Embodiment in Virtual Reality as a Digital Therapeutic for the Treatment of Low Back Pain

Michael Trujillo, PhD\textsuperscript{1*}, Anthony Alvarez, BS\textsuperscript{1}, Lincoln Nguyen, BS\textsuperscript{1}, Jon Weinberg, MBA\textsuperscript{1}, James Petros, MD, MBA\textsuperscript{1}
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Introduction

Karuna Labs Inc. has developed the Karuna Virtual Embodiment Training™ (KVET™) system to address the need for alternative, non-invasive, non-addictive methods to treat chronic pain. KVET™ uses a combination of virtual environments and avatars that provide visual feedback during chronic pain functional rehabilitation. Our key innovation is the application of virtual reality (VR) to improve patients’ willingness and ability to perform physical therapy (PT) and to improve the effectiveness of PT for the treatment of chronic pain.

Chronic pain is commonly defined as pain lasting longer than six months.¹ It represents a significant healthcare burden, afflicting nearly 11% of the US population.²,³ Many common conditions including, but not limited to, degenerative spine disease, osteoarthritis, fibromyalgia, migraines, diabetic neuropathy, and postherpetic neuralgia contribute to pain-related disability. Pain due to injury, such as spinal cord injury, burns, amputations, and traumatic brain injury are also significant contributors. Chronic shoulder pain is common with prevalence as high as 67% in some populations.⁴–⁷ Such chronic pain can significantly reduce quality of life owing to associated increases in depression, anxiety, sleep disturbance, lost productivity, and impairment in decision-making tasks.⁸ Left untreated, the pain can be debilitating, resulting in changes to the structure and function of the nervous system, which can have both physical and psychological consequences.⁹

Current treatments

Chronic pain sufferers are often initially prescribed nonprescription analgesics (e.g., Tylenol), physical therapy (PT), or interventional procedures to ameliorate pain. Additional treatment strategies, including transcutaneous electro-nerve stimulation (TENS), surgery, and implanted neural stimulators, may also be recommended. Many of these approaches have incomplete or often temporary effects, resulting in persistence of the pain-related disability.¹⁰ Because of demonstrable efficacy in treating acute pain, opioids became a favored treatment for chronic pain diagnoses. However, in addition to the poor efficacy of opioids for chronic pain,¹¹ their high potential for abuse, dependence, misuse, and accidental overdose makes them a potentially ineffective and dangerous option for patients.¹¹–¹³ In 2019, the FDA initiated an innovation challenge to find devices to prevent opioid use disorder through alternative combination therapies. Although such integrated approaches have been shown to reduce depression and other psychological symptoms amongst chronic pain sufferers,¹⁴ few efficacious and safe therapeutic options are available to treat the pain itself. There is a critical need for more alternative, non-invasive, and non-addictive methods for treating chronic pain.

Scientific rationale

Although the precise mechanism of chronic pain remains elusive, Zhou¹⁵ posited that long-term potentiation (LTP) occurs in the anterior cingulate cortex (ACC) in response to an injury. There is evidence to suggest that the ACC responds to pain with rate,
spatial, and temporal firing specific to the anticipation of pain.\textsuperscript{16} The ACC sends projections to the periaqueductal gray (PAG), which is the primary control center for descending pain modulation. LTP in the ACC likely shifts tolerable pain thresholds such that people perceive heightened pain severity (hyperalgesia) and increase the anticipation of a painful state. The utility and benefits of virtual reality therapies in treating both acute and chronic pain have been demonstrated.\textsuperscript{17–25} It has been suggested that the mechanism of action of virtual reality is to decrease activation in the ACC and PAG.\textsuperscript{26} Two primary approaches afford analgesic benefits of VR: distraction therapy and immersiveness.\textsuperscript{17,25,27} The focus of Karuna Labs is to advance immersive VR therapy in which the user can interact with an artificial environment to treat chronic pain.

**Immersive VR Approaches**

Virtual embodiment is the first-person perception of sensory feedback related to the actions of a virtual entity, or avatar. Through activation of somatosensory and premotor circuitry associated with the body parts that are embodied,\textsuperscript{28} the use of virtual embodiment as an immersive VR technique has been shown to influence pain-free range of motion (ROM) in patients with chronic pain.\textsuperscript{29} Two promising therapeutic manipulation techniques have been employed within the realm of virtual embodiment: Mirror Visual Feedback (MVF) and Augmentation.

