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Use of virtual reality (immersive vs. non immersive) for pain management in children and adults: A systematic review of evidence from randomized controlled trials

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ABSTRACT

Pain impacts negatively on physical, psychological, and social function and reduces quality of life. Over the past decade there has been a growing increase in the use of virtual reality (VR) in rehabilitation in general and for pain management specifically. To determine the scientific evidence for the effectiveness of VR therapy (immersive vs. non immersive) for pain management in individuals with acute (less than or equal to 6 weeks clinical pain or thermal procedural pain), or chronic pain (more than 12 weeks). An extensive review of the scientific literature involving all major health care databases was performed by two of the investigators in a systematic way within the framework of the Cochrane Collaboration to identify studies focusing on the effectiveness of VR therapy as an intervention aimed at pain reduction in children and adults with acute (less than or equal to 6 weeks, or thermal procedural pain), or chronic (more than 12 weeks) pain. Randomized controlled trials (RCT), quasi-randomized trials, crossover studies, clinical controlled trials, observational study, pre-post studies, cohort studies, descriptive studies, and case- control studies were included. Retrieved articles were rated for methodological quality using PEDro scoring to assess the internal validity of randomized trials. Levels of evidence were from the Sackett criteria. 42 studies were identified that fulfilled the inclusion criteria. Inter-rater agreement for all stages of the studies selection and quality assessment was moderate to perfect (Crude agreement ranged from 85- 100%; kappa's coefficient from 0.8- 1). For adults, there was level 1a evidence exploring the effectiveness of immersive VR therapy in reducing acute pain, level 2a evidence suggesting the potential role of immersive VR for reducing chronic pain and non-immersive VR for reducing acute pain, and level 5 evidence indicating that there is no study to investigate the effectiveness of non-immersive VR for chronic pain. For children, a level 5 of evidence indicates that there are no experimental studies to investigate the effectiveness of either immersive or non-immersive VR compared to conventional therapy or no therapy for chronic pain; however, level 2a evidence suggesting an advantage of immersive and non-immersive VR in reducing acute pain. Results of the present study recommend VR therapy as a clinical intervention for pain reduction with minimal side effects.

Keywords: Virtual reality, pain, RCT, systematic review, immersive and non immersive VR, rehabilitation, level of evidence.

INTRODUCTION

Pain is a common health problem in modern society. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant emotional experience or physical sensation of discomfort or distress primarily associated with tissue damage, resulting from the stimulation of specialized nerve endings due to a derangement of functions, disease, or injury". [1] Pain is recognized to have a negative impact on physical, psychological and social dimensions of quality of life (QOL). The way in which pain is perceived depends on many factors such as past experiences, mood, cultural differences, and individuals' pain threshold. [2] Although numerous treatments are available for pain reduction, people suffering moderate to severe pain are often unable to find adequate pain relief. This has led to a great interest in finding novel strategies to reduce pain in both acute and chronic stages.

In the past, the major focus around pain management has centered on pharmacological treatments, whereas the literature published during the last decade has increasingly focused on non-pharmacological techniques. One cognitive behavioral strategy is called distraction - a technique used in clinical practice to reduce pain associated with painful medical conditions, procedures, and surgeries. Distraction is based on the notion of a human's limited capacity for attention. [3] It has been found that distraction from pain itself, and attention to another experience can affect pain perception: attention to pain increases pain perception and distraction decreases pain perception. [4] The characteristics of pain that interrupt attention include the intensity, the unpredictability and the threat value. [4] Distraction techniques range from passive to active interventions, with the belief that the more interactive the distraction technique, involving visual, auditory and tactile stimuli, the greater the potential for distraction from pain. [5]

In recent years, virtual reality (VR) has become popular in clinical research studies as an innovative distractor technique. VR is a non-invasive simulation technology that allows a user to interact with a computer- generated environment, [6] in the three dimensions (3D) of width, height, and depth. The scenes are primarily visual experiences, displayed either on a computer screen or through special head mounted display (HMD) consisting of two display screens. The interactivity of VR is made possible by a head tracking system attached to the HMD that tracks the user's head movements, and permits the user to feel engaged in the virtual environment, providing a sense of presence that is the feeling of being in VR environment as it was a real environment. [7] Non-immersive VR environment refer to the least interactive implementation of VR techniques such that interaction with the VR environment can occur commonly by 2D interaction devices such as keyboards and mice without fully immersing into the environment, while immersive VR environments and specially the 3D immersive environments are considered to be as the highest interactive implementation of VR techniques, [8] in which subjects fully immersed in and interact with the VR environment. For practicing the real world tasks, immersive virtual environments are more relevant than non immersive ones as they also have the capability of providing feedback for the participants. [9] Interaction and presence in 3D is a key characteristic that distinguishes an immersive VR experience from other technologies.

VR has often been used in conjunction with other distraction interventions for pain reduction either a passive distraction, such as watching a movie, [10] or an interactive distraction activity, such as playing a computer game. [11] Moreover, in a study on pain perception to thermal pain with and without VR immersion [12, 13], experimental pain ratings of thermal stimuli were validated by functional magnetic resonance imaging, which showed that the effectiveness of VR is not only associated with subjective reports of less pain sensation but also with significantly reduced activity in pain involved regions of the brain. However, the evidence of benefits of VR technology over the benefits of the other distracting techniques on pain reduction have not been adequately determined with limited research studies. For example, it has been found that an immersive virtual environment resulted in lower subjective pain ratings during painful dental procedures compare to watching a Movie or playing a game [12, 14, 15] without the addition of any VR technology. However, little is known regarding why some distraction strategies fail or which one of the VR techniques is more effective than others. [10, 11]

It is also thought that the quality of distraction technique is related to the quality of VR impressiveness which itself depends on the quality of the VR experiences [16], and quality of the VR equipment [17]. However, not all studies have been reached to the similar results. For example, the results of a study by Hoffman [17] suggested that a higher quality VR helmet was more effective than a lower quality VR helmet in reducing pain. On the other hand, in another study authors tested the benefits of using a VR helmet versus playing the same video game without a VR helmet for acute pain in children and found no difference in pulse rate and pain intensity that nurse rated during the

procedure for children in the experimental group and control group. [18] The results were consistent with another study [19] that showed ratings of pain intensity in children having an intravenous needle placed were not affected by the VR type. In addition, Dahlquist [11] showed that VR helmet did not appear to uniformly enhance patients' pain tolerance, and simply adding high tech equipment to a distraction task would not necessarily make the intervention more effective.

