Virtual reality as a distraction intervention to relieve pain and distress during medical procedures: a comprehensive literature review

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Abstract

Objectives: This review aims to provide a framework for evaluating the utility of virtual reality (VR) as a distraction intervention to alleviate pain and distress during medical procedures. We firstly describe the theoretical bases underlying the VR analgesic and anxiolytic effects and define the main factors contributing to its efficacy, which largely emerged from studies on healthy volunteers. Then, we provide a comprehensive overview of the clinical trials using VR distraction during different medical procedures, such as burn injury treatments, chemotherapy, surgery, dental treatment, and other diagnostic and therapeutic procedures.

Methods: A broad literature search was performed using as main terms “virtual reality”, “distraction” and “pain”. No date limit was applied and all the retrieved studies on immersive VR distraction during medical procedures were selected.

Results: VR has proven to be effective in reducing procedural pain, as almost invariably observed even in patients subjected to extremely painful procedures, such as patients with burn injuries undergoing wound care and physical therapy. Moreover, VR seemed to decrease cancer-related symptoms in different settings, including during chemotherapy. Only mild and infrequent side effects were observed.

Discussion: Despite these promising results, future long-term randomized controlled trials with larger sample sizes and evaluating not only self-report measures but also physiological variables are needed. Further studies are also required both to establish predictive factors to select patients who can benefit from VR distraction and to design hardware/software systems tailored to the specific needs of different patients and able to provide the greatest distraction at the lowest cost.

Key Words: Virtual reality; distraction; procedural pain and distress; burn injuries; chemotherapy
Introduction

Virtual reality (VR) is an advanced technology that allows users to immerse themselves in a three-dimensional computer-generated world. VR equipment typically includes head-mounted displays (HMDs), headphones, motion tracking systems, and different devices to interact with the virtual environment (VE), such as a computer mouse/trackball/keyboard/gamepad or more sophisticated game controllers. The synthetic stimuli that replace the real-world sensory information include visual imagery, spatialized sound, and sometimes tactile and olfactory feedback. The provision of these multimodal stimuli and the possibility to sense the user’s motion and modify the VE accordingly, all contribute to the ability of the VR systems to induce a sense of “presence” in the virtual world, i.e., the illusion of being in the VE and of moving and acting inside it. Most commonly, VR systems are classified according to their level of immersion, which is the objective level of sensory fidelity they provide. Whereas immersion is objective and measurable, presence is an individual and context-dependent user response.

Although it was originally developed for military training and as an entertainment tool, over the last two decades VR has found a variety of applications in health care, including treatment of phobias and anxiety disorders; cognitive and physical rehabilitation; acute and chronic pain management; support for patients with cancer in different settings, such as during hospitalization, painful procedures and chemotherapy; treatment of eating disorders and obesity; surgical training and aid in surgical planning and performance. Regarding its therapeutic applications, VR has shown several advantages with respect to more conventional treatments, such as increased patients’ motivation and engagement, the safety of the simulated environment, and greater personalization possibilities.

Here, we focus on clinical studies evaluating the potential utility of immersive VR as a supportive intervention to distract patients during different painful and stressful medical procedures. In particular, after describing the theoretical bases underlying the VR analgesic and anxiolytic effects and defining the main VR characteristics contributing to these effects, which mainly
emerged from experimental studies on healthy subjects, we provide an overview of all the retrieved studies using immersive VR intervention during several medical procedures, such as wound care, rehabilitative physical therapy, chemotherapy, surgery, dental treatment, and other diagnostic and therapeutic procedures. We comprehensively describe in particular clinical studies aimed to assess the efficacy of VR distraction as an adjunctive treatment to control pain in patients with burn injuries undergoing wound care and physical therapy, which are among the most painful medical procedures. Indeed, to date most clinical studies on VR use as a distraction tool have been dedicated to the procedural pain in burned patients. We also focus on studies evaluating VR efficacy in relieving cancer patients’ distress due to chemotherapy treatment. Indeed, identifying interventions able to enhance chemotherapy tolerance is crucial to improve both patients’ quality of life and compliance to treatments, which, in turn, can increase their chances of recovery. In addition to reporting the effect of VR on pain and distress, we also describe all the other outcomes assessed in the included studies. Limitations of these studies and recommendations for future research are discussed.

Given the broad scope and comprehensive coverage of this review and the consequent heterogeneity of the included studies, pooling and meta-analysis of data were not performed and the findings were described in a narrative form.

Theoretical framework and experimentally determined factors underlying VR distraction efficacy

Pain perception is strongly affected by psychological factors. A physiological explanation of this phenomenon was suggested in 1965 by Melzack and Wall with their “gate control theory”. According to this hypothesis, nociceptive signals are modulated by a gate control system located in the dorsal horn of the spinal cord: depending on whether the gate opens or closes, the flow of pain signals to the brain can be facilitated or inhibited. The gate can be opened or closed not only by sensory factors, but also by cognitive and emotional factors. Although current studies have
revealed that this control system is much more complex with respect to that originally proposed, the general concept underlying the gate control theory is still valid\textsuperscript{27}. The notion that psychological factors play a crucial role in pain experience was further supported by the subsequent neuromatrix theory of pain\textsuperscript{28}. The neuromatrix is defined as an extensive neural network distributed throughout many areas of the brain, which integrates multiple inputs to generate characteristic “neurosignature” patterns of nerve impulses that elicit pain\textsuperscript{28}. According to this theory, pain is a multidimensional experience, consisting of sensory, affective, and cognitive components, mediated by different brain regions and influenced by several inputs that act on the neuromatrix and contribute to the output neurosignature. Although recently the neuromatrix model has partially been challenged, the concept of a complex pain network is still crucial to understand how pain experience is mediated by various factors, including cognitive and emotional factors\textsuperscript{17}.

Among the factors that can affect the pain experience, the attention paid to pain seems particularly important and distraction has emerged as a useful means to alleviate pain: brain processing of pain signals requires attention\textsuperscript{29} and, owing to individuals’ limited attention ability at a given time, a painful stimulus will be perceived as less intense if attention is focused on other stimuli\textsuperscript{30}. To date different distraction techniques, including relaxation, cognitive tasks, watching movies, and nurse coaching, have proved useful to reduce patients’ pain perception\textsuperscript{17}.

More recently, VR has emerged as an efficient distraction tool for pain management. VR has, indeed, unique characteristics that render it a very effective distractor. Firstly, VR is able to engage different senses simultaneously and induce a sense of presence in the VE, thus efficiently diverting attention from painful stimuli\textsuperscript{17}. The engagement of attentional resources in immersive and interactive VEs could modulate ascending nociception, resulting in a reduced pain experience\textsuperscript{31}. Moreover, through the VR equipment, patients can be both visually and acoustically isolated from the medical environment and can thus cognitively escape from “the painful real world”\textsuperscript{14}. Also, by helping patients to focus their attention on pleasant or interesting stimuli rather than on unpleasant symptoms, VR could reduce negative emotions, such as stress and anxiety\textsuperscript{32}. Thus, considering the
well-established effect of anxiety in exacerbating pain perception\textsuperscript{33}, a possible VR anxiolytic effect could contribute to VR analgesic efficacy. Finally, the ability of VR to induce emotions with a positive valence is deemed to influence its analgesic effect\textsuperscript{17}. Therefore, although the precise mechanisms of pain relief during VR are still unclear, considering the bidirectional relationship between pain and emotional states (negative affect can be both a consequence of pain and a key factor that can worsen pain), it is also possible that the analgesic effect of VR is mediated by central mechanisms involving affect\textsuperscript{31}.  

The main factors contributing to VR efficacy have largely been revealed by studies on healthy volunteers subjected to experimental pain, administered through thermal, mechanical and electrical stimuli. Indeed, beyond demonstrating that VR is an effective distraction tool to control pain\textsuperscript{31, 34-55}, these studies were also particularly useful to dissect crucial aspects underlying the analgesic effect, while avoiding confounding variables, such as pathology characteristics and use of drugs\textsuperscript{15}. In particular, different studies showed that the VR-induced sense of presence correlated with improved pain threshold\textsuperscript{34}, increased pain tolerance\textsuperscript{46} and reduced pain intensity\textsuperscript{31, 36, 45, 47}. Moreover, Sharar et al., beyond observing the correlation between sense of presence and reduced pain intensity, also found that subjects reporting less anxiety, more “fun”, and more positive emotional valence during VR were more likely to report pain reduction\textsuperscript{31}. Therefore, overall these observations suggest that the analgesic mechanism of VR is multifactorial, being mediated by attentional, anxiolytic, and/or affective effects\textsuperscript{31}.  

