# Simulation through virtual reality for the management of anxiety and neuropathic pain - Protocol for a randomized clinical study design

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## *Abstract*

**Background:** Neuropathic pain is a complex chronic pain condition often accompanied by affective symptoms such as anxiety and depression. This comorbidity is associated with increased pain severity, disability, and diminished quality of life, complicating treatment. Virtual Reality (VR) is an innovative non-pharmacological intervention gaining attention for its potential to alleviate pain and anxiety through immersive distraction.

**Objective:** To evaluate the efficacy of VR in reducing pain and anxiety in patients with persistent neuropathic pain.

**Methods:** This randomized, controlled, multicenter, open-label trial involves two groups: an intervention group receiving VR sessions and a control group receiving standard pharmacological treatment. Participants are adults aged 30-61 years diagnosed with neuropathic pain, unresponsive to flexible doses of gabapentin. Pain and anxiety levels are assessed using the Pain Detect Questionnaire, Visual Analog Scale (VAS), and Goldberg Anxiety Scale at baseline and follow-up points. VR sessions are conducted weekly for three weeks, each lasting 30-35 minutes. Perceived time during VR sessions is recorded as an indirect measure of distraction effectiveness.

**Results:** The primary outcome is the reduction in pain intensity and anxiety levels post-intervention compared to baseline. A sample size of 30 patients (15 per group) was calculated to achieve 80% statistical power, considering a 2-point mean difference in VAS scores.

**Conclusions:** This study hypothesizes that VR will significantly reduce pain and anxiety in patients with persistent neuropathic pain. By providing new insights into non-pharmacological pain management strategies, this research aims to enhance the quality of life for these patients. The findings could support the broader application of VR in clinical pain management. Clinical Trial: approval code: ID.2017/167

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# Original Manuscript

# Simulation through virtual reality for the management of anxiety and neuropathic pain. Protocol for a randomized clinical study

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## Abstract

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**Keywords:** Neuropathic pain, Virtual Reality, Pain management, Anxiety, Randomized controlled trial, Non-pharmacological intervention.

# Introduction

Pain is defined as a complex and multidimensional sensory experience that includes cognitive, behavioral, and psychological elements, often associated with unpleasant and subjective experiences. It has an adaptive function that initiates protective responses. Neuropathic pain is a form of chronic pain resulting from injury to the peripheral or central nervous systems. It is characterized as pain directly caused by an injury or disease affecting the somatosensory system (1).

Neuropathic pain frequently coexists with affective symptoms and negative emotions (anxiety, depression, fear, etc.). It is estimated that 20-30% of chronic pain patients also experience anxiety-depressive symptoms. Specifically, 50% of chronic pain patients will suffer from major anxiety-depression at some point, with 34% in the case of neuropathic pain (3).

The comorbidity of chronic pain and affective disorders is closely associated with higher pain severity, greater disability, and a substantial decline in patient quality of life (4), complicating treatment significantly. Persistent long-term pain and associated suffering seem to be key factors in developing secondary affective and emotional disorders. Long-term neuropathic pain has been shown to hyperactivate the LC-BLA pathway, responsible for anxiety symptoms secondary to the pain process (5).

Treating neuropathic pain is challenging. Pain management programs, therapeutic education, and physical training are fundamental for improving this type of pain. Therefore, it is crucial for patients to understand their pain process to change erroneous beliefs about it, as difficult-to-treat neuropathic pain is related to various psychosocial factors such as high stress or anxiety levels and various emotions caused by the pain.

Techniques aimed at reducing pain and anxiety are being introduced. One non-pharmacological, safe, and innovative technique that could potentially reduce pain and anxiety and is gaining interest in the scientific community in the "new technologies era" is Virtual Reality (VR). VR findings have helped to better understand the underlying processes of pain experiences and the analgesic role such strategies can play (6).

VR provides a three-dimensional, multisensory, and immersive environment that allows individuals to have modified reality experiences by creating a sense of "presence," making it an excellent candidate for distraction-based therapy. This is suggested to decrease attention to painful stimuli, which could affect the emotional interpretation associated with it, thus reducing perceived intensity.

Distractions help reduce anxiety by preventing painful stimuli from being transmitted to the thalamus (i.e., the limbic system) or the sensory cortex as effectively, helping to focus attention on external and internal stimuli rather than nociceptive stimuli. Sometimes, distractions surpass the capability of local anesthetics to control pain and discomfort associated with medical interventions. Distractions can be active (immersive), involving patient participation by manipulating the environment, or passive (non-immersive), involving only observation (7).

