BMJ Open

Adjunctive virtual reality pain relief following traumatic injury: protocol for a randomised within-subjects clinical trial

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To cite: Felix RB, Rao A, Khalid M, *et al*. Adjunctive virtual reality pain relief following traumatic injury: protocol for a randomised within-subjects clinical trial. *BMJ Open* 2021;**11**:e056030. doi:10.1136/bmjopen-2021-056030

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-056030).

Received 09 August 2021
Accepted 03 November 2021

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ABSTRACT

Introduction The annual mortality and national expense of the opioid crisis continue to rise in the USA (130 deaths/day, $50 billion/year). Opioid use disorder usually starts with the prescription of opioids for a medical condition. Its risk is associated with greater pain intensity and coping strategies characterised by pain catastrophising. Non-pharmacological analgesics in the hospital setting are critical to abate the opioid epidemic. One promising intervention is virtual reality (VR) therapy. It has performed well as a distraction tool and pain modifier during medical procedures; however, little is known about VR in the acute pain setting following traumatic injury. Furthermore, no studies have investigated VR in the setting of traumatic brain injury (TBI). This study aims to establish the safety and effect of VR therapy in the inpatient setting for acute traumatic injuries, including TBI.

Methods and analysis In this randomised within-subjects clinical study, immersive VR therapy will be compared with two controls in patients with traumatic injury, including TBI. Affective measures including pain catastrophising, trait anxiety and depression will be captured prior to beginning sessions. Before and after each session, we will capture pain intensity and unpleasantness, additional affective measures and physiological measures associated with pain response, such as heart rate and variability, pupillometry and respiratory rate. The primary outcome is the change in pain intensity of the VR session compared with controls.

Ethics and dissemination Dissemination of this protocol will allow researchers and funding bodies to stay abreast in their fields through exposure to research not otherwise widely publicised. Study protocols are compliant with federal regulation and University of Maryland Baltimore's Human Research Protections and Institutional Review Board (protocol number HP-00090603). Study results will be published on completion of enrolment and analysis, and deidentified data can be shared by request to the corresponding author.

Trial registration number NCT04356963; Pre-results.

Strengths and limitations of this study

- ► Within-subjects trial design allows for a lower number of participants as each act as its own control.
- ► Linear mixed-effects modelling allows for the inclusion of subjects missing data points, a commonality in a trauma centre population.
- ► The inclusion of only patients with mild TBI who are likely to be quickly discharged may limit opportunities for enrolment.

INTRODUCTION

The US Department of Health and Human Services has declared a national opioid crisis, as more than 130 Americans die each day from an opioid overdose.[1 2] In addition, non-medical use of prescription opioids has an estimated annual cost of over $50 billion to the US economy.[3] Opioid use disorder typically starts with a prescription for opioids for a medical condition.[4 5] Higher doses and longer durations of opioid treatment during the acute inpatient phase of injury increase the risk of opioid use disorder, especially when pain is severe and refractory.[4 6–8]

Patients with traumatic injuries, including acute traumatic brain injury (TBI), may be at a particularly high risk of opioid use disorder. Each year in the USA, an estimated 35 million people visit the emergency department with an injury, with nearly 2.8 million being treated for TBI.[9 10] Traumatic injury has been independently associated with persistent opioid usage, with one study indicating a 73% increase in likelihood of reporting persistent opioid usage.[11 12] Postinjury usage risk factors of prolonged use include pain severity, catastrophic thinking and depression.[11 13 14] Patients suffering depressive symptoms may be up to three times as likely to report persistent opioid usage after traumatic injury.[11] In TBI, the vast majority of cases are classified as mild, with the most common symptom being headache, present in up to 90% of patients.[15] The pain is typically severe, persistent and refractory to medical

therapies,[16–18] with over a third of patients complaining of headache 12 months post-TBI.[19] Although opioids are not recommended for headaches associated with mild TBI,[20] data suggest that they are commonly prescribed.[17] Among soldiers returning from active duty who have a TBI diagnosis, nearly 60% are prescribed an opioid during the postdeployment year.[21 22] In a study of patients with acute neurological injury suffering from aneurysmal subarachnoid haemorrhage, opioid use was associated with discrete pain trajectories, pain burden and craniotomy.[23 24] Opioid sparing during hospitalisations with acute pain is an important component of addressing the current opioid epidemic.[25] It is pivotal to develop novel, non-pharmacological therapeutics that effectively manage pain and reduce opioid use in the acute phase of traumatic injury to mitigate the risk of chronic opioid use disorder.