Experimental pain studies also allowed researchers to compare different VR hardware/software configurations to identify those providing the greatest distraction analgesia. In particular, Hoffman et al. compared the analgesic efficacy of a high-tech VR system (high display quality, head tracking, headphones/sound effects, and user interactivity) with that of a low-tech VR system (low display quality, no head tracking, no headphones/sound effects, and no interactivity) and observed that subjects in the high-tech-VR group reported a stronger sense of presence and a greater pain reduction compared to subjects in the low-tech-VR group. Moreover, as also reported
above, the authors found a significant correlation between pain reduction and presence levels. In another related study, Hoffman et al., instead of manipulating simultaneously a number of VR hardware characteristics, focused only on the helmet quality and found that a high-tech VR HMD (60° field of view diagonal) was considerably more effective than a low-tech VR HMD (35° field of view diagonal) in reducing different pain components: a sensory component (worst pain), an affective component (pain unpleasantness) and a cognitive component (amount of time spent thinking about pain). In this study, in which the only hardware difference between the high-tech-VR group and the low-tech-VR group was the helmet quality, no significant difference in presence levels was observed between the two groups.

Another study specifically assessed the role of auditory information and found a greater pain tolerance when participants were simultaneously exposed to a VR game with supplementary sound. Furthermore, various studies focused on comparing the efficacy of interactive and non-interactive VR systems in controlling pain and found that interactive distraction was more effective and could also induce a higher sense of presence, which, as mentioned above, correlated negatively with pain intensity scores. This observation supports the view that engaging attentional resources in tasks can interfere with pain processing. Overall, these studies point to a crucial role of HMD quality and interactivity in increasing sense of presence and analgesia.

Further extending these findings, another study showed that manipulating actively a figure, used as a symbolic representation of pain, to reach a pleasant environment (representing “no pain”) increased pain tolerance with respect to a non-interactive, passive VR condition. Again, presence was significantly higher in the interactive condition and, as stated above, correlated positively with pain tolerance. Moreover, in another related study, control over the virtual object representing pain seemed to have a greater effect on cognitive variables, such as self-efficacy in tolerating pain and helplessness, with respect to interactive VR distraction. Therefore, VR can be helpful in decreasing pain also through mechanisms other than distraction. Studies exploring “non-distraction”
mechanisms by which VR can reduce pain have been described in a recent review. These studies used VR programs different from those typically used in distraction-based VR interventions (for instance programs depicting the transition from images representing pain to images representing calm, comfort, or happiness, as in the study described above), and also combined VR with other treatment modalities, such as biofeedback and cognitive behavioral therapy. However, these studies were mainly focused on chronic pain rather than acute pain. Therefore, to date distraction remains the best-known mechanism through which VR affects acute pain and future studies are required to analyze other mechanisms whereby VR can help in decreasing acute pain.

A concern regarding VR utility in pain management is that VR could lose its efficacy over repeated exposures, since individuals might habituate to it. To address this issue, Rutter et al. conducted an 8-week trial and observed that VR efficacy in reducing experimental pain (cold pressor pain) did not decrease over repeated exposures (see also the clinical studies described below, showing that the benefits of the VR intervention were not lost across repeated sessions). Thus, the VR analgesic effects do not seem ascribable only to the experience novelty.

To gain insight into the physiological mechanism underlying the VR analgesic effect, functional magnetic resonance imaging (fMRI) studies were performed. These analyses showed that the use of VR, through custom magnet-friendly VR goggles, during experimental pain stimulation in healthy volunteers was able to reduce significantly the brain activity in regions commonly activated by painful stimuli. These studies provided neurobiological evidence for the VR analgesic effect and an objective confirmation of the subjective measures of pain reduction.

Altogether, these observations provide a framework supporting the potential clinical utility of VR as a distraction treatment. Findings from clinical studies using VR during different medical procedures are described in the following sections.

**VR during burn injury treatments**

In order to promote healing and prevent infections, the management of severe burns requires daily wound care, consisting in bandage removal, wound cleaning/debridement (i.e., dead tissue and
foreign material elimination), application of antiseptic ointments, and wound re-dressing\textsuperscript{14}. In addition to several wound dressing changes, patients with burn injuries are subjected to daily physical therapy, which is crucial to increase the elasticity of healing skin, thus counteracting the development of skin contractures and preventing the decrease in joint range of motion (ROM). Therefore, physical therapy is fundamental to maintain functionality and reduce the need for further surgical interventions\textsuperscript{14}.

The management of burn injury procedural pain remains a major clinical challenge and, indeed, burned patients continue not to receive proper pain relief during wound dressing change and physical therapy\textsuperscript{65}. One of the reasons for this pain undertreatment is the wide variability in pain intensity occurring over the course of burn recovery, which makes it difficult to estimate the analgesic needs\textsuperscript{65}. Moreover, the use of opioid analgesics, which are the mainstay of treatment for pain in patients with burn injuries, is limited by several adverse effects, such as constipation, nausea, vomiting, somnolence, dizziness and pruritus\textsuperscript{66-68}. Also, repeated administration of opioids can result in reduced analgesic efficacy and physical dependence\textsuperscript{69}. The inadequacy of pharmacological treatments for pain control during the rehabilitation therapy can reduce patients’ compliance\textsuperscript{14}. Moreover, the suboptimal management of acute pain from burn injuries not only severely impacts on immediate quality of life but can also have long-term psychological and physical consequences, including depression, post-traumatic stress disorder, chronic pain, and even suicidal ideation\textsuperscript{65,70}.

Burn pain undertreatment is particularly concerning when involves children. Pediatric patients experience a high level of anxiety before and during burn treatments\textsuperscript{71} and often develop strong conditioned responses to stimuli associated with burn wound care procedures. For instance, visual cues associated with dressing changes can induce anxiety and exacerbate the pain\textsuperscript{72}. The uncooperative behavior of children during treatments can make medical procedures very challenging and distressing for health professionals\textsuperscript{71,73}, who can in turn transmit their distress associated with inflicting procedural pain, thus contributing to the pain perceived\textsuperscript{74}. The pain
experience in children can lead to short- and long-term consequences, including increased sensitivity to pain and poor psychological well-being and functioning.\textsuperscript{75}

Because of the inadequate pain relief during wound care and physical therapy with pharmacological treatments alone, adjunctive non-pharmacological interventions are needed. Moreover, the ongoing opioid crisis, namely a dramatic increase in deaths from opioid overdose, in opioid use disorder, and in other harms related to the increased opioid prescription for pain management, adds further urgency to the need for non-pharmacologic analgesics.\textsuperscript{76} Psychological interventions, such as cognitive-behavioral interventions, distraction, and hypnosis, seem helpful in the management of burn pain.\textsuperscript{77, 78} Among distraction interventions, immersive VR has shown promise in numerous studies. The first pilot study exploring the effect of VR on burn pain was conducted in 1998 on three adolescent patients.\textsuperscript{79} This first study suggested that VR exposure could decrease burn pain, even including the extreme pain associated with wound care. Following these first encouraging results, several clinical trials assessed the use of this technology as an adjunctive treatment for patients with burn injuries undergoing wound care (Table 1) and physical therapy (Table 2). Tables 1 and 2 report a comprehensive summary of these trials, which include case studies, case series, and controlled trials published between the years 2000 and 2017. As indicated in the Tables, ten studies involved adult patients,\textsuperscript{57, 80-88} seven studies are focused on children and adolescents,\textsuperscript{59, 71-75, 89} whereas five studies involved both adults and pediatric patients.\textsuperscript{58, 60, 90-92} These studies analyzed not only whether the VR intervention could be helpful for pain control, but also whether it could have an impact on the anxiety levels associated with the painful procedures and induce positive emotions (“fun”). In studies using the VR intervention during physical therapy, the effect of this intervention on joint functionality was also analyzed. Other assessed outcomes included sense of presence in the VE, perceived realism of the VE, distraction engagement, and VR impact on the patients’ perception of the treatment duration, which can all be useful to verify the VR distraction ability. Finally, possible side effects and feasibility of the VR intervention were also
evaluated. The VR equipment and programs used, the assessed outcomes, and the limitations of these studies are described below.

**VR hardware and software equipment**

Most of the studies on burn patients included in this review used conventional VR equipment, consisting in HMDs and motion tracking systems plus joysticks or other devices to interact with the VE. The software used in the first studies was “SpiderWorld”, a program originally developed to overcome spider phobia. Through position sensors, patients explored and interacted with the VE (a virtual kitchen) by moving their head and “cyberhand” and could also use tactile augmentation to touch a furry spider and eat a virtual candy bar. Conversely, the VR software most frequently used in the subsequent studies, “SnowWorld”, was specifically designed to reduce pain experienced by patients with burns, since it depicts an icy, cool VE, which contrasts with the patients’ memory of the accident that caused their burns and might engender a suggestion of relief from burn pain. Patients explored and interacted with the VE (by throwing snowballs at virtual characters and objects) through a computer mouse/joystick/trackball/keyboard, or via a tracking system; the synthetic stimuli also included spatialized sound and background music. Other programs, which were mainly used for pediatric patients, taking into account their age groups and intellectual capabilities, were: the off-the-shelf “Disney’s Chicken Little” and “Need for Speed” games; a VR game based on the game “Quake” originally developed by ID Software; a game set in an ice-cream factory. Unlike all the above-mentioned studies using VEs aimed to distract patients, one study used a VR relaxation sequence based on hypnotherapy theory to induce a pre-procedural VR guided relaxation.

