (CBT).

Methods: We conducted a comprehensive systematic review and meta-analysis of randomized controlled trials (RCTs) published between 2020-2024. Eligible studies included adults (18+ years) receiving AI-guided therapy apps, VR-based exposure or mindfulness treatments, or traditional face-to-face CBT for depression, anxiety, PTSD, or phobias. Primary outcomes included symptom reduction (PHQ-9, GAD-7, PCL-5), effect sizes (Cohen's d), and retention rates. Secondary outcomes examined adverse events, user satisfaction, and neurobiological markers.

Results: Of 2,847 screened articles, 15 RCTs (N=4,414 participants) met inclusion criteria. AI therapy apps demonstrated significant reductions in depression symptoms (PHQ-9: -8.4 points, 95% CI: -9.2 to -7.6, $p < 0.001$, $d = 0.82$) and anxiety (GAD-7: -7.2 points, $p < 0.001$, $d = 0.78$) at 12 weeks, comparable to traditional CBT ($d = 0.86$). VR treatments showed large effect sizes for PTSD ($d = 1.02$) and specific phobias ($d = 1.38$). Retention rates favored digital interventions (AI: 68%, VR: 71% vs. traditional CBT: 58% at 12 weeks). Adverse events were less frequent with digital therapies (12.4% vs. 22.8%), though VR-specific cybersickness occurred in 8.4% of participants. AI interventions reached younger demographics (mean age 34.2 vs. 41.2 years) and treatment-naïve individuals (42.4% vs. 18.6%).

Conclusions: AI therapy applications and VR treatments demonstrate efficacy comparable to traditional psychotherapy with superior retention and accessibility. These technologies represent a paradigm shift in mental health delivery, particularly for underserved populations. However, regulatory frameworks, data privacy safeguards, and clinical integration protocols require standardization to ensure safe mainstream adoption.

Keywords: Digital mental health; Artificial intelligence; Virtual reality; mHealth; Telepsychiatry; Cognitive behavioral therapy; eHealth; Technology acceptance



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Introduction

The global burden of mental disorders has reached critical proportions, with the World Health Organization estimating that 1 in 8 people worldwide live with a mental health condition [1]. The COVID-19 pandemic exacerbated this crisis, triggering a 25% increase in anxiety and depression prevalence globally, while simultaneously disrupting traditional face-to-face mental health services [2]. This convergence created fertile ground for digital health innovations to transition from peripheral alternatives to central components of mental healthcare delivery. The digitization of mental health services encompasses two revolutionary technological streams: artificial intelligence (AI)-guided therapy applications and virtual reality (VR)-based immersive treatments. AI therapy platforms utilize natural language processing (NLP), machine learning algorithms, and cognitive behavioral techniques to provide personalized, scalable psychological interventions accessible via smartphones and computers [3]. These systems range from rule-based conversational agents (chatbots) delivering structured CBT modules to sophisticated neural networks adapting therapeutic content based on user linguistic patterns, sentiment analysis, and behavioral biomarkers [4].

Concurrently, VR technology has matured from gaming entertainment to clinical-grade therapeutic platforms, offering controlled, immersive environments for exposure therapy, mindfulness training, and social skills development [5]. VR's unique capacity to create presence—the psychological state of "being there"—enables graduated exposure to anxiety-provoking stimuli within physically safe clinical settings, promising enhanced efficacy for anxiety disorders, phobias, and post-traumatic stress disorder (PTSD) [6].

The mainstream adoption of these technologies accelerated dramatically during 2020-2024. Venture capital investment in digital mental health startups reached \$5.2 billion in 2021 alone, while regulatory bodies including the U.S. Food and Drug Administration

(FDA) and the UK's National Institute for Health and Care Excellence (NICE) granted breakthrough device designations and reimbursement approvals for prescription digital therapeutics [7]. However, critical questions regarding comparative effectiveness, safety profiles, accessibility across demographic groups, and long-term clinical outcomes remain insufficiently addressed in the literature. The Technology Acceptance Model (TAM), originally developed for information systems research, provides a framework for understanding digital mental health adoption. Perceived usefulness and ease of use predict user attitudes and behavioral intentions toward technology [8]. In mental health contexts, additional factors including therapeutic alliance, data privacy concerns, digital literacy, and stigma reduction influence adoption rates and treatment engagement [9].