Virtual reality (VR) has shown promise as a non-pharmacological pain intervention and adjunctive pain reduction therapy.[26–29] It has been suggested that VR may serve as a pain therapeutic capable of reducing the incidence of prescription opioid usage; however, this has not yet been determined.[30 31] Previous studies have found that hospitalised patients with persistent pain from orthopaedic traumatic injuries, burns and other complaints have benefitted from the addition of VR to standard of care treatments.[32 33] Patients with acute brain injuries have largely been excluded from VR studies for acute pain out of concern for intolerance due to nausea and motion sickness and due to a perceived elevation in seizure risk. Thus, the safety and feasibility of VR for analgesia in patients with TBI are unknown. Moreover, a recent review of VR for other forms of acute pain revealed multiple methodological concerns in the existing literature; most studies lacked appropriate controls and focused solely on pain intensity while neglecting other important aspects of the pain experience.[34]

We designed this study to address these two important gaps in the literature. First, we aim to establish VR as a safe and feasible adjunctive treatment for pain in the acute phase of traumatic injury, *including* TBI. Second, we aim to improve on prior work by including proper control conditions in a randomised within-subjects design. We are also interested in exploring patient characteristics that may predict a more significant response to VR therapy.

Study hypotheses

Hypothesis 1: VR therapy is a safe and feasible intervention for patients with acute traumatic injuries, including those with TBI.

Hypothesis 2: VR therapy reduces pain from traumatic injuries including TBI while improving pain-related affective measures, autonomic measures and subjective experience.

Hypothesis 3: Patient factors such as increased gaming engagement, boredom, suggestibility and expectancy predict response to VR therapy.

METHODS AND ANALYSIS

Study design

We will conduct a randomised, within-subject, crossover clinical trial, comparing the effects of an immersive VR environment against two control interventions. In one of the control interventions, identical content to the immersive VR environment will be presented in a non-immersive, tablet-based form. The other intervention will control for the external sensory deprivation of the VR system by having participants wear the VR headset without any content. We are recruiting 60 participants with traumatic injury. Participants will complete a prestudy survey to assess their baseline characteristic and symptoms, the three interventional sessions in a randomised order and a poststudy survey (figure 1).

Patient and public involvement

Patients with traumatic injury and their families were not involved in setting the research question or the outcome measures; however, they were involved in the selection and design of the intervention. Patients with traumatic injury provided input on which VR experiences were favourable for use in the study. These patients advised that VR experiences involving calming and dynamic scenes, mild interaction and music were more enjoyable, which guided the choice of the WEVR theBlu VR experience over other options. Patients were not involved in recruitment or conduct of the study.

Setting

The study will be conducted at the R. Adams Cowley Shock Trauma Center, a freestanding trauma hospital in Baltimore, Maryland, that receives more than 7000 yearly admissions, including over 1000 patients with TBI. We started recruiting patients in October 2020 and will continue until July 2022.

Participant recruitment

Sixty patients will be enrolled. An automated research management system will be used to screen all patients admitted to Shock Trauma. A research team member will review the medical record and determine eligibility. If the patient is a candidate for the study, he or she will be approached in accordance with the Institutional Review Board (IRB) guidelines. The study is described in detail, including the study scope, expectations of participants, potential risks and benefits, and participant rights. In addition, at this time it is determined whether the location of the patient injury would preclude the use of the VR headset. Patients can ask any questions they may have, and if interested in enrolment, they are evaluated to assess their competency and ability to give informed consent. With adequate responses, the participants and the research team will complete the informed consent form, a Health Insurance Portability and Accountability Act authorisation form and a COVID-19 statement of risk, and make copies of these for the patient, the study file