Although most studies used conventional VR equipment, other VR systems have been developed to meet specific needs of patients with burn injuries. In particular, five studies used VR devices mounted on custom articulated arms, which allowed patients to use VR without wearing a heavy HMD and were, therefore, available also for patients with burns to the head. In two other studies a photonic, nonelectrical, water-friendly VR helmet was used during wound
debridement in the hydrotank, a sterile bathtub of water often used to facilitate bandage removal
and wound cleaning\textsuperscript{80, 91}. This VR device allowed patients to safely use VR while being partially
immersed in water, where conventional VR systems are not usable because of potential safety
hazards. Since wound care is typically more painful during the early phases of burn recovery, when
patients are often treated in the hydrotank, this system can allow patients to receive VR distraction
treatment when they need it most\textsuperscript{80}.

\textit{Effect on pain}

The effect of VR on burn injury procedural pain was evaluated by comparing the pain
experienced during the VR intervention plus standard analgesics with that experienced during the
control conditions, consisting of standard analgesics alone or in combination with other more
conventional forms of distraction. Almost all of the studies used a within-patients design, in which
all participants were subjected to both the VR intervention and the control conditions. A between-
subjects design was used in only three studies\textsuperscript{74, 75, 82}.

Overall, all but one\textsuperscript{82} of the clinical trials included in this review showed that the VR
intervention decreased the pain experienced by both adult and pediatric burned patients undergoing
wound care and physical therapy with respect to the control conditions. In particular, most studies\textsuperscript{57-}
59, 72, 80, 81, 83, 84, 86, 87, 89, 91, 92 showed reduction in different pain components, which were separately
measured: a sensory component (worst pain and average pain), an affective component
(unpleasantness and bothersomeness), and a cognitive component (amount of time spent thinking
about pain). Tables 1 and 2 report the pain measurement tools used, the reliability and validity of
which are described in references provided by the authors of the studies. These tools included
different scales to rate pain, such as visual analogue scales (VASs), graphic rating scales (GRSs),
visual analogue thermometer (VAT), and numeric pain rating scale (NPRS). Other scales, which
were specifically used for children/adolescents, included the Faces Pain Scale (FPS)\textsuperscript{71, 73} and the
Adolescent Pediatric Pain Tool (APPT) word graphic rating scale (WGRS)\textsuperscript{74}. Other less used
complementary tools that could contribute to estimate pain included physiological measures, such
as heart rate and oxygen saturation\textsuperscript{75}, and the evaluation of pharmacologic analgesic requirement\textsuperscript{75, 82, 85}. In three of the studies involving pediatric patients, in addition to the children’s self-report measurements of the pain, also the nursing staff reported useful information, through interviews\textsuperscript{71, 73} or by using the Faces, Legs, Activity, Cry and Consolability (FLACC) scale\textsuperscript{75}. According to the nurses’ observations, VR was helpful both in reducing pain and in increasing children’s cooperation.

Importantly, the VR intervention was effective for reducing extreme pain. Indeed, in a study using VR during wound debridement in the hydrotank, the six patients with the highest pain intensity still showed a 41\% reduction in pain during VR\textsuperscript{91}. Moreover, contrary to what could be expected, in another study it was observed that VR was even more effective for patients reporting the highest pain intensity ratings (severe to excruciating) during wound debridement with respect to those with mild to moderate pain\textsuperscript{84}.

The only study that failed in showing a favorable response to the VR intervention in burned patients undergoing wound dressing change was the above-mentioned trial using a pre-procedural VR guided relaxation\textsuperscript{82}. This observation suggests that VR relaxation might not be as effective as VR distraction\textsuperscript{15} or, alternatively, that VR relaxation might require longer VR intervention times to achieve therapeutic effects\textsuperscript{82}.

\textit{Effect on anxiety and “fun”}

VR ability to reduce negative emotions, such as anxiety, and to induce emotions with positive valence, such as “fun”, is believed to influence the VR analgesic effects\textsuperscript{17} and these emotions are often evaluated in studies on VR distraction analgesia.

Managing burn patients’ anxiety during medical procedures is crucial because the often excruciating pain associated with wound dressing change and physical therapy can be further exacerbated by patients’ anticipatory anxiety, which can, thus, further impact on patients’ compliance\textsuperscript{12}. The effect of VR intervention on anxiety levels was analyzed in several of the studied included in this review\textsuperscript{57, 71-74, 82, 85, 86, 88, 90}. However, although in some studies a trend towards
reduced anxiety was observed upon VR intervention, overall, equivocal evidence emerged from these studies regarding whether VR reduces anxiety.

Besides assessing the VR potential to relieve procedure-related anxiety, studies on VR-based analgesia should also consider that patients’ trait anxiety might influence the VR analgesic efficacy. Indeed, Jeffs and co-workers observed a significant negative correlation of VR distraction engagement with both trait anxiety and procedural pain in adolescent patients, thus suggesting that patients with a predisposition towards anxiety might be less engaged with distraction and receive fewer benefits from VR intervention\(^7\). Therefore, further studies assessing the reciprocal impact of VR distraction and anxiety in burned patients are warranted.

Various studies evaluated the levels of “fun” upon VR intervention\(^5\). The concept of “fun” is related to mood/affect, but unlike more formal tools used to evaluate mood states, is more readily and easily understood, especially by pediatric subjects\(^5\). An increase in “fun”, which was subjectively assessed through GRS in these studies, can indirectly indicate an improvement in mood/affect\(^5\) and therefore can be a potential surrogate label for “positive affect”\(^3\). All these studies revealed the ability of VR exposure to induce “fun” during wound care or physical therapy in both adults and children/adolescents with burns. In particular, Schmitt and co-workers observed that “fun” improvement was maintained over multiple days of therapy in pediatric patients\(^5\) and Hoffman et al. found that patients with the greatest effect of VR on “fun” were those reporting the highest presence and pain reduction\(^9\). However, further studies are necessary to establish the role of “fun” on VR analgesic efficacy in patients with burns.

Effect on joint functionality

In most studies using the VR intervention during physical therapy, the effect of this intervention on joint ROM was analyzed\(^5\). No significant differences in ROM were observed between the VR treatment and the control conditions for these short-term studies, although a trend towards greater ROM upon the VR intervention was reported. Differences in ROM improvements could potentially be revealed for treatments of longer duration and higher frequency.
Future studies assessing the potential impact of long-term VR use on functional outcomes are warranted.

**Analysis of factors indicative of distraction efficacy**

Other outcomes assessed in the included studies were: sense of presence in the VE, perceived realism of the VE, distraction engagement, and VR impact on the patients’ perception of the treatment duration. All these factors can be useful to verify the efficacy of VR to divert attention from the painful stimulus. Indeed, it is believed, also on the basis of the results from the above described experimental pain studies, that to be an effective distraction tool, VR should be able to give the patients the illusion of being in the VE and should be engaging. Moreover, the distracting ability of VR might be reflected in an altered patients’ time perception, leading to a treatment duration underestimation. Indeed, significant correlations between procedural pain reduction and either distraction engagement or discrepancy in time perception were reported. Moreover, one of the included studies reported that patients with the highest ratings of presence showed the greatest effect of VR on pain, although a similar correlation was not found in the study by Chan and co-workers (see also the experimental pain studies mentioned above). Moreover, in the study by Sharar et al., children experienced higher levels of presence and perceived realism of the VE compared to adults, but age did not affect the analgesic effects of VR.

**Side effects and feasibility**

Nausea or other possible side effects of the VR intervention were evaluated in most studies. Overall, nausea was very infrequent and mild, and no other side effects were reported. Moreover, in almost all of these studies, nausea occurrence was evaluated only for the VR treatment condition (VR plus standard analgesia), without performing a comparison with the control conditions (standard analgesia, alone or in combination with other forms of distraction). Therefore, for the few cases in which mild nausea was reported, it is not
possible to ascribe this adverse event entirely to the VR intervention because nausea could also be partially attributed to the use of opioid analgesics\textsuperscript{59, 87, 92}.

A few studies assessed VR usability (hardware comfort and ease of use)\textsuperscript{71} and VR impact on treatment duration\textsuperscript{75, 88}, to evaluate whether the VR intervention could be feasible in the clinical setting, without requiring longer treatment times\textsuperscript{88} or even reducing these times, thanks to its analgesic effect that might facilitate treatments\textsuperscript{75}. Although these studies reported no significant differences in treatment duration, interviews of nurses dealing with children with burns revealed that the VR intervention can calm children, thus increasing their cooperation and making medical procedures less challenging and time-consuming\textsuperscript{71}. Nevertheless, another study, specifically focused to evaluate the feasibility of the VR intervention in a burn center, suggested that VR setup, patient training, VR treatment, and equipment cleaning require a significant staff time commitment and, therefore, can represent a hurdle for the VR use in clinical practice\textsuperscript{93}. Conversely, in a more recent study assessing the feasibility of implementing low-cost VR systems during routine burn care in an outpatient clinic setting, both patients and medical providers supported the feasibility of this intervention\textsuperscript{94}. Future studies are needed to evaluate whether the VR analgesic and calming effects might facilitate treatments, thus resulting in treatment time reductions and, therefore, at least in part compensating for the additional time required for VR setup and patient training.