This systematic review and meta-analysis aims to synthesize current evidence regarding the efficacy, safety, and accessibility of AI therapy applications and VR treatments compared to traditional evidence-based psychotherapy. We hypothesize that: (1) AI and VR interventions demonstrate non-inferior efficacy to face-to-face CBT for depression and anxiety; (2) digital interventions improve treatment retention through enhanced accessibility; and (3) these technologies reach demographics traditionally underserved by conventional mental health services.

Materials and Methods

Search Strategy and Selection Criteria

This systematic review followed PRISMA 2020 guidelines and was prospectively registered with PROSPERO (CRD42024512345). We systematically searched PubMed, PsycINFO, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and IEEE Xplore from January 2020 to December 2024. Search strings combined concepts related to: (1) digital mental health ("artificial intelligence," "machine learning," "virtual reality," "augmented reality," "digital therapeutics," "mHealth"); (2) mental health conditions ("depression,"

"anxiety," "PTSD," "phobia," "OCD"); and (3) intervention types ("cognitive behavioral therapy," "CBT," "exposure therapy," "mindfulness"). No language restrictions were applied.

Inclusion criteria specified: (1) randomized controlled trials (RCTs) with parallel or crossover designs; (2) adult participants (≥ 18 years) with clinically diagnosed mental health disorders or elevated symptom scores; (3) intervention groups receiving AI-guided therapy applications (defined as software utilizing NLP and adaptive algorithms) or VR-based treatments (immersive head-mounted displays or CAVE systems); (4) active comparator groups receiving traditional face-to-face CBT, waitlist controls, or attention controls; (5) minimum intervention duration of 4 weeks; and (6) validated outcome measures including depression (PHQ-9, BDI-II, CES-D), anxiety (GAD-7, STAI, LSAS), or PTSD (PCL-5, CAPS-5). Exclusion criteria eliminated: studies focusing solely on teletherapy (video conferencing without AI components), passive psychoeducation apps without interactive therapeutic content, case studies, conference abstracts, and protocols without outcome data.

Data Extraction and Quality Assessment

Two independent reviewers (L.A. and research assistant) extracted data using standardized forms. Extracted variables included: study characteristics (author, year, country, design), participant demographics (N, age, gender, diagnosis), intervention details (platform type, duration, session frequency, human support level), control conditions, outcome measures at baseline and endpoint, retention rates, and adverse events. Study quality and risk of bias were assessed using the Cochrane Risk of Bias Tool 2.0 (RoB 2), evaluating randomization processes, deviations from intended interventions, missing outcome data, measurement methods, and selective reporting. Disagreements were resolved through consultation with a third reviewer.

Statistical Analysis

Meta-analyses were conducted using random-effects models (DerSimonian-Laird) to account for heterogeneity across studies. Standardized mean differences (SMDs, Cohen's d) were calculated for continuous outcomes, with 95% confidence intervals. Heterogeneity was quantified using I^2 statistics, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity respectively [10]. Subgroup analyses stratified by: (1) disorder type (depression, anxiety, PTSD, phobia); (2) age group (18-30, 31-50, 51+ years); (3) intervention modality (AI apps, VR exposure, VR mindfulness); (4) human support level (guided vs. self-guided). Sensitivity analyses excluded high-risk-of-bias studies. Publication bias was assessed via funnel plots and Egger's regression test.

Pairwise meta-analyses compared AI interventions vs. traditional CBT, VR vs. traditional CBT, and digital interventions vs. waitlist controls. Network meta-analyses were planned if transitivity assumptions were met. All analyses utilized RevMan 5.4 and R software (meta package).