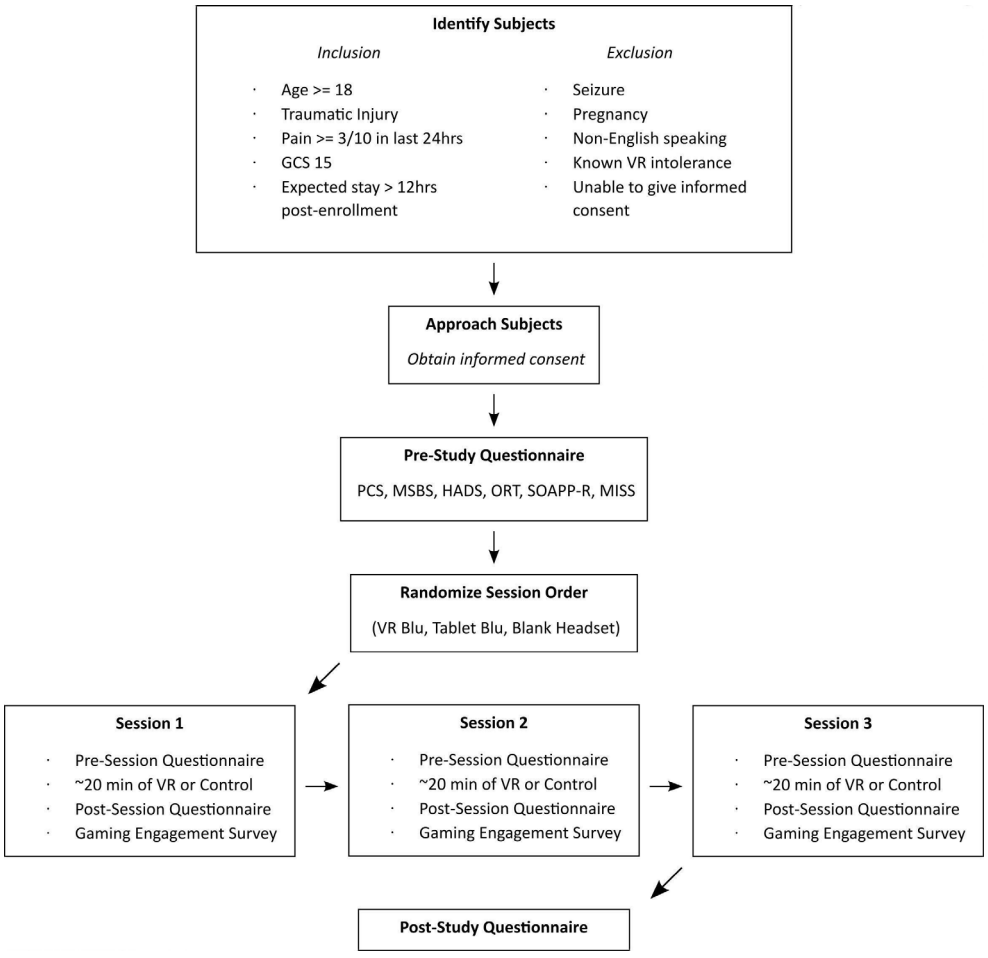

Figure 1 Study flow sheet. GCS, Glasgow Coma Score; HADS, Hospital Anxiety and Depression Survey; MISS, Multidimensional Iowa Suggestibility Scale; MSBS, Multidimensional State Boredom Scale; ORT, Opioid Risk Tool; PCS, Pain Catastrophizing Scale; SOAPP-R, Screener and Opioid Assessment for Patients with Pain- Revised; VR, virtual reality

and the patient chart. Participants may withdraw from the study at any point.

Eligibility

Inclusion criteria

Participants must (1) have a diagnosis of traumatic injury, (2) be at least 18 years of age, (3) have a Glasgow Coma Score of 15, (4) report a numerical pain score of at least 3/10 within 24 hours of enrolment and (5) be expected to remain hospitalised for at least 12 hours after enrolment to complete the study protocol.

Exclusion criteria

Excluded are participants (1) who cannot consent for themselves, (2) who have a medical history of seizure or a known intolerance of VR, (3) who are pregnant and (4) who are non-English-speaking. 'Known inability to use VR' has typically presented itself as patients self-reporting dizziness after their previous VR experiences. Although the study has not yet encountered it to date, any report of past acute stress disorder or seizure secondary to immersive VR would also be excluded.

