VIRTUAL REALITY TREATMENT IN A METHADONE MAINTENANCE TREATMENT PROGRAM FOR CHRONIC PAIN AND OUD: A PILOT RANDOMIZED CONTROLLED TRIAL

IRB number: 2022-14257

NCT05546749

Documents updated 04/20/2023

VIRTUAL REALITY TREATMENT IN A METHADONE MAINTENANCE TREATMENT PROGRAM FOR CHRONIC PAIN AND OUD: A PILOT RANDOMIZED CONTROLLED TRIAL (VR-OUD PILOT)
Protocol V 1.6

BACKGROUND

A. Opioid use disorder (OUD) is highly associated with comorbid chronic pain. Opioid use disorder, a condition affecting 2 million persons in the United States, is defined by a pattern of opioid use with significant personal, professional, and social consequences. In addition to being highly associated with health outcomes such as overdose related to opioid use, OUD is also highly related to poor general health, low quality of life, and debilitating chronic pain.[1,2] Among patients receiving medications for OUD, over half report at least moderate chronic pain, and more than a quarter report at least severe chronic pain.[3–5] Evidence suggests that poorly controlled chronic pain may impact OUD outcomes, likely mediated through increased opioid craving to relieve pain and/or reduce depression and anxiety symptoms.[5–8]

B. New and innovative treatments for chronic pain are needed. Despite the burden of chronic pain, established treatments are ineffective, laden with severe side effects, or inaccessible. Opioid therapy is common but ineffective for the treatment of chronic pain and, moreover, carries significant risk of severe adverse events including overdose.[9,10] For these reasons, non-pharmacologic treatment for chronic pain is recommended by numerous clinical practice guidelines. However, numerous barriers, including local availability and perceived lack of efficacy, impede access to non-pharmacologic treatment options.[11] For these reasons, studies of new and innovative treatments are needed.

C. Barriers and facilitators to non-pharmacologic treatment for chronic pain among persons with OUD. Accessing non-pharmacologic treatment among persons with OUD is further compounded by several unique barriers, including stigma and federal requirements requiring persons to visit MMTPs daily or very regularly.[12–16] Integrating on-site non-pharmacologic treatments for chronic pain into MMTPs is an innovative strategy to reduce systemic and logistical barriers to treatment of chronic pain and has the potential to reduce stigma.[17,18]

C. VR treatments for chronic pain. VR treatments represent a relatively new and highly innovative treatment paradigm for chronic pain. VR treatments already have established efficacy in mood disorders, anxiety, phobias, and acute pain.[19,20] Multiple systematic reviews have established that VR interventions for the treatment of chronic pain are promising, but interventions to date are heterogenous and further study is needed to demonstrate efficacy.[21–23] For example, immersive VR in a virtual environment tends to be associated with higher pain reduction and greater satisfaction.[24–26] Relevant to this application, the immersive VR intervention (RelieVRx) proposed for use in the current study was tested in a sample of 179 adults with chronic low back pain and shown to be effective in an 8-week trial in reducing pain and improving sleep, mood, and stress; most changes persisted up to 3 months.[27,28]

D. VR treatments have been used in substance use disorders, and early evidence suggests VR treatments can be effective in OUD. A recent systematic review concluded that VR treatments can provide benefits in substance use disorder treatment, mainly owing to the ability of a therapeutic, immersive environment.[29] In persons with nicotine addiction and alcohol use disorder, VR treatments found mixed to positive results on a number of nicotine and alcohol outcomes, including decreased craving.[30–39] A recent non-randomized pilot study of a VR meditative intervention with 15 persons on methadone for OUD showed reductions in pain, opioid craving, anxiety, and depression in addition to reduced saliva cortisol, and changes in brain activation in the postcentral gyrus region of the brain on pain related tasks.[40]

E. Immersive mindfulness VR can lead to improved pain and OUD outcomes through its targeted effects on stress and inflammation. Mindfulness exercises have been associated with a myriad of positive outcomes that are relevant to the current study, including improved quality of life, pain interference, mood and anxiety symptoms, sleep quality, opioid craving, and opioid use.[41–49] We propose

these positive outcomes work through targeted effects on stress and inflammation, as mindfulness therapies have been associated with reductions in both patient reported stress and inflammation and in biomarkers linked to stress (such as cortisol) and inflammation (such as C-reactive protein and cytokine levels).[45,50–52] Reductions in both stress and inflammation, in turn, are associated with improved pain and OUD outcomes.[53–56]