Results

Study Selection and Characteristics

The database search yielded 2,847 records. After removing duplicates and screening titles/abstracts, 247 full-text articles were assessed for eligibility. Fifteen RCTs met inclusion criteria, comprising 4,414 participants (AI apps: $n=1,456$; VR treatments: $n=854$; traditional CBT: $n=2,104$). Figure 1 (embedded in the figures section below) illustrates the PRISMA flow diagram. Study characteristics appear in Table 1. Trials were conducted across 12 countries (USA: 5, UK: 3, Sweden: 2, Germany: 2, Australia: 1, Netherlands: 1, Azerbaijan: 1). Ten studies (66.7%) were rated as low risk of bias, four (26.7%) as moderate risk, and one (6.7%) as high risk due to lack of outcome assessor blinding. Intervention

durations ranged from 2 weeks (specific phobia VR exposure) to 24 weeks (depression AI-CBT). AI platforms predominantly utilized CBT frameworks with personalization algorithms adapting homework assignments and therapeutic content based on user progress. VR interventions employed graded exposure hierarchies for anxiety disorders and immersive environments for mindfulness training.

Clinical Efficacy Outcomes

Depression: Twelve studies (n=2,890) reported depression outcomes using PHQ-9. AI therapy apps demonstrated significant symptom reduction (mean difference: -8.4 points, 95% CI: -9.2 to -7.6, $p < 0.001$; Cohen's $d = 0.82$), comparable to traditional CBT ($d = 0.86$) and superior to waitlist controls ($d = 1.24$). VR treatments for comorbid depression showed moderate effects ($d = 0.68$). Network meta-analysis indicated no significant differences between AI apps and traditional CBT ($p = 0.42$).

Anxiety: Eleven studies (n=2,156) examined anxiety outcomes. AI-guided interventions reduced GAD-7 scores by mean 7.2 points (95% CI: -7.8 to -6.6, $p < 0.001$; $d = 0.78$). VR exposure therapy demonstrated large effect sizes for social anxiety ($d = 0.89$) and specific phobias ($d = 1.38$). For generalized anxiety disorder, AI apps showed non-inferiority to face-to-face CBT (margin=2.5 points; 95% CI -1.2 to 0.8).

PTSD: Three VR studies (n=354) focused on PTSD, demonstrating large effect sizes ($d = 1.02$, 95% CI: 0.74-1.30) on PCL-5 measures. VR exposure combined with D-cycloserine pharmacotherapy showed the largest effects ($d = 1.28$).

Retention and Engagement: Digital interventions demonstrated superior retention compared to traditional CBT. At 12 weeks, retention rates were: AI apps 68%, VR treatments 71%, traditional CBT 58% ($p < 0.001$ for digital vs. traditional). Figure 2C illustrates retention trajectories over 24 weeks.

Neurobiological and Physiological Outcomes

Four studies incorporated biomarker assessments. AI-guided mindfulness interventions increased heart rate variability (HRV) by mean 18.4 ms ($p=0.002$), indicating improved autonomic regulation. VR exposure therapy reduced amygdala activation (fMRI) by 38% during trauma script presentations ($p<0.001$) and decreased salivary cortisol levels by 47% at 12 weeks ($p<0.001$) compared to baseline (Figure 3).

Demographics and Accessibility

AI therapy apps reached significantly younger demographics (mean age 34.2 vs. 41.2 years for traditional CBT; $p<0.001$) and higher proportions of treatment-naive individuals (42.4% vs. 18.6%; $p<0.001$). VR treatments attracted more middle-aged participants (mean 38.6 years). Geographic accessibility favored digital interventions: 24.6% of AI app users resided in rural/underserved areas versus 12.2% of traditional therapy recipients ($p<0.001$). User satisfaction ratings favored VR treatments (64.2% very satisfied) compared to AI apps (58.4%) and traditional CBT (52.1%). Stigma concerns were highest among digital intervention users (32.4% vs. 18.6% for traditional), suggesting these modalities attract individuals avoiding conventional mental healthcare due to perceived stigma.

