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Multidisciplinary Continuing Education for Pain Management Practice

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Virtual Reality Therapy for Chronic Pain: A Scoping Review on Indications, Mechanisms of Action, and Effectiveness

Richard W. Kim, DO, MBA, Ahish Chitneni, DO, John Edwin Rubin, MD, Robert White, MD, and Rohan Jotwani, MD, MBA

Learning Objectives: After participating in this continuing professional development activity, the provider should be better able to:

1. Distinguish chronic pain populations best suited for head-mounted display-based virtual reality (VR) interventions.
2. Evaluate current evidence regarding the efficacy of VR interventions on pain score reduction.
3. Explain the mechanisms of action underlying the efficacy of VR interventions for relief of chronic pain.

Key Words: Chronic pain, Extended reality, Virtual reality, Kinesiophobia, Pain psychology

Abstract

Background: The application of virtual reality (VR) technology as a nonpharmacologic treatment option for chronic pain has been increasingly studied. However, the mechanisms underlying this treatment modality's potential positive effects and appropriate indications are not well understood or summarized in the literature.

Objectives: This scoping review aims to better understand the chronic pain populations best indicated for head-mounted display-based VR interventions, explore their efficacy on pain score reduction, and characterize the mechanisms of action underlying their efficacy.

Methods: PubMed database systematic searches were conducted including articles from January 2010 to August 2023 with primary qualifying criteria including but not limited to use of head-mounted display VR and adequate VR treatment dosage. Mechanisms of action(s) were deduced via an exploratory approach whereby characteristics of VR

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treatment interventions were analyzed and categorized.

Results: Fourteen studies met qualifying criteria, representing a total treatment group of 327. Study data extracted were solely relative to VR treatment group participants. VR intervention mechanisms of action were best characterized via 2 broad but distinct categories: addressing kinesophobia and psychobehavioral modulation. Three studies investigating chronic neck pain used addressing kinesophobia as a mechanism of action and demonstrated a significant improvement [weighted average numerical rating scale (NRS): 4.6 at baseline, 2.5 post-intervention, and 2.5 3 months post-intervention]. Six studies investigated chronic low back pain, for which 5 studies, representing 99% of the subgroup, used psychobehavioral modulation. Each demonstrated significant reduction in pain (weighted average NRS: 5.1 baseline and 3.2 post-intervention).

Conclusion: This large-scale within-group analysis review proposes 2 broad mechanisms of action underlying the efficacy of VR interventions for chronic pain indications. VR interventions addressing kinesophobia seem to be significantly effective in nontraumatic chronic neck pain patients. Psychobehavioral VR interventions demonstrate significant efficacy in the chronic low back pain population. Studies with interventions targeting nonspecific chronic pain populations did not show significant results.

Extended reality (XR) is an umbrella term describing a spectrum of immersive technologies including virtual reality (VR), augmented reality (AR), and mixed reality (MR).¹ Applications for immersive technologies have been increasingly investigated across

industries with the rapid advancement of commercially available XR products.¹ One potential application for XR is as a therapeutic nonpharmacologic modality for patients suffering from chronic pain. Currently, VR therapeutics have limited reach in that they are mainly in the testing phase via clinical investigations; nevertheless, as VR technology becomes more powerful and the cost of the technology decreases, widespread implementation to all chronic pain patients becomes increasingly possible. However, investigating the mechanisms of action underlying VR's clinical efficacy in treating chronic pain is still required and remains a major limitation to properly prescribe the technology to the right patient at the right time.

VR involves simulated experiences intentionally presented to an individual's senses via a computer-generated environment.² In pain medicine today, VR delivery systems are varied, spanning from 2-dimensional (2D) screen/projector setups to head-mounted devices providing a 3-dimensional (3D) stereoscopic view of a digital environment. VR can be characterized based on the 3 key domains (pillars): presence, immersion, and interactivity.² Presence refers to the subjective experience of being in a certain place or environment when physically situated in another. Immersion describes the sense of being "caught up and absorbed" in a virtual world.² Interactivity is the degree to which the user can influence and manipulate their virtual environment.² Consistent with the appeal of high-definition television and movie theater experiences, early immersive technology systems involved large screens or projectors to induce the sense of presence and immersion for the

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user. Interactivity was often limited and sometimes involved infrared motion feedback or bespoke body-worn sensors. The release of high-quality, 3D VR headsets represents a stepwise advancement in a potentially paradigm-shifting technology, motivating investigation across fields. The ability to offer users with virtual experiences where cognitive dissonance is less a prerequisite to efficacy creates a promising, but largely uncharted avenue for potential medical applications, particularly in chronic pain.

Recent systematic reviews and meta-analyses have investigated VR applications for the chronic pain population, describing overall promising and clinically significant results.³⁻⁹ However, these reviews have shown a significant deal of heterogeneity in methodology, making generalizations for clinical practice difficult. In particular, a broad range of conditions were studied, including nociceptive, nociplastic, and neuropathic pain conditions and markedly different baseline characteristics between treatment groups. Furthermore, a wide range of outcome measures were used to quantify outcomes, including both pain and psychologic metrics, and variable postintervention follow-up protocols.

Due to the significant heterogeneity within chronic pain VR research, there remains limited understanding related to best practices in prescribing VR for treatment. In this scoping review, we aim to bridge the gap in understanding for VR interventions to assist in delineating underlying mechanisms of action of VR interventions and identification of indications for specific VR therapy based on patient symptomatology.

Methods

PubMed database searches were conducted from June 2023 to August 2023 using the following search terms: ((virtual reality) AND (chronic) AND (pain)). A filter for "human studies" and studies published since January 2010 were applied. MeSH translated search terms: virtual reality: "virtual reality"[MeSH Terms] OR ("virtual"[All Fields] AND "reality"[All Fields]) OR "virtual reality"[All Fields]; chronic: "chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]; pain: "pain"[MeSH Terms] OR "pain"[All Fields]. The search returned 185 English language articles. Each result with an available full-text, English language article was reviewed. Inclusion criteria included trial type (randomized control, quasi-experimental, or case series), use of a head-mounted display (HMD)-based VR intervention, patient history of chronic pain, adult patient (18 years and older). Exclusion criteria included VR intervention administered solely in a single session or administered in total on a single day, VR intervention used as part of an exercise rehabilitation program or physical therapy program, or patient history of phantom limb pain. Figure 1 shows the PRISMA diagram outlining the identification of studies.