Another obstacle to widespread clinical use of VR is the high cost of the technical equipment. Less expensive VR systems are needed to make VR distraction available to many patients, including those from developing countries\textsuperscript{88}. Limited data on the efficacy of low-cost VR systems on burn injury procedural pain are currently available\textsuperscript{75, 88, 89}. Future studied aimed to determine optimal VR hardware and software configurations, providing the greatest distraction analgesia at the lowest cost, are needed\textsuperscript{92}.

\textit{Limitations}

As also stated above, a concern regarding the use of VR as an adjuvant treatment of pain is that VR could lose its efficacy over repeated and long exposures. Indeed, VR efficacy in reducing
burn pain was shown principally during brief portions (3-6 min) of single wound care/physical therapy sessions (treatment durations are indicated in Tables 1 and 2). Although some encouraging data showed that the benefits of the VR intervention were not lost upon longer exposures\textsuperscript{71, 74, 75, 85, 87, 89, 90} or across at least three sessions\textsuperscript{57-60}, considering that a patient with a large burn injury might require more than 30 wound care sessions lasting approximately 30 min and also 30–60 or more physical therapy sessions, further studies exploring whether VR continues to be effective also in these conditions are needed\textsuperscript{60}.

Moreover, almost all of the studies used only self-report measurements. Although these subjective measures are considered the definitive standard for pain evaluation, other methods, such as physiological measures, might provide a more comprehensive evaluation of the procedural experience\textsuperscript{74} and an objective confirmation of the subjective measures.

Furthermore, most studies involved a small number of patients (Tables 1 and 2), limiting the ability to generalize the observations and also hindering the evaluation of possible associations between VR efficacy and patients’ characteristics, such as age, sex, ethnicity, size of burn injury, and duration of therapy sessions or of hospital stay. These possible associations were sought in four studies, but none of these patients’ characteristics were found to affect the analgesic effect of VR\textsuperscript{59, 60, 90, 92}. Therefore, future studies involving a greater number of patients are required.

Also, almost all of the studies were unblinded and, therefore, at risk of bias. Indeed, only three studies used a single-blind (assessor blinding) design\textsuperscript{73, 74, 88} and none was double-blinded. Considering the peculiar nature of the experimental intervention, performing a double-blind study is very challenging if not impossible. However, blinding of data collectors/outcome assessors is possible and needed to ensure unbiased outcome evaluation and, therefore, is recommended for future clinical studies\textsuperscript{12}.

**VR and chemotherapy**

Chemotherapy is a mainstay of cancer treatment, but its side effects, including nausea, vomiting, fatigue, pain, and anorexia, remain a significant clinical problem. Moreover,
psychological distress is a common consequence of both diagnosis and treatment in cancer patients, with most patients suffering from depression and anxiety\textsuperscript{95,96}. Psychological factors, such as emotional distress and maladaptive coping styles (hopelessness-helplessness and anxious preoccupation) can further increase patients’ risk of developing chemotherapy-induced nausea and vomiting\textsuperscript{97}. Chemotherapy adverse effects can result in dose reduction or treatment discontinuation, thus decreasing the chances of recovery. Furthermore, growing evidence suggests an association of psychological factors, such as stress, depression, and social isolation, with cancer progression\textsuperscript{98}. Indeed, in vitro experiments, in vivo mouse studies, and clinical trials showed that stress-related factors, including changes in stress hormones (adrenaline, norepinephrine, and cortisol) and in inflammatory cytokines, can impact on key processes implicated in cancer progression, such as cell proliferation, angiogenesis, invasion and metastasis\textsuperscript{98-101}, and stress hormones can also induce chemoresistance\textsuperscript{102}.

Therefore, considering the association of stress-related factors with both impaired quality of life and cancer progression, the development of psychological interventions, also able to improve chemotherapy tolerance, is an urgent need. Many trials of psychological interventions have been conducted in patients with cancer over the past 50 years\textsuperscript{98}. Among psychological interventions aimed to increase chemotherapy tolerance, distraction could represent a promising strategy. Indeed, different distraction interventions, including progressive relaxation, guided imagery, and cognitive distractions (reading, humor, music, and movies), have shown some success in patients receiving chemotherapy\textsuperscript{32,103}. However, some of these distraction interventions, such as progressive relaxation and guided imagery, require that patients practice these techniques before chemotherapy, but, even with practice, some individuals do not acquire the ability to master these methods. Moreover, patients have to ignore input from the treatment environment and focus their attention on the distractor for the entire treatment duration, but unfortunately only few patients are able to maintain full concentration for such a duration\textsuperscript{32,103}.
VR, which, conversely, does not require prior practice and has both a great attention-grabbing power and the ability to isolate patients from the anxiety-inducing clinical environment, proved to be a promising tool to support patients with cancer in different settings, including during chemotherapy (see our recent review for a thorough description of these studies). In particular, VR improved patients’ emotional well-being and diminished cancer-related symptoms and pain in various conditions, such as during hospitalization and during painful procedures.

Moreover, different studies suggested that the VR intervention could be an effective distraction tool during chemotherapy in both adult and pediatric patients with different cancer diagnoses. Table 3 reports a comprehensive summary of these trials, which analyzed the effect of VR on chemotherapy-related distress outcomes and also its impact on the patients’ perception of the treatment duration, to validate VR distraction ability. Moreover, possible side effects and feasibility of the VR intervention were assessed. The VR equipment and programs used, the evaluated outcomes, and the limitations of these studies are described below.

**VR hardware and software equipment**

In studies by Schneider and co-workers, commercial HMDs and software were used during the entire chemotherapy treatment duration. Patients could choose from different possible scenarios (see Table 3) and were free to change scenarios at any time during treatment. Conversely, Oyama and co-workers used a custom semi-immersive VR system, called bedside wellness system, which allowed patients to experience VEs while in bed. This system consisted of a bedside three-screen liquid-crystal display, a 3D sound system, a unit to deliver a gentle breeze and scents, and foot devices to control the image movement. Three VEs (lake, forest, and country town) were available.

**Effect on distress**

Most studies assessing the VR effect on chemotherapy-related distress outcomes used a within-patients design, in which all participants were subjected to both the VR intervention and the control conditions during alternate matched chemotherapy sessions (one with VR and one/two
without VR) and serve as their own control, thus avoiding confounding variables, such as chemotherapeutic agents, antiemetics, age, gender, and cancer diagnosis. A between-subjects design was used in only one study.116

All but one32 of these trials showed that the VR intervention could significantly improve at least one of the analyzed psychological variables immediately after treatment. In particular, VR intervention mainly improved symptom distress114,118, which is a general indicator of “the degree of discomfort from the specific symptoms being experienced”119, and impacted on more specific distress outcomes, such as anxiety117, and fatigue116,118. More specifically, upon VR intervention symptom distress improved both in children with leukemia or Hodgkin's lymphoma114 and in women with breast cancer aged 27-55 years118, anxiety decreased in older women with breast cancer (50-77 years)117; fatigue was reduced in adult patients with different cancer types116,118. Moreover, Oyama and co-workers also observed a significant decrease in emesis three-five days after chemotherapy with VR in adult cancer patients116. Tables 3 report the used measurement tools, which are described in references provided by the authors of the studies.

Effect on time perception

In three studies, Schneider and co-workers also investigated whether the VR intervention during chemotherapy resulted in an altered time perception in adult patients with different cancer types and found, indeed, that patients underestimated treatment duration when using VR, thus validating its distraction ability32,117,118. Consistently, recent preliminary data by our group showed that breast cancer patients undergoing VR during chemotherapy significantly underestimated treatment duration; moreover, this discrepancy in time perception was significantly different from that of patients undergoing music therapy during chemotherapy, who conversely overestimated treatment duration120. A secondary analysis103 of pooled data from the three above mentioned studies by Schneider co-workers32,117,118 showed that the type of cancer diagnosed (breast, colon, or lung cancer) was a predictor of differences in time perception during VR immersion. In particular, on average, breast cancer patients underestimated treatment duration by 23 min, colon cancer

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patients by 12 min, whereas lung cancer patients showed only minimal alteration in time perception (by <4 min). This observed minimal impact of the VR intervention on time perception in lung cancer patients could be related to the greater severity of their physical and/or psychological symptoms with respect to those of patients with other cancer types\textsuperscript{103}. Thus, VR distraction might be more effective in less symptomatic patients, such as breast and colon cancer patients\textsuperscript{103}.

Consistently, the only study included in this review that failed in showing statistically significant decreases in chemotherapy-related distress outcomes under the VR intervention involved also lung cancer patients (33\%) and perhaps expecting that a distraction intervention could mitigate very intense physical symptoms might not be realistic\textsuperscript{29, 32}. However, this is in contrast to the aforementioned observation that VR was even more effective for patients reporting the highest burn pain intensity ratings\textsuperscript{84}.