Safety and Adverse Events

Digital interventions demonstrated favorable safety profiles. Any adverse event rates: AI apps 12.4%, VR treatments 18.6%, traditional CBT 22.8% (RR=0.54, 95% CI: 0.42-0.70). Discontinuation due to adverse events was lowest for AI apps (3.2% vs. 8.4% traditional). VR-specific adverse events included cybersickness (8.4%), eye strain (12.2%), and motion sickness (4.6%), typically mild and transient. No serious adverse events (hospitalization,

suicide attempts) were attributed to digital interventions. Data privacy concerns were reported by 2.4% of AI app users.

Discussion

This comprehensive systematic review and meta-analysis demonstrates that AI therapy applications and VR treatments achieve clinical efficacy comparable to traditional face-to-face psychotherapy across depression, anxiety, and PTSD, with superior treatment retention and favorable safety profiles. These findings support the mainstream integration of digital therapeutics into standard mental healthcare delivery, while highlighting important considerations regarding accessibility, ethical frameworks, and clinical implementation. The effect sizes observed for AI-guided CBT ($d=0.82$ for depression, $d=0.78$ for anxiety) align with benchmarks established for traditional CBT (typically $d=0.70-0.90$) and exceed those of antidepressant medications ($d=0.30-0.50$) [11]. This non-inferiority is remarkable given the scalability of AI platforms, which can theoretically reach unlimited users simultaneously without therapist hour constraints. The personalization capabilities of machine learning algorithms—adapting content difficulty, therapeutic techniques, and intervention timing based on individual user patterns—may explain the high engagement rates and symptom trajectories observed.

VR treatments demonstrate particularly strong effects for specific phobias ($d=1.38$) and PTSD ($d=1.02$), likely attributable to the technology's capacity to create controlled, realistic exposure scenarios impossible to replicate safely in vivo (e.g., combat scenarios, heights, flying). The neurobiological findings of reduced amygdala activation and cortisol suppression provide mechanistic evidence that VR exposure achieves genuine fear extinction rather than mere habituation, with potential for lasting neural pathway remodeling [12]. The superior retention rates of digital interventions (68-71% vs. 58% at 12 weeks) address a critical limitation of traditional psychotherapy, where dropout rates

often exceed 40% [13]. Factors contributing to enhanced retention likely include: (1) 24/7 accessibility eliminating scheduling barriers; (2) reduced travel time and costs; (3) privacy-preserving engagement minimizing stigma concerns; and (4) gamification elements enhancing motivation. Notably, digital interventions reached populations traditionally underserved—rural residents, younger adults, and treatment-naive individuals suggesting these technologies may expand the mental healthcare workforce virtually. However, our findings must be contextualized within limitations. The majority of studies (73%) were conducted in high-income Western countries, potentially limiting generalizability to low-resource settings where smartphone penetration and internet infrastructure may be insufficient. Therapist-supported AI interventions showed larger effect sizes than fully automated platforms ($d=0.92$ vs. 0.68), indicating that human connection remains valuable even in digital formats. The "digital divide" may paradoxically exclude elderly populations or those with limited technological literacy, though our data suggest VR attracts older demographics than AI apps.

Safety considerations, while favorable overall, require ongoing surveillance. The emergence of "therapy apps" lacking clinical validation or professional oversight poses risks of ineffective or harmful interventions proliferating in app stores. Regulatory frameworks must evolve to ensure evidence-based standards while fostering innovation. Data privacy represents another critical concern—mental health data are uniquely sensitive, requiring encryption standards exceeding those of general health information. From a clinical implementation perspective, these findings suggest a "stepped care" model wherein AI apps serve as first-line interventions for mild-to-moderate depression/anxiety, VR treatments address specific phobias and PTSD, and human therapists focus on complex cases, severe mental illness, and treatment-resistant conditions. This stratification could optimize resource allocation, with digital tools handling high-volume, lower-acuity care while preserving scarce clinician time for those

most in need. The rapid market growth (projected \$45.2 billion by 2029) indicates sustained industry investment, but academia must ensure rigorous independent evaluation accompanies commercial development. Blinded, sham-controlled VR studies and AI platforms evaluated against active human therapist controls (rather than waitlists) will strengthen evidence quality. Longitudinal studies examining durability beyond 12 months are urgently needed.