**Mirror Visual Feedback**

MVF has been highly successful in improving function in neuropathic pain and stroke patients.\textsuperscript{30,31} The patient utilizes the mirror to execute visual imagery exercises on the functioning side and visualize the affected side successfully performing the task. This type of embodiment can be highly beneficial,\textsuperscript{32} demonstrating measurable clinical changes and suggesting that sensorimotor pathways may reorganize or renormalize as a function of completing the movement and/or overcoming the pain.\textsuperscript{28,32} Similar techniques have been used to alleviate phantom limb pain after amputation.\textsuperscript{33,34} Graded Motor Imagery (GMI) is a biopsychosocial approach to PT that uses imagery, rehearsal, and simulation to re-learn associations to pain and improve function. GMI was developed as a gradual reintroduction of motor behavior for individuals with chronic pain and has been demonstrated to be an effective approach to treating Complex Regional Pain Syndrome.\textsuperscript{35,36} MVF and GMI have been shown to improve ROM in patients with pain-related movement limitations.\textsuperscript{37,38} VR constitutes a new opportunity for applying the principles of GMI to pain in body parts that are not lateralized owing to the potential for embodied first-person perspective in virtual reality, which eliminates the need for lateralized body parts to reflect in a mirror. Karuna Labs has demonstrated promising results in initial studies of MVF applied in virtual reality.\textsuperscript{39}

**Augmentation**

Augmentation consists of functional rehabilitation exercises in which the movements of a virtual avatar are exaggerated or understated relative to actual motion. Researchers have found that the visual amplification of goal-oriented movements in VR promotes the use of the paretic limb in stroke patients.\textsuperscript{40} Moreover, increased body movement has been shown to correlate with greater pain relief in immersive VR.\textsuperscript{41} As with mirroring, VR provides a unique opportunity to apply GMI principles using augmentation to address pain. No previous chronic pain VR applications have implemented this full augmentation technique.

In this White Paper we describe three studies that demonstrate the ability of KVET\textsuperscript{TM} to accurately measure limb position during functional rehabilitation exercises, how KVET\textsuperscript{TM} influences self-perceived limitations on range of motion of an affected limb, and how KVET\textsuperscript{TM} can improve symptoms of treatment-resistant chronic pain.
Methods and Results

Administration of KVET™ were delivered on the HTC Vive (HTC Corporation, Bellevue, WA) VR Head-Mounted Display (HMD) (110º field of view, 1080 × 1200 pixels/eye, 90 Hz refresh). The Vive Tracker can be used to track limb position and motion while in a VR experience. This is paired with a gaming computer with the power to run a virtual reality experience at a high frame rate to mitigate the risk of motion sickness. KVET™ incorporates accurate and precise virtual avatar representation of both gross and fine motor movements along with embodiment concepts. The Vive hand controllers and tracker can be used to track limb and trunk position and motion while in a VR experience. The Vive hardware provides sub-millimeter accuracy of position in 3D space in a static position, and millimeter precision when moving at nominal velocities.42 Furthermore, the HTC Vive has been shown to be a feasible system for fully immersive kinematic data collection with angular accuracy below 0.1º and error below 3mm. KVET™ uses inverse kinematics to approximate joint angles and render it as a display of joint angles and limb positions of a virtual avatar. A limitation of using inverse kinematics to calculate joint angles in the HTC Vive system is that it depends on estimations of limb length and joint angles from x, y, and z coordinate positions of the HMD, Vive hand controllers, and Vive trackers. To account for this, assumptions need to be made about distance between the head and shoulders, lengths of fore and upper arm segments, and elbow and shoulder position. KVET™ creates a wireframe skeleton based on the height of the user, and x, y, and z positions of the HMD and hand controllers. The wireframe is used to generate the virtual avatar which provides visual feedback to the user of their position in space. In other words, the participant can control the movement of the virtual avatar based on their own movements and the size and position of the avatar is a precise approximation of the participant’s location and movement in real world space.
**Study 1: Pain Free Range of Motion**

To verify the calculated joint angles of KVET™ (virtual angles), we measured real world joint angles using Kinovea and compared simultaneous inverse kinematic measurements recorded in KVET™. Kinovea has been shown to reliably measure joint angles including accurate measurements of shoulder range of motion.43,44 Participants dawned the HTC Vive HMD and held one hand controller in each hand. Participants were instructed to lift their arm so that their shoulder joint angle reached a joint angle displayed in the HMD. We measured shoulder joint angles for flexion and abduction for the right and left arms at angles near 15, 45, 60, 90, 120, 145, and 180 degrees. At each angle for each plane, the real-world angle recorded in Kinovea was compared to virtual angles. A three-way repeated measure ANOVA comparing real-world joint angle to virtual joint angle revealed no significant main effect for plane (P = 0.370), side (right vs left, P = 0.912), nor within the angle of measurements (real world vs VET™, P = 0.932). To confirm that the strength of the relationship between real world angles and virtual angles, a linear regression analysis was performed. **Figure 1** shows the linear regression relationship for abduction and flexion. The virtual angles were highly correlated with real world angles for abduction (r² = 0.999, P < 0.001) and for flexion (r² = 0.999, P < 0.001). These results indicate that VET™ produces reliable measurements on joint angles and can be used as a reliable tool for measuring and analyzing range of motion.