F. Summary. Chronic pain is highly prevalent in patients with OUD, and new and innovative treatments and onsite treatment paradigms are needed. We propose an innovative, on-site immersive mindfulness VR treatment targeting stress and inflammation to improve pain and OUD outcomes. The proposed trial will be the first pilot RCT study of VR treatment in a methadone maintenance treatment program (MMTP), and has the potential for widespread application.

STUDY DESIGN

Overview. In a 6-week pilot RCT, we will assess the feasibility and preliminary efficacy of an immersive mindfulness VR treatment (RelieVRx) versus a non-immersive sham VR control (sham VR) for the treatment of pain and OUD. We will recruit 40 adults with OUD and chronic pain enrolled in an MMTP and randomize 1:1 to RelieVRx vs sham VR. Over 6 weeks, participants in both groups will participate in 20-30 minute VR sessions twice per week at the MMTP. Over the course of the study, the research team will conduct pain and psychological assessments at baseline, 3 weeks, and at the study conclusion at 6 weeks. We will also explore changes in stress and inflammatory saliva and blood biomarkers at baseline, 3 weeks and 6 weeks. To assess feasibility, we will examine recruitment and retention and assess patient satisfaction. Our preliminary efficacy co-primary outcomes are (1) change in pain intensity and (2) change in opioid craving between treatment groups at 6 weeks. Secondary outcomes will include changes in pain interference, physical functioning, depression, anxiety, sleep quality, illicit opioid use, and prescription opioid use. In a separate aim, we will also explore changes in stress and inflammatory markers over the course of the trial.

Setting and Participants. We will recruit and conduct study visits at one Montefiore Opioid Treatment Program (OTP). Montefiore has the largest network of OTPs in New York State. Three of the five Montefiore OTPs comprise the Montefiore Division of Substance Abuse (DoSA) Wellness Centers; in total, these sites serve approximately 3,000 individuals. Electronic health data indicates that of 945 people with a chronic pain diagnosis who are on methadone for OUD, 555 (59%) are Male, mean age is 58.3, 566 (60%) are Hispanic, 170 (18%) are Black, and 140 (15%) are White.

Participants: We will enroll 40 participants. As the narration of the VR device is only provided in English at this time, we require English proficiency for this pilot trial. **Inclusion criteria**: 1) ≥18 years old, 2) English proficiency; 3) receiving methadone treatment for DSM-5 confirmed OUD in the Montefiore network for at least 12 weeks, with no dose change in 14 days to ensure treatment stability; 4) chronic pain of at least moderate pain severity (score ≥4 on the Pain, Enjoyment of Life, and General Activity (PEG) scale);[57] 5) willingness to participate in all study components; and 6) ability to provide informed consent, assessed using consent teach-back. **Exclusion criteria**: 1) conditions that could make participation in VR hazardous or cause adverse effects (current or prior diagnosis of epilepsy, seizure disorder, dementia, or migraines, any medical condition predisposing to nausea or dizziness, hypersensitivity to flashing light or motion), 2) conditions that could prevent proper use of the VR headset (stereoscopic vision or severe hearing impairment, or injury to eyes, face, or neck that prevents use of the VR headset), and 3) acute exacerbation of psychiatric conditions that preclude the ability to participate in the study. Pregnant patients are NOT excluded from the trial as there are no contraindications to their use of a VR device, but we are not specifically targeting pregnant patients for this study nor are we testing for pregnancy.

Recruitment, Screening, and Randomization. Recruitment will be active and passive in the OTP. Based on our team's prior DoSA trials and the scope of this current project, we anticipate enrolling 1-2

participants weekly. Research staff will enroll from one DoSA site for the duration of the trial; we will plan our recruitment strategy in conjunction with other IMPOWR-ME trials as to not recruit from the same pool of patients at a site at the same time. We expect retention of approximately 85% based on our groups prior DoSA trials.[58,59] **Screening:** After obtaining written consent, we will administer a screening questionnaire. Potentially eligible subjects will then complete a written informed consent process including discussion of procedures and risks and benefits before being randomized. Consent will occur in a private area of the OTP. **Randomization**: Randomization will occur using block randomization (blocks of 4) to two conditions in a 1:1 ratio.