Current technological advances, especially in the field of VR, have resulted

in new types of distractions that can be used alongside traditional distractions to achieve better pain control in patients.

In VR technology, users interact with a computer-simulated three-dimensional environment. VR provides multisensory information (visual, auditory, tactile, and olfactory stimuli) that helps individuals interact in the simulated world. A literature review by Lopez-Valverde et al. (8) concluded that VR has shown its utility in reducing chronic pain and related issues such as anxiety, hopelessness, time spent thinking about pain, and perceived time during a procedure.

The concept of "Virtual Reality" lacks a unique and homogeneous definition among authors who have worked on it. We believe the most appropriate definition is by Riva (9), who conceptualizes VR as a communication interface based on interactive three-dimensional visualization capable of collecting and integrating different datasets into a single realistic experience. Various theories have been proposed regarding pain-modulating effects to explain VR's effects. To understand VR-induced hypoalgesia mechanisms, it is necessary to integrate neurobiological and neurochemical interactions with cognitive-attentional and affective-emotional aspects of the "painful experience" (10).

One of the main hypotheses states that humans have a limited capacity to pay attention to stimuli, so experiencing pain requires some attention to it (11). Additionally, patients suffering from both acute and chronic pain may experience excessive attention and vigilance towards pain, potentially increasing perceived intensity (or sensitivity to painful stimuli). VR could have an analgesic effect by distracting from the pain focus (12), producing a pain modulation response via neurophysiological activity in brain areas related to analgesia.

However, distraction is not the only proposed effect. The neuromatrix theory suggests that the pain experience results from a complex interaction between attentional, neurobiochemical, and emotional factors specific to each person. Therefore, pain depends on the interpretation and response of the brain matrix. In this context, VR could promote intercortical analgesia by modulating attentional and emotional networks, stimulating areas related to pain inhibition.

Many aspects remain unclear; however, VR use for pain treatment has shown significant benefits.

This study protocol aims to evaluate the outcomes in terms of pain and anxiety relief with VR application in this group of patients with persistent neuropathic pain.

# Materials and Methods

## *Study Design*

*Trial Design*

We will conduct a randomized, controlled, multicenter, open-label, parallel-group trial with two assigned groups (intervention group and control group).

*Scope and Study Period*

The study population will include adults aged 30 to 61 years. The study will

be conducted over one year, from 2024 to 2025.

*Participants*

All patients were evaluated and deemed suitable by a specialist in the Pain Unit. Neuropathic pain diagnosis was made using the Pain Detect Questionnaire (13).

Neuropathic pain symptoms and signs were assessed, including sensitivity alterations history such as tingling, numbness, stabbing, burning, shooting, or electric-like pain, paresthesia, allodynia, hyperalgesia, hyperpathia, and motor dysfunction (foot or wrist drop, symmetric motor weakness, difficulty buttoning a shirt or holding a pencil), myalgia, or muscle cramps. Neurological assessment included motor evaluation (muscle strength in limbs), sensory evaluation (touch, pain [pinprick test], cold, heat, vibration, and position, and allodynia test for dynamic and static mechanical stimuli), balance test, coordination, and deep tendon reflexes.

After diagnosing persistent neuropathic pain, oral gabapentin treatment was prescribed up to 1200 mg/day.

*Inclusion Criteria*

Patients with moderate to severe pain intensity despite treatment with flexible doses of gabapentin for 3 months up to 1200 mg/24h, understanding VR operation and use of validated scales, and signing informed consent.

*Exclusion Criteria*

Exclusion criteria include known hypersensitivity to gabapentin, inability to tolerate 1200 mg/24h doses (dizziness and drowsiness), pregnant or lactating women, any relative or absolute contraindication to VR treatment, patients with unstable or poorly controlled hypertension, recent cardiovascular events (6 months) before starting treatment, long-term diabetics with cardiovascular autonomic neuropathy, elderly patients, or those with cognitive deficits who cannot understand or apply the scales or answer the questions correctly.

## *Randomization*

*Sequence Generation*

Randomization will be performed using the RandomizedR computer system, a randomization tool in the R Studio program.

*Implementation*

Participants will be selected from a daily patient registry. Both the sequence and participant assignment to interventions will be generated by the RandomizedR computer system.

