BABEŞ-BOLYAI UNIVERSITY

FACULTY OF PSYCHOLOGY AND EDUCATIONAL SCIENCES

DOCTORAL SCHOOL "EVIDENCE-BASED PSYCHOLOGICAL ASSESSMENT AND INTERVENTIONS"

Ph.D. THESIS

IS PAIN MANAGEMENT READY FOR THE NEW INTERVENTIONS? A CRITICAL ANALYSIS OF THE PSYCHOLOGICAL STRATEGIES -SUMMARY-

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CLUJ-NAPOCA 2020

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CHAPTER I. THEORETICAL BACKGROUND

1.1. Introduction and Research Problem

1.1.1. Understanding pain

Currently pain symptoms are the most frequent reason why people address to physicians (Gregory & McGowan, 2016). Consequently, an enormous effort has been put in the understanding of the factors which are triggering and maintain pain symptoms. However, in the process of pain understanding is important to acknowledge that what pain means today is considerably broader, as compared with what was valued before. Specifically, early theories of pain valued the cartesian concept of pain as a simple sensory stimulus response model. According to this concept, pain was described as an immediate response to the degree of bodily injury resulting from a negative sensory stimulus. However, new models of pain ratify that pain and pain experience are far more complicated (Koyama et al., 2005). It was described that pain experience depends on the influence of individual and external factors which could have both beneficial and detrimental effects (Hansen & Streltzer, 2005; Świeboda et al., 2013). At the same time,it was described that although every human experience pain during his lifetime, it is not a universal experience impacting the whole population, but rather a divisive and unique private phenomenon (Skevington, 1995).

In this vein, Melzack claims that "Pain is whatever the experiencing person says it is, existing whenever he says it does" (R. Melzack, 1983, p. 71). This perspective of pain is also empathized by the International Association for the Study of Pain (IASP) which states that biological, psychological and social factors influence pain in different degrees. Additionally, the IASP, distinguishes between two different phenomena: pain experience and nociception[1]. Specifically, IASP describe pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey, 1979; Treede, 2018). Consequently, rather than a purely physiological phenomenon, pain is curently regarded as a psychological phenomenon. Thus, the newer appouches of pain understanding describe that pain reflects a perceptive process related to consciousness, selective abstraction, meaning assignment, assessments, and learning (Apkarian, 2018). In addition, in order to be perceived, pain demands attention (C. Eccleston & Crombez, 1999) respectively have emotional and motivational componets (Becker et al., 2018; Ronald Melzack & Wall, 1965).

To better understand this phenomen, lets consider that one unintentionally hits his/her foot in the door. In this context, the process of pain experience tipically starts with nociception (i.e., detection of noxious stimuli) that affects healthy tissues. Subsequently, through

[1] The process of nociception refers to the neurophysiological treatment of occurrences that cause nociceptors and can be experienced as pain (Turk & Melzack, 2011). The analysis of the nociceptive system and brain processing have always been the biological substrates of experienced pain.

transduction (i.e., a process which transforms the physical/mechanical, chemical and thermal stimuli into electric impulses), the information is transmitted to our peripheral nervous system. The impulses are then carried to the spinal cord through ion-gated channels, and then to the brain. When information is reached by the brain are modulated by descending chemical and neural mediators[2] and further perceived as pain (Hurley et al., 2014). Specifically in the brain, the information received activates a series of bain areas such as the anterior cingulate cortex (ACC), primary and secondary somatosensory cortex (Greenspan et al., 1999; Ploner et al., 1999), insula, amygdala (Baliki et al., 2010; Becerra et al., 2001) prefrontal cortex, thalamus (Apkarian et al., 2005), and cerebellum (Moulton et al., 2010). So far, the ACC, insula, and amygdala are recognized as the brain regions responsible for the *affective and cognitive processing of pain*, while the primary and secondary somatosensory cortex are considered to be responsible for the processing of the *sensory components of pain* - such as location and duration (Fuchs et al., 2014). Thus, when we smash our foot in the door, the pain occurrence is not linear, and along with the physiological pathway, the pain perception is modulated by our emotions and beliefs regarding the situation. In fact, what makes that pain (under the form of an electric impulse) to be interpreted as unpleasant and have qualities as intensity and tolerance are the processes of the ACC (Fuchs et al., 2014).

In addition, specifically related to the ACC contributions on pain perception, previous studies found that different cognitive processes, such as negative expectations can increase pain even after the treatment is administrated (i.e., opioids) (Bingel et al., 2011). Similarly, other studies emphasizing the importance of emotional state prove that negative emotions are associated with increased levels of pain whereas positive emotions with lower levels of pain (Villemure & Bushnell, 2009). Moreover, through ACC processes we can understand why in some contexts (e.g., phantom pain) we experience pain in the absence of a nociceptive stimulus or in other insatances we are able to postpone[3] the occurrence of perceived pain (De Ridder et al., 2011; Willoch et al., 2000).

Taken together, these evidences emphasize the multidimensionality of pain experience by acknowledging the biological, psychological and social factors in the perception of pain. Moreover, theese evidences bind us to understand that pain experience is more than a nociceptive process - as it was previously regarded.

1.1.2 Theoretical Foundation and Research Problem

Described as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey, 1979; Treede, 2018) pain is a clinical, economic and social major issue throughout all ages, with monthly prevalence estimates ranging from 1% to more than 60% (Henschke et al., 2015). In addition,

[2] Literature state that there are different pathways of the pain signals to the brain and there is not a straightforward line between the peripheral nociceptive inputs and the final cortical representation.
[3] Studies on soldiers shows that when in battle, they report little aches while having massive fractures on limbs (Beecher, 1956; Horstman & Flax, 1999)

pain conditions show up to have the largest negative impact on people's lives relative to any other health problem and to add the most to disability (Kyu et al., 2018). The effect of pain on the economy in Europe is tremendous, with an estimated total pain cost up to 3 % of GDP (Phillips, 2006), higher than the cost spent to treating any other type of diseases (Liedgens et al., 2016). Similarly, the overall cost of pain in the United States exceeds the cost of treatments for cancer or heart disease (Gaskin & Richard, 2012).

The status of pain theories is mature, explaining the occurrence of pain whether it is acute or chronic. In addition, current pain theories (i.e., The Gate Control Theory, Neuromatrix Theory of Pain) explain the individualized influence of biological, psychological and sociological factors, as well as the interaction between them, in the occurrence and maintaining of pain (see (R. Melzack, 1999; Ronald Melzack & Wall, 1965).

However, the research data are mixed regarding the efficacy of the interventions in pain treatment. In this sense, the field recognized the pharmacological interventions as the most used form of treatment, with modest efficacy (Finnerup et al., 2015) with an large array of side effects as a consequence of the opioids usage (Aronson, 2009) and associated with opioids crises (Kolodny et al., 2015; Vadivelu et al., 2018). Consequently new interventions were proposed, respectively, protocols that combine opioids with nonsteroidal anti-inflammatory drugs and the multi-modal interventions as a combination of pharmacological and psychological interventions (Manchikanti et al., 2017). These multi-modal interventions proved to be more efficient then pharmacological strategy alone (Markozannes et al., 2017). Thus, it has been proposed that psychological interventions could be the answer need it to end the opioid crisis overdose (Majeed et al., 2019; Meldrum, 2016).

Still, a closer examination at the psychological interventions, such as Cognitive Behavioral Therapy (CBT) leads the pain sufferers to a large array of options with different degrees of evidence regarding their efficacy (Ebert & Kerns, 2010). For instance, under the umbrella concept of CBT, different authors discuss the efficacy of the interventions based on classical CBT, such as Rational Evaluative Behavioral Therapy (REBT) interventions or interventions based on new perspectives, such as Aceptance and Commitment Therapy (ACT) interventions. Although there exist numerous studies assessing the efficacy of these psychological interventions compared with standard treatments (usually pharmacological treatment alone), comparisons between these two approaches are scarcity investigated; this is especially true for some outcomes, such as pain intensity or tolerance (as an important factor in improved everyday functionality at patients with chronic pain). Consequently, for a certain pain sufferer is confusing and misleading which psychological approach works better and for whom.

Moreover, among the non-pharmacological interventions, pain literature discusses the efficacy of different strategies used alone, not part a larger CBT protocol. In the field are disputed the efficacy of certain strategies such as distraction, relaxation, hypnosis and biofeedback (Dobbin et al., 2013; Haase et al., 2005; Johnson, 2005; Montgomery et al., 2000). Importantly, these techniques are presented to be delivered in classical formats or new formats, such as through Virtual Reality (VR). While for the classical format, meta analytical studies confirmed that these strategies have positive effect in reducing pain and distress with medium

effect sizes, for the new format the existent meta-analysis address only the effect on pain intensity. By precluding analyses estimating the efficacy of distress limit the reader's understanding concerning the overall efficacy of these VR based strategies. Consequently, the analyses of the adjuvant effect of non-pharmacological intervention and especially of the VR-based interventions is need it. These analyses are even important as a simulation of economic burden among hospitalized patients shows that for each patient $5,39 (95% CI -$11.00 - $156.17) can be saved when are treated with a VR-based intervention compared with standard treatment. Importantly, this analysis was invariant across opioids usage, highlighting even further the potential cost-saving (Delshad, Almario, Fuller, Luong, & Spiegel, 2018).

CHAPTER II. RESEARCH OBJECTIVES AND OVERALL METHODOLOGY

The aims of the present thesis were bi-folded. On the one hand, we were interested in improving the pain methodology by employing analyses that advance the understanding regarding the quality of instruments that assess pain outcomes. Respectively, on the other side by using a critical perspective we were interested to evaluate the efficacy of the psychological strategies in alleviating pain. In this matter, more specifically, we were interested in assessing the efficacy and the effectiveness of the newer strategies compared with the standard treatment in pain as in the last two decades new psychological approaches were proposed.

Thus, the first major objective of the present thesis was to quantify the efficacy of VR-based intervention compared with control conditions (standard treatments or active controls). To do this, in the first study we conducted a quantitative meta-analysis of 27 studies, assessing the efficacy of VR based interventions in reducing pain intensity as well as the affective and cognitive components of pain during painful episodes or immediately after. In addition, we analyzed the evidence for small-study effects and assessed the quality of the included studies.

Next, given that pain catastrophizing is one of the most prominent cognitive factors in the etiopathology of pain, in the second study we aimed to investigate the psychometric properties of Pain Catastrophizing Scale (PCS) in a Romanian sample. Specifically, we tested the measurement invariance across difference samples (i.e., persistent and chronic headaches suffer) and the construct validity upholding the scale factor structure.

The third major goal of this thesis was to evaluate the efficacy of cognitive restructuring techniques as compared with acceptance and distraction strategies in decreasing pain intensity and increasing tolerance. Moreover, in the third study we were interested to evaluate the effect of these strategies on pain immediately after the strategies were presented and after one week of practice as the pain tolerance is an important factor in the treatment of chronic pain.

Our last objective was to assess the efficacy of a VR-based intervention in a sample of acute pain suffers. To do this, we employed a prospective, randomized controlled Phase II trial to assess pain outcomes of a VR-based intervention as an adjuvant to pharmacological treatment compared with treatment as usual in patients following surgeries under general anesthesia. In addition, we were interested in assessing the adverse effects and satisfaction with the VR intervention.

In sum, the structure of this thesis, as presented in Figure 1 had as a theoretical objective to quantify the effectiveness of VR based interventions for pain (Study 1). As a methodological objective, we were interested in validating the Pain Catastrophizing scale on Romanian population and, as a practical objective, we were interested in evaluating the efficacy of new psychological strategies on treating pain as compared to the classical approaches (Study 3 and Study 4).

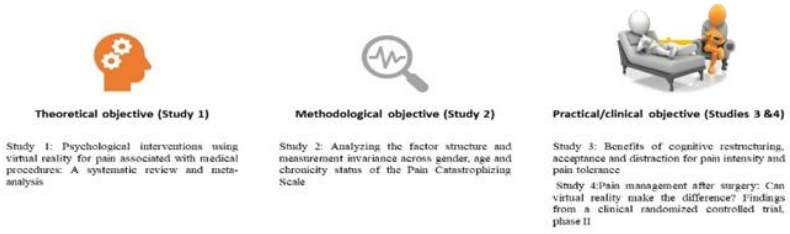


Figure 1. Overview of the thesis objectives and studies

CHAPTER III. ORIGINAL RESEARCH

3.1. STUDY 1: PSYCHOLOGICAL INTERVENTIONS USING VIRTUAL REALITY FOR PAIN ASSOCIATED WITH MEDICAL PROCEDURES: A SYSTEMATIC REVIEW AND META-ANALYSIS[4]

3.1.1. Introduction

Acute pain is an often unavoidable side-effect of medical procedures, such as treatment for burns (Norman & Judkins, 2004; Tsirigotou, 1993), cancer (van den Beuken-van Everdingen et al., 2016), dental (Costa et al., 2012; Pak & White, 2011), surgery (Sommer et al., 2008), or intensive care procedures (Barr et al., 2013). Inappropriate management of acute pain is accompanied by protracted hospitalization (E. Y. Chan et al., 2013), short-and long-term costs (Torrati et al., 2000) and represents a risk factor for developing chronic or persistent pain (Breivik et al., 2013; Turk & Okifuji, 2002).

Psychological interventions for acute pain management, such as relaxation (K. Seers & Carroll, 1998) or distraction (Kleiber & Harper, 1999) attempt to disrupt the process of allocating attentional resources to pain. However, not all patients are equally capable of making use of these techniques and effectively regulating their attention (K. Seers & Carroll, 1998), particularly in situations of increased pain salience and in the absence of goal directed motivation (Verhoeven et al., 2010).

Virtual reality (VR) technology is a promising development for enhancing the effectiveness of traditional interventions, such as distraction or relaxation, for acute pain. An immersive (Brooks, 1999) and multi-sensorial experience (Gallace et al., 2012), achieved through a combination of technologies (i.e., head-mounted displays, vibro-tactile gloves, individualized sounds, and gesture-sensing joysticks), along with the possibility of active exploration could facilitate the shift of attention away from the painful stimuli or the experience of pain, aiding effective distraction and reshaped pain perception (Gold et al., 2007; Piskorz & Czub, 2014). The technology could be effectively exported in medical care settings (Li et al., 2017) as a potentially cost-effective tool (Malloy & Milling, 2010), particularly since recent user-friendly developments (e.g., smaller headsets, intuitive controllers) do not require special training and could easily be used by medical providers (e.g., nurses).

Single trials of VR-based interventions for acute pain are accruing, with both encouraging (Gold & Mahrer, 2018; Schmitt et al., 2011) and mixed results (Walker et al., 2014; Wint et al., 2002). One meta-analysis (Scheffler et al., 2017) of non-pharmacological treatments in general for adults undergoing burn care reported large effects for distraction interventions, particularly when these used VR, but the number of studies in this subgroup was small and outcomes of pain intensity, affective and cognitive components were combined.

[4] This study has been published: Georgescu, R., Fodor, L. A., Dobrean, A., & Cristea, I. A. (2019). Psychological interventions using virtual reality for pain associated with medical procedures: a systematic review and meta-analysis. Psychological medicine, 1-13.