Table 1. Overview of Data Collection

Domain	Measure	Source
Feasibility Outcomes		
Percent screened	Proportion of total participants contacted who are screened	RL
Percent consented	Proportion of total participants screened who consent	RL
Percent retained	Proportion of total participants consented who complete study	RL
Patient satisfaction	Global impression of change scale[60]	S
Preliminary Efficacy Outcomes and Covariates		
Pain intensity (co-primary)	PEG,[57] PROMIS Pain Intensity subscale[61]	S
Opioid craving (co-primary)	Opioid Craving Visual Analog Scale[62]	S
Quality of life	PROMIS Physical Functioning, PROMIS PROPr Fatigue, Cognitive Function, Social Function[61]	S
Stress	Perceived stress scale[63,64]	S
Pain interference	PROMIS Pain Interference Subscale,[61] PEG[57]	S
Pain history and characteristics	Pain screening questions, Michigan pain body map[65], use of medications and treatments, chronic pain acceptance,[66] pain self-efficacy[67], pain catastrophizing[68]	S
Mood symptoms	PROMIS PROPr Depression, Anxiety[61]	S
Sleep quality	PROMIS Sleep Disturbance 6A + Sleep Duration[69]	S
Illicit opioid use and substance use	Modified Addiction severity index[70], Narcan use and overdose	S
Prescription opioid use	Opioid prescriptions, including methadone dose	S, EMR, PMP
Sociodemographics	Age, gender, insurance, race/ethnicity, education, marital status, socioeconomic status, social support[71], social risk assessment questionnaire	S
Perceived discrimination	Adapted perceived discrimination scale[71]	S
Mindfulness	Mindful attention awareness scale[72]	S
Technology Attitudes	VR Knowledge, Media and Technology Use and Attitudes subscale[73]	S
Stress and Inflammation Outcomes		
Cortisol	Morning salivary cortisol, serum morning cortisol	L
C-reactive protein	Serum CRP	L
Cytokine panel	Serum cytokines	L
Before/After VR Surveys		
Pain	Pain intensity score	S
Mood	Brief Mood Introspection Scale[74]	S
Mindfulness	State Mindfulness Scale[75]	S
Immersion & Distraction	Adapted Immersion Scale[76], Adapted Distraction Scale[76]	S

RL: Recruitment logs; S: Surveys; EMR: Electronic Medical Record; PMP: Prescription Monitoring Program; L: Lab tests

Description of intervention and control. Both intervention and control arms will utilize a Pico G2 head-mounted VR device with pre-installed software. RelieVRx incorporates evidence-based principles of cognitive behavioral therapy and mindfulness to provide pain neuroscience education and to train users on evidence-based pain and stress management strategies with interactive and immersive exercises and experiences. In total, RelieVRx combines biopsychosocial pain education, diaphragmatic breathing training, relaxation exercises, and executive functioning and attentional games to strengthen pain coping skills. RelieVRx is typically delivered in a 56-day program through daily virtual experiences, with each experience lasting between 2 and 16 minutes; in this pilot study, we will conduct in-office virtual experiences twice weekly. Each session will last about 20-30 minutes and go through 1-5 virtual experiences. The sham VR control is a non-immersive set of 56 daily virtual experiences, tuned to the length of the RelieVRx. Control participants will similarly experience 1-5 virtual experiences in each 20-30 session.