For each study meeting criteria, data were solely collected from VR treatment group arms. That is, baseline characteristics and outcome measures from study subjects who underwent a VR intervention were extracted, and no

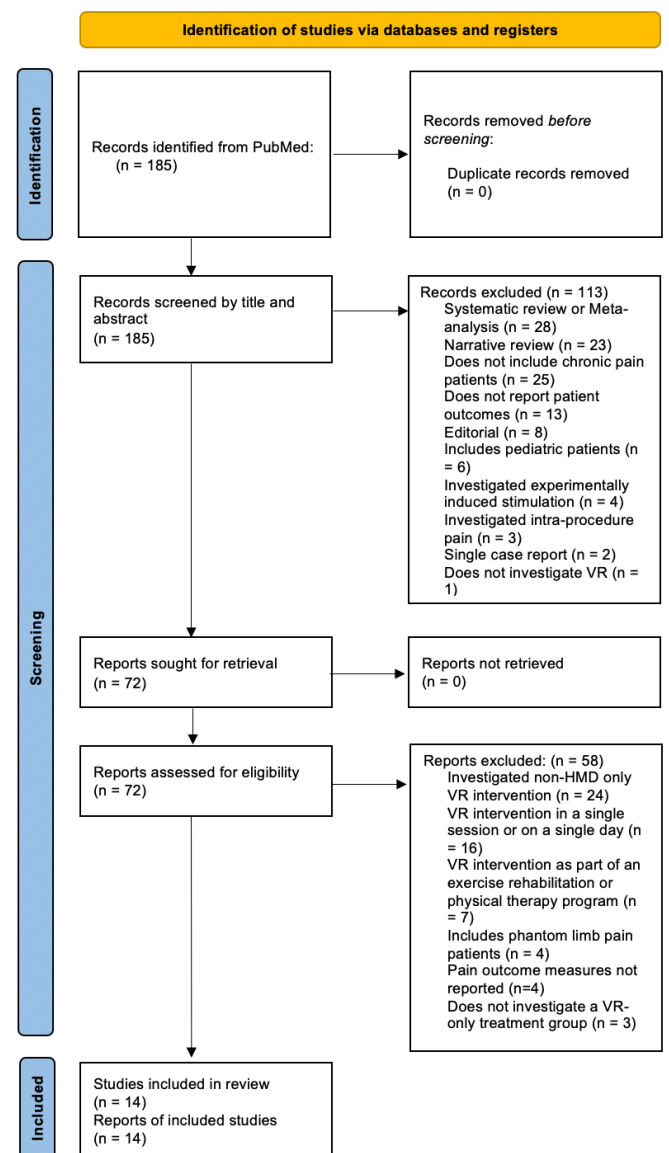


Figure 1. PRISMA flow diagram with identification of studies.³⁶

control or comparison group data were included in the analysis. This addresses the challenge of generalizing efficacy of VR interventions among heterogeneous study designs (eg, VR vs exercise, VR vs sham VR, and pretest vs posttest) by solely gathering data from VR treatment group arms for each study and analyzing within-group significance of relevant outcome measures. Data collected from identified studies included study design, number of participants analyzed in the VR treatment group, chronic pain population(s), psychological comorbidity inclusion/exclusion criteria, baseline Tampa Scale of Kinesiophobia (TSK) scores, dosage (total number of minutes/sessions and overall duration of VR intervention, if included), VR intervention characteristics, VR treatment within-group outcomes (ie, baseline vs post-intervention vs follow-up) for pain, kinesiophobia, and psychological measures, and VR intervention mechanism(s) of action. The mechanism of action(s) (MOA) for each VR intervention was deduced based on an exploratory approach whereby the characteristics of VR treatment interventions, as described in each article, were analyzed and categorized.

Weighted average pain scores for subgroups were calculated by taking the respective studies resulting the scale of 10 pain score [eg, numerical rating scale (NRS) and visual analog scale (VAS)], multiplying by the proportion of subjects represented by the respective study's VR treatment group participants in the subgroup described, and then taking the sum of these values. Confidence intervals, if sufficiently reported by studies in the described subgroup, were calculated in the same manner.

Results

Study Characteristics and Patient Demographics

A total of 45 retrieved studies met inclusion criteria, and 27 studies were removed for meeting exclusion criteria. Four studies were removed due to not reporting pain outcome measures. Fourteen studies qualified criteria, representing a total of 327 participants who participated in a VR therapy. Eight of 14 studies used a randomized controlled trial study design,^{10,11,13,15,18,19,21,22} 3 had a quasi-experimental trial design (eg, pre-/post-intervention),^{12,17,23} and 3 were case series.^{14,16,20} The patient populations examined included traumatic and non-traumatic chronic neck pain, chronic low back pain, chronic neuropathic pain in spinal cord injury patients, chronic neuropathic pain in cancer patients, and nonspecific chronic pain.

Seven of 14 studies contained exclusion criteria for psychological comorbidities such as untreated psychological or

psychiatric disorder, depressive symptoms, severe anxiety, or prior psychotherapy.^{12,15,17,19,21-23} Six studies included baseline kinesiophobia (TSK) scores.^{10,11,13-15,23} The reporting metric for VR intervention treatment dose varied widely, with studies reporting in a specific time frame (minutes or days) whereas others reported over a range of time (minutes or days) (Table 1). The characteristics of VR intervention were wide-ranging and included the following: promoting cervical active range of motion, promoting movement, promoting lumbar gross and fine motor movement, promoting motor movement via graded motor imagery, embodiment, cognitive behavioral therapy, desensitization and reprocessing, relaxation, mindfulness, pain visualization, and hypnotherapy.