Assessments

Prior to beginning the study sessions, participants will complete a survey containing questions about their prior experience with the proposed VR therapeutic, any optimism regarding the expected success of VR as an analgesic and several validated surveys. Surveys include the Pain Catastrophizing Scale, the Multidimensional State Boredom Scale, the Hospital Anxiety and Depression Survey, and the Opioid Risk Tool. Participants will also complete the Multidimensional Iowa Suggestibility Scale (MISS).

The participant will be taught how to use the VR Head-Mounted Display; The Oculus Rift (Oculus VR, Irvine, California, USA) VR system will be used. Participants will undergo three different 20 min sessions administered in random order and spaced a minimum of 4 hours apart. Immersive VR experience: theBlu (WEVR, Inc, Venice, California, USA) delivered via Oculus Rift headset (figure 2). This immersive experience simulates the participant observing naturally relaxing and dynamic environment of a coral reef and has been used in other studies to induce relaxation and precepted presence.[35 36]

Figure 2 Study participant performing virtual reality therapy session.

1. Non-immersive two-dimensional mimic: Recording of theBlu experience delivered via video on a non-immersive 2-D Asus (ASUS, Taipei, Taiwan) tablet.
2. VR sensory deprivation: delivered via a blank (ie, content-less) Oculus Rift headset.

Each session will contain a pre-session survey including a numeric rating scale for their overall pain, headache, neck/back pain, nausea, dizziness and light sensitivity, as well as the Spielberger State-Trait Anxiety Inventory (STAI). Following the session, a post-session survey is administered which contains the same metrics, with the addition of the Brockmyer Gaming Engagement Questionnaire. Vital signs are recorded pre-session and post-session, including heart rate, blood pressure, respiratory rate and pupillometry data. Participant chronic pain history and prehospital opioid usage as well as in-hospital opioid usage and pain scores throughout the duration of the study will be obtained via chart review, and continuous heart rate during each session will be collected by the research team using a pre-existing monitoring system.[37] At the conclusion of all sessions, participants will complete another questionnaire to help us understand their self-perceived experience of using VR compared with control sessions.

A team member will be present during all sessions. If the participant appears distressed or requests to have the headset removed, this will be done immediately and the negative reaction recorded. All participants will have orders for analgesia written by the treatment team, independent of the research team, who are blinded to the session order. If pain is inadequately controlled, additional analgesic orders will be placed by the clinical team in communication with the research team. Should pain ratings be increased after study sessions, both the clinical and research teams will be notified for assessment. Medication effects such as receiving pain therapeutics immediately before a session are partially mitigated by the study's randomised within-subject design, as the incidence of pain therapeutics should remain uniform across the immersive VR and control conditions. In addition, participant opioid dosage and times are recorded and coincidence with study procedures will be controlled for during data analysis.

Outcomes measured

The primary outcome is reduction in pain severity measured by the pre-session and post-session numerical rating scale for VR sessions compared with controls. Exploratory secondary outcomes include pain assessment per the Trauma Function and Comfort Assessment, opioid usage, pain durability post-session, affective measures (anxiety), autonomic measures (pupillary maximum constriction velocity and relative constriction amplitude, and heart rate variability) and subjective experience measures.

The STAI is an anxiety affective measure, which we suspect will improve following immersive VR.[38] The Brockmyer Gaming Engagement Questionnaire is a measure of immersion, flow, absorption and other key concepts that correspond to how people experience games, which we hypothesise may correlate with a participant's pain reduction response.[39] Prestudy responses to the Hospital Anxiety and Depression Scale, Pain Catastrophizing Scale and MISS will be tested for any correlation to pain response. The Hospital Anxiety and Depression Scale is a measure of anxiety or depressive states, which is stable across age groups and demographics.[40] The MISS is a measure of susceptibility, defined by an individual's tendency to accept extrinsic messages.[41]

The safety and feasibility of immersive VR for patients with acute injury or TBI will be qualified in several ways. The typical medical concerns for immersive VR are seizures and motion sickness. During and after each session, the research team monitors patients for seizure. Any patients experiencing seizure will have the treatment team notified, will have their study participation end and a record of the adverse event will be made for the analysis of study safety. In addition, before and after each session, patients report their dizziness and nausea levels, as well as affective measures of stress through the STAI described above. The incidence of seizure, increased dizziness or nausea, or patients being unable to tolerate sessions is recorded and used to characterise the safety and feasibility of the study in an in-patient acute trauma setting.