Data sources, measures, and management. Study assessments will take place onsite at the OTP at weeks 0, 3, and 6 and last 30-60 minutes. Participants will receive $50 compensation at each study assessment. We will track the number of patients screened, eligible, consented, and retained. During assessments, participants will answer surveys and submit saliva and blood. In addition, we will extract information from the Montefiore EMR, SMART EMR (methadone dosage), and from the New York State Prescription Monitoring Program (PMP). Study measures are listed in Table 1; where possible we align our measures with IMPOWR CDEs and with IMMPACT recommendations for study of chronic pain.[77] All measures will be examined at each study visit, at 0, 3 and 6 weeks. All study assessment data will be managed in REDCAP, a well-established, HIPAA-compliant web-based surveying platform and database.[78] During twice weekly VR sessions, we will also conduct before and after surveys to ask about experiences during VR exercises not taking more than 5 minutes; these will be paper based, scanned, and uploaded to Montefiore BOX, a HIPAA-compliant online cloud storage service. A portion of blood will also be bio-banked to facilitate future biomarker analyses. We will conduct an optional qualitative interview exploring experiences in the trial at the conclusion of the trial; participant interviews will be recorded and transcribed for analysis.

Informed Consent. The RA will screen all potential participants for inclusion and exclusion criteria in a private area of the MMTP. First, we will obtain written consent to administer a screening questionnaire. Screening questionnaire questions will focus on inclusion and exclusion criteria, pain history, and also ask about prior use of virtual reality devices. The initial screening questionnaire will take 15 minutes. Participants will not be reimbursed for the screening questionnaire. Written consent and the initial screening questionnaire will occur in a private area of the MMTP.

Potentially eligible subjects will then complete a written informed consent process with HIPAA authorization including discussion of procedures and risks and benefits before being randomized. Consent will occur in a private area of the OTP. The RA will perform consent teach-back to assure that participants are aware of the details of the consent. Participants who give consent and are randomized will then complete the first study visit at a convenient time. Participants will be reimbursed $50 for their participation at each study assessment. If they choose to participate in the optional qualitative component, they will be reimbursed an additional $30.

Tests and procedures, including blood draws and saliva samples, performed at study assessments will not be billed to participants.

Patient privacy protection. We will strip patients' protected health information from all data before conducting analyses. As in prior studies we have conducted, we will have a "name-based" and an "ID-based" identification system that will remain separate. In the name-based system, all documents that have patient identifiers will be filed together. Some of these documents will have participants' signatures (e.g., consent forms). In the ID-based system, all documents that do not include identifying information or signatures will use participants' unique study IDs (rather than names) and will be filed together. All forms will contain either a "name-based" or an "ID-based" identifier, but never both. There will be only one electronic document that links participants' names to their study IDs; only the study staff will have access to this document, which will be password protected and kept on password-protected servers.

Study data will be kept in a password-protected, encrypted file on password-protected servers that are backed up daily. No one but the study team will have access to study data. Publication or presentation of study results will not include information that would allow for identification of providers or patients.

Analytic plan. *Feasibility*: Feasibility outcomes will be measured as proportions. *Preliminary Efficacy*: To examine the association between treatment arm and the co-primary outcomes, we will use separate 2-level mixed-effects linear regression model with the treatment arm as a mixed effect with participant-specific random intercepts to account for hierarchical data. The difference in trends of pain intensity and opioid craving will be represented by the time-by-arm interaction. For secondary outcomes and stress and inflammation exploratory outcomes, we will use a similar strategy; where outcomes are dichotomous, we will use 2-level mixed effects logistic regression models.

We will use thematic analysis to analyze transcripts in the qualitative study.

Power analysis. The primary purpose of this study is to test feasibility and to generate preliminary data for a future R01 application. We are able to enroll 40 participants in the pilot RCT given our resources and given the time of this study. We base our conservative power analysis on t-tests of change in our pain intensity preliminary efficacy outcome and use effect size estimates from a study of RelieVRx.[27] In that study, the pre-post difference in pain intensity was 2.2 in the treatment group and 1.2 in the control group. Given the effect size of d=0.49, and 20 participants in each arm, we will have 70% power to detect a difference of this magnitude or larger. We expect to have greater statistical power using mixed effects linear regression models with repeated measures over time.

Risks/Benefits. We expect the major risks to be associated with the VR technology. VR can sometimes cause "cybersickness" in some patients, especially when playing or experiencing fast moving games or videos. RelieVRx is a much less intense program designed to minimize these sensations. In the clinical trial of RelieVRx, about 10% of participants reported some nausea and/or motion sickness, but these symptoms were temporary and none decided to terminate their use of the technology because of adverse events. In our preliminary data of 20 patients, no patients have reported any issues with cybersickness. Nonetheless, this will be an important risk to discuss with patients.