Today's, VR technology advancement and cost reduction have supported the development of more accessible VR systems which increases its potential for widespread use in clinical practice and rehabilitation field. Now, it is important to identify the effectiveness of VR for difference age groups and for different types of pain. This information on effectiveness will direct clinicians and health care providers regarding the usefulness of VR for pain management.

Scientific questions of the study:
The PICO (Population, Intervention, Comparison, and Outcomes) format of questions was:

1. Is the use of ***VR*** (***immersive and non-immersive***) more effective than no therapy or other conservative treatments in reducing pain in ***children*** with ***acute*** (less than or equal to 6 weeks clinical pain/ thermal procedural pain), or ***chronic*** (more than 12 weeks) pain?

2. Is the use of ***VR*** (***immersive and non-immersive***) more effective than no therapy or other conservative treatments in reducing pain in ***adults*** with **acute** (less than or equal to 6 weeks clinical pain/ thermal procedural pain), or **chronic** (more than 12 weeks) pain?

MATERIALS AND METHODS

Systematic review of the literature
An extensive review of the scientific literature was performed by two of the investigators in a systematic way within the framework of the Cochrane Collaboration to identify studies focusing on the effectiveness of VR therapy as an intervention aimed at pain reduction in children and adults with acute (less than or equal to 6 weeks, or thermal procedural pain), or chronic (more than 12 weeks) pain.

In this study we defined VR as an artificial sensory simulation of either reality-based or imaginary scenes created by computers viewed through a HMD or on the computer screen. We considered a VR environment as an immersive when the environment is viewed through a device such as HMD to create the illusion that one is inside the environment, and to allow for 3D interaction. In addition, a head tracking system should be employed to create a dynamic perception of the VR world in correspondence with the subject's head movements in the real word. We included studies if they had an independent no-treatment (control) or other-conservative-treatment comparison groups.
The sensation of pain in the context of this review was considered to be acute, or chronic, intermittent or continual, resulting from either a biological recognizable cause or thermal stimulus. So, pain might be contained to a discrete area, or it could be more diffuse, as in diseases like fibromyalgia. Studies using other types of training interfaces, performed in non-VR environments such as robotics and guided imagery were excluded.

Only full publications in peer reviewed journals were considered. Unpublished data and abstracts were not sought. We did not restrict the searches or inclusion criteria to any specific language. In addition, as VR is a new technology there were no date restriction, and so all citations in each database were search. The following databases were searched: MEDLINE (Pub Med), EMBASE, Cochrane Central Register of Controlled Clinical Trials and Cochrane Database of Systematic Review, Database of Abstracts of Reviews of Effectiveness (DARE), PsycInfo, CINAHL, Web of Science, Oxford Pain Database, Proceedings of the World Congress on Pain, AMED (Allied and Complementary Medicine Database), Scopus, and OT Seeker.

These databases were searched using the following key terms: VR, VR environment, VR therapy, computer simulated environment, VR exposure, user-Computer Interface, pain, discomfort, and analgesia. In addition, the reference lists of all retrieved papers were reviewed to identify other pertinent articles. We also hand searched VR relevant conference proceedings and medical journals. For all relevant trials lacking data, we attempted to contact

the corresponding author by email for further information. To minimize the risk of bias, all methods were developed and documented prior to commencement.

Data abstraction and analysis

Two reviewers (SS and XM) read all potentially relevant abstracts to identify publications that appeared to be eligible for this review. From the chosen abstracts, they later read the full texts, and selected studies for the review according to the inclusion and exclusion criteria. All discrepancies between the two reviewers were discussed and if a consensus wasn't reached, a co-author (MS) was approached to decide. Retrieved articles from all searches were first grouped according to whether immersive or non-immersive VR was used, whether patient population included adults or children, and whether pain was considered acute or chronic. To ease the comparison of findings across studies, the following information was extracted from each study: authors (name, year), type of study, participants' characteristics (sample size, age range, gender), duration of pain (acute, chronic), reason of pain (i.e. burn, dental, cancer, chemotherapy, stroke), VR type: (immersive, non-immersive, nature and name of VR environment); VR administration (duration, frequency); comparison (conventional therapy, no therapy), outcome measures, results and adverse effects (if provided).

Quality Assessment

We examined the methodological quality of the articles using the Physiotherapy Evidence Database Scale (PEDro) (www.pedro.fhs.usyd.edu.au). The PEDro scale has adequate interrater reliability (ICC=0.68) for total scores. This scale was developed by the *Physiotherapy Evidence Database* to be employed in experimental studies and has a total score of 10 points, including internal validity evaluation criteria and statistical analyses presentation. For each criterion defined on the scale, one point (1) was attributed to the presence of the presented evidence quality indicators, and no point (0) to the absence of these indicators. Two reviewer authors (SS and XM) independently assessed the methodological quality of each study that fulfilled the inclusion criteria. We used consensus and a third reviewer (MS), if necessary, to resolve disagreements. PEDro results were interpreted using Foley and colleague's quality assessment, [20] where studies scoring 6-to-10 were considered methodologically "high," 4-5 were considered "fair" and ≤ 3 were considered "poor."

As it is presented in table 1, the level of evidence of effectiveness was determined based on Sackett [21] adapted to PEDro ratings (www.strokengine.ca). A level of evidence rating of 1a (strong) is given if well designed meta-analysis, or two or more "high" quality RCT's (PEDro ≥ 6) showing similar findings, 1b (moderate) if one RCT of "high" quality (PEDro ≥ 6), 2a (limited) if at least one "fair" quality RCT (PEDro = 4-5), and 2b (limited) at least one "poor" quality RCT (PEDro < 4) or well-designed non-experimental study (non-randomized controlled trial, quasi-experimental studies, cohort studies with multiple baselines, case studies, etc.) indicating VR to be effective. A level of evidence of 3 (consensus) is given if there is an agreement by an expert panel or a group of professionals in the field or a number of pre-post studies all with similar results, a level 4 (conflict) if there is conflicting evidence of two or more equally well designed studies, and a level 5 (no evidence) if there are no well-designed studies - only case studies/case descriptions, or cohort studies/single subject series with no multiple baselines).