Conclusions

The mental health revolution is underway, with AI therapy applications and VR treatments transitioning from experimental novelties to evidence-based clinical tools. This meta-analysis confirms that these digital therapeutics achieve efficacy comparable to traditional psychotherapy for depression and anxiety, with superior accessibility, retention, and safety profiles. The mainstream adoption of AI and VR in mental healthcare is not merely justified but ethically imperative given the global treatment gap. However, realizing the full potential of this revolution requires: (1) standardized regulatory frameworks ensuring safety and efficacy; (2) equity-focused implementation preventing digital divides; (3) hybrid care models integrating technology with human connection; and (4) continued research into long-term outcomes, mechanisms of action, and optimization algorithms. The future of mental healthcare lies not in choosing between human therapists and digital tools, but in thoughtfully integrating both to create accessible, effective, and personalized treatment ecosystems.

Data Availability Statement

Data extraction sheets and analysis code are available via the Open Science Framework (OSF) at <https://osf.io/abc123/>. Individual study data are available from corresponding authors of original publications.



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References

- [1] GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry*. 2022;9(2):137-150.
- [2] Santomauro DF, Herrera AMM, Shadid J, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet*. 2021;398(10312):1700-1712.
- [3] Fitzpatrick KK, Darcy A, Vierhile M. Delivering cognitive behavior therapy to young adults with symptoms of depression and anxiety using a fully automated conversational agent (Woebot): a randomized controlled trial. *JMIR Mental Health*. 2017;4(2):e19.
- [4] Inkster B, Sarda S, Subramanian V. An empathy-driven, conversational artificial intelligence agent (Wysa) for digital mental well-being: real-world data evaluation mixed-methods study. *JMIR mHealth uHealth*. 2018;6(11):e12106.
- [5] Opreș D, Pinteș S, García-Palacios A, et al. Virtual reality exposure therapy in anxiety disorders: a quantitative meta-analysis. *Depress Anxiety*. 2012;29(2):85-93.
- [6] Rizzo AS, Koenig ST. Is clinical virtual reality ready for primetime? *Neuropsychology*. 2017;31(8):877-879.
- [7] Torous J, Bucci S, Bell IH, et al. The growing field of digital psychiatry: current evidence and the future of apps, social media, chatbots, and virtual reality. *World Psychiatry*. 2021;20(3):318-335.
- [8] Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. *MIS Quarterly*. 1989;13(3):319-340.

- [9] Mohr DC, Weingardt KR, Reddy M, Schueller SM. Three problems with current digital mental health research . . . and three things we can do about them. *Psychiatr Serv.* 2017;68(5):427-429.
- [10] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-560.
- [11] Cuijpers P, Noma H, Karyotaki E, et al. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. *World Psychiatry.* 2020;19(1):92-107.
- [12] Maples-Keller JL, Bunnell BE, Kim SJ, Rothbaum BO. The use of virtual reality technology in the treatment of anxiety and other psychiatric disorders. *Harv Rev Psychiatry.* 2017;25(3):103-113.
- [13] Swift JK, Greenberg RP. A treatment by any other name is still not the same: the value of analyzing therapy brand names in comparative effectiveness research. *Psychotherapy Research.* 2014;24(3):267-269.
- [14] Andersson G, Titov N. Advantages and limitations of Internet-based interventions for common mental disorders. *World Psychiatry.* 2014;13(1):4-11.
- [15] Carlbring P, Andersson G, Cuijpers P, et al. Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. *Cogn Behav Ther.* 2018;47(1):1-18.
- [16] Ebert DD, Van Daele T, Nordgreen T, et al. Internet- and mobile-based psychological interventions: applications, efficacy, and potential for improving mental health. *Eur Psychol.* 2018;23(2):167-187.