VR Intervention Mechanisms of Action

Each VR intervention's MOA could be distilled into 2 broad, but distinct categories: addressing kinesiophobia and psychobehavioral modulation (Table 2). Although most studies evaluated one MOA, there were 2 studies that investigated both. The studies by both Fowler et al¹² and Eccleston et al¹⁵ investigated addressing kinesiophobia and psychobehavioral modulation, with the latter demonstrating significant results. Broadly, studies using VR interventions promoting active spine movement, with

Table 1. Research Studies by Study Design, Population, and Baseline Scores

Study	Design	VR Treatment Group, n	Population	Psychological Comorbidity: Included vs Excluded	Baseline Tampa Scale of Kinesiophobia (TSK) Score
Sarig Bahat et al ¹⁰	RCT	16	Chronic neck pain	N/A	32.75 ± 6.8
Sarig Bahat et al ¹¹	RCT	48	Chronic neck pain	N/A	35.1 ± 7.5
Fowler et al ¹²	QE	16	Chronic pain, nonspecific, inpatient setting	Excluded: aggression, depression, psychosis, suicidality	N/A
Tejera et al ¹³	RCT	22	Chronic neck pain	N/A	22.90 ± 7.11
Harvie et al ¹⁴	CS	8	Chronic neck pain due to trauma	N/A	39.2 ± 4.2
Eccleston et al ¹⁵	RCT	14	Chronic low back pain + kinesiophobia	Exclusion: psychotherapy in prior 2 yr	41.9 ± 4.4
Trujillo et al ¹⁶	CS	2	Chronic low back pain	N/A	N/A
Trost et al ¹⁷	QE	17	Chronic neuropathic pain + SCI	Exclusion: diagnosis of severe psychiatric disorder	N/A
Darnall et al ¹⁸	RCT	35	Chronic low back pain and/or fibromyalgia	N/A	N/A
Garcia et al ¹⁹	RCT	94	Chronic low back pain	Exclusion: depressive symptoms ≥2 on PHQ9	N/A
Garrett et al ²⁰	CS	8	Chronic pain, nonspecific	N/A	N/A
Chuan et al ²¹	RCT	19	Chronic neuropathic cancer pain	Exclusion: psychological or psychiatric illness not stabilized with therapy or medications	N/A
Groenveld et al ²²	RCT	20	Chronic low back pain	Exclusion: severe anxiety or depression	N/A
de Vries et al ²³	QE	8	Chronic low back pain	Exclusion: severe psychopathology (eg, mood, anxiety, or psychotic disorders and/or suicidal risk)	42.6 ± 6.6

CS, case series; N/A, not available; PHQ9, Patient Health Questionnaire-9; QE, quasi-experimental; RCT, randomized controlled trial; SCI, spinal cord injury; VR, virtual reality.

Table 2. Research Studies by Total Duration, Characteristics of Treatment, and Mechanisms of Action of Treatment

Study	Total VRI Duration, d	Characteristics of VRI	MOA of VRI
Sarig Bahat et al ¹⁰	120–180 min, 35 d	Promote cervical active range of motion (clinic-supervised)	Address kinesiophobia
Sarig Bahat et al ¹¹	320 min, 28 d	Promote cervical active range of motion (clinic-supervised)	Address kinesiophobia
Fowler et al ¹²	380 min, 19 d	Promote movement, mindful meditation (hospital-supervised)	Address kinesiophobia Psychobehavioral modulation
Tejera et al ¹³	8 sessions, 28 d	Promote cervical active range of motion (clinic-supervised)	Address kinesiophobia
Harvie et al ¹⁴	50–84 sessions, 25–42 d	Promote cervical active range of motion via graded motor imagery (home-unsupervised)	Address kinesiophobia Embodiment
Eccleston et al ¹⁵	450–1800 min, 42–56 d	Promote lumbar gross and fine motor movement, behavior change (home-unsupervised)	Address kinesiophobia Psychobehavioral modulation
Trujillo et al ¹⁶	140–315 min, 28 d	Promote motor movement via graded motor imagery (clinic-supervised)	Address kinesiophobia Embodiment
Trost et al ¹⁷	600 min, 10 d	Promote motor movement, embodiment (home-supervised)	Address kinesiophobia Embodiment
Darnall et al ¹⁸	21–315 min, 21 d	Cognitive behavioral therapy, relaxation, mindfulness (home-unsupervised)	Psychobehavioral modulation
Garcia et al ¹⁹	336 min, 56 d	Cognitive behavioral therapy, relaxation, mindfulness (home-unsupervised)	Psychobehavioral modulation
Garrett et al ²⁰	360 min, 30 d	Relaxation, mindfulness (home-unsupervised)	Psychobehavioral modulation
Chuan et al ²¹	90 min, 28 d	Relaxation, pain visualization (clinic-supervised)	Psychobehavioral modulation
Groenveld et al ²²	280–2520 min, 28 d	Pain visualization mindfulness, hypnotherapy, desensitization, and reprocessing (home-unsupervised)	Psychobehavioral modulation
de Vries et al ²³	405–540 min, 21 d	Pain visualization mindfulness, hypnotherapy, desensitization, and reprocessing (clinic supervised)	Psychobehavioral modulation

MOA, mechanism of action; VRI, virtual reality intervention.

or without graded motor imagery or embodiment incorporated, were categorized as addressing kinesiophobia (Table 3). Eight of 14 studies addressed kinesiophobia, representing a total treatment group of 143 patients.^{10–17} Among 6 of these 8 studies [representing 83% (119/143) of treatment group participants], there was a statistically significant improvement in pain scores from baseline to post-intervention.^{10,11,13,15–17}

Studies using VR for psychological interventions were categorized as using psychobehavioral modulation. Eight of 14 studies used psychobehavioral modulation as the underlying VR intervention MOA, with a total treatment group of 214 patients.^{12,15,18–23} Among 5 of these 8 studies [representing 80% (171/214) of treatment group participants], there was a statistically significant improvement in pain scores from baseline to post-intervention.^{15,18,19,22,23}