Two reviewers (SS and XM) independently assessed methodological quality of all relevant studies. Disagreements were resolved by consensus. Crude agreement and Cohen's Kappa coefficient was used to assess the inter-rater agreement between the two reviewers at the major steps of the review from study selection to quality assessment. [22]

Table 1: Level of evidence based on Sackett grading system adapted to PEDro ratings [21]

Level	Description
1a	Two or more well- designed RCTs with similar findings of high quality (PEDro ≥6)
1b	One well- designed RCT of high quality (PEDro ≥ 6)
2a	One or more fair quality RCTs with similar findings of high quality (PEDro = 4-5)
2b	Non- Randomized trials and strong single subject designs (i.e., multiple baselines)
3	Agreement by an expert panel or a group of professionals in the field; also applied to the findings of a number of well-designed (pre-/post-) studies showing similar results
4	Conflicting evidence of two or more equally well- designed studies
5	No RCT, no consensus, no studies other than observation

RESULTS

As it is presented in figure 1, 104 studies were retrieved from databases: 36 in MEDLINE (PubMed), 15 in Cochrane Central Register of Controlled Clinical Trials, 14 in Cochrane Database of Systematic Review, 1 in Database of Abstracts of Reviews of Effectiveness (DARE), 2 in PsycInfo, 24 in Web of Science, 8 in CINAHL, 2 in EMBASE, and 2 in PEDro and OT seeker databases. Four additional studies were obtained from examining the reference lists of our retrieved studies. No new citations were retrieved from the Oxford Pain Database, and proceedings of the World Congress on Pain. 43 studies were excluded because they were repeated in different databases. 23 studies were excluded because they did not fit the inclusion criteria. At the end 42 studies were included in the systematic review including 16 RCTs, 14 randomized crossover design study, 6 single-case research studies (it often involves using large number of subjects in a study, where individuals in the study serve as their own control)**,** 4 case studies (it focuses on one individual), 1 study with uncontrolled clinical series of cases, and 1 randomized mixed factorial design. The studies were grouped according to the type of VR used for the intervention- immersive versus non-immersive, subjects' age group- adult versus children, and duration of pain- acute versus chronic. Inter-rater agreement for all stages of the studies selection and quality assessment generally was moderate to perfect (Crude agreement ranged from 85-100%; kappa's coefficient from 0.8 – 1).

Tables 2 to 7 provide a brief summary of the studies and, if the study was an RCT or randomized crossover design the corresponding PEDro score. Plus sign shows if VR has positive effect or not. Here we provide a conclusion regarding the level of evidence for the type of VR under question.

Evidence for the effectiveness of immersive VR compared to conventional therapy or no therapy for adults with acute pain (Table 2)
16 articles including three RCTs, five randomized cross-over design, three case studies, four single case studies, and one uncontrolled clinical series of cases investigated the use of immersive VR versus conventional or no therapy.

Finding 1: comparing immersive VR to no therapy or conventional therapy
Three "high" quality RCT [13], [17], [23], and five "fair" randomized cross over studies [24-28] have investigated the effectiveness of immersive VR therapy to no therapy or conventional therapy in pain reduction. So, there is strong (Level 1a) evidence from Three "high" quality RCT, and six randomized cross over studies suggesting that VR pain distraction is a promising tool for decreasing pain in adults undergoing acute pain.

Finding 2: comparing immersive VR using a Low-Tech-VR helmet to the immersive VR using a High-Tech-VR helmet
Two "high" quality (PEDro = 7) randomized control trials (RCT) [13], [17], have investigated the effectiveness of High Tech VR in comparison to Low Tech VR, regardless of the mechanism of VR analgesia, in reducing pain components. So, there is strong (Level 1a) evidence from two "high" quality randomized control trials (RCT) suggesting that subjects' illusion of 'going into' the 3D virtual world (i.e. VR presence) is greater for the High Tech VR group, and the High Tech VR produce more pain reduction than the Low Tech VR.

Evidence for the effectiveness of immersive VR compared to conventional therapy or no therapy for adult with chronic pain (Table 3)
There are two peer review published studies explored the usage of VR among individuals with chronic pain: one randomized cross over study, and one case study.

Finding: comparing immersive VR to no therapy or conventional therapy for pain relief in adults with chronic pain
Only one "fair" quality randomized cross over study [29] has investigated the effectiveness of immersive VR therapy to no therapy in reducing chronic clinical pain. So, there is limited (Level 2a) evidence from at least one "fair" quality study and one single case study suggesting that VR distraction therapy is effective for decreasing pain in patients with chronic pain.

Table 2: Summery of studies involving adults with acute pain under immersive VR environment