Another meta-analysis (E. Chan et al., 2018) examined VR-based treatments for painful clinical interventions and reported a moderate ES of 0.49 for maximum self-rated pain. Yet several clinically and theoretically important aspects were not investigated. Trials often also include additional measures of pain intensity (e.g., pain threshold), as well other pain-related outcomes (e.g., distress) and involve other assessors beside self-report. Moreover, the timepoint of pain assessment is subject to a clinically important distinction, between real-time assessments "during", and retrospective evaluations "after ", medical procedures. Comparisons between VR and other active treatments were not examined, though these could indicate whether observed effects are specific to VR or rather attributable to non-specific factors like novelty. Several potential moderators of clinical or theoretical importance were not examined. VR-enhanced interventions might be particularly effective for young participants, less able to engage in standard distraction. An important theoretical question is whether VR enhances the effectiveness of regular distraction. Possible moderating effects could result from concomitant analgesic use or the type of VR system employed. Finally, possible publication bias, as well potential adverse effects were not previously reported.

Hence, our goal was to assess the efficacy and safety of VR-based psychological interventions for pain associated to medical procedures, expanding on the issues identified above.

3.1.2 Method

Data Sources and Searches

We searched the National Library of Medicine via PubMed, Embase, PsycInfo and Cochrane Library databases in June 2018, using the following keywords: "virtual reality", "game", "interface", "immersion", "virtual reality exposure therapy", "pain", "burn", "wound", and "injuries". We also searched the references of narrative and systematic previous reviews.

Study Selection

Eligible studies were: (1) randomized controlled trials (RCTs), in (2) patients of any age undergoing a painful procedure delivered in a medical setting comparing (3) a VR-based psychological intervention (4) with treatment as usual, (e.g., analgesics alone, standard distraction) or an active comparator devised by investigators (psychological, pharmacological), (5) reporting any pain outcomes, (6) published in peer-reviewed journals. VR interventions could be stand-alone or combined with another intervention (e.g. pain medication), provided the same ancillary intervention was also administered to the control group. Both crossover and parallel designs were eligible. No language restrictions were used.We excluded the dissertations and conferences abstracts. For multiple reports of the same trial, we used the most complete one.

Data extraction

The primary outcome of interest was pain intensity (i.e., mean pain intensity, pain threshold and worst pain), measured by Visual Analogue Scale (VAS) or other clinical rating scales (e.g. Graphical Rating Scale/GRS, Faces Pain Scale), assessed real-time (i.e., during the medical procedure) or retrospectively (i.e., after the procedure). For outcomes assessed by more

observers (e.g., child, parent, nurse), we extracted data for each. Secondary outcomes were cognitive (e.g., time spent thinking about pain and worry), and affective components of pain (e.g., pain unpleasantness, anxiety and distress) as assessed by VAS, GRS or other clinical rating scales (e.g., Symptom Distress Scale; Face, Leg, Activity, Cry, Consolability Scale).

For each included trial, we extracted information about: (a) study design (i.e., parallel, crossover); (b) medical procedure (e.g., dressing change, physical therapy); (c) condition requiring medical procedure (e.g., burn, cancer, dental treatment); (d) age group (i.e., children, adults or mixed); (e) recruitment (i.e., clinical, community); (f) VR-based intervention (e.g., distraction, psycho-education); (g) TAU or active comparator condition; (h) numbers of patients randomized in the treatment groups; (i) number of sessions; (j) concomitant analgesic use, and, if present the class of drugs (e.g., opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), local); (k) VR system (e.g., head-mounted display/HMD, video glasses) and the number of interactive components (e.g., visual feedback, sound, navigation); (l) assessment of presence and immersion, if present; (m) adverse effects associated with VR; (n) number of drop-outs in the treatment groups; (p) VR program developer trial investigator (yes/no); (o) country of provenience.

Risk of bias (Rob) assessment

RoB was assessed with the revised Cochrane Collaboration tool (J.P.T. Higgins et al., 2016), separately for parallel and crossover designs, using templates with incorporated decision algorithms (*available at:* http://www.riskofbias.info/welcome/rob-2-0-tool). We evaluated sources of bias in five domains: (a) the adequate generation of the allocation sequence, (b) deviations from intended interventions (including blinding of participants and research personnel), (c) handling of incomplete outcome data, (d) measurement of the outcome (blinding of outcome assessors) and (d) selection of the reported results.

Data Synthesis and Analysis

Meta-analyses

We used the software packages Comprehensive Meta-Analysis (CMA v. 2.2.064) for computing study-level effect estimates and Stata SE 14.0 (STATA Corp., Inc., College Station, TX) packages *Admetan* (D. Fisher, 2019; D. J. Fisher, 2015) for pooling, *Metabias* (Harbord et al., 2009) for testing small study effects and *Confunnel* (Palmer et al., 2008) for visualization. Effect sizes (ESs) were calculated as standardized mean difference (SMD) for each comparison, transformed in the adjusted Hedges' *g* (Hedges & Olkin, 1985) to correct for the small sample size of most studies. In parallel designs, SMDs represent the difference between the means of the VR and the control group at each timepoint (real-time, retrospective), divided by the pooled standard deviations of the two groups, with positive values indicating superiority of VR-based interventions. When means and standard deviations were not reported, we computed the SMD from alternative statistics (Borenstein et al., 2009), such as *t* values or *p* values from independent group comparisons at the time-point of interest, and sample sizes.

In crossover designs, we primarily relied on individual participant means in each period and derived SMDs by computing within-participant mean differences, corresponding standard errors (SEs) for the differences, and the correlation between intervention and control

(Elbourne et al., 2002). When individual participants means were not available, we computed the SMD from the within-subject mean differences, SD of differences and sample size, paired-sample *t* values or *p* values (Borenstein et al., 2009; Elbourne et al., 2002).

In the case of multiple VR intervention groups, we computed and averaged separate ESs for each comparison with a control group. If an outcome (e.g., pain intensity) was assessed by more observers (e.g., self-report, others), we computed ESs both separately and across all assessors. To facilitate the clinical interpretation, we also report absolute benefits as numbers-needed-to-be treated (NNT), the number of patients that have to be treated in order to generate one additional positive outcome (Laupacis et al., 1988), computed with the Kraemer and Kupfer formula (Kraemer & Kupfer, 2006).

We aggregated individual ESs separately for: pain intensity as sensory component of pain measured real-time and, respectively, retrospectively; time spent thinking about pain and worry as cognitive components of pain; and pain unpleasantness, anxiety, distress as affective components of pain. Comparisons against TAU or other active competitors were aggregated separately.

We pooled studies with a random-effect model. Based on previous systematic reviews and the particularities of the population and setting, we expected most studies to use small samples. Therefore, we used the Paule and Mandel estimator (Paule & Mandel, 1982) for between-study variance (τ^2), as recommended by a recent review of estimation methods (Veroniki et al., 2016). We also applied the Hartung-Knapp-Sidik-Jonkman (HKSJ) variance correction (Hartung & Knapp, 2001; Sidik & Jonkman, 2002), with truncation of correction factor at 1, recommended for random-effects meta-analysis with few studies (Röver et al., 2015). We evaluated statistical heterogeneity with the I^2 statistic, which shows the percentage of total variation across studies due to heterogeneity. We used the Q-profile (QP) method for constructing the confidence intervals around heterogeneity estimates, shown to be adequate in terms of coverage probabilities even in small samples (Viechtbauer, 2007). We also report predictive intervals (PI) (Julian P T Higgins et al., 2009), as the confidence interval of the approximate predictive distribution of future trial, considering heterogeneity.

Sensitivity and subgroup analyses

As we expected high heterogeneity and few studies with low RoB across domains, we computed two additional meta-analysis models: the Henmi-Copas approximate exact distribution, which produces a confidence interval for the pooled effect robust to publication bias (Henmi & Copas, 2010), and the Quality Effects model, which integrates study quality into pooled estimate, favoring (i.e., assigns larger weights) both larger and better trials (Doi et al., 2015). We used the overall RoB score as a proxy for study quality.

We also conducted sensitivity analyses: i) excluding outliers (no overlap between the 95% CIs of the pooled ES with those of single trials); ii) excluding trials using the new technology MMD; iii) excluding comparisons where the control group received no treatment; iv) for burns dressing change; v) for children participants; vi) separately for outcome assessors (self-report, other-reports); vii) separately by design (parallel, crossover); viii) for trials with at

least 20 participants randomized/arm; ix) excluding trials characterized by their authors as pilot or feasibility studies.

Small study effects and publication bias

We visually examined funnel plot asymmetry and constructed contour enhanced funnel plots (Peters et al., 2008), with contour lines indicating regions where the test of treatment effects was significant for various statistical significance levels. For comparisons with at least 10 ESs, we also conducted Eggers` test of the intercept (Egger et al., 1997). We also addressed publication bias in sensitivity analysis with the Henmi-Copas estimate.

3.1.3 Results

Study selection (Figure 2)

We identified 3381 records and screened 1943 after the removal of duplicates. We retrieved full-texts of 68 reports and further selected a total of 36 RCTs for inclusion. Figure 1 represents the flowchart of the inclusion process following the PRISMA guidelines (Moher et al., 2009). For 12 RCTs, data was insufficient for ES calculation and authors were contacted, with a second reminder if necessary. Data for ES calculation were retrieved in 3/12 cases (Bentsen et al., 2001; Maani et al., 2011; Schmitt et al., 2011). In total, 27 included trials had sufficient information for ES calculation, and were included in the meta-analysis.

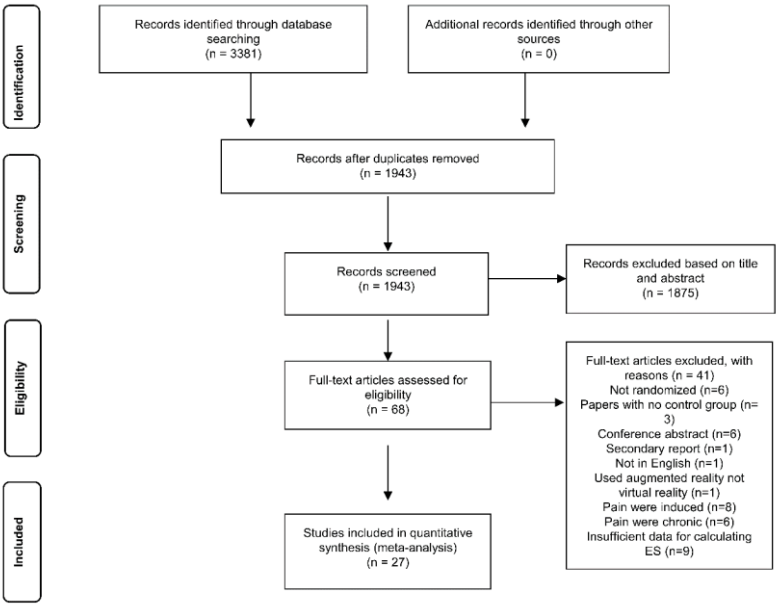


Figure 2. PRISMA flow-diagram of the study selection process

Characteristics of included studies (Table 1)

1452 patients were treated (659 with VR-based interventions and 793 with TAU or another active intervention). The average number of randomized participants in the VR arm was 25, and the average number of drop-outs was less than 1. Five trials had 10 or fewer participants per arm. Fourteen trials had parallel design and thirteen had crossover design (AB|BA format). Most trials were focused on burns, for new or chronic wounds, either for dressing change (12), or physical therapy (5), with Total Burn Surface Area (TBSA) ranging from 1% to 15%. Five studies were conducted for pain and distress related to needle procedures (e.g. during intravenous (IV) port access placement or phlebotomy), two with dental treatment and another two with chemotherapy. Most participants were recruited from clinical settings (26). Thirteen studies targeted children and youth, ten, adults and four, mixed samples. All but one of the VR-based interventions used distraction. Twenty-seven trials had a TAU comparison: no treatment (5), analgesics alone (16), distraction (2), analgesics plus distraction (4). Additionally, four trials also included an active comparator arm, designed for the purpose of the trial (e.g., external cold and vibration group (Gerçeker et al., 2018) or video game group (Gershon et al., 2004). Interventions ranged from one to five sessions and were all conducted individually. In eighteen studies, all participants received concomitant analgesics, most frequently Oxycodone opioids. The most used VR system was HMD (15), followed by video glasses (8) and MMD (3). The VR developer was also an investigator in twelve trials.

Risk of bias in the included studies (Figure 3)

Most of the included studies were rated as having some concerns or high risk of bias for both parallel and crossover (marked with * in *Figure S1*) designs. Random sequence generation was rated as some concerns in 13 trials and high risk in 8 trials. For deviations from intended interventions, 13 studies were rated as some concerns, and 8 studies as high risk. All studies were rated as low risk for missing outcome data. All studies used self-report measures. For bias due to selective reporting, based on the trial report and available protocols, 6 trials were rated at high risk and 21 as having some concerns. Only 3 trials were registered (Brown et al., 2014; JahaniShoorab et al., 2015; Schmitt et al., 2011), all retrospectively. Only two trials (Jeffs et al., 2014; Miller et al., 2011) could be rated as low RoB on at least 3 domains.

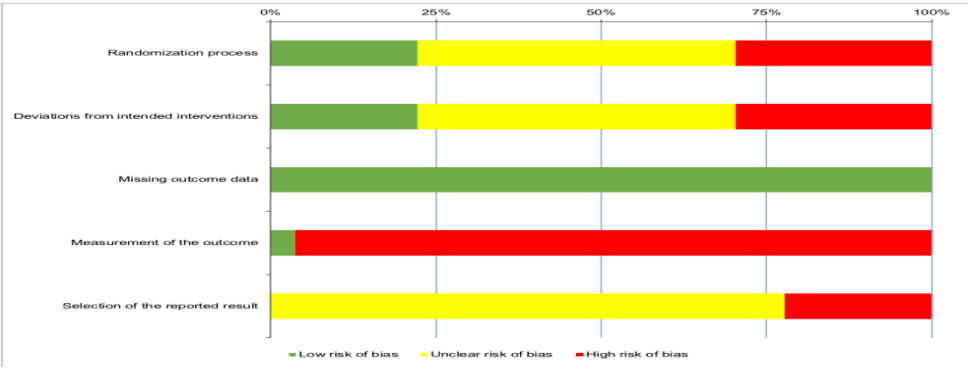


Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

VR-based interventions versus TAU (Table 1)

Pain intensity (primary outcome)

Real-time

Nine RCTs (7 parallel) resulted into a Hedges' *g* of 0.95 (95% CI 0.32 to 1.57), NNT= 2.00, with high heterogeneity (I^2 = 86%; 95% CI 65 to 96). Sensitivity analyses indicated smaller effects with the Henmi-Copas model, *g*= 0.77, 95% CI 0.22 to 1.33, and larger with the Quality Effects model, *g*= 1.13, 95% CI 0.66 to 1.60, with heterogeneity remaining high (I^2 = 79%). The effect was reduced in a sensitivity analysis excluding outliers (n= 1), *g*= 0.74 (95% CI 0.25 to 1.24), I^2 = 74% (95% CI 20 to 94) and when only self-report was considered (n= 5), *g*= 0.65 (95% CI 0.32 to 0.98), I^2 =0 % (95% CI 0 to 82). Analyses restricted to children participants, for burns' dressing change, or in parallel designs yielded similar estimations. Six trials with 20 or more participants randomized per arm resulted into a similarly large *g* of 1.11 (95% CI 0.07 to 2.15), I^2= 90% (95% CI 72 to 98). Owing to the high heterogeneity, all PIs, except for self-reported pain, included 0.

Retrospective

Twenty-two trials resulted into a pooled ES of *g*= 0.87 (95% CI 0.54 to 1.21), NNT= 2.16 with very high heterogeneity, I^2 = 89% (95% CI 78 to 95). Effects were smaller with the Henmi-Copas, *g*= 0.69, 95% CI 0.36 to 1.01, and similar with the Quality Effects models, *g*= 0.89, 95% CI 0.61 to 1.16, with heterogeneity remaining high (I^2 = 82%).