Chronic Neck Pain

Three studies investigated nontraumatic chronic neck pain in a nonhospital setting and used kinesiophobia as the MOA for their VR intervention.^{10,11,13} These studies demonstrated statistically significant reductions in pain scores after VR therapy. The VAS pain score-weighted average for these patients was 4.6 ± 2.0 at baseline, 2.5 ± 2.1 post-intervention, and 2.5 ± 2.1 at 3 months post-intervention. In 2 studies, there was a sustained reduction in pain scores on follow-up at 3 months after therapy and improvement in TSK scores and behavioral health anxiety measures.^{11,13}

Chronic Low Back Pain

Six studies investigated chronic low back pain, for which 5 studies (representing 99% of the cohort) used psychobehavioral modulation as the MOA.^{18–23} All studies demonstrated a statistically significant reduction in pain scores after VR therapy. Mean pain scores demonstrated a weighted-average scale of 10 pain scores of 5.1 at baseline and 3.2 post-intervention (confident interval data were not sufficiently reported). In addition, 83% of patients studied also had a statistically significant improvement in pain interference outcome measures.

Chronic Neuropathic Pain

Two studies investigated the chronic neuropathic pain population, representing 36 total participants. Trost and colleagues¹⁷ evaluated chronic neuropathic pain in spinal cord injury patients, addressing kinesiophobia as their VR intervention MOA. They demonstrated a statistically significant reduction in pain scores from 5.9 ± 3.0 at baseline to 3.9 ± 3.1 post-intervention. By contrast, Chuan and colleagues²¹ evaluated cancer patients with chronic neuropathic pain ($n = 19$) and used psychobehavioral modulation as their intervention's MOA. No statistically significant changes in pain scores were observed post-intervention.

Nonspecific Chronic Pain

Two studies targeted a nonspecific chronic pain population, representing 24 subjects, with both investigations reporting no significant improvement in pain scores after

Table 3. Results of Research Studies

VRI Group Outcomes				
Study	Significantly Improved Outcomes	Pain	Kinesiophobia	Psychological Measures
Sarig Bahat et al ¹⁰	Pain	VAS pain: 35.72 ± 17.7 (baseline) → 22.10 ± 24.1 (post-VR)* → 26.95 ± 16.5 (3-mo f/u)*	TSK: 32.75 ± 6.8 (baseline) → 30.13 ± 5.7 (post-VR) → 31.23 ± 6.5 (3-mo f/u)	N/A
Sarig Bahat et al ¹¹	Pain, kinesiophobia, psychologic measure	VAS pain: 47.11 ± 21.1 (baseline) → 25.83 ± 21.1 (post-VR)* → 25.43 ± 23.1 (3-mo f/u)*	TSK: 35.1 ± 7.5 (baseline) → 31.77 ± 6.94 (post-VR)* → 30.47 ± 7.67 (3-mo f/u)*	EQ5D health status: 66.28 ± 20.6 (baseline) → 76.74 ± 17.2 (post-VR)*
Fowler et al ¹²	N/A	NRS: 6.88 ± 1.26 (baseline) → 6.38 ± 1.59 (post-VR)	FDAQ Fear of Daily Activities: 59.20 ± 24.83 (baseline) → 56.45 ± 21.02 (post-VR)	POQ-VA pain interference: no significant improvement (post-VR)
Tejera et al ¹³	Pain, kinesiophobia, psychologic measures	VAS pain: 4.97 ± 1.88 (baseline) → 2.67 ± 1.91 (post-VR)* → 2.17 ± 1.99 (3-mo f/u)*	TSK: 22.90 ± 7.11 (baseline) → 18.90 ± 10.73 (post-VR) → 12.09 ± 7.77 (3-mo f/u)*	PCS pain catastrophizing: 17.36 ± 11.49 (baseline) → 8.52 ± 9.77 (post-VR)* → 4.95 ± 8.08 (3-mo f/u)* PASS20 anxiety: 27.52 ± 20.52 (baseline) → 17.33 ± 16.71 (post-VR)* → 12.33 ± 16.09 (3-mo f/u)*
Harvie et al ¹⁴	N/A	NRS pain: no significant change from baseline	TSK: no significant change from baseline	N/A
Eccleston et al ¹⁵	Pain, kinesiophobia, psychologic measure	NRS pain: 6.0 ± 1.4 (baseline) → 4.1 ± 1.7 (post-VR)* → 4.4 ± 1.9 (5-mo f/u)	TSK: 41.9 ± 4.4 (baseline) → 33.7 ± 7.4 (post-VR)* → 33.7 ± 9.2 (5-mo f/u)	PROMIS 6B Pain Interference: 64.5 ± 3.7 (baseline) → 59.0 ± 6.6 (post-VR)*
Trujillo et al ¹⁶	Pain	VAS pain: improvement from baseline (post-VR)*	N/A	PCS pain catastrophizing: 26.5 (baseline) → 17 (post-VR)
Trost et al ¹⁷	Pain, psychologic measures	NRS pain: 5.88 ± 2.98 (baseline) → 3.88 ± 3.11 (post-VR)* → 4.06 ± 2.0 (1-wk f/u)	N/A	PHQ9: 6.5 ± 5.38 (baseline) → 5.19 ± 4.40 (post-VR)* NRS pain interference: 3.75 ± 3.08 (baseline) → 2.62 ± 3.11 (post-VR)*
Darnall et al ¹⁸	Pain, psychologic measures	DVPRS pain: 4.6 (baseline) → 3.2 (post-VR)*	N/A	DVPRS pain-related interference measures—activity, mood, sleep, stress: significant improvement in all measures (post-VR)*
Garcia et al ¹⁹	Pain, psychologic measures	DVPRS pain: 5.1 ± 1.2 (baseline) → 3.0 (post-VR)* → 3.7 (3-mo f/u)*	N/A	DVPRS pain-related interference measures—activity, sleep, stress: significant improvement in all measures (post-VR and 3-mo f/u)*
Garrett et al ²⁰	N/A	N/A	N/A	N/A
Chuan et al ²¹	N/A	mBPI pain: 4.9 ± 1.1 (baseline) → 4.5 ± 1.6 (1-mo f/u)	N/A	mBPI pain interference: 4.7 ± 2.4 (baseline) → 3.7 ± 2.4 (1-mo f/u)
Groenveld et al ²²	Pain	VAS pain: improvement in daily worst and least experienced pain (post-VR)*	N/A	HADS depression subscale and Short Form-12 mental score: no significant mean group improvement (post-VR)
de Vries et al ²³	Pain	NRS pain: improvement from baseline (post-VR)*	TSK: no significant change from baseline (post-VR)	SCL-90-R psychometric and PCI pain Coping inventory: no significant mean group improvement (post-VR)