Authors / PEDro	Design	Participants	Intervention	Outcome	Results
Hoffman et al., 2000a / 5	Randomized and counter-balanced cross over study	12 burn patients (19-47 years old)	Immersive VR (Spider-world) vs. no distraction	Time spent thinking about pain, average and worst pain, pain bothersome and unpleasant/ 0-100 VAS	(+) All pain ratings for all pain measures were significantly lower during VR than in the control condition.
Hoffman et al., 2001a / 5	Case study with order randomization	2 dental patients (51 & 56 year old)	Immersive VR Vs. Movie distraction vs. No-distraction	Sensory and affective pain ratings, time spent thinking about the pain on VAS	(+) While in VR environment, both patients improved on all outcomes
Hoffman et al., 2004a	Case study	1 burn patient (40-year-old)	Water-friendly 'Snow World' Immersive VR vs. No distraction	Sensory and affective pain ratings and amount of time spent thinking about the pain on 0-10 VAS. Amount of fun / Nausea	(+) VR decreased the 3 pain components No report of Nausea
Hoffman et al., 2004b / 7	RCT	39 healthy adult	One of the two Immersive VR conditions (Low-tech VR vs. High-tech VR) vs. No VR distraction	Pain was measured by 0-10 graphic rating scales for cognitive, sensory and affective components.	(+) High-Tech-VR helmet group, showed a clinically significant reduction in pain intensity and a stronger presence during VR
Hoffman et al., 2006 / 7	RCT	77 healthy adult (19-23 year old)	Immersive VR Using a Low-Tech-VR helmet Vs. High-Tech-VR Vs. No distraction	Worst pain, pain unpleasantness, time spent thinking about pain.	(+) High-Tech-VR helmet group, showed a clinically significant effects on all pain related outcomes during virtual reality.
Hoffman et al., 2007 / 5	Cross over	9 Healthy subjects thermal pain stimulation (20-38 years old)	Immersive VR distraction vs. Opioid administration vs. Combined opioid+ VR vs. Control.	0-10 GRS was used for measuring pain intensity, pain affective, and time spends thinking about pain.	(+) Combined opioid + VR reduced pain reports more effectively than opioid alone or VR distraction alone, on all subjective pain measures.
Hoffman et al., 2008a	Single case study (within-subjects design, order randomized)	32-year-old male patient with multiple blunt trauma injuries	Adjunctive use of immersive VR No VR	The outcomes included 0-10 graphic rating scale for pain intensity and pain unpleasantness / Nausea	(+)The patient reported a significant reduction in pain when distracted with VR. Nausea from VR was negligible.
Maani et al., 2008	Case study	2 patients / Combat-related injuries	Immersive VR distraction Vs. No VR (standard pre-medication only)	Worst pain, pain unpleasantness, time spent thinking about pain. Nausea/ Fun during VR Using Graphic rating scales	(+) less pain scores when in VR except for worst pain intensity in patient1. More fun, Nausea was negligible
Magora et al., 2006 / 5	Cross over	20 healthy adults ischemic pain (10 women and 10 men aged 20 to 62 years (mean 32.5 years)	The Immersive VR game and a forced feedback joystick to destroy enemy aliens. Vs. Lively Music video	3 pain components Tolerance time of ischemia Nausea (cyber –sickness) Enjoyment of VR Presence VAS (0 to 10)	(+)Pain components were significantly lower in VR. (+) Tolerance time in VR was significantly longer than No VR. (+) Minimal adverse effects (only 2 women with mild nausea)
Mosso et al. 2007	Case reports	18 heart surgery, 2 pregnant women, 1kidney patient (14 yrs)	Immersive VR (Enchanted Forest and Icy Cool World) vs. No distraction	Well- being Pain (discomfort) Amount of medication dosage	(+) Pain reduced significantly. Patients reported higher well- being. There was the reduction of medication dosage that predicts the usefulness of VR.
Muhlberger et al., 2007 / 4	Cross over	48 healthy (18-26 year ago) heat or cold stimuli	Immersive virtual "walks" through a winter vs. An autumn landscape vs. Static exposure a neutral landscape.	Affective and sensory pain perception using a 0-10 VAS scale; simulator sickness with SSQ questionnaire; and PANAS scale for mood.	(+) Both VR environments reduced pain for heat and cold pain stimuli when compared to the control (-) No significant changes in measures of Cyber sickness were detected.
Patterson et	Single case study	1 burn patient	1 (Immersive VR	0-100 mm graphic rating	(+) Relative to pre

al., 2004		37-year-old male	Hypnosis), 2 (Audio Hypnosis), 3 (Control).	scales were used to measure his pain and anxiety.	intervention baseline, the patient's subjective pain ratings dropped after VR hypnosis.
Patterson et al., 2006 / 6	RCT	103 volunteers thermal pain (18-40 year old)	1) No PH (posthypnotic) – No VR (Immersive Snow World) 2) No PH _Yes VR 3)Yes PH _ No VR 4)Yes PH_ Yes VR	Worst pain intensity, pain unpleasantness, time spent thinking about pain were rated with 0-10 cm graphic rating scale	(+)VR group showed significant reduction in pain intensity regardless whether it combined with hypnosis or not. Combined of PHS with VR reduced worst pain and unpleasantness more.
Patterson, et al., 2006	Clinical study	13 burn-injury patients	Immersive VR-induced hypnosis (Snow World) vs. Hypnotic analgesia alone	Worst pain intensity, pain unpleasantness, time spent thinking about pain with 0-10 cm graphic rating scale	(+) Results showed that combination of VR and hypnosis more effectively decreased all GRS pain scores than hypnosis alone.
Shahrbanian et al., 2008 / 5	Crossover randomized and counterbalance	24 stroke patients (with and without pain) and 12 healthy adult	3 immersive VRs: Cold (Snow World), Hot (Dante's Canyon World), and Neutral (black and white pillars) vs. No VR	While presented to the thermal hot and cold pain stimuli Experimental Pain rating was rated using 0-100 VAS Scale.	(+) All VR conditions decreased pain ratings compared to the control condition. VR appeared to differentially influence pain rating to both hot and cold stimuli.
Wright et al., 2005	Case study	1 cancer patient (67 years old man)	Immersive VR (Snow World) vs. No VR	VAS for time thinking about pain, average pain, peak pain, enjoyment, anxiety	(+) Virtual reality reduced all pain and anxiety measures

Table 3: Summery of studies involving adults with chronic pain under immersive VR environment

Authors / PEDro	Design	Participants	Intervention	Outcome	Results
Oneal et al, 2008	Single case study	one 36-year-old female patient with chronic neuropathic pain	Immersive (Snow World) VR vs. audio recording of a hypnotic induction for pain relief	0-10 VAS for average pain intensity and unpleasantness	(+) pain intensity and unpleasantness average reduction of 36% and 33% respectively.
Simmonds et al., 2008 / 5	Cross over Counterbalance randomized	12 stroke patients (5 females, 7 males) went under thermal pain stimuli.	3 different immersive VR Cold (Snow World), Hot (Dante's Canyon World), and Neutral (black and white pillars) vs. No VR	Experimental pain threshold Clinical pain rating Engagement, Mood 0-100 NRS	(+) All VR conditions increased pain threshold, and were more engaging than control condition.

Evidence for the effectiveness of immersive VR compared to conventional therapy or no therapy for children with acute pain (Table 4)

Five RCTs, two cross over designs, one case study, and two single case studies were found to evaluate the use of VR compared to conventional therapy or no therapy for children with acute pain.

Finding: comparing immersive VR to no therapy or conventional therapy for children suffering acute pain

Five "fair" quality randomized control trials (RCT) [10, 18, 19, 30, 31], and two "fair" randomized cross over studies [32, 33] have investigated the effectiveness of immersive VR therapy to no therapy or conventional therapy for pain management in children with acute pain. So, there is limited (Level 2a) evidence from five "fair" quality randomized control trials (RCT) and two "fair" randomized cross over studies that identifies virtual reality distraction techniques as a promising non-pharmacologic approach to pain management for children suffering acute pain.