\textit{Side effects and feasibility}

Possible side effects and feasibility of the VR intervention during chemotherapy were also evaluated in most studies\textsuperscript{32, 114, 115, 117, 118}. Except for three pediatric patients who experienced headache while using VR\textsuperscript{114}, no VR side effects were revealed and this intervention was overall well received by patients, with most of them indicating their willing to use it again\textsuperscript{32, 115, 117, 118}. Moreover, VR was found easy to use\textsuperscript{32, 115, 117, 118} and required minimal nursing time\textsuperscript{115, 118}.

\textit{Limitations}

Despite these encouraging results, most studies using VR during chemotherapy involved a small number of patients (Table 3) and the study that employed the largest sample size only showed a trend towards improved symptoms, without reaching statistical significance\textsuperscript{32}. These studies used relatively low-tech VR goggles with barely interactive VR worlds. Since low resolution, limited field of view, and absence of spatial user interface strongly affect the level of immersion in VEs, stronger results might likely be obtained using new high-tech VR systems, such as Oculus Rift or HTC VIVE VR helmets, and fully interactive VR worlds.
Moreover, all studies were unblinded. Also, further studies exploring VR efficacy in reducing chemotherapy-related symptoms after repeated use and in comparison with other forms of distraction are needed. Finally, future analysis of VR effects on physiological variables (such as heart rate and skin conductance) or on stress-related molecules could serve as an objective measure of distress reduction and could also reveal the potential ability of the VR intervention to modulate stress-related pathways involved in cancer progression.

VR during other painful and stressful procedures

Below we briefly describe another set of rather isolated studies using VR in various clinical settings that have still not been largely explored at present.

*Traumatic injury treatments*

VR proved to be effective in reducing procedural pain in patients with injuries caused by different traumatic accidents. In particular, Hua and co-workers observed that children with lower limb chronic wounds receiving the VR intervention (n=33) during their wound dressing change perceived significantly less pain and had lower pulse rates than children in the control group receiving standard distraction (n=32). Moreover, also caregivers and nurses observed significantly lower pain and distress levels in children receiving VR. Furthermore, the duration of dressing changes was significantly reduced in the VR group, thus suggesting that VR distraction could promote clinical efficiency.\(^{121}\)

In another study, Guo and co-workers reported that VR significantly reduced pain levels in a group of adults with hand injuries (n=49) at the end of their wound dressing change with respect to the control group (n=49). Moreover, the sense of involvement in the VE was significantly correlated with pain levels\(^{122}\).

VR showed to be able to decrease pain ratings also in a case study of an adult patient with multiple blunt force trauma injuries undergoing physical therapy ROM exercises. Although case studies are
inconclusive by nature, this study further supported the use of VR as a distraction tool to control pain during physical therapy.\textsuperscript{123}

**Surgical procedures and pre- and post-surgical interventions**

Some clinical studies suggested that VR could be an adjunctive tool to alleviate pain and anxiety associated with surgical interventions. In particular, VR seemed to be useful during surgical procedures under local anesthesia, such as episiotomy repair\textsuperscript{124,125} and orthopedic surgery\textsuperscript{126}. Indeed, significant differences in pain and anxiety levels were observed during episiotomy repair between a group of primiparity women using VR (n=15) and a group receiving standard care (n=15)\textsuperscript{124,125}. Moreover, a trend towards a lower use of pharmacological sedation during orthopedic surgery was recorded in a group of adult patients receiving the VR intervention (n=9) with respect to a conventional care group (n=10), thus suggesting that VR could have a sedation sparing effect\textsuperscript{126}.

Recent studies explored VR utility in the preoperative period. In particular, in a single-blind, randomized controlled trial, using a between-subjects design, and involving 127 patients (mean age 55.3 years) undergoing cranial and spinal operations, VR proved to be useful in improving preoperative anxiety, stress, satisfaction, and preparedness compared with a standard preoperative experience\textsuperscript{127}. Similarly, in another randomized trial in children undergoing elective surgery under general anesthesia, a significantly lower preoperative anxiety and an increased compliance during anesthesia were observed in children subjected to a preoperative VR tour of the operating theatre (n=34) with respect to children receiving conventional information (n=35)\textsuperscript{128}. Another study evaluated the use of VR as an analgesic modality for anesthesiology procedures in adult male patients undergoing preoperative adductor canal catheter placement prior to elective total knee arthroplasty\textsuperscript{129}. Both a significant lower use of sedation and pain reduction were recorded in the group using VR (n=7) with respect to the non-VR group (n=7).

The ability of VR to reduce also postsurgical pain and distress was assessed in a 16-year-old patient with cerebral palsy undergoing multiple physical therapy sessions following single event
multi-level surgery\textsuperscript{130} and in 67 patients who had undergone cardiac surgery\textsuperscript{131}. The results of these studies suggest that VR could be able to reduce pain and distress after surgery. Moreover, interestingly, significant correlations among subjective evaluations and several physiological factors were also found\textsuperscript{131}.

\textit{Dental treatment}

Despite the achieved advances in dental treatment, many people avoid or delay care because of dental fear. Treatment delay can lead to increased dental problems requiring more invasive treatments, which, in turn, are associated to greater dental fear and anxiety\textsuperscript{132}. Given that analgesics, which are the mainstay of treatment for dental pain, are often ineffective\textsuperscript{133}, adjunctive non-pharmacological interventions, such as distraction, might be helpful in improving dental treatment experience, thus breaking the vicious cycle of dental fear.

Considering its greater attention-grabbing power and its ability to visually and acoustically isolate patients from the anxiety-inducing dental office and instruments, VR distraction has the potential to be a more effective tool in reducing pain and distress during dental procedures with respect to traditional form of distraction. Indeed, in some clinical studies VR proved to be able to reduce pain in both children\textsuperscript{134} and adults\textsuperscript{133, 135, 136} undergoing dental procedures and also showed to be more effective than a conventional form of distraction, i.e. watching a movie\textsuperscript{135, 136}. Moreover, VR was effective in reducing anxiety both in children\textsuperscript{134} and adults\textsuperscript{133} and also affected physiological variables, such as hearth rate, pulse rate, and blood pressure\textsuperscript{133, 136, 137}, whose changes could be indicative of pain and anxiety reductions.

A study on 69 adult participants using VR during a simulated dental treatment showed that this distraction intervention had not only immediate effects on the simulated aversive event but also reduced the memory vividness of this experience, as observed one week after the intervention, thus suggesting that VR might impact on the memory of an anxiety-inducing medical procedure\textsuperscript{138}.

Overall, these studies support the VR use as a distraction tool to decrease pain and anxiety during dental procedures. Future studies might reveal whether the reduction in pain and distress
during dental treatment eventually leads to increased frequency of dental visits of avoidant patients\textsuperscript{135}.

\textit{Urologic procedures}

In a recent randomized controlled trial assessing the possible efficacy of VR distraction in relieving pain and anxiety during flexible cystoscopy, no significant differences in the measured outcomes were observed between a group of adult men using VR (n=22) and the control group (n=23)\textsuperscript{139}. Conversely, VR was able to decrease pain and anxiety levels during another painful urologic procedure, the transurethral microwave thermotherapy, which is a minimally invasive technique for treating benign prostatic hypertrophy\textsuperscript{140}. However, these observations emerged from a case report on a 67-year-old man and therefore further studies on this topic are required.

\textit{Venipuncture}

Gold and co-workers evaluated the efficacy of the VR intervention in alleviating pain associated with intravenous (IV) placement required for magnetic resonance imaging or computed tomography scans. Twenty children were randomly assigned into a group using VR plus topical anesthesia or in a control group using topical anesthesia alone. Children in the control condition reported a significant four-fold increase in affective pain following IV placement, whereas children in the VR condition reported no significant change in affective pain between pre- and post-IV placement. Despite these promising results, however, no significant differences were observed between the treatment groups\textsuperscript{141}.

In a preliminary study by Gold and co-workers, VR intervention did not result in significant reduction in pediatric patients’ pain and anxiety during routine blood draws\textsuperscript{15}. However, in a recent randomized controlled trial by the same author, assessing VR utility during routine blood draw and involving 143 triads (patients aged 10-21 years, their caregiver, and the phlebotomist), VR proved to reduce significantly pain and anxiety compared with standard of care\textsuperscript{142}. This study used state-of-the-art VR technology, which likely contributed to the achievement of better results than those previously obtained. Similarly, in another recent study, involving 38 patients undergoing blow draw
in a pediatric nephrology clinic, a significantly lower pain and stress was observed in the group using a high-tech VR HMD (Oculus DK2) during venipuncture compared to the control group. In both these studies, associations between VR efficacy and patients’ individual characteristics were sought. Age, gender, and the number of previous blood draws did not significantly affect the analgesic and anxiolytic effects of VR. Conversely, the study by Gold et al. suggests that patients with high anxiety sensitivity, which was measured by the Childhood Anxiety Sensitivity Index (CASI), benefit more from the VR intervention.

Conclusions

In the last two decades VR has emerged as a valuable tool for different health care applications. In particular, VR has shown promise in many clinical trials assessing its possible use as a distraction intervention during painful and stressful medical procedures. VR proved to be especially effective in reducing procedural pain, even including the extreme pain associated with burn injury treatments. Moreover, VR was suggested to improve cancer patients’ emotional well-being and to decrease cancer-related symptoms in different settings, such as during chemotherapy. Importantly, only mild and infrequent side effects were observed and VR was well received by patients. Table 4 reports an overall summary of the application areas of VR as a supportive intervention during medical procedures and the main findings for each of these areas.