*Masking*

Due to the study's nature, it will not be possible to blind patients or healthcare professionals. Therefore, the trial will be open-label. However, a third-party blind evaluation will be conducted, as the data analysis responsible will not be involved in the intervention.

## Data Collection, Sources of Information, and Intervention

Pain intensity will be measured using the Pain Detect Questionnaire (13), which is self-administered with 9 descriptors. It detects neuropathic pain intensity and discriminates between possible neuropathic pain (scores between 12 and 19) and definite neuropathic pain (scores above 19). The Visual Analog Scale (VAS) is a one-dimensional quantitative scale, effective and easily reproducible. Patients mark a 100 mm segment with endpoints labeled as no pain (0 mm) and maximum pain (100 mm); the measure from 0 to the patient-marked point indicates pain intensity. A change of 20 mm (or 2 points on a 10-point pain intensity scale) is considered clinically significant.

Anxiety will be measured using the Goldberg Anxiety Scale (14), a test that not only guides diagnosis but also measures intensity. It contains 2 subscales with nine questions each: anxiety subscale (questions 1–9). The first 4 questions of each subscale (questions 1–4) act as a precondition to determine if the rest of the questions should be answered. Specifically, if fewer than 2 questions of the first 4 are answered affirmatively, the rest of the first subscale questions should not be answered. For the second subscale, it is sufficient to answer one of the questions 10–13 affirmatively to proceed with the rest of the questions.

Time perception will be analyzed as an indirect measure of distraction, with less attention to pain, greater tolerance, and possibly an early sensation of completing the treatment time (or Tprogrammed).

At the end of each VR session (30 to 35 minutes), patients will be asked how much time they think remains. This is called "perceived time" (Tperceived) and will be recorded in 10–15-minute intervals based on their responses.

A "significant" difference is defined as a time difference (Tprogrammed - Tperceived) ≥ 15 min and "no change" if ≤ 10 min. For patients who request to stop before completing the time, their "perceived time" is noted by adding the remaining time to the total programmed time.

For the virtual reality application, the Oculus Go VR 32GB model was used, featuring a head-mounted display. This headset provides a stereo visual image, thereby creating a sense of space and depth. A motion tracker in the headset's screen measures head position and adjusts the visual image accordingly. As a result, users perceive their surroundings and can move through the simulated environment. The headset is accompanied by headphones that provide sounds, further enhancing the user's immersion in the virtual world.

Participants in the control group underwent the usual pain assessment review during the two-week study period.

Eligible patients will be invited to participate in the study continuously, and the assignment to study groups will be randomized.

*Sample Size*

To detect a difference of 1 point between the two groups on the pain level scales, a sample of 50 patients is required, with 25 in each group, assuming an SD of 3 points, a 95% confidence level, a Z-score of 1.96, a margin of error $\alpha < 0.05$, and an estimated 10% dropout rate.

## Patient Recruitment for Study Participation

*Patient Selection*

Patients included in the study will be selected from individuals diagnosed with persistent neuropathic pain by Pain Units, with moderate to severe intensity. All will be duly informed about the nature and objectives of the study.

Twenty-five patients will be included, and their scores on the Visual Analog Scale (VAS), the “Pain Detect” Questionnaire, and perceived time will be analyzed.

*Control Selection*

Controls will be selected from patients in the Pain Unit diagnosed with moderate to severe neuropathic pain. All were duly informed about the nature and objectives of the study and were asked to provide signed consent.

Before the study begins, training on the use of the devices will be provided to all healthcare personnel involved.

*Data Collection, Information Sources, and Intervention*

Data collection will begin once the patient has provided written informed consent. Patient assignment to a study group will be randomized using the RandomizedR computer system.

The data collector will record the patients’ age, sex, study group, and type of intervention performed. Before contacting the patient with the virtual reality device, the patient's status and heart rate will be recorded upon arrival at the clinic, regardless of the assigned study group.

Patients in Group 1 will be the intervention group. They will undergo 10 virtual reality pain treatment sessions (Monday to Friday for two weeks), with each session lasting 30 minutes, while maintaining treatment with gabapentin at a dose of 1,200 mg/24 h. Their clinical history, pain situation, and anxiety will be assessed in each session.

Patients in Group 2 will be the control group. Their clinical history, pain situation, and anxiety will be assessed in each session. They will receive pain treatment with oral gabapentin at a dose of 1,200 mg/24 h.

## *Data Analysis*

Data entry for anxiety and pain test scores through VAS, Pain Project, and perceived time will be performed using Microsoft Excel and analyzed using SPSS statistical software (version 16.0).