Sensitivity analyses showed decreased ESs with the exclusion of potential outliers (n= 4), *g*= 0.66 (95% CI 0.46 to 0.85), I^2 = 53% (95% CI 8 to 81), of MMD trials (n= 3), *g*= 0.77 (95% CI 0.51 to 1.02), I^2 = 78% (95% CI 60 to 90), or of trials with a no intervention control (n= 4), *g*= 0.77 (95% CI 0.41 to 1.14), I^2 = 87% (95% 68 to 95). Effects were also considerably smaller across crossover trials (n= 11), *g*= 0.61 (95% CI 0.34 to 0.88), I^2 = 57% (95% CI 1 to 89). Pain was self-reported in all but two trials. Analyses restricted to burns dressing change (n=11), *g*=1.03 (95% CI 0.37 to 1.68), I^2 = 91% (95% 78 to 97) or in parallel designs (n= 11), *g*=1.08 (95% CI 0.46 to 1.70), I^2 = 92% (95% CI 82 to 98) led to slightly higher effects. Effects were similar for children participants (n=11), *g*=0.87 (95% CI 0.17 to 1.57), I^2 = 94% (95% 85 to 98), or in trials with at least 20 randomized participants per arm (n= 14), *g*=0.97 (95% CI 0.44 to 1.51), I^2 = 94% (95% CI 87 to 98). All PIs except for the analysis without outliers included 0.

Table 1. VR-based interventions compared with treatment as usual (TAU)

	N	g^a	95% CI	I^2	I^2 95% CI	Predictive interval 95% CI	NNT
Sensory component of pain (pain intensity) measured							
					65 to 96	-0.93 to 2.82	2.00
Real-time (all assessors)	9	0.95	0.32 to 1.57	86			
Henmi-Copas	9	0.77	0.22 to 1.33	79	65 to 96	N/A	2.41
Quality Effects model	9	1.13	0.66 to 1.60	79	N/A	N/A	1.73
Outliers excluded[c]	8	0.74	0.25 to 1.24	74	20 to 94	-0.59 to 2.07	2.50
Only burns' dressing change	7	1.01	0.16 to 1.87	90	72 to 98	-1.40 to 3.42	1.90
Children participants	7	1.01	0.14 to 1.88	88	70 to 98	-1.41 to 3.43	1.90
Self-report	5	0.65	0.32 to 0.98	0	0 to 82	0.27 to 1.03	2.82
Other-report	4	1.34	-0.61 to 3.28	91	71 to 99	-4.31 to 6.99	1.52
Parallel design	7	1.09	0.25 to 1.92	88	67 to 98	-1.23 to 3.41	1.78
N>/= 20 randomized/arm	6	1.11	0.07 to 2.15	90	72 to 98	-1.70 to 3.93	1.76
						-0.61 to 2.35	
Retrospective (all assessors)	22	0.87	0.54 to 1.21	89	78 to 95		2.16
Henmi-Copas	22	0.69	0.36 to 1.01	82	80 to 95	N/A	2.67
Quality Effects model	22	0.89	0.61 to 1.16	82			2.12
Outliers excluded[e]	18	0.66	0.46 to 0.85	53	8 to 81	0.06 to 1.25	2.78
Excluding MMD	19	0.77	0.51 to 1.02	78	60 to 90	-0.22 to 1.75	2.41
Excluding no tx ctrl	18	0.77	0.41 to 1.14	87	68 to 95	-0.66 to 2.21	2.41
Only burns' dressing change	11	1.03	0.37 to 1.68	91	78 to 97	-1.15 to 3.21	1.87
Children participants	11	0.87	0.17 to 1.57	94	85 to 98	-1.48 to 3.23	2.16
Self-report	20	0.84	0.50 to 1.17	89	79 to 95	-0.66 to 2.33	2.23
					1 to 89	-0.07 to 1.28	2.99
Crossover design	10	0.61	0.34 to 0.88	57			
Parallel design	12	1.08	0.46 to 1.70	92	82 to 98	-1.06 to 3.22	1.80
N>/= 20 randomized/arm	14	0.97	0.44 to 1.51	94	87 to 98	-1.03 to 2.98	1.97

Excluding pilots or feasibility studies	20	0.93	0.58 to 1.29	90	79 to 96	-0.59 to 2.4	2.04
Cognitive component of pain measured							
Retrospective	8	0.82	0.39 to 1.26	75	24 to 95	-0.29 to 1.94	2.28
Affective component of pain measured							
Real-time	5	0.94	0.33 to 1.56	51	0 to 94	-0.37 to 2.25	2.02
Retrospective	14	0.55	0.34 to 0.77	58	4 to 86	-0.08 to 1.19	3.30

Note.

N = number of studies; NNT= numbers needed to treat; Child= children; Dress Ch = dressing change; Phys = Physical; Tx = Therapy; Ctrl = control; Conc = concomitent; Analg = analgesic; Distr= distraction; VR = Virtual Reality; HMD = Head-Mounted Display; VG = Video Glasses; MMD = Multi-modal device, RoB = risk of bias, N/A = not available.

[a] All results are reported with Hedges' *g*, using a random effects model, positive effect indicates superiority of the experimental group over control group (significant results are marked with italic).

[c] Miller, 2011

[d] The two crossover studies were both identified by the authors as pilot or feasibility studies

[e] Bensen, 2001; Gerceker, 2018; Guo, 2014, Miller, 2010

[f] Excluding trials with a no treatment control arm

Affective and cognitive components of pain (secondary outcome)

Five studies assessed the affective component of pain real-time, g= 0.94 (95% CI 0.33 to 1.56), NTT= 2.02, I^2 = 51% (95%, 0 to 94) and 14 trials retrospectively, g= 0.55 (95% CI 0.34 to 0.77), NNT= 3.30, I^2 = 58% (95% CI 4 to 86). The cognitive component was assessed only retrospectively in eight trials, g= 0.82 (95% CI 0.39 to 1.26), NTT= 2.28, I^2 = 75% (95% CI 24 to 95).

VR-based interventions versus active comparators

Two studies assessed pain intensity real-time and four studies retrospectively, g = 0.69 (95% CI -0.58 to 1.97), I^2 = 83% (95% CI 43 to 99), PI -2.86 to 4.25. The affective component was assessed in 2 studies.

Adverse effects

Twelve studies evaluated potential nausea or simulator sickness associated with VR interventions. In one, 15% of the participants reported nausea, and in another 5.2% reported nausea and 8% simulator sickness. In the remaining trials, none or under 5% of participants reported nausea.

Subgroup analysis

We only conducted planned subgroup analyses for VR-based interventions versus TAU for pain intensity assessed retrospectively. The two characteristics planned were correlated (Cramér's V= -0.57), therefore analyses were only conducted with analgesic use. Differences between studies using concomitant analgesic (n= 16, g= 0.78, 95% CI 0.37 to 1.19) versus those that did not (n= 6 g= 1.09, 95% CI 0.33 to 1.86) were not significant, F (1, 20)= 0.86, p= 0.36.

Small study effects (Figure 4)

These were gauged for pain intensity assessed retrospectively (22 trials). The funnel plot appeared asymmetrical (*Figure 4,A*), and visualization with contour enhanced funnel plot (*Figure 4, B*) suggested that most studies were significant at the conventional threshold of $p<$ .05. Egger's test was significant (intercept = 3.09, 95% CI 0.50 to 5.67, p= 0.021).

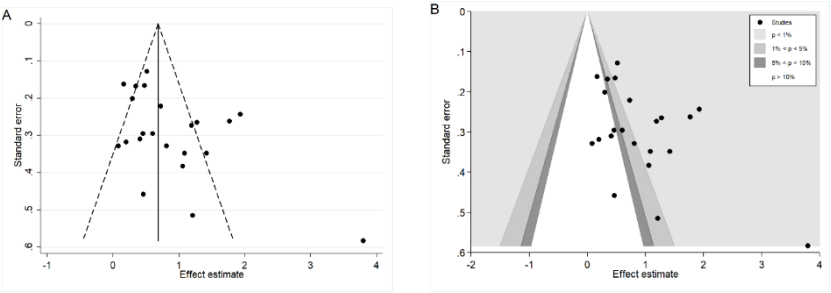


Figure 4- Figure A – funnel plot; Figure B - contour enhanced funnel plot

3.1.4 Discussion and conclusions

In a meta-analysis of twenty-seven randomized trials, VR-based distraction interventions for procedural pain demonstrated reductions in pain intensity, assessed either real-time or retrospectively, compared to treatment as usual. Though effects appeared generally large, they were associated by high heterogeneity, with all predictive intervals including zero. Effectively, this implies that the effects of 95% of future similar trials fluctuate across a wide range of effects, both favorable and not to VR-based interventions. Across several sensitivity analyses, involving both alternative statistical models (i.e., robust to publication bias, considering study quality), and restricted to the largest, clinically relevant and more homogenous categories (e.g., children participants, burn dressing change procedures), heterogeneity remained high and effect estimates largely similar. VR-based interventions were also effective for the affective and cognitive components of pain, assessed retrospectively, though the number of trials was more limited. Only four studies contrasted VR-based interventions with active comparators with a non-significant but large effect. Adverse effects were reported in a minority of participants and mostly consisted of nausea and simulator sickness.

Despite these seemingly promising effects, serious methodological and reporting issues across the entire evidence base preclude any inferences regarding clinical effectiveness. First, trial risk of bias was rated as high or raising some concerns for most of the included trials for randomization, deviations from the intended intervention and selective reporting. In most instances, ratings were motivated by the absence of essential information for the assessment of these domains. Moreover, as the VR-based intervention involved specialized equipment, it was generally impossible to blind participants and the personnel administering it. Also, owing to the

outcome (pain) or the assessment timepoint (real-time), all studies relied on self-report measures or used unblinded observers (i.e., parent, nurse, researchers).

3.1. 4. Conclusions

Interpreting these results is a glass half-full/half-empty conundrum. The setting is challenging, with large trials absent and difficult to conduct. For several indications, such as burns, particularly with children, recruiting a reasonably large number of participants to be randomized is difficult. Moreover, VR-based interventions were, until recently, difficult to scale. Not coincidentally, half of the trials we included were cross-over. Procedural pain is an unavoidable side-effect in settings such as burn care, compelling medical staff, patients and caregivers to try to alleviate it by any intervention that appears safe. Distraction intervention are generally effective (Scheffler et al., 2017) for adults, but less so for children and adolescents (Birnie et al., 2014). A new technology like VR, purported to enhance the effectiveness of "regular" distraction, will likely be embraced. Moreover, a cost analysis simulation estimated a using adjuvant VR therapy for pain management in hospitalized patients would reduce costs by $5.4/patient (95% CI $11 to $156) compared with TAU (Delshad et al., 2018). Hence, our meta-analysis provides reassurance VR-based distraction interventions appear safe and with some benefits in reducing procedural pain.

3.2. ANALYZING THE FACTOR STRUCTURE AND MEASUREMENT INVARIANCE ACROSS GENDER, AGE AND CHRONICITY STATUS OF THE PAIN CATASTROPHIZING SCALE

3.2.1 Introduction

Pain catastrophizing has been described as the tendency to distort the risk associated with a painful stimulus, along with the feeling of powerless and inability to hamper pain-related thoughts in painful episodes (Quartana et al., 2009). Previous studies have showed that pain catastrophizing is strongly associated with negative affects and is a strong predictor of pain intensity and pain-related disability (see (M. J. Sullivan et al., 2001; M. J. L. Sullivan et al., 2005; Turner et al., 2002) for a review). In acute samples, the predictive value attributed to catastrophic thinking for treatment outcome, exceeded the values assigned to the pain intensity, diseases characteristics, or type of medical interventions (Abbott et al., 2011; M. O. Martel et al., 2013; Spinhoven et al., 2004; Wertli et al., 2014). Moreover, it was positively linked with inadequate response to opioids (Weissman-Fogel et al., 2008) increased usage of opioids in acute and long term postoperative settings (Helmerhorst et al., 2014), and chronic pain intensity (R. Severeijns et al., 2001). Likewise, in chronic pain patients, an increased level of pain catastrophizing was associated with fear of movement (Picavet et al., 2002), poor outcomes of pain treatment (Edwards, Bingham, et al., 2006), reduced health-related quality of life (Bakshi et al., 2018; Hayashi et al., 2018) and was found to be a vulnerability factor for suicidal ideation (Edwards, Smith, et al., 2006), and depression (Lee et al., 2008).

Initially, pain catastrophizing was measured with the Coping Strategies Questionnaire (CSQ), proposed by Rosenstiel and Keefe (Rosenstiel & Keefe, 1983). The CSQ included six items aiming to assess the helplessness and pessimism in painful contexts. However, other dimensions of catastrophizing were not targeted (see Albert Ellis (Ellis, 1962) and Aaron Beck (Beck, 1979) for discussions). Thus, Sullivan et al. designed the Pain Catastrophizing Scale (PCS) (M. J. L. Sullivan et al., 1995) by including items covering other dimensions of catastrophic thinking in pain contexts, with a resultant of a 13-items instrument measuring more precisely the construct of pain catastrophizing.

Regarding its psychometric properties, in his validation study on healthy participants, Sullivan (M. J. L. Sullivan et al., 1995) identified three factors, second-order structure with a general pain catastrophizing factor behind the three components (i.e., rumination, magnification and helplessness). Since then, a large proportion of the further validation studies choose this model as a default model. Although none of the studies had headaches participants, the original factor solution has been replicated in both, pain-free samples (Karpinski et al., 2013; Augustine Osman et al., 2000; Pallegama et al., 2014, sec. Study 1; Van Damme et al., 2002) as well as pain suffers samples (Bansal et al., 2016; Cho et al., 2013; Kemani et al., 2019; Meyer et al., 2008; Pallegama et al., 2014, sec. Study 2; Sehn et al., 2012; Rudy Severeijns et al., 2002; Ugurlu et al., 2017; Van Damme et al., 2002; Yap et al., 2008). However, some of these replications found similar indices for the one-factor first-order solution or better solution when item 12 was dropped. Moreover, alternative solutions have also been recommended, as the two-

factor solution, represented by the factors rumination (7 items) and powerlessness (6 items) (Chibnall & Tait, 2005; A. Osman et al., 1997, sec. Study 1).

One may argue that finding similar fits between different structures can be due to sampling facts. Conversely, the previous studies of CFA rely on Confirmatory Factor Analysis (CFA) as a primary method in testing the construct validity, and only a small fraction on Exploratory Factor Analysis (EFA) (see table 1). In the lights of recent studies, when CFA is applied on multidimensional scale (as the case of PCS) biased results may returned (Asparouhov & Muthén, 2009; Booth & Hughes, 2014; Marsh et al., 2014; Mu & Duan, 2017; Tóth-Király, Bőthe, et al., 2017). By its methodology, CFA forces all the cross-loadings to zero, allowing loadings only on the defined latent factors (Marsh et al., 2009). In consequence, besides unsatisfactory goodness of fit, inflated factor correlations may be retrieved. As in the snowball effect, these inflated factor correlations may further affect the results of the discriminant validity of the instrument (Asparouhov & Muthén, 2009; Marsh et al., 2009, 2014).

For the last years, a growing body of researchers recommends exploratory structural equation modeling (ESEM) to be used as an alternative method to assess the construct validity of multidimensional instruments. The advantage of the ESEM methodology is that it can offer better estimates of the factor structure by allowing cross-loadings (features retrieved from EFA analysis) while the advanced statistical methods of CFA can be employed (e.g., factor invariance).