DVPRS, Defense and Veterans Pain Rating Scale; f/u, follow-up; HADS, Hospital Anxiety and Depression Scale; mBPI, modified Brief Pain Inventory; N/A, not available; NRS, numerical rating scale; PCI, percutaneous coronary intervention; PCS, Pain Catastrophizing Scale; SCL-90-R, Symptom Checklist-90-Revised; TSK, Tampa Scale of Kinesiophobia; VAS, visual analog scale; VR, virtual reality; VRI

VR intervention. Fowler and colleagues¹² evaluated patients in the inpatient setting using a combination of addressing kinesiophobia and psychobehavioral modulation, whereas Garrett and colleagues²⁰ evaluated patients in the outpatient setting and used psychobehavioral modulation as the MOA.¹²

Discussion

This scoping review identified studies using 3D HMD-based VR interventions for chronic pain and assessed both the MOA and efficacy of each intervention. Based on the current extent of the literature, VR therapy is currently being used to treat 2 broad MOAs: kinesiophobia and psychobehavioral modulation.

Kinesiophobia

Kinesiophobia has previously been described as a predictor of pain, proprioception, and functional performance for patients with various chronic pain conditions, including chronic neck pain.²⁴ Broadly speaking, kinesiophobia refers to an unwarranted fear of physical movement due to concerns for reinjury and/or pain that results in avoidance-type behaviors. It is associated with a pronounced negative cognitive and affective response after exposure to pain, also known as a pain-catastrophizing response.²⁵ Persistent chronic neck pain, and changes in the somatosensory system, can be induced by kinesiophobia and its associated catastrophizing behaviors.²⁴ This, in turn, could theoretically delay rehabilitation and reduce activity levels, leading to a cycle of further deterioration of function and possibly worsening pain.

All of the studies related to chronic neck pain reviewed here used avoiding kinesiophobia as the MOA for the VR therapy. On average, there was a nearly 50% reduction in pain scores after VR therapy, and the effect was sustained 3 months after therapy. Based on the recent IMMPACT guidelines for clinically important differences in pain studies, this reduction would be categorized as a “substantial improvement” based on responder analysis.²⁶ Interestingly, a separate cross-sectional study analyzing chronic neck pain patients by Asiri and colleagues²⁴ demonstrated that kinesiophobia, as measured by TSK scores, robustly correlated with predicted pain scores in that patient cohort. Thus, VR seems to be a particularly effective therapy for the treatment of chronic neck pain, and effective VR treatments should be aimed at avoiding kinesiophobia.

Psychobehavioral Modulation

Low back pain is one of the most common causes of chronic pain. Although nonopioid multimodal therapies along with physical therapy have become the standard of care for these patients, largely in response to the opioid epidemic, there continues to be a need for the development of further nonopioid pharmacologic and nonpharmacologic modalities to further treat patients.^{27–30} There are many nonpharmacologic interventions for chronic low back pain, but most are currently aimed at psychological interventions, such as cognitive behavioral therapy. A recent review by Chou and colleagues²⁷ demonstrated that many of these existing modalities are effective at long-term pain intensity. However, many of these interventions require a significant

time commitment on the part of the patient and can be logistically challenging, limiting sustainability and scalability to further treat patients.

Here, we demonstrate that VR is an effective tool for reduction of pain scores in patients suffering from chronic low back pain, and that psychobehavioral modulation is the MOA used for this intervention. The average reduction in pain scores found in studies using VR results in clinically important differences that would be categorized as a “substantial improvement” based on responder analysis.²⁶ One helpful feature of VR as a therapeutic modality is that headsets can be prescribed by a provider at minimal cost and setup burden for the patient, but they can be used asynchronously by the patient at a time and place that is convenient with minimal need for clinician oversight. Thus, VR as a treatment option for psychobehavioral modification in patients with chronic low back pain may be a more effective and scalable modality than options currently being offered to patients. Further robust studies in this area will be required to directly compare the efficacy of VR therapies compared with current outpatient psychological interventions.

A recent review by Foster and colleagues³¹ describes the importance of early incorporation of psychobehavioral therapy into the treatment paradigm, suggesting that cognitive behavioral therapy and patient education should be first-line treatments for chronic low back pain. Currently, VR therapy is used as an adjunct treatment option, either in conjunction with existing traditional therapy or after other therapies have been tried and failed. Thus, VR therapy should also be used early on in the treatment of chronic low back pain for optimal impact.

Chronic Neuropathic Pain

Chronic neuropathic pain has increasingly been investigated as a target for VR interventions. Although the neurophysiology of chronic neuropathic pain is complex and multifactorial, interventions that “correct” altered body perceptions through bodily illusions are considered a promising therapeutic avenue.^{32,33} Here, we found that VR therapies are effective at treating chronic neuropathic pain. Two studies were evaluated here, and both studies used separate MOAs for their VR therapy (kinesiophobia and psychobehavioral modulation). Given that the treatment of neuropathic pain involves modulating neural circuitry gone awry, it is not surprising that VR interventions aimed at addressing the interplay between the way one perceives the world and the central processing of stimuli via the central nervous system is effective.