A sample t-test will be used. Before applying the t-test, the Kolmogorov-Smirnov test will be used to evaluate the normality of the mean scores obtained.

Likert-type statements will be analyzed such that a score below three indicates disagreement and a score above three indicates agreement with a positive statement and vice versa for a negative statement.

Intervention group patients will be informed that they can use the virtual reality device. They will be assisted in putting on the device and given a brief explanation of the content to be displayed.

Data collected from the control group will be compared with those from the intervention group (heart rate, pain perception level, anxiety level).

The mentioned data will be collected by an IT professional through a web questionnaire generated by Microsoft Forms on a tablet and will be stored on a computer server.

### *Statistical Analysis*

Subjects will be analyzed according to the group to which they were assigned.

Data will be collected through Microsoft Forms (an application included in Office 365 by Microsoft Corporation that allows for creating customized questionnaires, surveys, and records) and analyzed with R software (version 4.0.3). Categorical variables will be described using absolute frequencies and percentages, and continuous variables will be described using means and standard deviations or medians and quartiles. A two-tailed t-test will be used to compare values related to pain, anxiety, and satisfaction between the two groups. Correlations between pain perception and anxiety values reported by patients will be assessed using Pearson's correlation. The significance level will be set at 5%, and all confidence intervals will be set at 95%.

Data will be stored in a database. Pearson's chi-square test will be used to calculate statistical significance.

## Ethical Considerations

This study will adhere to the principles outlined in the Declaration of Helsinki and has been approved by the Institutional Review Board of the participating centers. Informed consent will be obtained from all participants before study enrollment.

The Protocol Committee of the University of Salamanca (Spain) has approved the study protocol (approval code: ID.2017/167). Written informed consent will be requested from all patients participating in the study.

## Results

The study is scheduled to begin in 2024. In a preliminary study (15), a total of 16 patients were recruited, of whom 9 used virtual reality.

With the distraction chosen by each of them, pain was reduced (considered significant with a VAS drop ≥ 2 compared to their previous experience) in 3 patients; while 5 patients did not notice any changes (VAS difference of 0 or 1 points compared to their previous experience) and for 1 patient, the experience worsened, leading them to discontinue participation.

Moreover, anxiety measured by the Goldberg Scale decreased during the

session in 4 cases (considered "significant anxiety" with a score >2 points).

Regarding the perception of time passage, 50% of the patients experienced a significant difference (considered significant if the treatment time was perceived as 30 minutes) in time perception 30 days after the treatment.

We hope to obtain sufficient evidence to demonstrate that the use of virtual reality is effective in reducing anxiety and difficult-to-treat neuropathic pain. In this context, the use of virtual reality could be introduced into routine practices and extended to other potentially painful processes. Statistically significant differences in heart rate and the reduction of pain perception in favor of the intervention group will be considered a satisfactory outcome.

## Discussion

Our study aims to demonstrate that the use of VR glasses reduces chronic neuropathic pain. The use of virtual reality glasses may also reduce anxiety after such procedures, thereby generating greater patient satisfaction.

It has also been observed in several studies that VR focused on distraction reduces pain levels and anxiety (a parameter extensively studied in pediatric patients undergoing various medical procedures) . Anxiety is widely correlated with pain, as an increase in pain can exacerbate underlying anxiety, which in turn may influence the degree of immersion in VR therapy, potentially leading to reduced effectiveness due to decreased distraction.

Studies have already used virtual reality, especially in children, for painful procedures and during vaccine administration. However, to date, there is no literature describing studies focusing on the population with treatment-resistant neuropathic pain. Obtaining favorable results could lead to the use of virtual reality as a routine practice in chronic painful procedures.

The main limitation of the study is the lack of VR systems that patients can use at home. There may be limitations due to not reaching the required sample size or the emergence of unexpected biases.

Other limitations are associated with the study design, patient recruitment, and inclusion and exclusion criteria. Firstly, patients being treated for mixed nociceptive-neuropathic pain will be excluded. Another weakness of the study design, which could be improved in the future, is that patients could not choose from a range of videos or scenes for their immersive experience. The device used comes with pre-recorded environments and does not allow for editing, inclusion, or deletion of these environments. With active choice, patients take control of the themes they like or are attracted to, which is theorized to increase the degree of distraction or abstraction. Lastly, patients who have already received interventional treatment will be excluded.

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