Evidence for the effectiveness of immersive VR compared to conventional therapy or no therapy for children with chronic pain

There is no evidence (level 5) that suggest immersive VR therapy in compared to conventional therapy or no therapy is effective for reducing pain in children with chronic pain. As currently there is no study explores this research area, it would be useful to use VR therapy in combination with conventional treatment or alone for pain management in children suffering chronic pain.

Table 4: Summary of studies involving children with acute pain under immersive VR

Authors / PEDro	Design	Participants	Intervention	Outcome	Results
Chan et al., 2007 / 4	Crossover	8 burn children	Immersive VR compared with no VR	The pain scores before, during and after changing the dressing were measured by 0-100 Face Scale Rating / Presence	(+) The findings suggested that a significant difference was found in the children's reported pain, with or without VR, over the three phases.
Dahlquist et al., 2007 / 5	Randomized controlled trial with a within- subject cross over design	40 healthy children (5-13 years old)	Iinteractive distraction (played a 3D video game through VR HMD) vs. passive distraction (only watched someone playing the game) vs. no distraction	Pain threshold (PTh) Pain tolerance (PT)	(+) either passive or interactive distraction caused improvements in both pain tolerance & threshold Interactive distraction was more effective than the passive.
Dahlquist et al., 2008 / 5	RCT	41 healthy children (6-14 year old) Thermal pain	Distraction with the VR helmet vs. Distraction without the VR helmet vs. no distraction	Outcomes included pain threshold and tolerance, and pain intensity measured by a 0- 100 mm VAS scale.	(+) There was a significant increase in pain tolerance and pain threshold in both passive and interactive distraction. Distraction helmet showed more effect.
Das et al., 2005 / 5	Randomized counterbalanced crossover design	7 burn Children aged 5-18	Immersive VR coupled with pharmacological analgesia vs. pharmacological analgesia only The VR game involved a visual simulation giving the children a feeling of shooting monsters.	Pain and anxiety were measured with a self-report face pain scale.	(+) It showed that VR coupled with pharmacological analgesia were more effective than pharmacological analgesia alone.
Gershon et al., 2003	Single Case study	An 8-year-old male cancer patient	Immersive VR (Gorilla program with HMD) vs. No distraction vs. non-VR distraction	Reports of pain and anxiety by the patient, parent, and nurse VAS measures of pain	(+)virtual game with HMD was found to be as the most effective condition to reduce pain related behaviors during the medical procedure.
Gershon et al., 2004 / 5	RCT	59 Children with cancer (7-19 years old)	Immersive VR distraction VS. Non- VR distraction VS. regular treatment without distraction	Child's pain and anxiety from the parent, child, and nurse's point of view.	(+) Children in the VR and Non VR distraction conditions experienced less pain than those in the control group. (+) A more significant decrease in pain experience in VR distraction condition.
Gold et al., 2006 / 5	RCT	20 children with IV placement (12 M, 8 W)	Immersive VR distraction (Street Luge -5DT, via a HMD) Vs. Standard of care with no distraction.	Anxiety, affective pain, pain intensity, and simulator sickness by Faces Pain Scale.	(+) All these outcome scores were reduced for children in the VR group. No simulator sickness
Hoffman et al., 2000b	Case study	2 burn patients (16 and 17 years old males)	Immersive VR vs. Video game "Spider World" was used as immersive VR game.	3 pain components Anxiety Several 0-100 mm VAS scales were used	(+) Both patients experienced significant less pain and anxiety, and more feeling of presence in immersive VR compared to playing the video game.
Sander Wint et al., 2002 / 5	RCT	30 adolescents with cancer (53% male)	Immersive VR (3D skiing down the Swiss Alps) plus standard care (n=17) vs. standard care (n=13).	Pain rating	(-) Less pain was reported by those in the VR group but it was not significant
Steele et al., 2003	Single case study	One patient with cerebral palsy 16-year-old	Immersive VR plus usual pharmacologic analgesics vs. the usual pharmacologic analgesics alone The patient spent half of the session.	Rating of pain intensity twice during each physiotherapy session using the Faces scales.	(+) There was significant pain reduction from VR session compared to that of PT session without VR.

Table 5: Summary of studies involving adult with acute pain under non-immersive VR

Authors / PEDro	Design of study	Participants	Intervention	Outcome	Results
Bentsen et al., 1999 / 4	RCT	24 Healthy adults cold pressor stimulus (11 females, 13 males)	3D video glasses VR VS. No VR vs. 3D Movie	Pain intensity and pain unpleasantness were rated with 0-100 mm VAS.	(+) 3D video provided a significant reduction in both pain and unpleasantness compared with control in the male, but in the female, a significant reduction in unpleasantness with 2D video
Bentsen et al., 2000 /5	RCT	39 healthy volunteer cold pressor stimulus (24 women, 15 men, 19-28 years old)	Assigned to one of these groups: positive/ neutral/ negative information about the effect of 3D video on pain, then Watching 3D movie vs. No distraction	Rating of the intensity of pain and unpleasantness using 0-10 VAS	(-) no significant effect on perceived pain or unpleasantness for 3 information groups. (+) a significant effect of 3D video on perceived pain but not on unpleasantness
Bentsen et al., 2001 / 5	Cross over by randomization	23 dental patients (17f & 6m, age 20±49 yrs)	Non- Immersive 3D video glasses Rolling skater VE vs. without video glasses (control situation).	Pain intensity Pain unpleasantness 0- 100 (VAS)	(-) There was no significant effect on the perceived pain or unpleasantness
Bentsen et al., 2002 /5	RCT	26 dental patients (12 f and 14 m, mean age of 55 years, 29–92yrs	video glasses ((VG, I-Glasses, Virtual i-O) vs. N2O –analgesia vs. Control	intensity of pain pain unpleasantness 0-10 VAS	(-) No significant VAS scores of VG on the perceived pain or unpleasantness. (-) No difference between VG and N2O
Frere, et al., 2001 / 5	Randomized mixed factorial design	27 Adult patients Dental procedure pain :13 M and 14 F, mean age: 44.3± 20.2	Use of A/V eyeglasses Vs. Control condition to view various video scenes with sound, various scenic, and activity segments.	Verbal report of pain and anxiety were measured using a 5-point Likert scale.	(+) The results showed that using A/V eyeglasses decreased anxiety and pain discomfort more than using no eyeglasses.
Lee et al., 2004 / 4	RCT	145 patients (16-75 years old) underwent elective colonoscopy	Visual distraction (Eyetrek system) & patient-controlled sedation (PCS) vs. audio-visual distraction & PCS Vs. PCS alone	Complications Recovery time / Pain score/ Satisfaction score 0-10 VAS	(+) The mean pain score and the dose of sedative medication required in group 2 was significantly lower compare to group 1 and 3
Tse, et al., 2002a /4	randomized controlled cross-over	72 healthy modified tourniquet pain (36 female, 36 male; age 20.97±1.97 years)	A soundless video display of a natural environment such as mountains (V-session) Vs. a static blank screen via the eyeglass.	Pain threshold and tolerance using 0 to 6 rating scale/ Simulation sickness and immersion using a 0 to 10 NRS	(+) Significant increase in pain threshold and pain Tolerance in visual stimuli group. Slight degree of nausea (4 out of 72).
Tse, et al., 2002b /4	randomized controlled cross-over study	46 healthy subjects tourniquet pain (32 females, 14 males; age 21.7 ± 1.58 years)	V-session: visual content of a video of a natural environment. Vs. static blank screen.	Pain threshold and pain tolerance were measured using the 0-6 rating scale where zero means no pain and 6 means intolerable pain.	(+) There was a significant increase in pain threshold and pain tolerance
Tse, et al., 2003 /4	randomized, controlled, cross-over design	33 patients with leg ulcers (17 male, 16 female, age 75.8 ± 9.8 years)	V-session: visual content of a video of a natural environment. Vs. Static blank screen.	0-10 VAS was used to measure pain intensity and 0 to 10 numerical ranging scales was used to measure enjoyment.	(+)more than twofold difference in pain scores while watching a video during the medical treatment compare to looking at the blank screen. Mean of enjoyment was 7.5 out of 10