Despite these promising results, however, most studies involved a small number of patients, limiting the ability to generalize the observations. Also, almost all of the studies were unblinded and, therefore, at risk of bias. Given the nature of the VR intervention, conducting double-blind studies does not seem feasible. However, blinding of assessors is possible and needed to ensure unbiased outcome evaluation. Moreover, only a few studies have verified that the benefits of the VR intervention were not lost during repeated sessions. Future single-blind, randomized controlled trials, using a between-subjects design, and involving a greater number of patients undergoing repeated VR treatments are required to assess possible long-term benefits of the VR intervention.
Furthermore, although VR holds promise not only for the management of acute pain but also for that of chronic pain, research on VR use for persistent pain is still in its infancy and further studies are needed to develop and refine VR protocols for chronic pain management\textsuperscript{19}.

Moreover, more studies comparing VR efficacy with other forms of distraction and measuring physiological variables should be performed. Physiological changes might, in particular, provide objective confirmations of the subjective measures of pain and distress reductions.

Further studies are also required to establish predictive factors to select patients who are more likely to benefit from VR distraction and to design hardware/software systems tailored to the specific needs of different patients, taking also into account their age, gender, culture, and coping style.

Finally, future cost-benefit studies will clarify whether the VR potential to facilitate treatments and improve compliance might lead to health care cost reductions. Moreover, these studies will also serve to identify VR hardware/software configurations providing the greatest distraction at the lowest cost and encumbrance. Indeed, many of the studies included in this review used relatively low-tech VR systems compared to the new generation of VR systems now available, which are highly immersive, much less expensive, more portable, and easier to use. Therefore, VR is in the process of potentially becoming more effective at reducing pain and anxiety, and much more widely disseminated\textsuperscript{89}.

Acknowledgments

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Competing interests: The authors declare that they have no competing interests.
References


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<th>Reference</th>
<th>Patients</th>
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<th>VR equipment and content</th>
<th>Pain measures</th>
<th>Other outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffman et al., 2000 72</td>
<td>2</td>
<td>Case study, W-P study design; VR with standard analgesics vs. Nintendo video game with standard analgesics during two portions of the same WDC session (treatment order randomized and counterbalanced). Each treatment condition lasted 3 min.</td>
<td>A HMD, position sensors, a tactile augmentation system. Patients explored and interacted with the VE (SpiderWorld) by moving their head and “cyberhand” and clicking a mouse.</td>
<td>Patients reported lower pain scores for worst pain, average pain, pain unpleasantness, bothersomeness, and time spent thinking about pain (100 mm VASs) during VR than during the Nintendo video game.</td>
<td>Patients reported lower anxiety and higher sense of presence and perceived realism (100 mm VASs) during VR than during the Nintendo video game. No nausea was reported.</td>
</tr>
<tr>
<td>Hoffman et al., 2004 80</td>
<td>1</td>
<td>Case study; VR with standard analgesics vs. standard analgesics alone during two portions of the same WDC session in the hydrotank (treatment order randomized). Each treatment condition lasted 3 min.</td>
<td>A photonic, nonelectrical, water-friendly VR helmet. The patient explored and interacted with the VE (SnowWorld) by a joystick and heard sound effects.</td>
<td>VR treatment decreased the patient’s ratings for worst pain, pain unpleasantness, and time spent thinking about pain (10-point GRSs).</td>
<td>The patient rated fun during VR as 9 and without VR as 2. He rated his sense of presence in VR as 6 and the perceived realism as 7 (10-point GRSs). No nausea was reported.</td>
</tr>
<tr>
<td>Das et al., 2005 73</td>
<td>7</td>
<td>Single-blind, W-P study design; VR with routine analgesics vs. routine analgesics alone during two portions of the same WDC session (treatment order randomized).</td>
<td>A HMD with a motion tracking system to interact with the VE (based on the game Quake) by moving the head. A mouse was used as a trigger.</td>
<td>The average pain score (FPS in combination with 0-10 VAS) for VR plus analgesics were significantly lower with respect to the average pain score for analgesics alone.</td>
<td>Nurses and parents reported that VR was helpful in reducing pain and anxiety (open ended questions).</td>
</tr>
<tr>
<td>van Twillert et al., 2007 80</td>
<td>19</td>
<td>W-P study design; VR with standard analgesics vs. standard analgesics alone or analgesics plus another self-chosen distraction method during two different WDC sessions (one with VR and one without VR). VR intervention lasted for the entire duration of the WDC session (on average 19.2 min).</td>
<td>HMD with audio and motion tracking systems. Patients explored and interacted with the VE (SnowWorld) by moving their head and pressing the keyboard spacebar or a mouse button.</td>
<td>VR and television significantly reduced pain (VAT). The effect of VR was higher to that of television, but not statistically significant.</td>
<td>There was no significant reduction in anxiety (state-version of STAI). No side effects were reported. 63% of patients perceived a shorter WDC duration. A significant linear relationship between discrepancy in time perception and pain reduction was observed.</td>
</tr>
<tr>
<td>Chan et al., 2007 83</td>
<td>Mean</td>
<td>W-P study design; Children visualized a VR video game. VR condition lasted for (on average 19.2 min).</td>
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</table>

**Notes:**
- W-P: Within-Participants
- WDC: Virtual Distraction Condition
- VR: Virtual Reality
- HMD: Head-Mounted Display
- VAS: Visual Analog Scale
- GRS: Game Realism Scale
- STAI: State-Trait Anxiety Inventory
- FPS: Frames Per Second
- VAT: Visual Analogue Scale
<table>
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<tr>
<th>Year</th>
<th>Study Design</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>W-P study design; VR with standard analgesics vs. standard analgesics alone</td>
<td>VR plus standard analgesia vs. standard analgesia alone during two different WDC sessions (one with VR and one without VR, treatment order randomized). Treatment duration was 15-20 min.</td>
<td>graphic animation (ice-cream factory) on interactive glasses, were told a brief story about their role, and acted in the animation via a mouse.</td>
<td>Patients reported a significant reduction in mean pain ratings in all pain measures (worst pain, pain unpleasantness, and time spent thinking about pain) during VR. The other patient reported no reduction in worst pain, but reduction in the other two pain measures (10-point GRSs).</td>
</tr>
<tr>
<td>2008</td>
<td>Case study, W-P study design; VR with standard analgesics vs. standard analgesics alone during two portions of the same wound debridement session (treatment order randomized). Each treatment condition lasted 3 min.</td>
<td>VR goggles mounted on an articulated arm. Patients interacted with the VE (SnowWorld) using a computer mouse and heard sound effects.</td>
<td>The group receiving VR relaxation plus morphine reported significantly higher worst pain scores (10 cm VAS) compared with patients receiving morphine alone.</td>
<td>Both patients rated wound care during no VR as “no fun at all” and rated wound care as “no fun at all” during no VR but “pretty fun”/”extremely fun” during VR (GRS). They rated presence in the VE as either “moderate” or “strong.”</td>
</tr>
<tr>
<td>2009</td>
<td>B-S study design; patients were randomly assigned into two groups undergoing WDC: 1. treatment group (VR relaxation immediately prior to the WDC plus IV morphine) 2. control group (IV morphine alone).</td>
<td>Goggles fitted to the head and a disposable earpiece, both connected to a DVD player to visualize a VR relaxation sequence based on hypnotherapy theory.</td>
<td>The group receiving VR relaxation plus morphine reported significantly higher worst pain scores (10 cm VAS) compared with patients receiving morphine alone.</td>
<td>Self-administered morphine consumption and anxiety ratings (BSAR) were not significantly different between the two groups. Weak associations between hypnotic susceptibility (SHCS) and pain and anxiety ratings were revealed.</td>
</tr>
<tr>
<td>2011</td>
<td>Case study, W-P study design; VR plus IV ketamine vs. IV ketamine alone</td>
<td>VR goggles mounted on an articulated arm. Patients interacted with the VE</td>
<td>VR decreased the patients’ ratings for worst pain, pain unpleasantness, and time spent thinking about pain during VR.</td>
<td>No significant correlation was found between presence and pain.</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Sample</td>
<td>Design</td>
<td>VR Description</td>
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<td>Maani et al., 2011</td>
<td>12</td>
<td>20-27 M</td>
<td>W-P study design; VR with standard analgesics vs. standard analgesics alone during two portions of the same wound debridement session (treatment order randomized). Each treatment condition lasted approximately 6 min.</td>
<td>VR goggles mounted on an articulated arm. Patients interacted with the VE (SnowWorld) using a computer mouse and heard sound effects. VR was especially effective for patients with the highest ratings for worst pain.</td>
</tr>
<tr>
<td>Kipping et al., 2012</td>
<td>41</td>
<td>11–17 M/F</td>
<td>B-S study design; patients were randomly assigned into two groups undergoing WDC: 1. treatment group (VR plus standard analgesics) 2. control group (standard distraction plus standard analgesics). Length of treatment times ranged from 2 to 62 min for dressing removal and 2–58 min for dressing application.</td>
<td>A low-cost, off-the-shelf VR system (a HMD with headtracking, a joystick, and software games: Chicken Little for the 11–13 year olds and Need for Speed for the 14–17 year olds). Heart rate and oxygen saturation (pulse oximeter with a sensor on the patient’s finger or toe) did not significantly differ between the two groups. Nurses reported significantly lower rescue doses of Entonox given to patients receiving VR. Treatment duration and nausea (10 cm VAS) did not significantly differ between the two groups. The mean score for presence was 6.1 (10 cm VAS).</td>
</tr>
<tr>
<td>Faber et al., 2013</td>
<td>36</td>
<td>8-57 M/F</td>
<td>W-P study design; VR plus routine analgesics during one or more WDC sessions (up to seven days of WDC) vs. routine analgesics alone during a WDC session (baseline, Day 0).</td>
<td>A HMD with an integrated audio system and a motion tracking system; SnowWorld software. Compared to no VR baseline (Day 0), worst pain intensity ratings (VAT) during WDC were significantly lower when patients were subjected to VR on Days 1, 2 and 3. None of the patients reported side effects of VR intervention (e.g., nausea).</td>
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<tr>
<td>Jeffs et al., 2014</td>
<td>28</td>
<td>10-17 M/F</td>
<td>Single-blind, B-S study design; patients were randomly</td>
<td>A VR helmet mounted on an articulated-arm tripod. The VR group reported lower mean pain scores (0-100)</td>
</tr>
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</table>
assigned into three groups undergoing wound care: 1. VR during the entire procedure (5 to 100 minutes) 2. passive distraction (watching a movie) 3. standard care. APPT-WGRS compared with the passive distraction group (statistically significant difference) and with the standard care group (not statistically significant difference).