As it is important to test the stability of the factor structure, is also important to test if the scales have the ability to return equivalent results across different subgroups. Particularly to PCS, although in pain literature exist evidence showing that males and females experience pain differently (Bartley & Fillingm, 2013) only few studies examined the ability to return reliable results across gender. In adittion, previous studies addressing this aspect used analysis of variance (ANOVA) in the attempt to establish the measurement equivalence. As measurement invariance literature disputes, traditional methods (i.e., *t* test or ANOVA) should be avoided and analysis of latent means should be used in the establishments of full or partial measurement invariance.

Impacting the clinical outcomes, another branch of studies found age as a mediator of the relationship between pain and cognitions (Oosterman et al., 2013; M. J. Sullivan et al., 2001). Unexpectedly, the analysis of previous validation studies shows that the measurement equivalence across age was precluded even though the instrument is extensively used in various age groups.

Consequently, the main aim of the present study is to solidify the psychometrics properties of PCS through ESEM framework in a sample of acute and chronic tension-type suffers and to test the measurement invariance of the retained model across the type of pain, gender and age groups. This study expects that the ESEM solution reveals a clear three-factor solution and show better goodness of fit than CFA solution, allowing a further test of the 13 taxonomy ESEM for measurement invariance.

3.2.2. Method

Participants

The total sample comprised 461 participants (M_{age} = 28,98; SD_{age}=9,74; range 18-62 years) and was recruited through an online platform. The frequent episodic tension-type headache (FTTH) sample comprised 376 participants (with a percent of females of 80,3; M_{age} = 28,95; SD_{age}=9,96; range 18-60 years). For being classified as an FTTH suffers, participants should have reported a minimum of ten episodes of pain occurring in 1 to 14 days /month in the last three months. The chronic tension-type headache (CTTH) sample comprised 83 participants (M_{age} = 29,13; SD_{age}=8,80; range 19-62; 89,2 % female) and reported more than 45 episodes in the last three months.

Procedure

To be included in the study, participants freely completed the questionnaire by accessing an online link. Before starting, they read and sign the formal consent and confirmed they were above 18 years old. At the end of the formal consent as during the study procedure, they had the chance to decline participation if any aspects of the study were in disagreement with his/her beliefs. The formal consent included information regarding the General Data Protection Regulation (GDPR) and study procedure. The study was conducted in accordance with the Declaration of Helsinki, and data collection was performed between June and September 2018.

Measure

As we earlier mentioned the PCS is a 13 items questionnaire. The scoring is on a 5-points Likert scale, ranging from 0 (“not at all”) to 4 (“all the time”) and items assess ruminative and exacerbated thoughts regarding the unpleasantness of painful situations, negative expectancies about pain and inability to handle such situations. The total score ranges from 0 to 52, with higher scores indicating greater levels of pain catastrophizing.

Statistical analysis

Analyses were performed in Mplus 8.2 (Muthén & Muthén, 1998) using robust maximum likelihood (RML) estimator on ordinal data (Meredith, 1993; Putnick & Bornstein, 2016). In the first phase of analysis, using the original structure proposed by Sullivan et al. (M. J. L. Sullivan et al., 1995), CFA and ESEM models were conducted simultaneously on the entire sample to evaluate the factor structure of PCS. In the CFA model, items could load only on their defined factors, while the cross-loadings were restricted at zero. In the ESEM model, target rotation (Asparouhov & Muthén, 2009) was applied while the cross-loadings were not restricted. To evaluate model fits of both solutions (i.e., CFA and ESEM), the chi-square test (χ^2) was used. Still, the χ^2 test is known to be sample size sensitive, and current practice emphasizes the importance of using multiple fit statistics (Kline, 2016) therefore the following alternative indices were included: Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), and Root-Mean-Square Error of Approximation (RMSEA). Values equal to or greater than 0.95 for the CFI and TLI indices were considered good, while values across 0.90 were considered acceptable (Hu & Bentler, 1999). For the RMSEA with a 90% confidence interval, a value lower or equal with 0.06 was retained as good and values between 0.06 and 0.08 as acceptable

(Hu & Bentler, 1999). Moreover, accounting that sometimes these indices can lead to Type 1 error, these cut of criteria were treated as general guidelines, and underlying theory was considered (Marsh et al., 2004).

In the next phase of analysis, the measurement invariance was tested across the type of tension-type, gender, and age (Meredith, 1993; Putnick & Bornstein, 2016). To do this, the age variable was dichotomized into two groups: emergent adults (18 – 26 years, N= 228) and adults (27 – 62 years, N= 202) and the taxonomy of 13 ESEM models were employed (Marsh et al., 2009). However, measurement invariance literature dispute four crucial level of invariance to be achieved: (1) configural invariance (i.e., no invariance; compare the similarity between pattern of free and fixed loadings in both groups as a precondition of the further invariances); (2) weak invariance (i.e., invariance of factor loadings across groups); (3) strong invariance (i.e., besides invariance of factor loadings, the intercepts of responses to individual items are constrained to be equal); and (4) strict invariance (invariance of factor loading, intercept, and item uniqueness). By reaching the strong invariance, the corrections for standard error are assumed and any change in the latent factors means can be interpreted as a change in latent construct. Further, by achieving the strict invariance, the uniqueness of the item (i.e., variances in reliability) is accounted. Next, we test the latent mean invariance (invariance of factor loading, intercept, latent factor means, and item uniqueness) important to be assumed in multifactorial constructs. Moreover, if the strong invariance was achieved, we computed the complete measurement invariance by testing the invariance of the factor loading, latent factor variance/covariance, intercept, latent factor means, and item uniqueness (model 13 from the ESEM taxonomy). In order to assess the goodness of fit of the nested models, non-significant *p* values of the chi-square difference along with the relative changes in fit indices (Chen, 2007): ΔCFI $\leq$0.01, ΔTLI $\leq$0.01, and ΔRMSEA $\leq$0.015 were interpreted as evidence of invariance.

In the last phase of analysis, the scale reliability (i.e., internal consistency) was estimated relying on two coefficients: Cronbach's alpha (Cronbach, 1951) with the general guidelines to translate the results (values as 0,70 interpreted as acceptable and 0.80 as good) and Omega (ω, (McDonald, 1999)). Choosing a second reliability index was based on the rationale that although the Cronbach alpha is the most reported index due to his practical reasons (e.g., serve as a comparative index with the previous studies) is also the most loathed and misunderstood from all internal consistency indexes (Bentler, 2008; Rodriguez et al., 2016; Yang & Green, 2011). By contrast, the omega coefficient is a factor analytic index which estimates the proportion of variance attributed to all source of variance (i.e., the global construct and specific factors) recommended to be used in multidimensional instruments such as PCS (Deng & Chan, 2017; Dunn et al., 2014).

3.2.2. Results

CFA vs. ESEM (Table 2, Table 3)

First, we examined the factor structure of CFA using both frameworks of analysis, ESEM and CFA. The fit indices are presented in Table 2. The fits of CFA on the original three-factor solution was good (χ^2 = 167.779, *df*=62, CFI = .957, TLI= .946, RMSEA =.061 (90% CI 0,050 – 0,072)). However, the corresponding solution retrieved from the ESEM model was notably better (χ^2 =89.181, *df*=42, CFI = .981, TLI= .965, RMSEA= .049 (90% CI 0,035 – 0,064)).

Table 2. Goodness of fit for the CFA and ESEM models

	χ^2	df	CFI	TLI	RMSEA[90%CI]
CFA	167.779	62	0.957	0.946	0.061[0.050, 0.072]
ESEM	89.181	42	0.981	0.965	0.049[0.035, 0.064]

Note: N=454. CFA=confirmatory factor analysis; ESEM=exploratory structural equation modeling; χ^2 =chi-sqaured; df= degree of freedom; CFI= Comparative Fit Index; TLI= Tucker-Lewis Index; RMSEA= Root-Mean-Square Error of Approximation; CI=confidence interval.

In the next step the factor loadings (see Table 3) were examined. As expected, in the CFA model the factor loadings are greater than the ones retrieved by the ESEM model, however in both analysis, factor loadings tend to range from medium to high, with few loadings greater than 0.80 (five in CFA model and two in ESEM model) and few loadings less than .40 (none in CFA model and two in the ESEM). On the other hand, comparable mean factorial loadings: .72 in CFA and .65 in ESEM were found. Next, the cross-loadings pattern in the ESEM model was examined finding that all were different from zero, ranging from -.04 to .34, with one item cross-loading higher than the target loading (item 1 also loaded on magnification factor). Examination of the pattern correlation presented in Table 1 relieves lower correlations in the ESEM model (range .561 - .616) comparative with the CFA model (range .733 to .780). For instance, the correlation between rumination and magnification was .733 on the basis of the CFA solution but not higher than 0.574 in the ESEM solution.

Table 3. Factor loadings extracted from confirmatory factor analysis and exploratory structural equation modeling, and factor corelations based on the resposnes to the Pain Catastrophzing Scale

	CFA solution[a]				**ESEM solution**			
	R	M	H	R^2	R	M	H	R^2
Factor loadings								
Rumination								
8. I anxiously want the pain to go away.	**0.600**	-	-	0.360	**0.637**	-0.035	-0.007	0.376
9. I can't seem to keep it out of my mind.	**0.806**	-	-	0.650	**0.688**	0.052	0.108	0.627
10. I keep thinking about how much it hurts.	**0.864**	-	-	0.747	**0.855**	0.020	-0.006	0.745
11. I keep thinking about how badly I want the pain to stop.	**0.794**	-	-	0.631	**0.843**	-0.041	-0.009	0.663
Magnification								
6. I become afraid that the pain may get worse.	-	**0.817**	-	0.668	0.286	**0.418**	0.159	0.550
7. I think of other painful experiences.	-	**0.564**	-	0.318	-0.015	**0.663**	-0.010	0.421
13. I wonder whether something serious may happen.	-	**0.690**	-	0.477	0.061	**0.724**	-0.015	0.565
Helplessness								
1. I worry all the time about whether the pain will end.	-	-	**0.651**	0.424	0.212	0.340	**0.244**	0.460
2. I feel I can't go on.	-	-	**0.798**	0.636	0.015	0.176	**0.677**	0.639
3. It's terrible and I think it's never going to get any better.	-	-	**0.751**	0.564	-0.046	0.279	**0.607**	0.590
4. It's awful and I feel that it overwhelms me.	-	-	**0.848**	0.719	0.131	0.009	**0.776**	0.754
5. I feel I can't stand it anymore.	-	-	**0.832**	0.693	0.216	-0.019	**0.710**	0.721
12. There is nothing I can do to reduce the intensity of the pain.	-	-	**0.488**	0.239	0.203	0.172	**0.209**	0.248
Factor correlations								
Rumination	-				-			
Magnification	0.733	-			0.574	-		
Helplessness		0.780	-		0.616	0.561	-	

Note. N=454. CFA=confirmatory factor analysis; ESEM=exploratory structural equation modeling; R=Rumination, M=Magnification, H=Helplessness; [a] Each item loaded on their respective specific factor, while cross-loadings were constrained to zero.

Measurement invariance (Tables 4, 5, 6)

In the next phase of analysis, we performed measurement invariance across the type of pain (FTTH vs. CTTH), gender (female vs. male) and age (emergent adults vs. adults) using the taxonomy of 13 ESEM models. After the examination of the goodness of fit in the configural invariance (M1) for all groups, constrains were gradually applied. Consequently, the full invariance (see *Appendix 3*, model 13) across the type of pain provides a good fit to the data: χ^2 =245.682, *df*=146, CFI=.963, TLI=.960, RMSEA=.055 (90% CI .042 - .066). Similar fit indices were founded for the factorial, strong, strict, and latent means invariance (see Table 4). As observed, the *p* value for the chi-squared difference was significant for the strong and strict invariance. However, as χ^2 is sample size dependent and the changes in fit indices (ΔCFI, ΔTLI, ΔRMSEA) were less than the value of .01 we concluded that the scores of PCS are invariant across the type of pain (frequent TTH or chronic TTH). Moreover, we found no significant differences in latent means.

Table 4. Summary of goodness-of-fit statistics for type of pain invariance models

Model	χ^2	*df*	CFI	TLI	RMSEA[90%CI]	Δχ2 / (Δ*df*)	ΔCFI	ΔTLI	ΔRMSEA	Decision
M1. Configural invariance	163.5	84	.970	.945	.064 [.049, .079]	-	-	-	-	-
M2. Factorial invariance	203.52	114	.966	.954	.058 [.045, .071]	40,02(30)	-0,004	+0,009	-0,006	Accepted
M3. Strong invariance	226.94	124	.961	.951	.060 [.048, .072]	20,76(4)*	-0,007	-0,007	+0,004	Accepted
M4. Strict invariance	241.03	137	.961	.956	.058 [.045, .069]	20,946(4)*	-0,006	-0,006	+0,005	Accepted
M5. Latent mean invariance	229.86	127	.961	.953	.059 [.047, .072]	-13,234(-16)	-0,001	-0,006	+0,004	Accepted
M5. Complete invariance	245.682	146	.963	.960	.055 [.042, .066]	14,895(13)*	0	+0,003	-0,002	Accepted

Note: Frequent tension type headaches, n=373; Chronic tension type headaches, n=81; χ^2 = model chi-square statistic; *df* = model degrees of freedom; CFI = Comparative Fit Index; TLI = Tucker–Lewis index; RMSEA = Root Mean Square Error of Approximation.

*p<0.001

Next, the examination of gender equivalence (see Table 5 and *Appendix 4*) was conducted. All fit indices for the factorial, strong, strict, latent mean were good as the fit indices for the most restrictive model (M13): χ^2 =229.88, *df*=146, CFI=.967, TLI=.965, RMSEA=.05 (90% CI .034 - .062). The *p* values for the chi-squared difference were non-significant in all instances, and none of the changes in fit indices exceed the value of .01, indicating that all constraints hold across gender. Latent mean differences were significant for rumination and magnification, indicating that females have more ruminative and exacerbated thoughts regarding pain than males.

Table 4. Summary of goodness-of-fit statistics for gender invariance models

Model	χ^2	*df*	CFI	TLI	RMSEA[90%CI]	$\Delta\chi^2/(\Delta df)$	ΔCFI	ΔTLI	ΔRMSEA	Decision
M1. Configural invariance	149.05	84	.975	.953	.058 [.043, .073]	-	-	-	-	-
M2. Factorial invariance	191.88	114	.97	.958	.055 [.041, .068]	42,83(30)	-0,005	+0,005	-0,003	Accepted
M3. Strong invariance	201.23	124	.97	.962	.052 [.039, .065]	5,52(4)	0	0	0	Accepted
M4. Strict invariance	214.34	137	.97	.966	.05 [.036, .062]	3,34(4)	0	+0,002	-0,001	Accepted
M5. Latent mean invariance	209.59	127	.968	.96	.053 [.04, .066]	-11(-16)	-0,002	-0,007	+0,004	Accepted
M6. Complete invariance	229.88	146	.967	.965	.05 [.037, .062]	16,17(13)	-0,001	+0,002	-0,001	Accepted

Note: Females, n=376; Males, n=83; χ^2 = model chi-square statistic; df = model degrees of freedom; CFI = Comparative Fit Index; TLI = Tucker–Lewis index; RMSEA = Root Mean Square Error of Approximation;

The examination of age invariance (see Table 6 and *Appendix 5*) provided good fit indices for the configural, factorial, strong, strict, and latent mean invariance and acceptable fit indices for the full measurement invariance (M13): χ^2 =261.98, *df*=146, CFI=.948, TLI=.944, RMSEA=.061 (90% CI .049 - .073). All values of *p* chi-squared differences were non-

significant, excepting the one for the latent mean invariance. All the changes in fit indices (ΔCFI, ΔTLI, ΔRMSEA) were less than the value of .01, indicating that the scores of PCS are invariant across age (emergent adults vs. adults). The examination of the latent mean difference was significant for the magnification and helplessness in young adults.