Table 6: Summary of studies involving children with acute pain under non-immersive VR

Authors / PEDro	Design of study	Participants	Intervention	Outcome	Results
Mott, et al., 2008 / 5	RCT	42 burn Children underwent wound care	Augmented VR (AR) vs. Basic cognitive therapy	Pain scores, Pulse rates, Respiratory rates, Oxygen saturations 0-10 VAS	(+) Compare to cognitive therapy, AVR was more significantly effective in reduction of pain scores.
Windich et al., 2007 / 5	RCT	50 children and adolescents with cancer ages 5 to 18	VR Distraction (3D skiing down the Swiss Alps) plus standard care vs. standard care	Pain and fear and distress were measured by 145 mm vertical Color Analogue Scale (CAS).	(-) Though there was no statistically significant difference between two groups on mean pain scores (P = .68), the scores in distraction groups reduced more than that of standard care.

Table 7: Summary of studies involving both children and adult tested in immersive VR

Authors / PEDro	Design of study	Participants	Intervention	Outcome	Results
Hoffman et al., 2001b / 5	Crossover	7 burn patients (9-32 years old)	Therapy with immersive VR "Snow World" vs. therapy with no VR	0-100 mm VAS for pain during PT, time spent thinking about pain, unpleasantness, bothersomeness, and worst pain.	(+) There was a significant reduction in all pain ratings while patients immersed in VR during PT. Magnitude of pain reduction did not diminish with repeated use of VR.
Hoffman et al., 2008b / 4	Crossover	11 burn patients (9 - 40 years old)	3 minutes immersive VR exposure (icy 3D canyon) and 3 minutes non-VR exposure during wound care.	0-10 pain GRS was used to measure the worst pain, time spent thinking about pain and pain unpleasantness.	(+) VR distraction showed significant reduction in pain for patients experiencing severe to excruciating pain during wound care.
Sharar et al., 2007 / 5	RCT	88 burn patients (6-65 years old)	Standard analgesic care Vs. Standard analgesic care plus immersive VR "Snow World"	Worst pain intensity, pain unpleasantness, time spent thinking about pain and side effects by 0-100 GRS.	(+) All pain ratings were significantly lower during the VR distraction than during non-VR. 255 of subjects reported nausea.
Twillert et al., 2007 / 4	randomized crossover, within-subject design study	19 burn subjects (8-65 years old)	Standard care alone vs. Standard care and Immersive VR vs. Standard care and TV	0-100 mm VAS was used to rate pain and anxiety	(+) Both VR and TV showed significant pain reductions (-) VR showed more effect on pain compared to television, but not significant. No side effects regarding VR application were reported.

Evidence for the effectiveness of non-immersive VR compared to conventional therapy or no therapy for adult participants with acute pain (Table 5)

Five "fair" quality RCTs, three "fair" quality randomized controlled cross-over study, and 1 randomized mixed factorial design were found in the literature to investigate the effectiveness of non- immersive VR therapy for acute pain relief in adults.

Finding: comparing immersive VR to no therapy or conventional therapy for adult participants with acute pain

Seven "fair" quality RCTs have investigated the effectiveness of non- immersive VR therapy to no therapy or conventional therapy for pain management in adults with acute pain. So, there is limited (Level 2a) evidence from eight "fair" quality trials suggesting that VR therapy may has the potential to be a feasible, non-pharmacologic adjunct to conventional standards of care in managing the pain in adults, but may not be a promising tool to be effective when it is used alone.

Evidence for the effectiveness of non-immersive VR compared to conventional therapy or no therapy for children participants with acute pain (Table 6)

There are two RCT studies found to support the evidence for the effectiveness of non-immersive VR compared to conventional therapy or no therapy for children participants with acute pain.

Finding: comparing immersive VR to no therapy or conventional therapy in children with acute pain
Two "fair" quality RCTs [33, 35] have investigated the effectiveness of non- immersive VR therapy to no therapy or conventional therapy for pain management in children participants with acute pain. So, there is limited (Level 2a) evidence from two "fair" quality trials suggesting that VR therapy may is effective compared to no therapy or conventional therapy.

Evidence for the effectiveness of immersive VR compared to conventional therapy or no therapy for the studies that recruited both children and adult participants with acute pain in the same study (Table 7)
Four randomized and counter-balanced cross over studies were found in the literature.