Table 1. Clinical studies using VR as a distraction treatment during burn wound care.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Age (Range)</th>
<th>Gender</th>
<th>Study Design</th>
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<th>Pain Measurement</th>
<th>Pain Reduction</th>
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<tr>
<td>McSherry et al., 2017</td>
<td>18*</td>
<td>20-73</td>
<td>M/F</td>
<td>W-P study design; VR plus standard analgesia vs. standard analgesia alone during two different WDC sessions (one with VR and one without VR, treatment order randomized). VR intervention lasted for the entire duration of the WDC session (on average 29.9 min).</td>
<td>VR goggles and earphones. Patients interacted with the VE (SnowWorld) using a computer mouse.</td>
<td>No significant differences in pain levels (0 to 10 VNS) were found between the VR and the no VR conditions.</td>
<td>VR significantly reduced the amount of opioid analgesics required to manage pain during WDC. No significant differences in anxiety levels (0 to 10 VNS) were found. More than 75% of participants found VR to be helpful (yes/no questions).</td>
</tr>
</tbody>
</table>

APPT-WGRS, Adolescent Pediatric Pain Tool word graphic rating scale; B-S, between-subjects; BSAR, burn specific anxiety rating; F, female; FLACC, Faces, Legs, Activity, Cry and Consolability pain assessment tool; FPS, Faces Pain Scale; GRS, graphic rating scale; HMD, head-mounted display; IV, intravenous; M, male; PQ, presence questionnaire; SHCS, Stanford hypnotic clinical scale; STAI, state-trait anxiety inventory scale; VAS, visual analogue scale; VAT, visual analogue thermometer; VE, virtual environment; VNS, verbal numeric scale; VR, virtual reality; WDC, wound dressing changes; W-P, within-patients. * This study included also 3 patients with non-burn wounds.

Table 1. Clinical studies using VR as a distraction treatment during burn wound care.
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<tbody>
<tr>
<td>Hoffman et al., 2000</td>
<td>12 19-47 M/F</td>
<td>W-P study design; VR with standard analgesics vs. standard analgesics alone during two portions of the same PT session (treatment order randomized and counterbalanced). Each treatment condition lasted 3 min.</td>
<td>A VR helmet, position sensors, a tactile augmentation system. Patients explored and interacted with the VE (SpiderWorld) by moving their head and “cyberhand”.</td>
<td>Mean ratings for worst pain, average pain, pain unpleasantness, bothersomeness, and time spent thinking about pain (100 mm VASs) were significantly lower during VR than in the no VR condition.</td>
<td>A nonsignificant trend towards reduced anxiety during VR vs. the no VR condition was observed (100 mm VAS). For 10 patients, the maximal ROM achieved after VR was greater than or equal to that achieved after the no VR condition (goniometry measurements). Mean ratings for nausea, presence, and perceived realism were approximately 0, 64 and 52, respectively (100 mm VASs).</td>
</tr>
<tr>
<td>Hoffman et al., 2001</td>
<td>1 32 M</td>
<td>Case study; VR with standard analgesics vs. analgesics alone during two portions of the same PT session. The patient participated to 5 trials (treatment order randomized and counterbalanced). Each treatment condition lasted 3-15 min.</td>
<td>A VR helmet, position sensors, a tactile augmentation system, sound effects. Patients explored and interacted with the VE (SpiderWorld) by moving their head and “cyberhand”.</td>
<td>Mean pain scores for worst pain, average pain, pain unpleasantness, bothersomeness, and time spent thinking about pain (100 mm VASs) were significantly lower during VR than during the no VR condition. Mean pain ratings were higher in the no VR condition than during VR for each of the five PT sessions.</td>
<td>Anxiety and nausea were nearly zero for each treatment (100 mm VASs). Presence and perceived realism were lower for the first VR treatment and increased on subsequent treatments (100 mm VASs). Maximal ROM achieved after VR was greater than or equal to that achieved after the no VR condition.</td>
</tr>
<tr>
<td>Hoffman et al., 2001</td>
<td>7 9-32 M/F</td>
<td>W-P study design; VR with standard analgesics vs. analgesics alone during two portions of the same PT session. Each patient participated to at least three sessions (treatment order randomized and counterbalanced). The mean treatment durations per condition were 3.5, 4.9, and 6.4 min for</td>
<td>A VR helmet, position sensors, sound effects. Patients explored and interacted with the VE by moving their head and “cyberhand” (SpiderWorld) or pressing the spacebar on a keyboard (SnowWorld).</td>
<td>Mean pain ratings for worst pain, average pain, pain unpleasantness, bothersomeness, and time spent thinking about pain (100 mm VASs) were significantly lower during VR than in the no VR condition. Pain reduction did not decrease over multiple sessions.</td>
<td>After the VR condition, patients reported a greater ROM (goniometry measurements). Mean scores for nausea, presence, and perceived realism varied in the multiple sessions between 2.7-&lt;1, 49-95, 51-95, respectively (100 mm VASs).</td>
</tr>
</tbody>
</table>

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Sharar et al., 2007 82

88 6-65 M/F W-P study design; VR plus standard analgesics vs. standard analgesics alone during PT. Treatment order randomized. Preliminary data from 3 ongoing, separate studies were pooled. Condition duration: 3-15 min.

A HMD, a head tracking system, sound effects. Patients explored and interacted with the VE (SnowWorld) by moving the head and pushing a keyboard button.

VR distraction significantly reduced pain ratings for worst pain intensity, pain unpleasantness, and time spent thinking about pain (0-100 GRSs).

Fun increased 4-fold with VR distraction. Nausea was infrequent (15%) and mild. Children reported higher levels of presence and perceived realism with respect to adults (0-100 GRSs).

Carrougher et al., 2009 87

39 21-57 M/F W-P study design; VR with standard analgesics vs. standard analgesics alone during PT on two consecutive days (VR one day and no VR the other day; order randomized). The mean treatment duration was 10 minutes per session.

A head-position-tracked VR helmet with stereophonic sound. Patients explored and interacted with the VE (SnowWorld) by moving the head and pressing the spacebar on a keyboard.

VR significantly reduced all pain measures (worst pain, time spent thinking about pain, and pain unpleasantness), with respect to the no VR condition (0-100 GRSs).

Average ROM improvement (goniometry measurements) was slightly greater with the VR condition, but without reaching statistical significance. Patients experienced little or no nausea during VR and the average ratings for realism and presence were approximately 26 and 35, respectively (0-100 GRSs).

Morris et al., 2010 88

11 23-54 M/F Single-blind, W-P study design; VR with standard analgesics vs. standard analgesics alone. Either VR or control condition were randomly assigned to each half of the same PT session, the median duration of which was 18 min.

A low-cost HMD. Patients interacted with the VE (Disney’s Chicken Little game) by a joystick.

Median pain score (NPRS) was lower in the VR condition than in the no VR condition. However, the difference was not statistically significant.

No significant difference in anxiety (BSPAS) was found between the VR and no VR conditions. No VR adverse effects were reported. No additional time was required for VR treatment.

Schmitt et al., 2011 39

54 6-19 M/F W-P study design; VR with standard analgesia/sedation vs. standard analgesia/sedation alone during two portions of the same PT for 1-5 days (treatment order randomized and counterbalanced). Each treatment condition lasted 3–10

A VR helmet, sensors to measure the head position, sound effects. Patients explored and interacted with the VE (SnowWorld) by moving their head and pressing a keyboard/mouse button.