Table 6. Summary of goodness-of-fit statistics for age invariance models

Model	χ^2	df	CFI	TLI	RMSEA[90%CI]	$\Delta\chi2$/ (Δdf)	ΔCFI	ΔTLI	ΔRMSEA	Decision
M1. Configural invariance	115.38	84	.986	.974	.042 [.02, .059]	-	-	-	-	-
M2. Factorial invariance	147.09	114	.985	.98	.037 [.015, .053]	31,71(30)	-0,001	+0,006	-0,005	Accepted
M3. Strong invariance	188.07	124	.971	.964	.049 [.034, .063]	33,5 (4)	-0,013	-0,016	+0,012	Accepted
M4. Strict invariance	230.93	137	.958	.952	.056 [.044, .069]	31,23(4)	-0,012	-0,013	+0,008	Accepted
M5. Latent mean invariance	209.62	127	.963	.954	.055 [.041, .068]	-31,67*(-16)	+0,007	+0,002	-0,002	Accepted
M5. Complete invariance	261.98	146	.948	.944	.061 [.049, .073]	44,64(13)	-0,014	-0,012	+0,007	Accepted

Note: Emergent adults, n=228; Adults, n=202; χ^2 = model chi-square statistic; *df* = model degrees of freedom; CFI = Comparative Fit Index; TLI = Tucker–Lewis index; RMSEA = Root Mean Square Error of Approximation;

Reliability analysis (Table 7)

The coefficients for the internal consistency are presented in Table 7. Acceptable Cronbach's alpha values were found for all subscales (α = 0.742 to 0.872). In any case, as some researchers argued the trustworthiness of this coefficient, especially on multidimensional instruments, the omega values were computed for each subscale. The resultant values were similar (ω = 0.745 to 0.876) indicating that the score successfully represents the proportion of variance attributed to the pain catastrophizing and his specific components (i.e., magnification, helplessness, and rumination).

Table 7. Reliability indices and descriptive statistics of the Pain Catastrophizing Scale

Sub-scales	N	McDonald's ω	Cronbach's α	Score range	M	SD
Rumination[a]	4	0.855	0.852	0-16	8,610	3,897
Magnification[b]	3	0.745	0.742	0-12	4,596	2,901
Helplessness[b]	6	0.876	0.872	0-24	8,561	5,242

Note: N= N of items number of items on the factor; M=mean, SD= standard deviation.

[a] Of the observations, 454 were used, 0 were excluded listwise, and 454 were provided.

[b] Of the observations, 452 were used, 2 were excluded listwise, and 455 were provided

3.2.4 Discussions and conclusions

In the present investigation, we used the ESEM framework to test the construct validity of the PCS scale scores. As disputed in the introduction, through estimating all the cross-loadings, ESEM gives us the possibility to overcome the limitations of the CFA in terms of inflated correlations among the latent factors. Our results sustain the previous studies using

ESEM methodology and return better fit indices than the CFA model. Furthermore, in the ESEM model, the correlations between rumination, magnification, and helplessness were notably lower than the ones retrieved from the CFA model, fitting better to the underlying theory of the irrational beliefs (i.e., catastrophizing) in painful situations.

Though ESEM, the present study sustains the previous findings offering support for the three-factor second-order structure of the PCS. Although in the ESEM model non-zero cross-loadings were present, besides the fact that when are suppressed (as in CFA model) could contribute to the multicollinearity problems, none of them were large enough to undermine the factors meaning. Analysis of the cross-loadings pattern revealed that some items positively load on their factor and negatively on others (items 7, 8, or 11). These situations exceeded our expectations based on theory and a possible explication might be that although all items as a construct measure pain catastrophizing, some of them tap into specific components of rumination, magnification, or helplessness processes. Moreover, similar situations were previously found in other validations studies on passion (Tóth-Király, Bõthe, et al., 2017), or academic motivation (Tóth-Király et al., 2016) scales, leading to the possibility that these situations could be a characteristic of multidimensional instruments rather than a specific one. However, more notably, from the cross-loadings pattern analysis was that item 1 (i.e., "I worry all the time about whether the pain will end") positively load on two factors: helplessness (as in the factor structure proposed by Sullivan et al., 1995) and magnification. This situation could be explained by the wording of the item and also through the underling theory. It is possible that the item not be compressed either in the helplessness nor magnification process and reflect more the concept of catastrophic thinking itself (see for a discussion (Flink et al., 2013)).

An important aspect of the present methodology was testing the measurement equivalence across the type of pain, gender, and age. A particular interest was allocated to the invariance across the type of pain as none of the previous validation studies on PCS were addressed to headaches sufferers. Our results show that either when we use an extensive model for measurement invariance (i.e., the 13 taxonomy of ESEM), PCS scores are completely invariant across the type of pain, gender, and age meaning that the scores difference are not due to error measurement or structural model. Our findings regarding gender invariance were in line with the ones founded by the previous studies (D'Eon et al., 2004; Augustine Osman et al., 2000; Van Damme et al., 2002) contributing thus to the generalizability of the results.

As regards the scale reliability, the results of the present study show modest internal consistency values for the magnification subscale (i.e., 0.745) and good for the rumination (i.e., 0.855) and helplessness (i.e., 0.876) subscales. However, as the author's scale argued is possible that this instance is a consequence of the small number of items gathered (i.e., three items for the magnification subscale).

A number of limitations for the present study are worthy of being discussed. First, relying only on self-reports in classifying the frequent and chronic tension type sufferers could contribute to a limited external validity. Further studies should include participants fulfilling all criteria listed in ICHD-3 for frequent and chronic headaches in order to confirm the present results. Second, although ESEM is a versatile framework, allowing us to incorporate features

from EFA and CFA and return better fits, one may argue that better coefficients are a consequence of a less parsimonious model. For this reason, although this study can be treated as a successful synergy between clinical and methodological aspects in inspecting the construct validity of PCS, further studies should use with precaution the ESEM framework. It must be noted that, although we found complete measurement equivalence across age, the age variable was dichotomized which may affect our conclusion. Likewise, further studies should also investigate other age groups, especially to test the scale ability in returning trustable results in old populations.

Notwithstanding the limitations discussed, this is the first study that tests the psychometric properties of PCS on a headache's population. Our findings, using a relatively new methodology confirm the three factors structure of PCS primarily important in clinical and research practice. Moreover, finding measurement equivalence across age and gender allows furthering studies to make comparisons across groups.

3.3. Benefits of cognitive restructuring, acceptance and distraction for pain intensity and pain tolerance[5]

3.3.1 Introduction

As defined by The International Association for the Study of Pain (IASP, 1994) pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". Episodes of acute pain last less than 3 months and their intensity tends to decrease along the healing process or response to treatment. However, unsuccessful management of acute pain led to persistent or chronic pain (Sinatra, 2010) with negative impact on individuals and society (Breivik et al., 2006; Patel et al., 2012; Reid et al., 2011; Tsang et al., 2008). Chronic pain is a condition that could be developed in the presence or absence of a known cause and persists more than expected healing time or against the treatment aims (typically more than 3 months).

In the view of the Gate Control Theory proposed by Melzack and Wall's (1965), pain can be modulated into the gates passed by the pain signals from the affected area to the brain. Thus, our thoughts, feelings and behaviours are mediators of the pain perception process (Turk & Rudy, 1992). Cognitive-behavioural therapy (CBT; Alford, Beck, & John V. Jones, 1997) through cognitive restructuring, active scheduling and goal setting, change the catastrophic thinking and maladaptive behaviour about pain (Vranceanu et al., 2017). Current evidence showed a medium effect size of CBT in reducing acute pain (Birnie et al., 2014; Tatrow & Montgomery, 2006), chronic pain (Bailey et al., 2010; Dysvik et al., 2010; Morley, 2011; Williams et al., 2012) and disability associated (Cosio, 2015; Sturgeon, 2014). Still, some patients have not equal benefits from CBT interventions, particularly in reducing pain disability (Christopher Eccleston et al., 2009; McCracken & Turk, 2002). This is particularly true for acute pain, possible due to the involvement of executive functions in the process of pain perception (Bjekić et al., 2018). From another point of view, Acceptance and Commitment Therapy (ACT) rooted in Functional Contextualism (Hayes,1993) claim that restructuring or challenging the content of dysfunctional pain beliefs may increase the patient's distress (Gagliese, 2007). Accordingly to ACT, between beliefs and behaviours is not a direct and causal relationship (Ruiz, 2012), meaning that the process of changing dysfunctional cognitions will not promote positive behavioural changes. Studies evaluated the efficacy of ACT showed small to medium effect size to reduce distress, not pain intensity and especially in chronic pain samples (Hughes et al., 2017; Wetherell et al., 2011). Besides, only few studies compare ACT strategies with other techniques such as cognitive restructuring or distraction for pain management.

Kohl, Rief, and Glombiewski (2013) conducted one of the first comparisons between acceptance, cognitive restructuring and distraction as strategies to reduce acute pain. In this study, a sample of 109 female students received a pain coping strategy during pain induction

[5] This study has been published: Georgescu, R., Dobrean, A., & Predescu, E. (2018). Benefits of cognitive restructuring, acceptance and distraction for pain intensity and pain tolerance. Journal of Evidence-Based Psychotherapies, 18(2).

using a thermode. No significant differences between groups were founded regarding pain intensity. However, means for pain tolerance were higher in the acceptance group than in the cognitive restructuring group. One subsequent study of Kohl and colleagues (2014) has further examined the effect of acceptance and cognitive restructuring after pain induction at fibromyalgia patients. Kohl et al., (2014) examined the effect of these techniques on two types of induced pain, cold and heat pain. Although results relived that both acceptance and cognitive restructuring were superior to distraction no significant results were founded between groups for pain intensity outcome. However, average values for pain tolerance were higher in the cognitive restructuring group.

Even though contrary, results of Kohl et al. (2013, 2014) highlights that cognitive restructuring and acceptance strategies could be promising strategies for pain management, especially for pain tolerance outcome. In spite of this, some questions remain unanswered, particularly regarding the effectiveness of these techniques on pain intensity. Additionally, in each study, pain intensity and pain tolerance were assessed immediately after the coping strategies were given, collecting all measures in 10–15 minutes. Although consistent with CBT and ACT literature to produce immediate effects, estimations about efficacy of these strategies after a middle term practiced remaining unclear.

Consequently, this study was conducted to replicate and extent the work of Kohl, Rief, & Glombiewski, 2013 with respect to the clinical utility of cognitive restructuring and acceptance for increasing pain tolerance. In addition, we were interested in evaluating the effects of strategies after one-week practice for both outcomes, pain intensity and pain tolerance. To examine this, participants were randomly assigned to receive either cognitive restructuring techniques, acceptance techniques or distraction techniques (as control group) and practice the assigned technique 1-week as daily homework.

3.3.2. Methods

Participants

Using G*Power 3.1.9.2 (Faul et al., 2007) an *a priori* analysis was performed to estimate the sample size. Analysis indicated a minimum of 95 participants needed to detect an effect size of 0.3, with $\alpha = 0.05$ and power =0.80. Participants were students recruited through announcements on social media with the following exclusion criteria 1) age below 18 years, 2) suffering for an acute or a chronic pain condition, 3) use of pain medication in the last 24 hours before the study participation and 4) any wounds at the dominant hand.

This study was approved by the Ethics Committee of the Babeș-Bolyai University and respect the recommendation of the Declaration of Helsinki regarding participants' safety.

Study design

A bifactorial mixt design was employed, with two independent variables and two dependent variables. The first independent variable was *time*, having three condition pre - test (time 1), immediately post-test (time 2) and after 1-week practice (time 3). The second independent variable was *group* with three conditions, namely a. cognitive restructuring; b. acceptance and c. distraction. The dependent variables were pain intensity measured on a VAS scale and pain tolerance measured in seconds. The flowchart of the study design is illustrated in Figure 5.

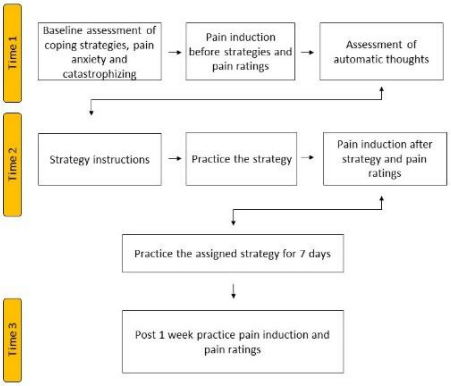


Figure 5 - Flowchart of study design

Procedure

Common procedures for all groups. At the first visit to the laboratory, informed consent was provided to participants and after all the questions regarding study principal were answered, the pre-strategy pain induction was employed. The instructions for the immersion were as follows: after the dominant hand is inserted in the tank water, please announce when the discomfort feeling starts and when pain feeling starts. When pain becomes intolerable please remove the hand. A stopwatch was started at the beginning of the immersion and stopped when the participants withdraw the hand. Following the pain induction, participants rated pain intensity on a Numerical Rating Scale (NRS) scale. Next, participants provided three pain related thoughts that were discussed and ranked in accordance with their frequency and impact. After that, the strategy was given (accordingly to groups), discussed and exercised on the first thought listed before. The length of the strategy instructions and discussions associated was approximately 15 minutes for all groups. Following this, the pain induction was repeated, and pain intensity rated. At the end of the first laboratory visit, the "homework" was presented, and we explained to the participants that for the next 7 days they should practice the rational assigned twice a day using the imagery. After that, participants completed the self-report scale for coping strategies in pain, anxiety and catastrophizing. To ensure that participants do not forget to practice their assigned strategies, they received two messages per day (in random order: morning, lunch and afternoon between 9:00AM and 9:00PM) that remained them as follow: "Remember to practice > the assigned strategies< and complete your ratings!" At the second laboratory visit, the pain induction was repeated, pain intensity rated, and participants were debriefed.

Cognitive restructuring training. Based on the Rational Emotive and Behavioural interventions (Ellis et al., 1975) participants were informed that pain sensation and pain tolerance are affected by our thoughts and these can be rational or irrational, respectively

functional and dysfunctional. Identifying and challenging dysfunctional thoughts were presented as the most effective strategy for coping with pain. Using the first thoughts listed after the pain induction, the experimenter guides the participants in disrupting these thoughts using the following sequence: a. acknowledges the situation; b. identification of the automatic thought; c. finding the evidence that supports the thought; d. finding the evidence that disproves the thought; e. extracting the conclusions and develop a new rational thought. The researcher guided the participants through the cognitive restructuring process in an individualized manner, considering the cognitive vulnerabilities of the participants.

Acceptance training. Based on the ACT manual (Hayes et al., 1999) participants were informed that the content of their pain thought does not cause pain nor distress. It was explained that language despite their advantages increase distress by offering the illusion to people that their thoughts are literally true. Moreover, is was explained that attempting to change or arguing the content is a source of the increased pain sensation. Consequently, accepting the content of their thoughts and trying to decrease his literality is the most effective strategy to cope with pain. Using the first thought listed after pain induction, the researcher guided the participants to view their thoughts as a cloud in the sky which is passing and nothing bad is happening. The researcher guided the participants in an individualized manner, considering the personal factors, such as, time needed to believe and apply the strategy.

Distraction training. Based on the attention theory, previously successfully applied on pain management (S. C. C. Chan et al., 2012; Johnson, 2005; Torta et al., 2017; Veldhuijzen et al., 2006) participants were informed that our attention has a limited capacity to process pain sensations. The researcher used the metaphor of a spotlight to illustrate the association between our thoughts and their actions. It was explained that depending on which thoughts we focus our attention the pain sensation could be influenced. It was explained that exists more types of distraction: internal and external and was presented the difference between them. The researcher guided the participants to successfully apply distraction to cope with pain and practice the distraction rational using the first thought listed before.