Another risk is breach of confidentiality of patient data. Such a breach is unlikely, because all study staff will be trained in confidentiality and secure data management, and the data collected as part of this study will be stripped of protected health information.

In the major clinical trials of RelieVRx, both intervention and sham VR groups had reduced pain at the end of the trial, with the magnitude being larger in the intervention arm. However, this trial is shorter and some of the parameters are not the same, including the number of weeks of the intervention. Therefore, it is possible, but not certain, participants will receive a direct benefit.

Data Safety Monitoring Plan. Monitoring of recruitment and retention, adverse events, protocol deviations, and protocol violations will be ongoing by the Principal Investigator. Additionally, the PI and co-investigators will meet every 2 months in person to discuss recruitment, retention, data quality, and any adverse events. Together, they will make corrective plans as necessary. No interim analyses are planned for this pilot trial.

REFERENCES

1. Aas CF, Vold JH, Skurtveit S, et al. Health-related quality of life of long-term patients receiving opioid agonist therapy: a nested prospective cohort study in Norway. *Subst Abuse Treat Prev Policy*. 2020;15(1):68.

2. Millson PE, Challacombe L, Villeneuve PJ, et al. Self-perceived health among Canadian opiate users: a comparison to the general population and to other chronic disease populations. *Can J Public Health*. 2004;95(2):99-103.

3. Dunn KE, Brooner RK, Clark MR. Severity and interference of chronic pain in methadone-maintained outpatients. *Pain Med*. 2014;15(9):1540-1548.

4. Jamison RN, Kauffman J, Katz NP. Characteristics of methadone maintenance patients with chronic pain. *J Pain Symptom Manage*. 2000;19(1):53-62.

5. Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. *JAMA*. 2003;289(18):2370-2378.

6. Tsui JI, Lira MC, Cheng DM, et al. Chronic pain, craving, and illicit opioid use among patients receiving opioid agonist therapy. *Drug Alcohol Depend*. 2016;166:26-31.

7. Martel MO, Dolman AJ, Edwards RR, Jamison RN, Wasan AD. The association between negative affect and prescription opioid misuse in patients with chronic pain: the mediating role of opioid craving. *J Pain*. 2014;15(1):90-100.

8. MacLean RR, Spinola S, Garcia-Vassallo G, Sofuoglu M. The Impact of Chronic Pain on Opioid Use Disorder Treatment Outcomes. *Current Addiction Reports*. Published online January 13, 2021. doi:10.1007/s40429-020-00352-6

9. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. *JAMA*. 2018;320(23):2448-2460.

10. Agency For Healthcare Research. *The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain*. AHRQ; 2014. http://www.effectivehealthcare.ahrq.gov/ehc/products/557/1971/chronic-pain-opioid-treatment-report-141007.pdf

11. Becker WC, Dorflinger L, Edmond SN, Islam L, Heapy AA, Fraenkel L. Barriers and facilitators to use of non-pharmacological treatments in chronic pain. *BMC Fam Pract*. 2017;18(1):41.

12. Beitel M, Oberleitner L, Kahn M, et al. Drug Counselor Responses to Patients' Pain Reports: A Qualitative Investigation of Barriers and Facilitators to Treating Patients with Chronic Pain in Methadone Maintenance Treatment. *Pain Med*. 2017;18(11):2152-2161.

13. Karasz A, Zallman L, Berg K, Gourevitch M, Selwyn P, Arnsten JH. The experience of chronic severe pain in patients undergoing methadone maintenance treatment. *J Pain Symptom Manage*. 2004;28(5):517-525.

14. Kunins HV. Structural Racism and the Opioid Overdose Epidemic: The Need for Antiracist Public Health Practice. *J Public Health Manag Pract*. 2020;26(3):201-205.

15. Woo J, Bhalerao A, Bawor M, et al. "Don't Judge a Book Its Cover": A Qualitative Study of Methadone Patients' Experiences of Stigma. *Subst Abuse*. 2017;11:1178221816685087.

16. Umbricht-Schneiter A, Ginn DH, Pabst KM, Bigelow GE. Providing medical care to methadone clinic patients: referral vs on-site care. *Am J Public Health*. 1994;84(2):207-210.