Finding: comparing immersive VR to no therapy or conventional therapy in children/ adolescents, and adult participants with acute pain
Four "fair" quality randomized cross over studies [15, 36, 37, 38] have investigated the effectiveness of immersive VR therapy to no therapy or conventional therapy for pain management in children/ adolescents, and adult participants with acute pain. So, there is limited (Level 2a) evidence from four "fair" quality trials suggesting that VR, a more novel distracter, could be a useful disporting strategy and an effective non-pharmacologic intervention for reducing pain in individuals with acute pain.

Evidence for the effectiveness of non-immersive VR compared to conventional therapy or no therapy for adult and/or children participants with chronic pain
Finally, a level of evidence of 5 indicates that there are no experimental studies to investigate the effectiveness of non-immersive VR compared to conventional therapy or no therapy for either adult or children participants with chronic pain. So, additional research on this modality with this kind of population is warranted.

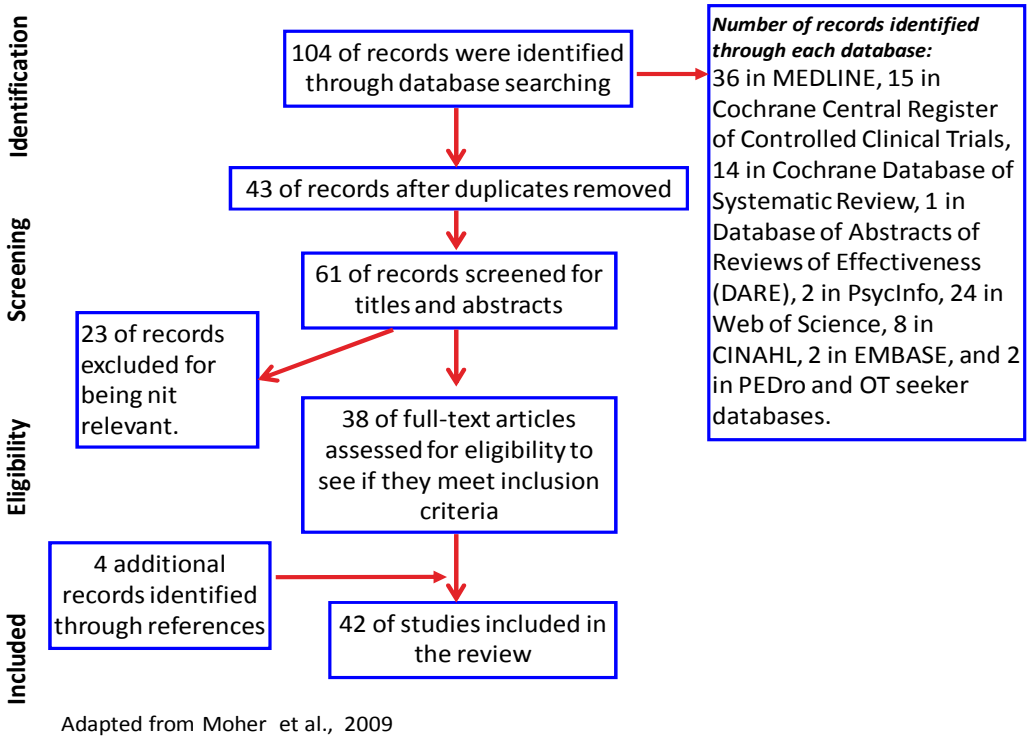

Figure1. Graphic or tabular display of study selection process

DISCUSSION

The results of the reviewed studies suggest that VR have an advantage over no therapy or other approaches in the management of pain in individuals suffering either acute or chronic pain. However, the ratings of pain that were

found on the 0-100 VAS, GRS, or NRS scales, were generally less than 50 of 100, suggesting that some subjects reported low levels of pain at baseline. So, due to this ceiling effect some subjects may be not able to demonstrate stronger effects for the VR therapy in comparison to control condition.

Our study has several strengths. This review was not restricted to type of pain either acute or chronic, to type of VR either immersive or non immersive, to age groups either children or adults, to gender differences, and to type of study. Many RCTs and cross over study designs informed our study, and we collected the data in a systematic way within the framework of the Cochrane Collaboration, suggesting that our comprehensive search strategy represents the current state of the literature. Another strength point of this systematic review is that there was no restriction in the language of related articles since it is possible that exclusion of non English studies would have influence the findings of systematic reviews. In addition, it is important to note that the validity of any findings resulted from a systematic review must obviously be evaluated in the context of the quality of the included studies themselves. [39] We therefore examined the methodological quality of the articles using qualitative synthesis strategy (PEDro scale) as an aid to assessing the validity of their conclusions, which was informative and can be considered as another strength point of this review. However, the qualitative synthesis was more challenging in assessing the evidence in chronic populations, where only few studies were available.

On the other hand, this study suffered from several limitations. One obvious limitation of this review is that many of the included studies suffered a small sample size that cause to limit the ability to generalize the results. More studies with larger sample size are needed to provide better understanding of the usefulness of VR as a treatment for pain relief. Another apparent limitation of this review is that many of the trials included were authored by the same authors, for example Hoffman with ten studies, Bentsen with four studies [40-43], and Patterson [44-46] and Tse [47-49] , each with three studies. It is possible that the results may be systematically biased in some way. It is imperative that trials of these VR interventions be repeated by other research groups and in different settings. Research has also suggested that studies with positive results are more likely to be published than studies with negative results [50]. However, outcomes of included studies in this review went in different directions, which indicate that negative results also are likely to be published in this field. Further, although some of the included studies were considered to have homogeneous pain populations (burn or dental pain population), statistical pooling of data was not possible due to heterogeneous interventions (different VR environments with different frequencies and equipments) and in some studies lack of reporting of sufficient raw data.

Learning effect can be another potential limitation for the most of VR studies as some subjects were tested more than once in same session; however, they were tested in a randomized crossover design. In these cases, there may have been a ceiling effect which modified the pain scores due to habituation. In addition, although it is possible that the novelty of the VR and unfamiliar sensations associated with VR have had an unanticipated effect of initially drawing the patients' attention away from their pain or anxiety, usually in many of VR studies all participants are provided an opportunity to practice with the VR environments before the data collection during the medical procedure. This practice could potentially reduce the novelty and the overall effects of VR distraction for all treatment groups. In future studies, researchers should try to find a way that participants in the VR group do not use exactly the same equipment before the medical procedure, thus keeping the novelty of treatment for subjects.