For their homework, participants were instructed to practice these strategies every day twice for the next 7 days and following the practiceto complete the journal.

Measures

Primary measures

The numerical rating scale (NRS) was used as a unidimensional scale measuring the intensity of pain. The score options ranged from 1 (“no pain at all”) to 10 (“the worst pain ever possible”). Previous studies that examined the validity of NRS showed strong correlations with other pain intensity scales and recommended the scale to be used as a valid measurement in most pain settings (Hjermstad et al., 2011).

Pain tolerance was defined as the time in seconds passed between the participant report that cold sensation had begun painful to the point when she/he withdrawn the hand from the cold water. To help participants to differentiate between cold sensations and pain we explained before the immersion in the cold water the feeling of both sensations. After that, we instructed the participants to report first the feel of cold sensation and next the moment when

pain sensation starts to hurt. The time reported between the feeling of cold sensation to the point when the participant decides to withdraw the hand from the cold water was not calculated nor included in the analysis.

Secondary measures

Pain acceptance. Chronic Pain Acceptance Questionnaire – Revised (CPAQ-R,(McCracken et al., 2006) is 20 items self-report scale measuring pain acceptance.

Pain coping strategies. The 27-item coping strategies Questionnaire – Revised(CSQ - R,(Riley & Robinson, 1997) is 27 items self-report scale measuring coping strategies in pain, structured in 6 subscales as follows: distraction, catastrophizing, ignoring the pain sensations, distracting from pain, coping self-statements and praying.

Pain Catastrophizing Scale (PCS,(M. J. L. Sullivan et al., 1995) is a self-report measure with 13 items measuring pain catastrophizing structured in three subscales, namely rumination, magnification and helplessness.

Pain anxiety. Pain anxiety symptoms scale (PASS-20,(McCracken & Dhingra, 2002) is a self-report scale with 20 items measuring anxiety and fear responses related to pain structured in four subscales respectively, cognitive, escape/avoidance, fear and physiological anxiety.

Homework diary: to ensure that participants believed in their assigned strategies they completed two times per day a journal with four questions designed for this study. The questions were as follows: (1) “On a scale from one to ten how easy was for you to practice the strategy?”; (2) “On a scale from one to ten how much can you believe that your pain is controlled?”; (3) “Did you have specific thoughts, physical sensations or specific emotions during the time you practice the strategy? Please mention”; (4) “Please note if you had any problems during the time you practiced your strategy”.

Pain induction apparatus: a circulating and cooling water tank, JSR model 13 (240 X 300 X 150) filled with water maintained at 1°C was used to induce pain sensation. The circulation pump enables the water to circulate and be maintained at the set temperature. This model of apparatus maintains the temperature within 0.1°C. The water was maintained constant due to drastically changes in pain ratings at different temperatures (Mitchell et al., 2004) .

Data analysis

Analyses were performed using *IMB SPSS* (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) based on the intention-to-treat principle. Descriptive analyses and baseline imbalances were computed for pain intensity, tolerance and cognitive measures (i.e., coping strategies to pain, catastrophizing and anxiety). Multivariate analysis of variance (MANOVA), 3 (time) x 3 (group) was employed to test the effects on pain intensity and tolerance. Post hoc analysis was conducted to determine the specific differences between groups.

3.3.3 Results

Participants

One hundred twenty students responded affirmatively on the social media announcements. Twenty-two students declined to participate after they received all the information about the study or could not be contacted. One participant was excluded for pain medication intake in the last 24 hours and two participants were excluded for having wounds at their dominant hand. The final sample size of the present study was 95 participants with a mean age of 21.39 years (*SD* = 4.20 years), ranged from 18 to 41 years. The flowchart of participants is presented in Figure 6.

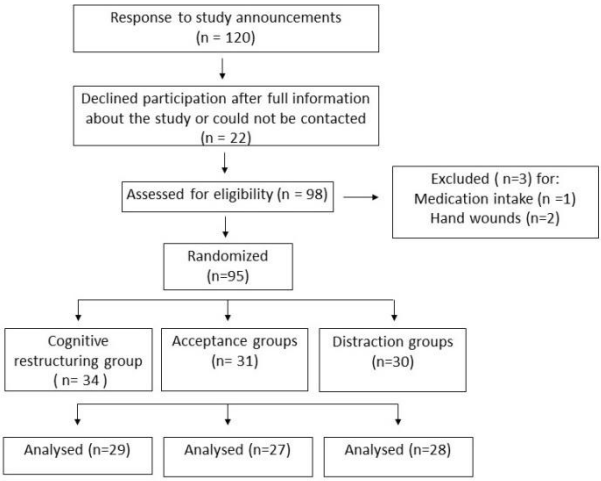


Figure 6: Flowchart of participants

Outlier Analysis and baseline imbalances (Table 8 & Table 9)

Using frequency analysis, we explore for extreme values in pain intensity and pain tolerance outcomes. To identify them, we calculate the Mean (*M)* and Standard Deviation (*SD*) and exclude all values above/below 2.5 *SD*. Excluded values are presented in Table 8.

Table 8: Outlier analysis for pain intensity and tolerance

	Condition	Intensity	Tolerance
Upper values excluded	Cognitive restructuring	-	892, 512, 651, 846
	Acceptance	-	888
	Distraction	-	700
Lower values excluded	Cognitive restructuring	2	-
	Acceptance	1,2,3	-
	Distraction	3	-

To evaluate if the process of randomization was balanced, we examined the baseline differences using different analyses of variance (ANOVA) for their gender, level of acceptance, cognitive restructuring, distraction, anxiety and pain catastrophizing. No significant differences were founded, leading to the conclusion that the randomization process succeed. Descriptive values for sample characteristics and *F* values are presented in Table 9.

Table 9: Sample characteristics

	Cognitive restructuring (N= 29)	Acceptance (N=27)	Distraction (N=28)	*F* Values*
Gender (M, SD)	0.76 (0.435)	0.85 (0.362)	0.71 (0.460)	0.759
Acceptance (M, SD)	68.10 (10.140)	64.63(10.36)	67.46(11.377)	0.834
Cognitive restructuring (M, SD)	17.48(4.469)	17.56(4.726)	16.71(3.876)	0.318
Distraction (M, SD)	18.17(6.465)	20.81(6.325)	21.86(5.772)	2.684
Pain anxiety (M, SD)	44.11(13.734)	49.00(11.455)	52.15(12.05)	2.453
Pain catastrophizing (M, SD)	16.66(8.953)	20.41(7.682)	19.50(10.99)	1.253

Note: N = number of participants; M= mean; SD = standard deviations.
All *F* values are nonsignificant(p_s>.05)

Effects on pain intensity and pain tolerance (Table 10)

Means and standard deviations for pain intensity and pain tolerance at pre-test, post-test and after 1-week are presented in Table 3.

Table 10: Means and standard deviation for pain intensity and tolerance measured at pre-test, post-test and post 1-week homework.

Pain intensity	Cognitive restructuring (N= 29)	Acceptance (N=27)	Distraction (N=28)
Pre-test	7.28 (1.38)	7.07(1.56)	6.71(1.56)
Post-test	6.41(2.44)	6.37(1.80)	6.29(1.51)
Post 1-week	6.45 (1.80)	6.30 (1.66)	6.07 (1.72)
Pain tolerance	Cognitive restructuring (n= 29)	Acceptance (n=27)	Distraction (n=28)
Pre-test	55.00 (78.04)	37.33 (58.08)	46.39 (56.95)
Post-test	100.79 (144.33)	45.52 (96.75)	59.39 (76.26)
Post 1-week	177.62 (244.48)	116.33 (164.78)	125.61 (204.77)

Note: N = numbers of participants; All values are means and standard deviations.

Results from mixed MANOVA led to a significant overall effect of time, Wilk's Λ = .622, F (4, 78) = 11.86, p = .00, η^2 = .37. Univariate test indicated a significant time effect for pain intensity, F (2, 162) = 9.429, p = .00, η^2 = .104, as well for pain tolerance outcome F (2, 162) = 25.02, p = .00, η^2 = .236. Pairwise comparisons for pain intensity shown that the significant result reflect significant differences between pre-test and post-test (p= .001), respectively pre-test and post 1-week (p= .000) with significant lower level of pain intensity at post-test and post 1-week homework and no significant results of time from post-test and post 1-week (p = 1.00).For pain tolerance, pairwise comparisons showed significant differences between pre-test to post 1-week homework (p= .000) and between post-test and post 1-week homework (p=.000). Comparative analyses of the cognitive restructuring, acceptance and distraction revealed that there are no significant effects between subjects for pain intensity nor for pain tolerance, Wilk's Λ = .949, F (4, 160) = 1.05, p = .379, η^2 = .026 and no significant interaction effect group x time, Wilk's Λ = 924, F (8, 156) = 0.785, p = .616, η^2 = .039.

3.3.4. Discussion and conclusions

Pain is a global problem, being an extremely serious clinical, social and economic problem, due to high rates of prevalence and negative impact on individuals and society (Henschke et al., 2015). Because of the negative consequences associated with opioids consumption, such as vomiting, nausea or respiratory depression (Baldini et al., 2012) nonpharmacological interventions are often preferred (Songer, 2005; Williams et al., 2012). Although CBT techniques are the non-pharmacological golden standards for pain (Ehde et al., 2014) and widely used in practice, more recently theories, such us ACT promote acceptance or cognitive diffusion as successful strategies to manage pain episodes.

The purpose of the present study was to compare the efficacy of restructuring, acceptance and distraction as techniques in reducing pain replicating the results of Kohl et al (2013), and after 1-week practice. As hypothesized, all techniques produced improvements in time at the pain tolerance level. In addition, our results suggest that higher levels of tolerance are achieved after the 1-week practice of the techniques. Finding greater improvement after 1-week is a chiefly encouraging result, expanding the knowledge about strategies efficacy on middle terms. In contrast with Kohl et al (2013), we found that in both active groups pain intensity decreases over time. Average pain intensity decreases from pre-test to post-test to post 1-week in cognitive restructuring, from pre to post 1-week in acceptance group, while in the distraction groupremain similar over time.

In line with previous studies (Kohl et al., 2014) we did not find differences between cognitive restructuring and acceptance instructions nor in pain intensity or pain tolerance outcomes. In addition, we did not find significant differences between restructuring, acceptance and distraction in reducing pain after practice. Although average pain tolerance at post-test and post 1-week in the cognitive restructuring group was double than in the acceptance or distraction group, the standard deviations were high affecting heterogeneity which could deflate our results.

Though finding no differences between groups limits our understanding, individual studies comparing cognitive restructuring or acceptance strategies in their attempts to change pain outcomes also found small evidence or no effects (Branstetter-Rost et al., 2009; Hayes et al., 1999; Masedo & Rosa Esteve, 2007). Counting these results, we believe that our results highlight the need for more focused studies on the mechanism of change and participants' characteristics. For example, one study conducted by Verhoeven et al., 2010 founded that absence of goal directed motivation increases pain intensity. Moreover, high level of catastrophizing, fear of pain, depression or perceived pain as a threat was directly associated with pain intensity (Arnow et al., 2006; Severeijns, Vlaeyen, van den Hout, & Weber, 2001).

The present study has some limitations worthily to be discussed. First, all techniques used were shorted and simplified. Studies employing CBT or ACT protocols used more than one strategy to ensure the management of pain variables (e.g.: for CBT protocols: (Morley, 2011); for ACT protocols: (Hughes et al., 2017). Second, although the laboratory sessions were highly standardized, we could not control the degree of technique applicability in the 1-week practice period, which could affect the pain ratings at the second laboratory visit. Even though two remainders to practice the strategies were sent daily, no strategy to measure adherence or credibility was included. Further research could include a questionnaire or apps with a series of multiple choice questions in order to gain better control (examples of questions for treatment adherence: (Jeffcoat & Hayes, 2012). This caveat is related to our next limitation, the assessment of pain intensity which was based exclusively on self-report measures. We believe that by including physiological measures of pain in further studies could offer a more objectively picture of pain intensity (examples of physiological measure applicably to experimental studies: heart rate variability, skin conductance; (Cowen et al., 2015). Next, our design din not include a follow up assessment, therefore we cannot draw any conclusion about the lasting effects of these strategies and finally, these results are based on a pain-induced pain sample, therefore the extrapolations to clinical pain should be done with precaution.

Despite the limitations, the present study is important in several ways. This results extent the previous research by analysing the effects of the techniques after a middle term practice and by using the REBT model of cognitive restructuring in pain settings. In addition, our results suggest that both, acceptance and cognitive restructuring techniques are effective in reducing pain intensity and increase pain tolerance. Findings on pain tolerance are particularly important for the management of persistent or chronic pain when daily functioning and quality of life are highly affected (Dueñas et al., 2016; Meeus et al., 2012; Turk & Okifuji, 2002). Moreover, it is useful to know that all strategies could reduce pain intensity, effects that were not previously founded. Altogether, these findings provide further empirical evidence that cognitive restructuring, acceptance and distraction are effective strategies for pain management.

3.4 PAIN MANAGEMENT AFTER SURGERY: CAN VIRTUAL REALITY MAKE THE DIFFERENCE? FINDINGS FROM A CLINICAL RANDOMIZED CONTROLLED TRIAL, PHASE II

3.4.1 Introduction

Surgeries have the role of treating a broad spectrum of diseases in the mitigation of human suffering (Rose et al., 2014). Each year 313 million surgical procedures are performed worldwide (Meara et al., 2015). Only in the United States, in the year 2014, 10 million surgical procedures were performed in hospital wards, to which is added an additional of 11,4 million surgeries in ambulatory settings (Hall et al., 2017). Although necessary and life-saving, most of the procedures are associated with high amounts of postsurgical pain which if inadequate treated is associated with poor outcomes treatment and, might lead to persistent postoperative pain (PPO) and chronic pain (CP) (Chapman & Vierck, 2017; Niraj & Rowbotham D.J., 2011).

Traditionally, the upper crust of postoperative pain management was the pharmacological approach. That is to say, a combination of opioids, nonsteroidal anti-inflammatory, and local anesthetics delivered in different modalities are used in the treatment of acute postoperative pain. However, this line of treatment is not without side effects (Hartling et al., 2016; Marc O. Martel et al., 2015), and some of these approaches failed to achieve the expectations. For instance, using local anesthesia was believed to reduce the risk of CP development, but the results of a meta-analysis show that CP is prevented in the utmost 1 of every 4 to 5 patients (Andreae & Andreae, 2013). Moreover, the prescriptions of opioids outside the hospital settings contributed to the opioids crisis (Dhalla et al., 2011; Soelberg et al., 2017; Vadivelu et al., 2018). According to the National Institute for Drug Abuse (NIDA), in 2015, one in three Americans used prescription-based opioids (Han et al., 2017). This is an alarming report since the deaths related to opioids exceded the number of motor vehicle accidents, was quadrupled from 1999 to 2017 (Hedegaard et al., 2018, fig. 1), and in almost half of cases, drugs were used as painkillers (Hedegaard et al., 2017). Although the true incidence of physical drug dependence is unknown, some researchers argue that opioids usage, particularly in CP patients is without clinical improvements regarding pain intensity or functionality (Ballantyne, 2017).