17. Batchelder AW, Brisbane M, Litwin AH, Nahvi S, Berg KM, Arnsten JH. "Damaging what wasn't damaged already": psychological tension and antiretroviral adherence among HIV-infected methadone-maintained drug users. *AIDS Care*. 2013;25(11):1370-1374.

18. Batchelder AW, Peyser D, Nahvi S, Arnsten JH, Litwin AH. "Hepatitis C treatment turned me around:" Psychological and behavioral transformation related to hepatitis C treatment. *Drug Alcohol Depend*. 2015;153:66-71.

19. Cieślik B, Mazurek J, Rutkowski S, Kiper P, Turolla A, Szczepańska-Gieracha J. Virtual reality in psychiatric disorders: A systematic review of reviews. *Complement Ther Med*. 2020;52:102480.

20. 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.

21. Nagpal AS, Raghunandan A, Tata F, Kibler D, McGeary D. Virtual Reality in the Management of Chronic Low Back Pain: A Scoping Review. *Front Pain Res (Lausanne)*. 2022;3:856935.

22. Austin PD. The Analgesic Effects of Virtual Reality for People with Chronic Pain: A Scoping Review. *Pain Med*. 2022;23(1):105-121.

23. Mallari B, Spaeth EK, Goh H, Boyd BS. Virtual reality as an analgesic for acute and chronic pain in adults: a systematic review and meta-analysis. *J Pain Res*. 2019;12:2053-2085.

24. Triberti S, Repetto C, Riva G. Psychological factors influencing the effectiveness of virtual reality-based analgesia: a systematic review. *Cyberpsychol Behav Soc Netw*. 2014;17(6):335-345.

25. Austin PD, Siddall PJ. Virtual reality for the treatment of neuropathic pain in people with spinal cord injuries: A scoping review. *J Spinal Cord Med*. 2021;44(1):8-18.

26. Austin PD, Siddall PJ, Lovell MR. Feasibility and acceptability of virtual reality for cancer pain in people receiving palliative care: a randomised cross-over study. *Support Care Cancer*. 2022;30(5):3995-4005.

27. Garcia LM, Birckhead BJ, Krishnamurthy P, et al. An 8-Week Self-Administered At-Home Behavioral Skills-Based Virtual Reality Program for Chronic Low Back Pain: Double-Blind, Randomized, Placebo-Controlled Trial Conducted During COVID-19. *J Med Internet Res*. 2021;23(2):e26292.

28. Garcia LM, Birckhead BJ, Krishnamurthy P, et al. Three-Month Follow-Up Results of a Double-Blind, Randomized Placebo-Controlled Trial of 8-Week Self-Administered At-Home Behavioral Skills-Based Virtual Reality (VR) for Chronic Low Back Pain. *J Pain*. Published online December 11, 2021. doi:10.1016/j.jpain.2021.12.002

29. Segawa T, Baudry T, Bourla A, et al. Virtual Reality (VR) in Assessment and Treatment of Addictive Disorders: A Systematic Review. *Front Neurosci*. 2019;13:1409.

30. Lee J, Lim Y, Graham SJ, et al. Nicotine craving and cue exposure therapy by using virtual environments. *Cyberpsychol Behav*. 2004;7(6):705-713.

31. Pericot-Valverde I, Secades-Villa R, Gutiérrez-Maldonado J. A randomized clinical trial of cue exposure treatment through virtual reality for smoking cessation. *J Subst Abuse Treat*. 2019;96:26-32.

32. Pericot-Valverde I, Secades-Villa R, Gutiérrez-Maldonado J, García-Rodríguez O. Effects of systematic cue exposure through virtual reality on cigarette craving. *Nicotine Tob Res*. 2014;16(11):1470-1477.

33. Pericot-Valverde I, García-Rodríguez O, Gutiérrez-Maldonado J, Secades-Villa R. Individual variables related to craving reduction in cue exposure treatment. *Addict Behav*. 2015;49:59-63.

34. Park CB, Choi JS, Park SM, et al. Comparison of the effectiveness of virtual cue exposure therapy and cognitive behavioral therapy for nicotine dependence. *Cyberpsychol Behav Soc Netw*. 2014;17(4):262-267.