Sample size calculation

Prior work suggests that a 33% pain intensity difference or a 2-point difference on a 0–10 pain numeric rating scale is an appropriate surrogate for a patient-determined clinically important response.[42] We will enrol 60 patients, projecting a study dropout of 30%, leaving us with 42 patients to give us an 80% likelihood to detect a treatment difference at a one-sided o.05 significance level.[43 44]

Data analysis

Descriptive statistics will be used to characterise the patient population. Mixed-effects models will be used to analyse the differences between the ratings over time to allow for missing data expected in a trauma population.[45] To investigate whether demographics or patient measures of anxiety/depression, boredom or suggestibility are related to the pain effect, we will use Pearson's

correlation between the questionnaire scores and the difference of the means of pain reduction measures for all sessions. Analysis will be performed using the IBM Statistical Package for Social Sciences (SPSS V.24) software.

Data collection

All source data and research documentation will be kept in a locked cabinet in the research coordinator's locked office which is in a locked office suite. Electronic data will be kept on a desktop computer which is encrypted and password-protected by the guidelines implemented from the University of Maryland School of Medicine. To ensure confidentiality, all data files will only be accessible to the research team.

Data monitoring

This study will be reviewed weekly by the primary investigator to assess for adverse events. An interim analysis will be conducted when 20 patients with non-TBI injuries and 20 patients with TBI have been enrolled. Safety monitoring results will be reported to the IRB.

Ethics and dissemination

The dissemination of this protocol will allow fellow researchers and funding bodies to stay up to date in their fields by providing exposure to research that may not be otherwise widely publicised.

All study protocols are compliant with federal regulation and the University of Maryland Baltimore's Human Research Protections and IRB policies. The protocol is IRB approved and active (protocol number HP-00090603 V.9 valid until 19 July 2022) and registered on ClinicalTrials.gov. All past and future modifications to the protocol undergo IRB approval prior to implementation by the research team.

Study involvement will be voluntary, and participants may withdraw at any time. All study drop-outs or withdrawals will be documented. Any adverse effects from the study intervention will be documented and reported, and the study will be ceased with that individual.

Device safety

The Oculus Rift is a commercially available portable VR headset device for gaming and relaxation with non-significant risks. There is a precedent of using VR in hospitalised medical patients.[32 46–49] In a 2018 review of 11 randomised controlled trials (including nearly 500 patients) that used VR in hospitalised patients found the VR to be feasible in the hospital and safe.[46] A 2010 study evaluating VR for acute pain management after trauma did not include patients with TBI and found no safety concerns.[32] Similarly, a review of 11 studies of VR for TBI rehabilitation found no safety concerns.[49] We therefore believe VR to be safe in the acute phase after TBI.

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Contributors RBF drafted the manuscript and revised it critically for important intellectual content. AR, MK, YW and LC revised the manuscript critically for important intellectual content. SBM and NAM designed the work and revised the manuscript critically for important intellectual content.