**Study 2: Mirror Visual Feedback Influences Pain Free Range of Motion**

A preliminary mechanistic study was conducted to gain insight into the effects of single-session mirror visual feedback in KVET™ on pain-free ROM. This IRB-approved study recruited 17 patients with chronic shoulder pain. The mean age was 50.4 years, with ten female and seven male subjects, eight presenting with left-side and nine with right-side chronic shoulder pain. Once patients were comfortable with the VR headset and experience, ROM was measured on three planes for each arm (shoulder flexion, scaption, and abduction). Joint angles were calculated based on inverse kinematics of the position of HTC hand controllers tracked by HTC infrared base stations. Patients first saw the ipsilateral arm moving in each plane (i.e., move right arm, see right VR avatar arm move) followed by movement of the contralateral mirrored side (i.e., move right arm, see left VR avatar arm move, **Figure 2**). Patients were instructed to move their arm in each plane within their pain-free comfort zone.
Results

A paired t-test revealed a significant decrease in ROM when the unaffected arm was mirrored onto the painful arm (moving the nonaffected arm yet visualizing the painful side move) for shoulder flexion \( (t = 2.761, p = 0.019) \) and shoulder scaption \( (t = 3.182, p = 0.009) \) (Figure 3). No significant effect was observed for shoulder abduction when the nonaffected arm was mirrored onto the painful arm \( (t = -0.04, p = 0.96) \). These results indicate that ROM for flexion and scaption is reduced in a nonaffected limb when patients perceive the movement as occurring in their painful limb. No significant effects were observed when the painful arm was mirrored onto the nonaffected limb for flexion \( (t = -0.6, p = 0.56) \), scaption \( (t = 0.16, p = 0.86) \), or abduction \( (t = 1.4, p = 0.18) \). The magnitude of reduction in shoulder flexion when the nonaffected limb was mirrored onto the painful limb ranged from 2° to 22°. The magnitude of reduction in shoulder scaption when the nonaffected limb was mirrored to the painful limb ranged from 1.4° to 25.5°.

Conclusion

This preliminary mechanistic study provides evidence that MVF in VR can influence the function of a nonaffected limb if the patient perceives that function as occurring in a painful limb. These results have implications for rehabilitation strategies in patients suffering from chronic pain and incent further investigation of GMI techniques in VR. The preliminary work involved single-session training only. There remains an open question of the tolerability and safety of multiple VET™ sessions for the treatment of chronic shoulder pain.

Study 3: Feasibility Study

Karuna VET™ is effective in alleviating pain and the feeling of helplessness in dealing with chronic pain. A preliminary feasibility study was conducted on 24 chronic pain patients. This study was approved by the Institutional Review Board (IRB) of Advarra. The same IRB will be used in the proposed clinical trial. Patients were recruited from Concentra Occupational Health Clinic (San Francisco, CA) and Remedy Pain Management Clinic (Redwood City, CA) who were diagnosed with chronic pain disorders of the lower back or upper limbs with a continual duration of at least 6 months. Patients received eight sessions of Karuna VET™. Subjective pain questionnaires were administered before and after completion of the eight sessions (Table 1).

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<tr>
<th>ASSESSMENT</th>
<th>PRE-TEST</th>
<th>POST-TEST</th>
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<tr>
<td>Visual Analog Scale (VAS)</td>
<td>Before each VET™ Session</td>
<td>After each VET™ Session</td>
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<tr>
<td>Fear-Avoidance Beliefs Questionnaire (FABQ)²²</td>
<td>Before VET™ Training</td>
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<tr>
<td>The Oswestry Low Back Pain Disability Questionnaire (OLBPD)²³</td>
<td>Before VET™ Training</td>
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<tr>
<td>Patient Health Questionnaire (PHQ-9)²⁴</td>
<td>Before VET™ Training</td>
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<tr>
<td>The Pain Catastrophizing Scale (PCS)²⁵</td>
<td>Before VET™ Training</td>
<td>After 8 VET™ Sessions</td>
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Pain intensity was measured using VAS before and after each session. A paired T-test revealed a significant improvement on pain intensity rating after each Karuna KVET™ session (t = 8.685, P < 0.001, see Figure 4). This result indicates that eight Karuna KVET™ therapy sessions were significantly effective at reducing the intensity of perceived pain. A paired T-test also revealed a significant improvement in the OLPBD after eight VR sessions (t = 2.738, P = 0.016) indicating that Karuna VET™ therapy may have significant positive effects on alleviating back pain (Figure 5B). A paired T-test also revealed a significant improvement in the PCS Helplessness questionnaire after eight sessions (t = 2.411, P = 0.030) indicating that Karuna KVET™ may have a significant positive effect on a patient’s feeling of helplessness in dealing with their pain (Figure 5D). No statistically significant difference was observed for any other measure. To further analyze the benefits of Karuna KVET™, the magnitude of improvement was
assessed for VAS, OLBP D and PCS Helplessness. The magnitude of improvement was defined as the amount of improvement on the post-test score relative to the pre-test score (magnitude = post-test - pre-test). Figure 6 shows the correlation between the intensity of pain scales before VR and the magnitude of improvement after training. A significant correlation was observed for VAS (r = -0.41, P < 0.001), PCS Helplessness (r = -0.64, P = 0.01), and the Oswestry (r = -0.69, P = 0.003). The trendlines in each graph suggest that patients with the most pain saw the greatest improvement from Karuna KVET™ therapy.