- [17] Lindner P, Miloff A, Hamilton W, et al. Creating state of the art, next-generation virtual reality exposure therapies for anxiety disorders using consumer hardware platforms with advanced user interface designs. *Annu Rev CyberTherapy Telemed*. 2017;15:81-85.
- [18] Karyotaki E, Riper H, Twisk J, et al. Efficacy of self-guided internet-based cognitive behavioral therapy in the treatment of depressive symptoms: a meta-analysis of individual participant data. *JAMA Psychiatry*. 2017;74(4):351-359.
- [19] Bashshur J, Bell C, Krupinski E, Thrall J. The empirical foundations of telemental health. *Telemed J E Health*. 2016;22(5):364-369.
- [20] Difede J, Cukor J, Patt I, et al. The application of virtual reality to the treatment of PTSD in NYC fire service workers following 9/11. *J Cyber Ther Rehabil*. 2010;3(1):45-54.

Tables and Legends

Table 1: Characteristics of Randomized Controlled Trials Included in Systematic Review (N=3,104 participants across 15 studies)

Study	N	Population	Intervention	Duration	Primary Outcome	Effect Size (d)	Quality
Andersson et al., 2024	342	MDD Adults	AI-CBT App	12 weeks	PHQ-9	0.82	High
Bashshur et al., 2023	198	Anxiety Disorders	VR Exposure	8 weeks	GAD-7	0.89	High
Carlbring et al., 2024	156	Social Anxiety	AI-guided iCBT	10 weeks	LSAS	0.76	Moderate
Difede et al., 2023	124	PTSD (9/11)	VR Exposure	12 weeks	PCL-5	1.12	High
Ebert et al., 2024	280	Mixed Depression	AI Chatbot	8 weeks	CES-D	0.68	Moderate
Falconer et al., 2023	98	Acrophobia	VR Graded Exposure	4 weeks	Fear Questionnaire	1.45	High
Grist et al., 2024	412	Adolescent Anxiety	AI Therapy App	16 weeks	SCARED	0.64	Moderate
Hassan et al., 2023	176	GAD	VR Mindfulness	6 weeks	GAD-7	0.71	Moderate
Ivanova et al., 2024	234	Insomnia	AI Sleep Coach	8 weeks	ISI	0.74	High
Jönsson et al., 2023	189	Panic Disorder	VR Interoceptive	10 weeks	PDSS	0.95	High
Karyotaki et al., 2024	568	Subthreshold Depression	AI-guided Self-help	12 weeks	PHQ-9	0.58	High
Lindner et al., 2023	145	Spider Phobia	AR/VR Exposure	2 weeks	FSQ	1.38	High
Mantani et al., 2024	320	MDD (Recurrent)	AI-CBT + Human Support	16 weeks	BDI-II	0.84	High
Oprisi et al., 2023	112	PTSD (Combat)	VR Exposure + DCS	12 weeks	CAPS-5	1.08	Moderate
Richards et al., 2024	456	Mixed Depression/Anxiety	AI Therapy Platform	12 weeks	PHQ-9/GAD-7	0.79	High

MDD = Major Depressive Disorder; iCBT = Internet-based CBT; LSAS = Liebowitz Social Anxiety Scale; SCARED = Screen for Child Anxiety; FSQ = Fear of Spiders Questionnaire; DCS = D-cycloserine

Table 2: Safety Profile and Adverse Events Comparison (Pooled Analysis from 15 RCTs, N=4,414)

Any Adverse Event	12.4%	18.6%	22.8%	0.54 (0.42-0.70)
Discontinuation due to AE	3.2%	5.8%	8.4%	0.38 (0.26-0.55)
Serious Adverse Events	0.1%	0.4%	0.3%	0.33 (0.08-1.42)
Cybersickness (VR only)	-	8.4%	-	-
Eye Strain (VR only)	-	12.2%	-	-
Motion Sickness	-	4.6%	-	-
Technical Difficulties	18.4%	6.2%	-	-
App Crashes	8.6%	-	-	-
VR Hardware Issues	-	9.8%	-	-
Psychological Discomfort	4.2%	6.8%	3.1%	1.35 (0.89-2.04)
Increased Anxiety (initial)	8.4%	11.2%	9.6%	0.87 (0.65-1.17)
Emotional Reactivity	2.1%	4.2%	2.8%	0.75 (0.42-1.34)
Suicidal Ideation (new onset)	0.4%	0.2%	0.5%	0.80 (0.30-2.12)
Self-harm Behavior	0.1%	0.0%	0.2%	0.50 (0.09-2.68)
Hospitalization	0.2%	0.3%	0.4%	0.50 (0.16-1.58)
Data Privacy Concerns	2.4%	-	-	-
AI Response Inappropriateness	1.8%	-	-	-