Subsequently to the opioid crisis and in the attempt to better fit the pain management into the biopsychosocial framework, the guideline on the postoperative pain management (Chou et al., 2016) chiefly recommend multimodal approaches including non-pharmacological interventions. To date, from the non-pharmacological options, the most studied were the strategies rooted in Cognitive Behavior Therapy (CBT) (Gordon et al., 2016). Different strategies, such as distraction (Good et al., 2001; Noguchi, 2006; Ullán et al., 2014), relaxation (Good et al., 2001; Kate Seers et al., 2008; Wells, 1982) or guided imagery (Antall & Kresevic, 2004; Haase et al., 2005; Tusek et al., 1997) have been successfully implemented as an adjuvant to pharmacological therapy with promising results and the gain of having no side effects. In addition, along with a reduced level of pain, encouraging results were found regarding drug consumption and anxiety. However, these interventions failed to meet the hospital settings requirements in terms of producing improvements immediately, and in consequence, are barely

implemented in the hospital's practices of treating postoperative pain. In consequence, the postoperative pain continues to be suboptimally treated, putting pain medicine again back into the corner, with pharmacological approaches as the only workable solution in treating pain after surgeries.

Still, sparkling lights in the non-pharmacological approaches are represented by the newer evidence showing that making use of technological progress, some techniques (i.e., based on distraction) can be successfully integrated into the computer world, creating virtual reality (VR)-based interventions. The VR-based interventions create a vivid three-dimensional experience through a head-mounted display, controllers with tactile vibrations, and an omnidirectional treadmill. These interventions are based on Gate Control Theory (Ronald Melzack & Wall, 1965) and forestall the attention away from painful stimuli, redirecting to more pleasant ones in order to dampen the transmission of pain impluses to the thalamus, limbic system, and cortex (Fong & Schug, 2014; Hunter G. Hoffman et al., 2004). As a direct consequence, the awareness of pain and intensity are reduced. A recent meta-analysis (Georgescu et al., 2019) relying on 27 randomized controlled trials (RCT) conducted in hospital settings, showed significant effects of VR-based interventions in reducing pain intensity during medical procedures (g= 0.87, 95% CI 0.54 to 1.21) and after the medical procedures (g= 0.87, 95% CI 0.54 to 1.21). Although these are promising results in the attempt to treat pain, none of the included studies aimed to reduce postoperative pain. To date, only one study (Mosso-Vázquez et al., 2014) assessed postoperative pain outcomes using VR-based interventions as an adjuvant to pharmacological treatment. It demonstrated that, after cardiac surgery, scores of pain intensity are lower in the experimental group, but the uncontrolled design of the study can lead to possible biases (Naudet et al., 2011; Schmoor et al., 1996).

Consequently, the literature of postoperative pain urgently needs Phase II and Phase III trials to assess the adjuvant effect of the non-pharmacological intervention and especially the VR-based interventions in pain management. These trials are even crucial as a simulation of economic burden among hospitalized patients shows that for each patient $5,39 can be saved when treated with a VR-based intervention compared with standard treatment. Hence, our goal was to assess the efficacy and safety of a VR-based psychological intervention for pain at patients following surgeries under general anesthesia. We also objectively evaluated relaxation, adverse events, and satisfaction with the intervention using patient questionnaires.

3.4.2 Methods

Design and setting

This was a single-center, randomized, controlled, blinded, and parallel group phase II trial comparing a VR-based intervention with standard care in the attempt to decrease pain in patients undergoing non-cancer surgeries. This study is registered on ClinicalTrals.gov, number NCT03776344 and was designed and conducted in agreement with the Declaration of Helsinki and with the approval of the Ethical Committee of Babeș-Bolyai University and Municipal Hospital of Cluj-Napoca.

Participants

Eligible participants were those on their second day following non-cancer surgeries under general anesthesia who meet the inclusion criteria of (1) aged 18-65 years; (2) were after varicose veins, hernia repair or gallbladder surgery; (3) inpatient in the acute care unit; (4) willing and able to provide informed consent and participate in the study visit and follow-up questionnaire. Exclusion of patients was determined by (1) age below 18 and above 65 years; (2) patients with neoplastic pathologies; (3) patients with a history of motion sickness; (4) patients with visual impairment; (5) patients with severe/profound cognitive impairments; (5) patients using strong opioids (i.e., morphine). Surgeries of varicose veins, hernia repair, and gallbladder, were aggregated due to similarities across (1) the incidence rate (Jenkins & O'Dwyer, 2008; Rabe et al., 2010; Shaffer, 2005); (2) levels of pain intensity after surgery (Bay-Nielsen et al., 2001; Bisgaard et al., 2005; Gloviczki et al., 2011); and (3) odds of acute pain to be translated into PPO or CP (Bay-Nielsen et al., 2001; Bisgaard et al., 2005; Gloviczki et al., 2011). Patients with a history of motion sickness and visual impairments were excluded due to incompatibilities with the VR device (Lu, 2016).

Randomization and blinding

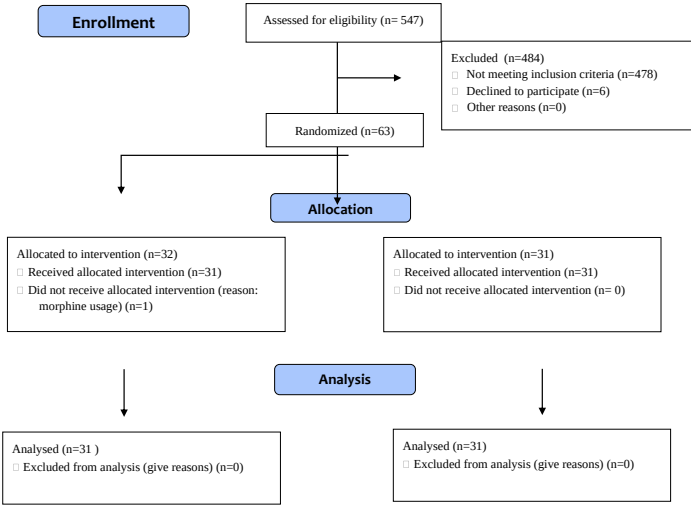
This study was the first randomized, phase II, parallel design conducted to assess the reduction of pain intensity after surgery; therefore, we had no previous studies to rely on estimating the drop-out rates or effect size. Therefore we relied on VR studies (Benbow & Anderson, 2019; Fodor et al., 2018) used to reduce anxiety in estimating the dropouts. Those studies found an attrition rate of 16%. The expected effect size (i.e., above 0.80) was based on VR studies aimed to reduce pain intensity after medical procedures (mainly for treating burn injuries). To estimate the number of participants in each group, G*Power software (Faul et al., 2007) was used resulting that a number of 54 participants (27/arm) are needed, accounting for an α of 0.05 and 1- β error of 0.80. After the attrition rate of 16% was considered, 31 participants were recruited in each arm. Randomization was stratified according to the type of surgery using numbers extracted from a random sequence generated by a computer.

Data collection and interventions

Starting October 2018 until September 2019, research assistants screened the weekly surgical schedule for potential participants graphically represented in Figure 1. Afterward, patients were approached in their hospital rooms in order to determine their interest and eligibility. Patients who were willing to participate were conducted in a separate room for the rest of the intervention to maintain blinding and similar conditions (e.g., setting, room temperature). Before the initialization of the first assessment, all participants signed the informed consent. The initial assessment involved the evaluation of pain intensity and relaxation through a semi-structured interview and evaluation of executive functions, as well as the baseline for physiological measure (i.e., skin conductance was measured for ~5 minutes). The initial assessment lasted approximately 30 minutes.

After the initial assessment, the patients were treated according to their group: (1) analgesic only as of the control group (SC) and (2) SC plus the VR-based intervention as the treatment group. The patients from the SC group, followed the pharmacological treatment as

recommended by their physician, and the level of skin conductance was measured for 15 minutes. Patients from the SC plus VR-based intervention group, in addition to the pharmacological treatment, after the initial assessment completed the cybersickness questionnaire and interacted with the VR application for 15 minutes. Before the exposure to the VR application, patients had several minutes to explore the VR world and get familiarized with the headset and controller. During the time when participants were immersed in the VR world, they were encouraged to enjoy the environment as much as they feel, with no other instruction. During the immersion in the VR world, the level of skin conductance was recorded. After the skin conductance measurements (in the control group) and VR exposure (in the treatment group) were completed, participants filled the measures of pain intensity, relaxation, and how much time they spent thinking about pain. The ones from the treatment group additionally completed the cybersickness, immersion, and satisfaction with the intervention questionnaires. Participants from both groups had no other instruction in order to prevent biases of pain outcomes.



VR application

Patients assigned to the VR treatment were exposed to the Nature Treks VR® using the Oculus Rift, a highly immersive device equipped with a headset, integrated headphones, and one hand controller. Nature TreksVR® is a commercially available application promoting relaxation. Patients from the treatment group had the opportunity to choose between fifteen environments (e.g., beach, mountains in the winter, sunset on Havana, marine life from oceans) and freely move 360 degrees. Each environment was populated with animals, flowers, or other

plants, and the weather was the most typical for the specific geographic zone recreated. Inside each environment, patients could interact with the elements or simply enjoy the location. For a better immersion, the environments were continuously kept fresh through interactive elements (i.e., growing flowers, rivers populated with fishes), and the possibility to create new ones in the environment (e.g., tree, rock). After each VR session was completed, the headset was cleaned out with sanitary wipes using alcohol in the prevention of spreading infections throughout patients.

Measures

The primary outcome was self-reported pain intensity (measured with the Numerical Pain Rating Scale, NPRS) and was blinded from participants. Self-reported pain intensity was complemented with the physiological measures (i.e., mean level of skin conductance), which was as well blinded from participants. For measuring skin conductance, a Biopac MP150 system (Biopac Systems, CA, USA) was used. Signal of SCs was recorded through two TSD203 electrodermal response electrodes previously filled with isotonic gel and attached to the first phalange of the index and medius fingers from the non-dominant hand.

The secondary outcome was relaxation (measured with the Numerical Rating Scale, NRS) as the VR-based intervention promotes a relaxed state of mind and time thinking about pain (measured with NRS). In the attempt to evaluate the feasibility of the VR-based intervention, satisfaction (measured with User Satisfaction Evaluation Questionnaire, USEQ), immersion (measured with I group Presence Questionnaire, IPQ), and adverse effects (measured with Simulator Sickness Questionnaire, SSQ) of VR usage was accounted. Other measures (e.g., demographic characteristics, pain catastrophizing, anxiety, and depression related to health, drug intake) were used to establish the equivalence between groups after randomization.

Statistical analysis

Preliminary analyses and preprocessing data of skin conductance

Demographic characteristics and psychological measures were explored for missing data, and distribution abnormalities. Means and standard deviations were used to characterize the sample. Baseline imbalances between groups regarding continuous variables (i.e., age, level of pain catastrophizing, anxiety and depression related to health problems) were explored using *t*-test statistics, and gender respectively the opioids usage using χ^2 test. Preprocessing of skin conductance measure was performed using AcqKnowledge 4.1 first through the visual inspection of the raw signal, and then applying the *Smoothing* function with a smoothing factor of three samples. This function has the same effect as the *low pass* filter by replacing the high-frequency signal with the mean values across three milliseconds in order to subtract the artifacts, without changing the waves form.

Main analyses

Behavioral data were analyzed using SPSS 20 (IBM Corporation, Armonk, NY) in accordance with the intent to treat principal (Gupta, 2011). Physiological data were processed using the AcqKnowledge 4.1 software, and for each patient, a difference score in the area under the curve between the last five minutes of measurement and baseline level of SC was extracted. In order to account for the changes in pain intensity and relaxation scores, separate repeated measure analysis of variance (RM-ANOVA) was employed. The effect size of intervention was estimated by computing a *d* value using the means and standard deviations (SD) of the control and treatment group. For clinical significance purposes, we coded for each patient the percentages of dropping in pain score, coding with 1 all pre-post differences above 30% on NPRS and 0 differences below this threshold. Subsequently, χ^2 test was employed to determine if are significant differences across the two groups. To estimate differences in time spent thinking about pain, treatment satisfaction, and adverse effects of VR intervention, *t*-test statistics were used. Pearson correlation was employed to examine the relationship between the level of skin conductance and pain intensity (as a difference score between pre-post intervention). A *P*-value was used to estimate statistical significance for all analyses.

3.4.3 Results

Preliminary analysis

Table 11 presents the descriptive statistics about study variables and demographic data in terms of means and standard deviations. There are no significant differences between the two groups as regards: age, gender, level of pain intensity and relaxation before the intervention, drug consumption, levels of pain catastrophizing, pain anxiety, and symptoms of anxiety and depression related to health (all p values $\geq .106$). Examination of the raw SC signal showed only a few drifts managed through the smoothing function.

Table 11. Descriptive statistics of study variables

		VR-intervention added to standard treatment	Standard treatment	
Variable	Type of varbiale	M(SD)	M(SD)	*P* values
Age	Cont.	46.71 (11.13)	51,81 (13.20)	1.000
Gender-female %	Cat.	45.2%	45.2%	0.106
Gender-male %	Cat.	54.8%	54.8%	
Painkillers usage %	Cat.	19.4%	16.1%	0.895
Type of surgery	Cat.			
Hernia repair %	Cat.	44.2%	55.8%	0.224
Varicose vein %	Cat.	61.4%	38.6%	0.265
Gallbladder %	Cat.	52.6%	47.4%	0.784
Pain intensity (baseline)	Cont.	5.94 (1.71)	5.52 (1.58)	0.321
Relaxation (baseline)	Cont.	6.23(2.27)	6.13 (1.96)	0.858
Mean SC (beasline)	Cont.	1.613 (0.19)	1.663 (0.26)	0.885
PCS	Cont.	15.03 (9.48)	12.77 (8.13)	0.318
PASS	Cont.	52.81 (16.81)	50,84 (19.22)	0.669
HADS -anxiety	Cont.	5.39 (3.45)	6.35 (4.22)	0.327
HADS- depression	Cont.	4.94 (3.36)	4.23 (3.07)	0.389
Pain intensity (after intervention)	Cont.	3.06 (1.73)	5.16(1.77)	
Relaxation (after intervention	Cont.	8.13(1.94)	7.06(2.23)	

Note: M= mean; SD= Standard deviation.

Main analyses

RM-ANOVA for pain scores revealed a significant effect of group, F(1, 60)= 92.54, p=0.000, d=1.93, indicating that patients from the treatment group reported a greater reduction in pain intensity scores than the patients treated with analgesic only (i.e., standard treatment). Regarding the clinical significance of this reduction, 22 from 31 patients aggregated to the treatment group reported a reduction of pain intensity scores higher than 30%. The χ^2 test (χ^2 (1) = 4.23, p=0.039) shows a significant association between group and odds to have such a reduction. Correlation between the pre-post difference in pain intensity and level of skin conductance was non-significant (p=.456).

With respect to our secondary outcome, RM-ANOVA for relaxation scores showed a significant effect of time, F(1, 60)=27,90 p=0.000, d=1.36 and a non-significant effect of group F(1, 60)=3.24, p=0.077 indicating that patients from both groups reported higher scores for relaxation after the intervention, but these scores are not a consequence of our VR-based intervention. Regarding time spent thinking about pain, there is a significant difference between groups, t(60) =3.422, p=.001, favoring the treatment group.

As for immersion, satisfaction and adverse effects with the VR-based intervention, patients report high levels of immersion (M=42,48, SD=3,98), and satisfaction (M=18.53,

SD=2.48) and 83,9%, rated that are willing to use VR-based interventions in further intervention for postoperative care. The presence or absence of adverse effects was analyzed through the pre-post differences of SSQ, as some of the adverse effects of VR interventions (e.g., nausea, dizziness, or abdominal discomfort) could be an effect of medication or surgery itself, not VR. The paired sample t-test ($t(30)= -1.41$, $p = .168$) showed non-significant differences indicating that there are no differences between the two endpoints.