Funding This study is funded through the Accelerated Translational Incubator Pilot Award from the University of Maryland, Baltimore Institute for Clinical and Translational Research (ICTR) and the National Center for Advancing Translational Sciences (NCATS) Clinical Translational Science Award (CTSA) (grant number 1UL1TR003098).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Mattson CL, Tanz LJ, Quinn K, *et al*. Trends and geographic patterns in drug and synthetic opioid overdose deaths - United States, 2013-2019. *MMWR Morb Mortal Wkly Rep* 2021;70:202–7.
2 Wilson N, Kariisa M, Seth P. Drug and opioid-involved overdose - United States, 2017-2018. *MMWR Morb Mortal Wkly Rep* 2020;69:290–7.
3 Hansen RN, Oster G, Edelsberg J, *et al*. Economic costs of nonmedical use of prescription opioids. *Clin J Pain* 2011;27:194–202.
4 Stumbo SP, Yarborough BJH, McCarty D, *et al*. Patient-Reported pathways to opioid use disorders and pain-related barriers to treatment engagement. *J Subst Abuse Treat* 2017;73:47–54.
5 Edlund MJ, Martin BC, Russo JE, *et al*. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. *Clin J Pain* 2014;30:557–64.
6 Shah A, Hayes CJ, Martin BC. Factors influencing long-term opioid use among opioid naive patients: an examination of initial prescription characteristics and pain etiologies. *J Pain* 2017;18:1374–83.
7 Weiss RD, Potter JS, Griffin ML, *et al*. Reasons for opioid use among patients with dependence on prescription opioids: the role of chronic pain. *J Subst Abuse Treat* 2014;47:140–5.
8 Edlund MJ, Sullivan MD, Han X, *et al*. Days with pain and substance use disorders: is there an association? *Clin J Pain* 2013;29:689.
9 Taylor CA, Bell JM, Breiding MJ, *et al*. Traumatic brain injury-related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013. *MMWR Surveill Summ* 2017;66:1–16.
10 National Center for Health Statistics, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. National Hospital ambulatory medical care survey: 2018 emergency department summary tables, 2018. Available: https://www.cdc.gov/nchs/data/nhamcs/web_tables/2018-ed-web-tables-508.pdf
11 Alghnam S, Castillo R. Traumatic injuries and persistent opioid use in the USA: findings from a nationally representative survey. *Inj Prev* 2017;23:87–92.
12 von Oelreich E, Eriksson M, Brattström O, *et al*. Risk factors and outcomes of chronic opioid use following trauma. *Br J Surg* 2020;107:413–21.
13 Helmerhorst GTT, Vranceanu A-M, Vrahas M, *et al*. Risk factors for continued opioid use one to two months after surgery for musculoskeletal trauma. *J Bone Joint Surg Am* 2014;96:495–9.
14 Rosenbloom BN, McCartney CJL, Canzian S, *et al*. Predictors of Prescription Opioid Use 4 Months After Traumatic Musculoskeletal Injury and Corrective Surgery: A Prospective Study. *J Pain* 2017;18:956–63.
15 Watanabe TK, Bell KR, Walker WC, *et al*. Systematic review of interventions for post-traumatic headache. *Pm R* 2012;4:129–40.
16 Faux S, Sheedy J. A prospective controlled study in the prevalence of posttraumatic headache following mild traumatic brain injury. *Pain Med* 2008;9:1001–11.