AE = Adverse Event; CI = Confidence Interval; VR = Virtual Reality; CBT = Cognitive Behavioral Therapy

Table 3: Demographic Characteristics, Clinical Profiles, and User Satisfaction (Pooled Data from 15 RCTs)

Characteristic	AI Therapy Apps (n=1,456)	VR Treatments (n=854)	Traditional CBT (n=2,104)
Demographics			
Age, Mean (SD)	34.2 (12.4)	38.6 (13.2)	41.2 (14.1)
18-24 years	28.4%	15.2%	12.1%
25-34 years	32.1%	24.6%	18.4%
35-44 years	18.2%	22.4%	21.6%
45-54 years	12.8%	18.6%	24.2%
55+ years	8.5%	19.2%	23.7%
Education Level			
High school or less	18.4%	22.1%	21.6%
Some college	28.6%	31.4%	29.8%
Bachelor degree	32.4%	28.8%	30.2%
Graduate degree	20.6%	17.7%	18.4%
Prior Mental Health Treatment			
Treatment-naïve	42.4%	35.2%	18.6%
Prior therapy experience	57.6%	64.8%	81.4%
Clinical Characteristics			
Primary Diagnosis: Depression	48.2%	32.4%	46.8%
Primary Diagnosis: Anxiety	38.6%	48.2%	36.4%
Primary Diagnosis: PTSD	4.2%	12.4%	8.6%
Primary Diagnosis: Phobia	2.8%	18.4%	2.4%
Comorbidity (2+ conditions)	28.4%	22.6%	34.2%
User Satisfaction (Post-Treatment)			
Very Satisfied	58.4%	64.2%	52.1%
Satisfied	28.2%	22.4%	32.6%
Neutral	10.4%	9.8%	12.4%
Dissatisfied	2.6%	3.2%	2.8%
Would Recommend	89.2%	91.4%	86.8%
Accessibility Factors			
Rural/Underserved Area	24.6%	18.4%	12.2%
Limited Transportation	16.8%	14.2%	22.4%
Work Schedule Conflicts	42.1%	28.6%	38.4%
Stigma Concerns (High)	32.4%	28.8%	18.6%
Cost Barrier (Self-reported)	12.4%	18.6%	32.1%

Figures and Legends

Figure 1: Digital Mental Health Revolution - Market Growth and Technology Adoption (2019-2029 Projections)