3.4.4 Discussions and conclusions

Treating pain after surgical interventions is a very complex and challenging process (Baratta et al., 2014; Hutchison, 2007), and the integration of non-pharmacological approaches has been one of the priorities of healthcare reform (Chou et al., 2016). This RCT is a first using a VR-based intervention as an adjuvant treatment to standard postoperative management of pain (i.e., multimodal pharmacological therapies). Reckoning the public excitement and eagerness for VR and its applications, particularly in health care, the present study was designed as a synergy between new developments in VR techniques and pain management, ensuring a crucial first step in the management of surgical pain. Results of our study show that a psychological intervention delivered trough immersive VR is highly effective in reducing pain after surgery (as measured with NPRS). Specifically, patients randomized to VR-based intervention as a complement to standard treatment compared with the ones randomized to standard care, reported significantly less pain (mean differences of 1.19). Our findings are consistent with the previous results aiming to decrease pain after cardiac surgeries (Mosso-Vázquez et al., 2014), as well as pain during burn treatments or related to needles. The effect size found for behavioral reports of pain intensity exceeded the values for other types of pain in hospitalized settings (i.e. burn treatment (Carrougher et al., 2009; H. G. Hoffman et al., 2000), dental treatment (Bentsen et al., 2001; Frere et al., 2001)). However, scores of pain intensity on NPRS wasn't significantly associated with the physiological measure (i.e. mean of SC). Not coincidently, this result is consistent with other studies (Ledowski et al., 2007), failing to find a significant correlation between physiological and self-reported measures, but showing that skin conductance is strongly associated with other factors not related to pain intensity. With respect to the secondary outcome, we observed a non-significant difference in relaxation between groups but a significant result for the effect of time, suggesting that the increment in relaxation is not due to our intervention. However, this is a phase II trial, and the sample size calculation was based on our primary outcome. Consequently, it is possible that the effects of VR on relaxation be smaller than the one on pain intensity, and our study did not have enough statistical power to detect significant differences. In fact, this hypothesis is sustained by the means after the intervention across the two groups (Table 1) and from the observed power as showed in the RM-ANOVA, respectively, 0.426.

Further results showed that patients randomized to treatment group report high levels of satisfaction as regards the VR intervention. This establishes is essential as previous studies showed that a higher level of satisfaction is associated with a more quick recovery, low risk of inpatient mortality (Glickman Seth W. et al., 2010), increased overall quality of life (Dobríková et al., 2018) and is mirrored in the hospital monetary. Consequently, using VR-based

interventions can be a potential avenue to improve care perception as there are a limited number of strategies targeting patient experience (Rau, 2015). Regarding ruminative thinking about pain as a significant predictor of pain intensity (Scheuren et al., 2014), our findings show that patients treated with VR spent less time thinking about pain as the ones randomized in the analgesic only group. Positive findings were also found concerning the level of immersion and side effects of VR.

While the effects of our VR based intervention regarding reductions in self-reported pain intensity are positive, there are several limitations worth to be discussed. First, the external validity of our trial is possibly affected as the recruitment was made from a single center, and we don't know if the characteristics of our participants are representative of a broader population of surgical pain sufferers. Moreover, our results cannot be extrapolated to other VR environments, being strictly linked to Nature TreksVR®. Second, this trial assesses only the effects of VR immediately after exposure without follow up endpoints. It is particularly important to know how long this effect lasts, and the next trials should aim to quantify this effect. Similar environments, designed to reduce anxiety, proved to have long term effects, but in the absence of RCTs regarding this endpoint we can draw any conslusion yet. In addition, as we previously mentioned, it will also be interesting to know if VR can substitute or reduce drug consumption. Lastly, is imperative to be mentioned that our results are obtained in the absence of other non-pharmacological treatment, thus, we can conclude that the Nature TreksVR® produce significant reductions in pain intensity but we cannot know the effects when other non-pharmacological interventions are applied or when VR-based interventions are integrated in more comprehensive treatments of pain intensity. For instance, encouraging results were found for CBT protocols applied in pre-surgical settings by offering more realistic expectations regarding functionality and level of pain intensity after surgeries. The integration of VR-based interventions in more extensive protocols could enhance the effectiveness and could have other relevant pain outcomes, as a reduced length of hospitalization.

Consequently, Nature TreksVR®, as a VR environment, significantly reduced postsurgical pain. Regarding its feasibility and acceptability, our trial produced encouraging results with no dropouts and a high rate of treatment uptake, but the maintenance of these results should be confirmed by a Phase III trial incorporating other outcomes and conducted in multi-site centers to increase the external validity.

CHAPTER IV: GENERAL CONCLUSIONS AND IMPLICATIONS

4.1. General Conclusions

Non-pharmacological interventions and particularly, CBT interventions were proposed to act as a catalysator in the attempts to stop the opioid crisis. In consequence, a substantial number of guidelines included CBT techniques as adjuvant interventions in decreasing pain (e.g., (Barr et al., 2013; Chou et al., 2016)). However, in pain literature the concept of CBT is represented by a mixture of old and new techniques without strong conclusions regarding their efficacy.

Consequently, the present research sought to evaluate the effectiveness of new psychological therapeutic approaches in the management of pain. As a result, we began from the goal of evaluating the effectiveness of VR based therapies in tandem with the evaluation of the core techniques (i.e. cognitive restructuring) of traditional CBT therapy as compared to the new ones (i.e. based on ACT). Subsequently, we focus on improving the tools of pain assessment by evaluating the psychometric properties of one of the most commonly used instruments in the evaluation of pain catastrophizing. To do this, a few logical steps had to be performed.

First, a systematic synthesis and meta-analyses of all the published literature on VR-based intervention for pain associated with medical procedures were performed. Thus, we found that VR-based interventions for procedural pain as compared to treatment as usual have large effects in pain intensity, assessed either in real time or retrospectively.

Subsequently, we found in the present meta-analysis that VR-based strategies were successful for the affective and cognitive dimensions of pain, measured retrospectively, although the number of trials was smaller. Moreover, four trials compared VR-based treatments to active comparators with a large but non-significant effect. In addition, we found that adverse effects were reported in a minority of participants and were mostly consistent with vomiting and simulator illness.

Next we conduct a methodological study by assessing the validity of PCS. Results showed that PCS has strong psychometric properties as regards the factorial structure and ability to return similar results either is applied in acute or chronic samples. These findings are particularly important as pain catastrophizing was proposed as one of the most important contributors to pain intensity and chronicity.

Next, through an experimental design, we conduct an RCT comparing the efficacy of classical strategies (i.e., cognitive restructuring) with new techniques (i.e., acceptance) and distraction as a standard alternative to reduce pain. Though this study we found no differences between CBT and ACT strategies, nor for outcomes of pain intensity or pain tolerance. In addition, there were no significant differences between cognitive restructuring, acceptance and distraction in the treatment of pain following a one-week practice. Although the average pain tolerance for post-test and post-1-week in the cognitive restructuring group was double that for

acceptance and distraction groups, high standard deviations were also observed, possible bended our results.

In the last study, aiming to assess the efficacy of the new way of delivering CBT strategies on pain sufferers we investigate a VR based intervention on pain following surgery under general anesthesia. This study leads us to the understanding that immersive VR is particularly effective in reducing pain following surgery (as assessed with Numerical Pain Rating Scale). This means that patients randomized to treatment based on VR as an alternative to traditional psychological intervention relative to those randomized to standard treatment (pharmacological treatment) show significantly less pain (mean differences of 1.19).

4.2 Implications of the present work

Methodological implications

Methodologically through this thesis we were able to fill some blind spots of the pain literature. In addition, considering the way of conducting our research we believe that we contributed to the improvement of pain methodology. That is to say, though the first study, which is a meta-analytical approach we improve the pain methodology by adjusting the plan analysis to the current status of pain literature. Most of the previous studies using VR had small sample sizes and was not uncommon to have different study designs (i.e., crossover or parallel trials). In this first study we accounted for these variations and employed specific analysis to offer unbiased results as well as specific results accounting for each variation (i.e., the mean ES for studies using crossover design). Next, in our second study, in our attempt to validate the PCS scale we employed along with the CFA the ESEM analysis. We decide to double the statistical analysis as the last evidence shows that CFA is sometimes an over restrictive analysis which could conduct to biased results (Asparouhov & Muthén, 2009; Marsh et al., 2009). Confirming results with old and new techniques we believe is an important methodological advance and further attempts to test the construct validity should incorporate both analyses in their statistical plan. Subsequently, we test for the first time in a randomized controlled trial the effects of cognitive restructuring, acceptance and distraction after 1-week of practice as well as the effectiveness of a VR-based intervention for postoperative pain. By employing randomized controlled designs, we were able to limit the bias often resulted from other methodologies (e.g., non-randomized trials) (Allain et al., 2017; Schmoor et al., 1996). Moreover, the database of the first study was published online on a data repository (i.e. Open Science Framework) and the fourth study was registered in an online database (i.e., ClinicalTrials.gov) respectively a detailed plan analysis was described (see Appendix 6) in advance.

Practical and clinical implications

Besides the methodological implications, the present thesis has a series of clinical implications. Thus, through finding that VR-based interventions are highly effective in reducing

pain intensity as well as the cognitive and emotional components of pain offer to patients as well as to practitioner's evidence-based tools in managing pain. Moreover, the findings are even important as these interventions proved to be cost-effective (Delshad et al., 2018). Moreover, we find in the first study that the effects of the VR interventions are particularly effective in treating burn pain. This finding is essential as we consider the burden of this pain on patients (Corry et al., 2010; Rimmer et al., 2015). Moreover, we found that Nature Treks VR® as a VR-based intervention reduces pain after surgery. Knowing to have evidence-based interventions in reducing pain immediately after surgery is an important contribution as these interventions could be used to reduce the suffering in the healing process and to prevent the transition to chronic pain. In present, the rates of transition to chronic pain after surgery are across 60% depending by the type of surgery (Gerbershagen, 2013). Thus, we believe that these interventions would help to decrease these rates and consequently to reduce the suffering in those patients.

Another important clinical implication is the fact that PCS is a stable instrument to measure pain catastrophizing. The importance of these contributions is linked with the fact that this type of thinking was associated with increased pain (across different types of pain) and disability (Leung, 2012). Finally, finding that there is no difference as regards efficacy in reducing pain intensity or increase tolerance when different CBT strategies are used increase the practitioner's options to use evidence-based strategies.

4.3 Limitations and further lines of research

Although the present thesis led to important findings and implications for research and practice, there also exist a series of limitation worthed to be discussed. Thus, in our first study we found that VR-based intervention has large effects on pain, however, these effects were also associated with high heterogeneity which could dampen our results. Although across a variety of sensitivity analyzes, including both alternative statistical models (i.e. publishing bias, research quality) and restricted to the highest, clinically relevant and more homogeneous groups (e.g. children participants, burn dressing change procedures), variability remained high.

Next, in the second study, our classification as acute or chronic relied on self-reported measures which could also influence the reliability of our results. Further studies should employ more exhaustive assessments in order to classify the subjects. In consequence, this methodological constraint could affect our external validity. This limitation is also related to the type of pain used in the third study. Using inducing pain, not clinical, is possible to affect our estimation and limit the generalizability of our results. Moreover, is important to be noted that in this study we used only different strategies representing different approaches from the umbrella of CBT interventions, and further studies should employ more extensive protocol in order to (1) confirm our results and (2) to test the superiority of one intervention.

Finally, in our fourth study we had patients only from one hospital. Thus, it is unknown if the participants' characteristics are representative of a larger surgical pain population. Furthermore, our results cannot be extrapolated to other VR environments, being

strictly linked to Nature Treks VR®. Next, our study assesses only the effects of VR immediately after exposure without further assessments. Knowing how long this effect lasts is particularly important, and next trials should aim to quantify this effect. Different VR applications, designed to reduce stress, have long-term effects, but we can draw no conclusion in the absence of an RCTs specifically designed with this endpoint. In addition, it will be interesting to know whether VR can replace or reduce drug consumption. Ultimately, it is important to acknowledge that our findings are collected in the absence of other non-pharmacological treatments, so we can infer that Nature TreksVR® shows significant reductions in pain severity, but we cannot know the effects when other non-pharmacological methods are implemented or when VR-based approaches are incorporated into more extensive pain interventions. For example, encouraging results were found for CBT protocols applied in pre-surgical settings by offering more realistic expectations of functionality and pain intensity after surgery. Integrating VR-based treatments into more comprehensive procedures can improve efficacy and have other significant pain benefits as a shortened duration of hospitalization.

GENERAL CONCLUSIONS

Summarizing and acknowledging the limitation of the present work we can draw a series of final conclusion regarding the innovation of the present studies, as follows:

1) Throughout the first study, the present work contributes to the pain literature by estimating the efficacy of all VR-based interventions for pain management related to medical procedures accounting for the characteristics of the actual studies.

2) These estimations are made for VR-based interventions as compared with standard treatment in two meaningful time points, respectively during the procedures and immediately after. These two-time points are especially important as the pain experience change substantially during the procedures and the treatment goal is to offer the best care with minimal invasion.

3) In addition in the first study a series of important estimation has been approximated, respectively the efficacy of VR based interventions based on different designs (e.g. crossover and parallel) and for several meaningful clinical outcomes (e.g. only for burn patients or when pain is reported by others or by the pain suffer).

4) Likewise, the first study estimated for the first time the efficacy of VR-based interventions when are compared with other non-pharmacological interventions.

5) Subsequently, through the second study, the present work contributes to the pain literature by offering information regarding the construct validity of one of the most used pain scale. Chiefly, our results showed that PCS has a factor structure of three subscales, namely rumination, magnification, and helplessness. In addition, by the analysis employed in the

present work, we concluded that the scores of PCS are invariant when are applied in different settings such as different types of pain (e.g. frequent or chronic pain, emerged adults or adults or to males or females). The conclusions based on this study advance the knowledge regarding the properties of PCS and offer the Romanian practitioners a valid instrument for measuring pain catastrophizing.

6) Next, through the third study, the present work offers important knowledge to practitioners as well as to patients by highlighting that there are no differences in efficacy when old or new strategies based on CBT principles are applied for pain intensity or pain tolerance. Accounting that both strategies produce positive results in decrease pain and increase tolerance practitioners can further use any of these strategies in pain treatment focusing more on the patients' needs offering at the same time evidence-based intervention.

7) Finally, through the last study, the present work expands the knowledge regarding the efficacy of VR-based intervention in settings not tested before in a randomized controlled manner. The analysis of the present work leads to the conclusion that specifically, Nature TreksVR® is an effective VR tool for reducing pain after surgery. This information is chiefly important as the intensity of pain after surgery it has been proved to be a significant preditor of chronicity. Consequently, besides better care during the hospitalization, this intervention could contribute to reducing these rates.

8) In addition, not lastly, the Nature TreksVR® proved that it can be used without side effects and patient reports showed that they are satisfied with the application. This knowledge is highly important as the patients' safety is the first criterium in the choice of certain medical treatment. Moreover, knowing that this VR based intervention, besides efficiently reduce pain intensity, increase the patients' satisfaction regarding treatment is extremely relevant as in some countries (see the case of USA) the hospital monetary is mirrored in these rates.

In conclusion, the present Ph.D. thesis contributes in several ways to pain understanding, particularly regarding the efficacy of new approaches of pain. That is to say, the present project has the ability to find the answer for a series of questions (e.g., has the non-pharmacological strategies based on VR an analgesia effect?) but it also rising other questions (e.g., have non-pharmacological interventions the ability to reduce the usage of opioids?). Putting in balance the advances in understanding, the limits, and implication of this thesis we are confident that the present work brings valuable information regarding the efficacy of the new psychological approaches in pain management.

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