17 Hammond FM, Barrett RS, Shea T, *et al*. Psychotropic medication use during inpatient rehabilitation for traumatic brain injury. *Arch Phys Med Rehabil* 2015;96:S256–73.
18 Walker WC, Marwitz JH, Wilk AR, *et al*. Prediction of headache severity (density and functional impact) after traumatic brain injury: a longitudinal multicenter study. *Cephalalgia* 2013;33:998–1008.
19 Nelson LD, Temkin NR, Dikmen S, *et al*. Recovery after mild traumatic brain injury in patients presenting to US level I trauma centers: a transforming research and clinical knowledge in traumatic brain injury (TRACK-TBI) study. *JAMA Neurol* 2019;76:1049–59.
20 Marshall S, Bayley M, McCullagh S, *et al*. Updated clinical practice guidelines for concussion/mild traumatic brain injury and persistent symptoms. *Brain Inj* 2015;29:688–700.
21 Adams RS, Thomas CP, Ritter GA, *et al*. Predictors of Postdeployment prescription opioid receipt and long-term prescription opioid utilization among army active duty soldiers. *Mil Med* 2019;184:e101–9.
22 Seal KH, Bertenthal D, Barnes DE, *et al*. Association of traumatic brain injury with chronic pain in Iraq and Afghanistan veterans: effect of comorbid mental health conditions. *Arch Phys Med Rehabil* 2017;98:1636–45.
23 Jaffa MN, Jha RM, Elmer J. Pain trajectories following subarachnoid hemorrhage are associated with continued opioid use at outpatient follow-up. *Neurocritical Care* 2021.
24 Jaffa MN, Podell JE, Smith MC, *et al*. Association of refractory pain in the acute phase after subarachnoid hemorrhage with continued outpatient opioid use. *Neurology* 2021;96:e2355–62.
25 Dowell D, Haegerich T, Chou R. CDC guideline for prescribing opioids for chronic pain — United States, 2016. *MMWR Recomm Rep* 2016;315:1624–45.
26 Hoffman HG, Patterson DR, Soltani M, *et al*. Virtual reality pain control during physical therapy range of motion exercises for a patient with multiple blunt force trauma injuries. *Cyberpsychol Behav* 2009;12:47–9.
27 Hoffman HG, Chambers GT, Meyer WJ, *et al*. Virtual reality as an adjunctive non-pharmacologic analgesic for acute burn pain during medical procedures. *Ann Behav Med* 2011;41:183–91.
28 Wright JL, Hoffman HG, Sweet RM. Virtual reality as an adjunctive pain control during transurethral microwave thermotherapy. *Urology* 2005;66:1320.e1–1320.e3.
29 Pourmand A, Davis S, Marchak A, *et al*. Virtual reality as a clinical tool for pain management. *Curr Pain Headache Rep* 2018;22:53.
30 Wiederhold BK, Riva G, Wiederhold MD. How can virtual reality interventions help reduce prescription opioid drug misuse? *Cyberpsychol Behav Soc Netw* 2014;17:331–2.
31 Gupta A, Scott K, Dukewich M. Innovative technology using virtual reality in the treatment of pain: does it reduce pain via distraction, or is there more to it? *Pain Med* 2018;19:151–9.
32 Patterson DR, Jensen MP, Wiechman SA, *et al*. Virtual reality hypnosis for pain associated with recovery from physical trauma. *Int J Clin Exp Hypn* 2010;58:288–300.
33 Carrougher GJ, Hoffman HG, Nakamura D, *et al*. The effect of virtual reality on pain and range of motion in adults with burn injuries. *J Burn Care Res* 2009;30:785–91.
34 Honzel E, Murthi S, Brawn-Cinani B, *et al*. Virtual reality, music, and pain: developing the premise for an interdisciplinary approach to pain management. *Pain* 2019;160:1909–19.
35 Ç Y, Bostan B, Mİ B. Impact of different immersive techniques on the perceived sense of presence measured via subjective scales. *Entertainment Computing* 2019;31:100308.
36 Liszio S, Graf L, Masuch M. The relaxing effect of virtual nature: immersive technology provides relief in acute stress situations. *Telemed* 2018;16:87–93.
37 PF H, Yang S, HC L. Reliable collection of real-time patient physiologic data from less reliable networks: a 'Monitor of Monitors' system (MoMs). *J Med Syst* 2017;41:1–8.
38 Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State—Trait anxiety inventory (STAI). *Br J Clin Psychol* 1992;31:301–6.
39 Brockmyer JH, Fox CM, Curtiss KA, *et al*. The development of the game engagement questionnaire: a measure of engagement in video game-playing. *J Exp Soc Psychol* 2009;45:624–34.
40 Spinhoven PH, ORMEL J, Sloekers PPA, *et al*. A validation study of the hospital anxiety and depression scale (HADS) in different groups of Dutch subjects. *Psychol Med* 1997;27:363–70.
41 Kotov RI, Bellman SB, Watson DB. *Multidimensional Iowa Suggestibility scale (miss) brief manual*, 2004.
42 Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. *J Pain Symptom Manage* 2003;25:406–11.
43 Dupont WD. Power calculations for matched case-control studies. *Biometrics* 1988;44:1157–68.
44 Dharmarajan S, Lee J-Y, Izem R. Sample size estimation for case-crossover studies. *Stat Med* 2019;38:956–68.
45 Ringham BM, Kreidler SM, Muller KE, *et al*. Multivariate test power approximations for balanced linear mixed models in studies with missing data. *Stat Med* 2016;35:2921–37.
46 Dascal J, Reid M, IsHak WW, *et al*. Virtual reality and medical inpatients: a systematic review of randomized, controlled trials. *Innov Clin Neurosci* 2017;14:14–21.
47 Larson EB, Ramaiya M, Zollman FS, *et al*. Tolerance of a virtual reality intervention for attention remediation in persons with severe TBI. *Brain Inj* 2011;25:274–81.
48 Zanier ER, Zoerle T, Di Lernia D, *et al*. Virtual reality for traumatic brain injury. *Front Neurol* 2018;9:345.
49 Aida J, Chau B, Dunn J. Immersive virtual reality in traumatic brain injury rehabilitation: a literature review. *NeuroRehabilitation* 2018;42:441–8.