Individual differences such as degree of ability to concentrate and immerse in VR environment, as well as anxiety, mood, and emotions level in the time of study, may also mediate the effectiveness of VR. [51] Therefore, in those studies that were not RCT, heterogeneity of population can be another issue that should be considered while exploring the results as we cannot confidently conclude that training in one type of VR environment is better than another. The quality of the VR equipment available at the time of study can also affect its effectiveness and therefore can be another issue that should be considered. For instance, in a study of 77 adults undergoing thermal pain, Hoffman found that more subjects reported less pain when they used a VR helmet with a larger field of view. [17] Further research is needed to determine how essential the sophistication of the equipment is important in obtaining VR results.

The 0-10 or 0-100 VAS scales were the most common outcome measures used to assess pain across studies. GRS and a NRS obtained the second and third place. Other pain measures included Faces Pain Scale, the McGill pain questionnaire, verbal color analogue scale, and FPQ-III. Range of sample size was from 1, single case study, to 103 subjects. Number of female patients was pretty much less than male, whereas in healthy subjects number of female was larger than male. Clinical population included: burn patients undergoing wound care, IV insertion and suturing,

patients undergoing dental treatment, patients undergoing port access, patients with cancer, patients undergoing a lumbar puncture, patients with leg ulcer, patients with cerebral plasy, patients requiring venipuncture, and patients with acute lymphocytic leukemia. Pain intensity, pain unpleasant and time spend thinking about pain were the most outcome measured in most studies which limits the ability to report on other important outcomes such as general health and mood. Only few studies [10, 11, 26, 29, 47, 48] have measured pain threshold or tolerance and other outcomes such as long-term efficacy (e.g., return to work and other social activities), and some short- term efficacy (e.g., physical function and mood) were not assessed in many of these trials. It is also important to determine if VR immersion will extend the pain-tolerance time because the amount of time that a patient can tolerate a painful procedure is of clinical significance. Only few studies such as Simmonds [29] worked on this. In addition, there are a limited number of studies which have worked on chronic pain. [29, 52] Likewise, most studies used immersive VR in comparison to No VR, and Snow World (www.vrpain.com), which is the first 3D immersive interactive virtual world designed by Hoffman, was the most common VR environment used to reduce pain experienced by patients during medical procedures.

Side effects of immersing in VR environments, such as nausea and motion sickness or cyber sickness, have been not reported in many of the studies. Likewise, a small percentage of adults immersed in VR experienced side effects. [26, 28, 37] Children experienced little to no nausea following immersion VR. [19, 25, 30, 37] Since reports of VR side effects in many of studies are limited, further research is needed to determine the probable side effects of VR distraction in different clinical settings.

There appears to be considerable scope for further research into the potential using of VR in clinical settings. Based on evidence provided in this systematic review, VR effectively reduces the pain perception of patients undergoing unpleasant procedures. VR distraction techniques could allow subjects to immerse themselves to an unreal world during procedural pain, decrease their attention to painful stimuli, reduce the need for analgesia during painful procedures, and improve their tolerance during painful medical procedures. Results of this systematic review also provide useful information for primary care clinicians in their patients' pain management and referral practices. Virtual reality could be widely applied today's, and VR equipment is reusable and requires minimal technical knowledge for use. So, it is suggested that given the effectiveness of VR for reducing pain and consequently anxiety, it should be offered to hospital patients in all situations that are known to be painful and stressful. It is definitely recommended that for clinical settings the VR equipment should be immersive, and interesting while in the same time is simple and involving various senses, such as visual, auditory and tactile.

Continued research should try to identify the aspects of technology that can enhance the effectiveness of VR environments for pain reduction. Research should also try to determine which types of VR environments are the most effective in different clinical populations. In addition, designing VR worlds to various individual characteristics of patient, such as gender, age, socio-cultural, and personal interests may result in producing much greater pain reduction.

Likewise, research should address the feasibility of VR for use in more distressing medical procedures. As many of studies have used VR in conjunction with other pain relief or in plus with standard care, another goal of future research would be to test VR alone against pharmacological pain relief. Along these lines, it would be important to investigate the exact mechanisms by which VR assists pain reduction.

It has been found that increasing or decreasing mood can modify pain responses in chronic illness [29], so it is possible that VR may reduce pain in part through its effect on mood. Clearly further investigation regarding this issue is recommended. Motivation also has been demonstrated to be important in VR therapy and pain reduction and it would be appropriated to assess or control its role in VR training program. Since emotions are known to modulate pain [51], more pleasant VR environments are also recommended to be produced and used for pain management.

As the VR interventions are reported to have very few side effects, more research is required to more extensively explore the safety of these environments. Besides, research on consistent and long time measurement of pain, anxiety, and other outcomes might be considered in future work. Additionally, although it has been found from this review that both genders have benefited from the interactive distraction with VR technology, the major number of subjects in most studies were male, suggesting more research to determine the gender differences in pain relief while immerse in VR environment. Finally, it is necessary to mention that as a consequence of small sample size, some

studies may have lacked the enough power to adequately detect beneficial outcomes, so more RCTs with larger sample sizes, for the varying age groups, are needed to generalize the VR analgesic efficacy to larger populations of patients.

CONCLUSION

The present study identifies VR distraction techniques as promising non-pharmacological approach for pain management in patients suffering pain. There is strong (Level 1a) evidence suggesting that immersive VR is a promising tool for decreasing pain in adults undergoing acute pain. A limited level of evidence of 2a indicates that immersive VR may is effective compared to no therapy or conventional therapy for pain relief in adults with chronic pain and children with acute pain. Moreover, there is limited (Level 2a) evidence suggesting that non- immersive VR distraction may has the potential to be a feasible, innovative distraction in managing the pain in adults and children with acute pain. Finally, a level of evidence of 5 indicates that there are no experimental studies to investigate the effectiveness of either immersive or non-immersive VR compared to conventional therapy or no therapy for children with chronic pain. The results of the present study also suggest that although some type of distraction is better than no distraction, interactive distraction is much more likely to provide effective pain management than passive distraction. In addition, results indicate that High Tech VR produce more pain reduction than the Low Tech VR. VR may also produce other beneficial outcomes; however, many of these outcomes require further investigation. To summarize, although in some parts the current evidence of the effectiveness of VR for pain management in individuals with pain is limited, it can be accepted that the combination of traditional and VR therapy is more effective than either approach alone.

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