Nonspecific Chronic Pain

Neither study investigating patients suffering from nonspecific chronic pain demonstrated any benefit for patients. It is not unsurprising that VR therapy was not helpful for patients suffering from nonspecific chronic pain given the MOA's utilized in the studies. Here, we found that patients benefited from VR therapy when there was a specific target for the intervention. For example, VR therapy aimed at avoiding kinesiophobia was effective at reducing chronic neck pain. For patients suffering from nonspecific chronic pain, these patients are likely to fall under the “nociplastic”

spectrum of chronic pain, in that there is no obvious lesion for their pain, but the patients still experience pain. Therefore, the VR interventions may not have been appropriately targeted for the underlying conditions. It remains unclear whether VR therapy leveraging a different MOA would be beneficial for this cohort of patients, or whether VR is simply not an effective tool for the treatment of non-specific chronic pain. Further research will be required to better characterize this discrepancy. Nevertheless, our findings from this scoping review demonstrate that VR therapy is not a panacea and may not be effective for every patient with chronic pain. Just as one would do with any other therapy, it is important to appropriately target the correct patients and establish them with the right MOA to best treat their pain.

The Current and Future Advantages of VR Interventions for Chronic Pain

VR emerges as a promising avenue for addressing critical issues in the context of chronic pain management, particularly in overcoming accessibility challenges. Home-based kinesiophobia training, facilitated by VR, obviates the need for direct clinician supervision, offering a scalable and potentially cost-effective solution. Health insurance-associated barriers to accessing pain psychologists are a pervasive difficulty faced by a large majority of patients, but VR interventions present a transformative opportunity to surmount this barrier.³⁴ As described by Darnall et al¹⁸ emphasizing the pivotal role of access, VR interventions can significantly augment the availability of psychological support for pain management. Furthermore, the entertainment and gamified elements of VR make adherence to treatment regimens potentially more favorable, as has been shown with technology-assisted medication adherence programs.³⁵ From an economic standpoint, the viability of VR interventions could be noteworthy, as they may eliminate the necessity for a reimbursed clinician to supervise each session through continued remote therapeutic monitoring, thereby reducing the burden of chronic pain management cost on the health care system.

This current scoping review, although contributing valuable insights into the potential of VR interventions for chronic pain, is not without significant limitations. Notably, the sample size of studies reviewed was limited, and there is considerable inconsistency in reporting key parameters such as dose as defined by duration and length of intervention. Baseline characteristics among similar pain populations/indications exhibit heterogeneity, impacting the generalizability of findings. Data reporting inconsistencies, including the presence or absence of 3-month follow-ups and the use of differing outcome measures, further complicate the synthesis of results. Heterogeneous exclusion criteria and variations in the administration of VR interventions, whether at home or at a facility, add layers of complexity. Additionally, the VR interventions themselves, although purportedly sharing a common MOA, display heterogeneity in terms of the programs used, with some being in-house developed and others off-the-shelf.

Nevertheless, to refine future study designs investigating VR for chronic pain, it is imperative to consider several key insights. The adoption of 3D HMDs and ensuring a sufficient

dose (ie, exceeding a single session per day) align with the trajectory of technological advancements and offer the most potential for widespread adoption. Precision in indicating the specific chronic pain condition is paramount, with the MOA of VR interventions tailored to address the nuances of each indication. Future studies could explore targeted interventions, such as investigating VR interventions for chronic neck pain patients with elevated baseline TSK scores related to kinesiophobia or exploring psychobehavioral modulation VR interventions for chronic low back pain patients with mild to moderate psychological comorbidity.

Several open questions warrant future investigations, including determining the optimal dose threshold for efficacy, pinpointing the ideal timing for deploying VR interventions within the treatment algorithm, and assessing the durability of results beyond the 3-month follow-up period. The importance of this scoping review and its findings lies in laying the groundwork for further exploration in these areas, paving the way for more refined and comprehensive investigations into the potential of VR interventions in the realm of chronic pain management.

The rapid advances in technology and decreasing costs of VR equipment are pivotal factors contributing to the burgeoning success of VR interventions. Improvements in immersion, presence, interactivity, tolerance, and societal acceptance are anticipated to further enhance the overall efficacy of these interventions. Additionally, the growing emphasis on nonpharmacologic treatment options for chronic pain, as evidenced by the NIH Heal Initiative's funding, underscores the significance of VR in this landscape. As technology continues to evolve and as more literature emerges, the potential for VR in chronic pain management is poised to expand further, offering a multifaceted approach to address the complex challenges associated with this pervasive health issue.

Conclusion

The results of this large-scale within-group analysis indicate VR interventions have significant analgesic effects, often durable at 3-month follow-ups. Furthermore, the results of this study identified 2 broad mechanisms of action underlying the efficacy of VR interventions for respective chronic pain indications. Notably, VR interventions addressing kinesiophobia seem to be significantly effective in nontraumatic, nonhospitalized chronic neck pain patients. Psychobehavioral VR interventions demonstrate significant efficacy in the chronic low back pain population. Studies with interventions targeting nonspecific chronic pain populations did not show significant results despite the use of 3D HMD headsets and sufficient dosing. It seems, as with any medical intervention, precision is key to efficacy. Along with providing actionable data for pain clinicians to incorporate VR interventions into treatment plans, the data gleaned can help guide the design of future VR interventions and clinical trials.

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ICYMI: IN CASE YOU MISSED IT

News from recent studies related to pain management, compiled by Elizabeth A.M. Frost, MD, co-editor of *Topics in Pain Management*

Practice Guidelines for Cannabis and Cannabinoid-Based Medicines in the Management of Chronic Pain and Co-occurring Conditions

In this extensive review of the uses and safety concerns of cannabis, the authors summarize findings from more than 130 studies.¹ In general, they demonstrated moderate effect of cannabis in many situations with strong recommendations for its incorporation in several situations.

Noting that 1 in 5 individuals live with chronic pain globally, which often co-occurs with sleep problems, anxiety,

depression, and substance use disorders, the researchers described how these conditions are commonly managed with cannabinoid-based medicines (CBMs). However health care providers often lack information on the risks, benefits, and appropriate use of CBM for therapeutic purposes.