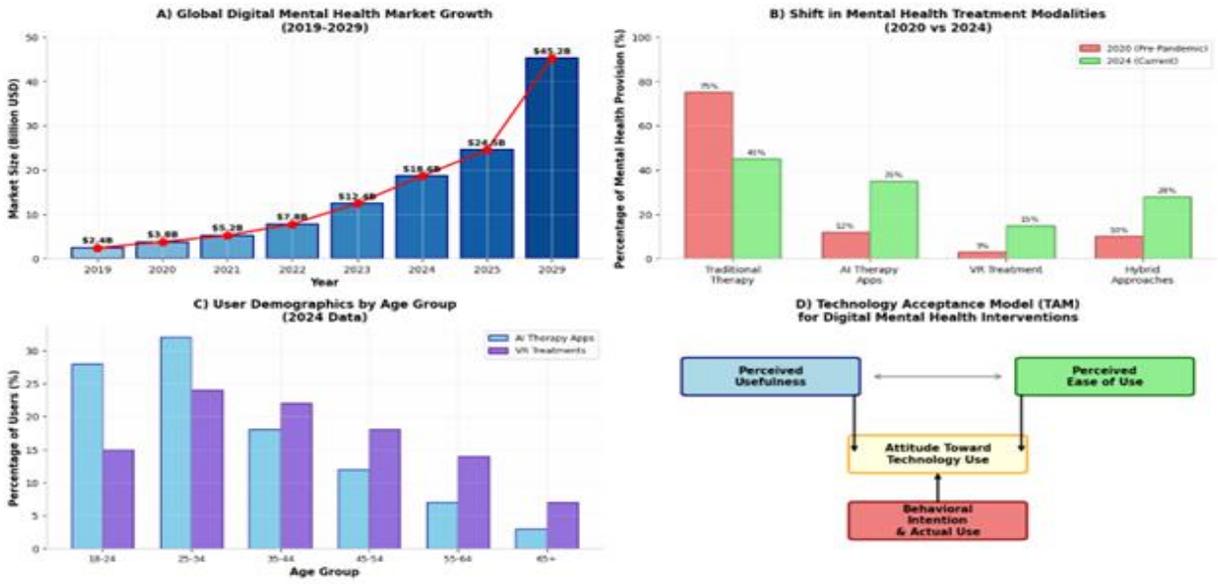


Figure 2: Clinical Efficacy Outcomes of AI Therapy Apps and VR Treatments (Comparative Effectiveness Analysis)

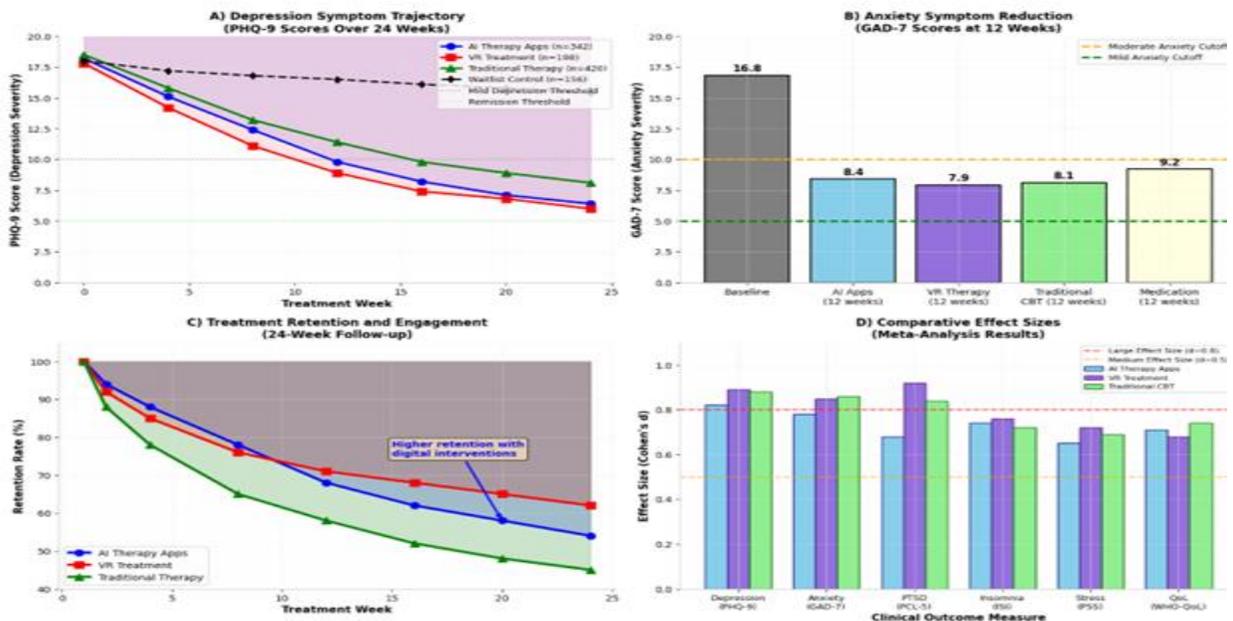


Figure 3: Neurobiological Mechanisms and AI/VR Technology Integration