35. Girard B, Turcotte V, Bouchard S, Girard B. Crushing virtual cigarettes reduces tobacco addiction and treatment discontinuation. *Cyberpsychol Behav*. 2009;12(5):477-483.

36. 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*. 2012;22(3):293-300.

37. Lee SH, Han DH, Oh S, et al. Quantitative electroencephalographic (qEEG) correlates of craving during virtual reality therapy in alcohol-dependent patients. *Pharmacol Biochem Behav*. 2009;91(3):393-397.

38. Son JH, Lee SH, Seok JW, et al. Virtual Reality Therapy for the Treatment of Alcohol Dependence: A Preliminary Investigation With Positron Emission Tomography/Computerized Tomography. *J Stud Alcohol Drugs*. 2015;76(4):620-627.

39. Choi YJ, Lee JH. The effect of virtual covert sensitization on reducing alcohol craving in heavy social drinkers. *Virtual Real*. 2015;19(2):111-117.

40. Faraj MM, Lipanski NM, Morales A, et al. A Virtual Reality Meditative Intervention Modulates Pain and the Pain Neuromatrix in Patients with Opioid Use Disorder. *Pain Med*. 2021;22(11):2739-2753.

41. Khanna S, Greeson JM. A narrative review of yoga and mindfulness as complementary therapies for addiction. *Complement Ther Med*. 2013;21(3):244-252.

42. Garland EL, Hudak J, Hanley AW, Nakamura Y. Mindfulness-oriented recovery enhancement reduces opioid dose in primary care by strengthening autonomic regulation during meditation. *Am Psychol*. 2020;75(6):840-852.

43. Hilton L, Hempel S, Ewing BA, et al. Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis. *Ann Behav Med*. 2017;51(2):199-213.

44. Garland EL, Hanley AW, Kline A, Cooperman NA. Mindfulness-Oriented Recovery Enhancement reduces opioid craving among individuals with opioid use disorder and chronic pain in medication assisted treatment: Ecological momentary assessments from a stage 1 randomized controlled trial. *Drug Alcohol Depend*. 2019;203:61-65.

45. Nyklícek I, Kuijpers KF. Effects of mindfulness-based stress reduction intervention on psychological well-being and quality of life: is increased mindfulness indeed the mechanism? *Ann Behav Med*. 2008;35(3):331-340.

46. Roth B, Robbins D. Mindfulness-based stress reduction and health-related quality of life: findings from a bilingual inner-city patient population. *Psychosom Med*. 2004;66(1):113-123.

47. Parisi A, Landicho HL, Hudak J, Leknes S, Froeliger B, Garland EL. Emotional distress and pain catastrophizing predict cue-elicited opioid craving among chronic pain patients on long-term opioid therapy. *Drug Alcohol Depend*. 2022;233:109361.

48. Parisi A, Hanley AW, Garland EL. Mindfulness-Oriented Recovery Enhancement reduces opioid craving, pain, and negative affect among chronic pain patients on long-term opioid therapy: An analysis of within- and between-person state effects. *Behav Res Ther*. 2022;152:104066.

49. Garland EL, Hanley AW, Nakamura Y, et al. Mindfulness-Oriented Recovery Enhancement vs Supportive Group Therapy for Co-occurring Opioid Misuse and Chronic Pain in Primary Care: A Randomized Clinical Trial. *JAMA Intern Med*. 2022;182(4):407-417.

50. O'Leary K, O'Neill S, Dockray S. A systematic review of the effects of mindfulness interventions on cortisol. *J Health Psychol*. 2016;21(9):2108-2121.

51. Matousek RH, Dobkin PL, Pruessner J. Cortisol as a marker for improvement in mindfulness-based stress reduction. *Complement Ther Clin Pract*. 2010;16(1):13-19.

52. Ng TKS, Fam J, Feng L, et al. Mindfulness improves inflammatory biomarker levels in older adults with mild cognitive impairment: a randomized controlled trial. *Transl Psychiatry*. 2020;10(1):21.

53. MacLean RR, Armstrong JL, Sofuoglu M. Stress and opioid use disorder: A systematic review. *Addict Behav*. 2019;98:106010.