A systematic review of 70 articles met inclusion criteria and were used in guideline development, including

19 systematic reviews and 51 original research studies. Studies investigating the use of CBM for the treatment of chronic pain were dually reviewed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Clinical recommendations were developed based on available evidence from the review. *Values and preferences* and *practical tips* have also been provided to support clinical application. The GRADE system was used to rate the strength of recommendations and quality of evidence.

Research typically demonstrated moderate benefit of CBM in chronic pain management. There is also evidence for efficacy of CBM in the management of comorbidities, including sleep problems, anxiety, appetite suppression, and for managing symptoms in some chronic conditions associated with pain including HIV, multiple sclerosis, fibromyalgia, and arthritis.

Clinical practice guidelines were then developed to help clinicians and patients navigate appropriate CBM use in the management of chronic pain and co-occurring conditions in this freely uploadable article.

The guidelines are summarized:

1. CBM use for people with chronic pain

Forty-seven studies were reviewed. Most studies (38/47) reported at least moderate benefits of CBM for chronic pain. Associated improvements in secondary outcomes, including quality of life, functionality, and mood, were also observed.

Recommendations: Use CBM as monotherapy, replacement, or adjunct treatment, in people living with chronic pain, for the management of chronic pain including central and/or peripheral neuropathic pain to improve pain outcomes. The recommendations place high value on the improvement in chronic pain, functionality, and secondary outcomes, including time to sleep, quality of sleep, anxiety, and depression, in those living with chronic pain and using CBM compared with placebo. The recommendations also outweigh the risks of nonserious adverse events with CBM (dizziness, disturbance in attention, somnolence, dry mouth, nausea, and diarrhea) as compared with adverse events from standard analgesia (opioids and serotonin-norepinephrine reuptake inhibitors or opioids monotherapy), including constipation, loss of appetite, unclear mentation, reduced affect, hemorrhoids, and substance use disorder. *Strong recommendation, moderate-quality evidence.*

2. The use of CBM as monotherapy, replacement, or adjunct treatment, in people living with chronic pain, for mobility in those not achieving adequate response to other modalities comes with. *Weak recommendation, low-quality evidence.*

3. CBM use for people with HIV and chronic pain

The use of CBM for the management of muscular and neuropathic pain in people living with HIV who are not achieving adequate response, including nausea, anxiety, depression, lack of appetite, and weight loss in people living with HIV has *Strong recommendation, moderate-quality evidence*. CBM use is for symptom management only and should not replace the use of antiretroviral therapies.

4. CBM use in multiple sclerosis and chronic pain

Most studies (9/12) reported improvements in pain, sleep disorders, and muscle spasm associated with CBM but were limited by small numbers of participants, short duration of treatment, and some crossover and blinding deficiencies. Use as an adjunct treatment, for pain management in people with multiple sclerosis not achieving adequate response to other modalities. *Strong recommendation, moderate-quality evidence.*

5. CBM with an arthritic condition experiencing chronic pain

One randomized controlled trial (RCT) and a published abstract demonstrated improvement in pain, sleep, and comorbid markers of inflammation in patients with an arthritic condition not achieving adequate response to other modalities. Use of CBM is recommended with *strong recommendation, low-quality evidence.*

6. CBM use for people living with fibromyalgia and chronic pain

In 4 of 6 studies that included participants with fibromyalgia and pain demonstrated improvements in pain across their wider study sample. In an open-label study, two-thirds of study participants living with fibromyalgia responded well to sublingual tetrahydrocannabinol (THC) treatment. Use of CBM, as an adjunct treatment, for management of back pain, fibromyalgia pain, or other chronic pain in people with fibromyalgia who are not achieving an adequate response to standard analgesics comes with *strong recommendation, low-quality evidence.*

7. CBM use for chronic headache and migraine

Four studies reported at least some improvement from cannabis in participants experiencing headaches, and its use is recommended as an adjunct treatment, for the management of chronic migraine or chronic headache, in those not achieving adequate response to other modalities. *Weak recommendation, low-quality evidence.*

8. CBM use for chronic pain and nausea

Five studies demonstrated improvements in nausea with cannabis use, whereas other studies demonstrated nausea to be an adverse event associated with cannabis use among some participants. All studies were limited by study design (case series or cross-sectional surveys), small numbers of patients, unknown duration or dosing of cannabis, and the possibility of selection and recall bias. It is also unclear which cannabis formulation or route of administration is optimal (smoked vs oral, THC vs cannabidiol (CBD) vs THC/CBD products) for nausea. Use could be considered to reduce nausea in people living with chronic pain as a monotherapy or adjunct treatment for those not achieving adequate response to other treatment modalities with *weak recommendation, low-quality evidence.*

9. CBM use for sleep problems and symptoms of sleep deprivation experiencing chronic pain.

Twenty-five studies demonstrated benefit for sleep in some or most participants with *strong recommendation, moderate-quality evidence.*

10. CBM use for chronic pain experiencing appetite loss

Of 7 studies, 2 did not demonstrate a significant difference between CBM and placebo. Use comes with *strong recommendation, low-quality evidence*.

11. CBM use in chronic pain patients experiencing posttraumatic stress disorder (PTSD)

Two studies demonstrated reporting of chronic pain decreased and ability to cope with pain and overall quality of life, mood, sleep, and concentration. Use of CBM to improve PTSD symptoms has *weak recommendation, low-quality evidence*.

12. CBM use for people living with chronic pain experiencing anxiety

Eight studies reported anxiolytic effects of cannabis. And the recommendation is *strong recommendation, moderate-quality evidence*.

13. CBM use for chronic pain and depression

Findings for depressive symptom outcomes seemed to be contingent on the types of CBMs used, with herbal cannabis appearing to be more effective than extracts. An RCT of smoked cannabis demonstrated that it improved depressive symptoms significantly with a medium-sized effect over placebo. Studies involving the use of cannabis extracts are generally less positive. The review comes with *weak recommendation, moderate-quality evidence*.