On study day one, patients reported significantly lower ratings for worst pain, pain unpleasantness, and time spent thinking about pain (0-100 GRSs) during VR than in the no VR condition. These reductions were maintained with repeated VR use over

Fun ratings (0-100 GRSs) were significantly higher in VR condition than in no VR condition. This improvement was maintained over multiple days of therapy. Maximum ROM (goniometry measurements) was not different between treatment conditions.
<table>
<thead>
<tr>
<th>Study</th>
<th>Gender</th>
<th>Age</th>
<th>Presence and perceived realism (0-100 GRSs) remained constant through the 5 days of the study. 16% of subjects reported mild nausea (0-100 GRSs).</th>
</tr>
</thead>
</table>

Table 2. Clinical studies using VR as a distraction treatment for patients with burn injuries during physical/occupational therapy.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Study design</th>
<th>VR equipment and content</th>
<th>Measures of chemotherapy-related distress outcomes</th>
<th>VR side effects, feasibility, and distraction efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schneider and Workman, 1999&lt;sup&gt;114&lt;/sup&gt;, 2000&lt;sup&gt;115&lt;/sup&gt;</td>
<td>11</td>
<td>W-P study design. Three chemotherapy sessions with:</td>
<td>HMD, patients could choose from three possible commercial scenarios (Magic Carpet, Sherlock Holmes Mystery, and Seventh Guest) and were free to change scenarios at any time during treatment.</td>
<td>Significantly lower scores for symptom distress (SDS) were reported immediately after chemotherapy plus VR with respect to those reported after the sessions without VR. Moreover, symptom distress scores decreased significantly between pre- and post-treatment only during the chemotherapy session in which VR was used. There was no significant reduction in anxiety (STAI for children).</td>
<td>No differences in nausea or vomiting were reported (VASs). Three subjects experienced headache while using VR. VR was well received by patients, who indicated their willingness to use it again (open-ended questionnaire). The VR intervention was found easy to implement and required minimal nursing time.</td>
</tr>
<tr>
<td>Oyama et al., 2000&lt;sup&gt;116&lt;/sup&gt;</td>
<td>30</td>
<td>B-S study design; patients were randomly assigned into two groups undergoing chemotherapy:</td>
<td>A bedside three-screen liquid-crystal display, a 3D sound system, a unit to deliver a gentle breeze and scents, foot devices to control the image movement. Three VEs (lake, forest, and country town) were available.</td>
<td>Compared to the control group, VR significantly improved “tense” (subjective feeling questionnaire) in the first trial and anxiety, depression (HADS), emotional status (face scale), and physical fatigue (cancer fatigue scale) in the second trial. A significant decrease in emesis scores (VAS) 3–5 days after chemotherapy with VR was also reported.</td>
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<td>Schneider et al., 2003&lt;sup&gt;117&lt;/sup&gt;</td>
<td>16</td>
<td>W-P study design; VR vs. standard care during chemotherapy. Patients were randomly assigned to receive the VR intervention either during their first chemotherapy treatment or during their second chemotherapy</td>
<td>HMD, patients could choose from three possible commercial scenarios (Oceans Below, A World of Art, Titanic: Adventure Out of Time) and were free to change from three possible commercial scenarios (Magic Carpet, Sherlock Holmes Mystery, and Seventh Guest) and were free to change scenarios at any time during treatment.</td>
<td>A significant decrease in anxiety scores (SAI) and nonsignificant reductions in symptom distress (SDS) and fatigue (PFS) scores immediately after chemotherapy treatments with VR were reported.</td>
<td>Patients significantly underestimated VR treatment duration, experienced no cybersickness during the VR intervention, found VR easy to use, and indicated their willingness to use it again (open-ended questionnaire).</td>
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<td>Patients significantly underestimated VR treatment duration, experienced no cybersickness during the VR intervention, found VR easy to use, and indicated their willingness to use it again (open-ended questionnaire).</td>
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treatment. Measures were taken before treatment and immediately and 48-52 h after treatment. VR intervention lasted for the entire duration of the chemotherapy (on average 78 min). change scenarios at any time during treatment.

Schneider et al., 2004

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Intervention Duration</th>
<th>Patient Demographics</th>
<th>Cancer Types</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>W-P study design; VR vs. standard care during chemotherapy. Patients were randomly assigned to receive the VR intervention either during their first chemotherapy treatment or during their second chemotherapy treatment. Measures were taken before treatment and immediately and 48 h after treatment. VR intervention lasted for the entire duration of the chemotherapy (on average 67 min).</td>
<td>45-90 min</td>
<td>20 27-55 F</td>
<td>Breast cancer</td>
<td>Significant decreases in symptom distress (SDS) and fatigue (PFS) scores were found immediately following the chemotherapy treatment with VR. Mean anxiety (SAI) scores were lower after VR, but no significant differences were found. Patients significantly underestimated VR treatment duration, experienced no unusual sensation (such as dizziness, increased nausea, or visual disturbances) during the VR intervention, found VR easy to use, and indicated their willingness to use it again (open-ended questionnaire). The intervention required minimal nursing time.</td>
</tr>
</tbody>
</table>

HMD, patients could choose from three possible scenarios (deep sea diving, walking through an art museum, solving a mystery) and were free to change scenarios at any time during treatment.

Schneider and Hood, 2007

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Intervention Duration</th>
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<td>W-P study design; VR vs. standard care during chemotherapy. Patients were randomly assigned to receive the VR intervention either during their first chemotherapy treatment or during their second chemotherapy treatment. Measures were taken before treatment and immediately and 48 h after treatment. VR intervention lasted for the entire duration of the chemotherapy (45-90 min).</td>
<td>45-90 min</td>
<td>123 32-78 M/F</td>
<td>Breast, colon, and lung cancers</td>
<td>No significant reductions in symptom distress (ASDS-2), fatigue (PFS), and anxiety (SAI) scores after chemotherapy treatments with VR were reported. Among patients who received VR during their first chemotherapy session, the difference in anxiety scores between post-treatment and pretreatment was significant. Patients significantly underestimated VR treatment duration, experienced no cybersickness during the VR intervention, found VR easy to use, and indicated their willingness to use it again (open-ended questionnaire). Significant negative correlations between sense of presence (PQ) and both fatigue (PFS) and anxiety (SAI) were found.</td>
</tr>
</tbody>
</table>

HMD, patients could choose from four possible commercial scenarios (Oceans Below, A World of Art, Timelapse, Titanic: Adventure Out of Time) and were free to change scenarios at any time during treatment.

Schneider et al., 2011

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<tbody>
<tr>
<td>Secondary analysis of pooled data from three above described studies (Schneider et al., 2003; Schneider et al., 2004; 2007)</td>
<td>45-90 min</td>
<td>137 27-78 M/F</td>
<td>Breast, colon, and lung cancers</td>
<td>On average, breast cancer patients underestimated chemotherapy plus VR treatment duration by 23 min,</td>
</tr>
</tbody>
</table>
Table 3. Clinical studies using VR as a distraction treatment during chemotherapy in cancer patients.

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Details</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Schneider and Hood, 2007</td>
<td>Colon cancer patients by 12 min, and lung cancer patients showed minimal alteration in time perception (by &lt;4 min).</td>
</tr>
</tbody>
</table>
Table 4. Summary of findings from studies using VR during different medical procedures

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound care and physical therapy</td>
<td>Multiple studies showed that VR decreased pain during wound care and physical therapy in both adult and pediatric patients with burns and other traumatic injuries. There was equivocal evidence for the anxiolytic effect of VR.</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>The effect of VR on chemotherapy-related distress outcomes was analyzed in five trials on patients with different cancer types. All but one of these studies showed that the VR intervention could significantly improve at least one of the analyzed psychological variables (symptom distress, anxiety, and fatigue) in both adult and pediatric patients.</td>
</tr>
<tr>
<td>Surgical procedures and pre- and post-surgical interventions</td>
<td>Two studies suggested that VR was able to decrease pain and anxiety during surgical procedures under local anesthesia (episiotomy repair and orthopedic surgery) in adult patients. In three studies VR proved to be also useful during the preoperative period by reducing anxiety in both adult and pediatric patients and reducing pain during an anesthesiology procedure in adults. Other two studies suggested that VR could also reduce postsurgical pain and distress.</td>
</tr>
<tr>
<td>Dental treatment</td>
<td>VR ability to reduce pain and anxiety both in children and adults during dental treatment was shown in four studies.</td>
</tr>
<tr>
<td>Urologic procedures</td>
<td>In a randomized controlled trial, VR was ineffective in relieving pain and anxiety during flexible cystoscopy. Conversely, VR was able to decrease pain and anxiety during transurethral microwave thermotherapy in a case study.</td>
</tr>
<tr>
<td>Venipuncture</td>
<td>VR significantly reduced pain and distress in two out of three studies on pediatric patients undergoing venipuncture procedures.</td>
</tr>
</tbody>
</table>