54. Lu RB, Wang TY, Lee SY, et al. Correlation between interleukin-6 levels and methadone maintenance therapy outcomes. *Drug Alcohol Depend*. 2019;204:107516.

55. Morris P, Ali K, Merritt M, Pelletier J, Macedo LG. A systematic review of the role of inflammatory biomarkers in acute, subacute and chronic non-specific low back pain. *BMC Musculoskelet Disord*. 2020;21(1):142.

56. Schell E, Theorell T, Hasson D, Arnetz B, Saraste H. Stress biomarkers' associations to pain in the neck, shoulder and back in healthy media workers: 12-month prospective follow-up. *Eur Spine J*. 2008;17(3):393-405.

57. Krebs EE, Lorenz KA, Bair MJ, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. *J Gen Intern Med*. 2009;24(6):733-738.

58. Nahvi S, Ning Y, Segal KS, Richter KP, Arnsten JH. Varenicline efficacy and safety among methadone maintained smokers: a randomized placebo-controlled trial. *Addiction*. 2014;109(9):1554-1563.

59. Nahvi S, Litwin AH, Heo M, Berg KM, Li X, Arnsten JH. Directly observed antiretroviral therapy eliminates adverse effects of active drug use on adherence. *Drug Alcohol Depend*. 2012;120(1-3):174-180.

60. Ferguson L, Scheman J. Patient global impression of change scores within the context of a chronic pain rehabilitation program. *J Pain*. 2009;10(4):S73.

61. Cook KF, Jensen SE, Schalet BD, et al. PROMIS measures of pain, fatigue, negative affect, physical function, and social function demonstrated clinical validity across a range of chronic conditions. *J Clin Epidemiol*. 2016;73:89-102.

62. Boyett B, Wiest K, McLeod LD, et al. Assessment of craving in opioid use disorder: Psychometric evaluation and predictive validity of the opioid craving VAS. *Drug Alcohol Depend*. 2021;229(Pt B):109057.

63. Lee EH. Review of the psychometric evidence of the perceived stress scale. *Asian Nurs Res* . 2012;6(4):121-127.

64. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. 1983;24(4):385-396.

65. Brummett CM, Bakshi RR, Goesling J, et al. Preliminary validation of the Michigan Body Map. *Pain*. 2016;157(6):1205-1212.

66. McCracken LM, Vowles KE, Eccleston C. Acceptance of chronic pain: component analysis and a revised assessment method. *Pain*. 2004;107(1-2):159-166.

67. Nicholas MK. The pain self-efficacy questionnaire: Taking pain into account. *Eur J Pain*. 2007;11(2):153-163.

68. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Psychol Assess*. 1995;7(4):524-532.

69. Buysse DJ, Yu L, Moul DE, et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep*. 2010;33(6):781-792.

70. McLellan AT, Kushner H, Metzger D, et al. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat*. 1992;9(3):199-213.

71. Zimet GD, Powell SS, Farley GK, Werkman S, Berkoff KA. Psychometric characteristics of the Multidimensional Scale of Perceived Social Support. *J Pers Assess*. 1990;55(3-4):610-617.

72. MacKillop J, Anderson EJ. Further Psychometric Validation of the Mindful Attention Awareness Scale (MAAS). *J Psychopathol Behav Assess*. 2007;29(4):289-293.

73. Rosen LD, Whaling K, Carrier LM, Cheever NA, Rokkum J. The Media and Technology Usage and Attitudes Scale: An empirical investigation. *Comput Human Behav*. 2013;29(6):2501-2511.

74. Mayer JD, Gaschke YN. The experience and meta-experience of mood. *J Pers Soc Psychol*. 1988;55(1):102-111.

75. Tanay G, Bernstein A. State Mindfulness Scale (SMS): development and initial validation. *Psychol Assess*. 2013;25(4):1286-1299.

76. Tcha-Tokey K, Christmann O, Loup-Escande E, Richir S. Proposition and validation of a questionnaire to measure the user experience in immersive virtual environments. *Int J Virtual Real*. 2016;16(1):33-48.

77. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9(2):105-121.

78. Emily F. Patridge TPB. Research Electronic Data Capture (REDCap). *J Med Libr Assoc*. 2018;106(1):142.