14. Adjunctive CBM use for chronic pain in patients experiencing unsatisfactory analgesia from opioid treatment

Four studies demonstrated a reduction in pain with the addition of CBM to an opioid regimen. Several additional studies demonstrated improvements in chronic pain associated with CBM use within samples that included participants concurrently using opioids to treat pain. In addition, 3 studies demonstrated positive associations between medical cannabis use and opioid sparing. Two other studies reported that most participants reduced their routine pain medications by 60%–70%; however, the extent to which opioid medications were specifically reduced was unclear. *Strong recommendation, moderate-quality evidence for combination*.

Additional Information

Drug Interactions

Both THC and CBD are predominantly metabolized, by the liver, through the action of the cytochrome P450 system. Few clinical studies consider the effect of cannabinoids on this enzyme system, but *in vitro* studies suggest that THC inhibits CYP3A4, CYP3A5, CYP2C9, and CYP2C19, whereas CBD inhibits CYP2C19, CYP3A4, and CYP3A5. Due to the weak inhibitory effect of these cannabinoids, higher concentrations than those seen clinically are likely to be required for clinical inhibitory effect.

Concern arises when cannabinoids are coadministered with drugs having a narrow therapeutic window and also

metabolized by these enzymes, such as direct-acting oral anticoagulants metabolized through CYP3A4 and clopidogrel requiring conversion to its active metabolite by CYP2C19. Significantly elevated levels of the antiepileptic clobazam and its metabolite, N-desmethyloclobazam, have been observed when coadministered with very high doses of CBD, likely due to cometabolism through CYP2C19 and CYP3A4.

A comprehensive overview of the pharmacokinetic interactions of cannabinoids has been reported by Alsherbiny and Li.² Pharmacodynamic interactions also need to be considered with CBM, particularly THC, administration. Additive effects can occur when cannabinoids are combined with sympathomimetics (eg, tachycardia and hypertension), central nervous system depressants such as alcohol and opioids (eg, drowsiness and ataxia), and anticholinergics (eg, tachycardia and confusion).³

Adverse Effects

The adverse effects most commonly associated with cannabis are related to THC dose and the route of administration.⁴ THC-related adverse effects include dizziness, cognitive impairment, dry mouth, tachycardia, anxiety, drowsiness, and fatigue. Although no definitive causal effects have been established, there are case reports of stroke, acute coronary syndrome, and cardiac arrhythmias associated with use of cannabis.¹ Maternal exposure to cannabis can adversely affect conception and/or maintenance of pregnancy. Significant decline in sperm count, concentration, and motility, and an increase in abnormal sperm morphology have been reported.¹

Smoking cannabis is associated with respiratory adverse effects such as cough, an increase in phlegm, and bronchitis. Long-term use is associated with risk of cannabis use disorder, hyperemesis syndrome, and withdrawal symptoms including insomnia, anxiety, depression, and tremulousness.

Conclusions

Although CBMs may be used for other purposes, these guidelines present recommendations for people living with chronic pain and for co-occurring conditions within the context of chronic pain during a period of cannabis regulation changes.

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CME/NCPD QUIZ: VOLUME 40, NUMBER 5

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1. You are managing a patient with chronic low back pain. Standard therapy has provided limited relief, and the patient is no longer interested in injections or surgery. The *most* appropriate VR-based intervention is
 - A. addressing kinesiophobia to reduce fear of movement.
 - B. embodiment therapy to modulate central pain processing.
 - C. psychobehavioral modulation focusing on cognitive restructuring and relaxation.
 - D. graded motor imagery to stimulate movement through virtual environments.
2. A patient with chronic neck pain can be counseled that
 - A. VR therapy helps by providing distraction from pain, reducing focus on physical discomfort.
 - B. VR therapy allows controlled exposure to movement without the immediate fear of real-life injury.
 - C. VR therapy alters sensory perceptions, tricking the brain into ignoring pain signals.
 - D. VR therapy encourages physical engagement with gamified environments rewarding movement.
3. A VR intervention should
 - A. focus on relaxation and mindfulness techniques.
 - B. maximize the frequency of VR sessions for appropriate dosage.
 - C. combine VR with physical therapy exercises.
 - D. be reconsidered, given the nonspecific nature of the patient's pain.
4. Generalization of results from existing studies is limited due to
 - A. lack of sufficient follow-up data in most studies.
 - B. heterogeneity in VR intervention mechanism, study design, and dosing.
 - C. the high cost of VR equipment used in most studies.
 - D. the exclusion of patients with comorbid conditions.
5. A patient has chronic low back pain and a history of psychological comorbidities.
 - A. VR therapy should be avoided in patients with psychological comorbid conditions.
 - B. VR therapy with psychobehavioral modulation may significantly reduce pain interference in daily activities.
 - C. VR therapy with psychobehavioral modulation is best suited for patients with severe depressive symptoms.
 - D. VR therapy with psychobehavioral modulation should be reserved for patients who have undergone psychotherapy interventions.
6. The 3 key domains (pillars) used to characterize VR are
 - A. setup, view point, and immersibility.
 - B. timing, avatars, and relatability.
 - C. presence, immersion, and interactivity.
 - D. realism, relatability, and interactability.
7. Most of the studies included in this review were
 - A. case reports.
 - B. quasi-experimental.
 - C. descriptive.
 - D. randomized controlled trials.
8. Each VR intervention's mechanism of action addresses
 - A. kinesiophobia and psychobehavioral modulation.
 - B. pain catastrophizing and activities of daily living.
 - C. pain coping and quality of life.
 - D. problem-solving and self-regulation skills.
9. The most potential for widespread adoption of VR for pain management is in
 - A. ensuring realistic scenarios based on specific mechanisms of action.
 - B. adoption of 3D head-mounted displays and ensuring a sufficient dose.
 - C. implementation on smartphones and integration in standard care.
 - D. having relatable virtual worlds and accessible platforms.
10. Which area of VR research was suggested by the authors as a need for future investigations?
 - A. determining how accessibility to VR improves pain-treatment outcomes
 - B. demonstrating that increased gamability improves adherence to pain treatment
 - C. assessing the durability of results beyond the 3-month follow-up period
 - D. understanding how early introduction to VR can reduce chronic low back pain