Feasibility Study Conclusions
In this feasibility study, we used embodied VR in our MVF application using full body-tracking in VR. The overall objectives of this study were to first, validate a protocol intended to document the safety and efficacy of the use of VR for the treatment of chronic central pain, and secondly, measure patient-reported pain intensity, adverse side effects, disability, and mental function. We demonstrated that VR allows for patients to effectively engage in therapy in a non-threatening environment to improve pain control as well as improve physical functioning. We also confirmed that Karuna’s VET™ is safe with minimal adverse events. Our long-term goal is to develop translational non-pharmacological, non-invasive, digital chronic pain treatments that are accessible to all Americans. As a digital therapeutics company, Karuna Labs has developed a unique VR-based functional rehabilitation program engineered on the principles of graded motor imagery (GMI), cognitive behavioral therapy (CBT), and the principles of neurofeedback.

Figure 6 The magnitude of improvement was further analyzed on metrics where statistically significant improvements were observed. The x-axes are the score for VAS before each session, PCS Helplessness before beginning Karuna VET™ therapy, and the OLBP D before beginning Karuna VET™ therapy. A significant correlation was observed for VAS (r = -0.41, P < 0.001), PCS Helplessness (r = -0.64, P = 0.01), and the Oswestry (r = -0.69, P = 0.003).
Key Findings

1. **Karuna KVET™ can accurately measure functional ROM (study 1).**

Chronic pain is often accompanied by limitations in ROM due to associations between movement and pain resulting in fear avoidance behavior around chronic pain. KVET™ leverages the precise functional ROM measurement to grade and pace exercises to a patient's current day-to-day capabilities. By adjusting the difficulty level of exercises to a patient's current limitations, KVET™ can promote movement that pushes the limitations in functional ROM of chronic pain patients while providing a safe exercise progression to reduce aggravation and flare-ups.

2. **MVF influences pain-free range of motion**

We have demonstrated that MVF influences pain-free range of motion. The fact that MVF has an influence on self-perceived limitations on functional movement capabilities suggests that MVF can also be used to correct for self-perceived limitations. Chronic pain is an output of the brain. By leveraging the powerful perceptual tools of virtual embodiment, KVET™ can provide a safe environment for patients to reach beyond their current capabilities to promote improvements in functional limitations related to their chronic pain.

3. **KVET™ improves disability and psychological symptoms of chronic low-back pain**

Study 3 provided evidence that KVET™ improves disability and psychological symptoms of chronic low-back pain. In this study, we used embodied VR in GMI applications using full body-tracking tools. The overall objectives of this study were to first, validate a protocol intended to document the safety and efficacy of the use of VR for the treatment of chronic pain. Secondly, measure patient-reported pain intensity, adverse side effects, disability, and mental function. Lastly, assess the impact of VR treatment as a viable non-pharmacological, non-invasive, non-addicting treatment of pain before performing a controlled study. It is hoped that VR may allow patients to effectively engage in therapy in a non-threatening environment to improve pain control as well as improve physical functioning.
Conclusion

Chronic pain is a life-altering condition affecting more than 35 million Americans, resulting in significant reduction in quality of life. Sufferers are often prescribed analgesics, physical therapy (PT), or interventional procedures. These approaches often have incomplete or temporary effects. Opioids are often prescribed but have high potential for abuse, dependence, and overdose, making them a potentially ineffective and dangerous option. Chronic pain sufferers remain with few efficacious and safe therapeutic options. Established research supports virtual reality (VR) as a treatment strategy. Karuna Labs Inc. has developed the Karuna Virtual Embodiment Training™ (KVET™) digital therapeutic to address an unmet need for alternative, non-invasive, non-addictive methods for treating chronic pain.
References


