White Paper

Reducept

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CONTENT

1. Introduction

It is estimated that worldwide, one in five adults suffers from moderate to severe pain that continues for more than 3 months (Goldberg & McGee, 2011, Mittinty et al., 2018). Chronic pain seriously affects social and working life quality (Dezutter, Dewitte, Thauvoye, & Vanhooren, 2017; Leadley et al., 2014; O'Brien & Breivik, 2012; Reid et al., 2011) and is the leading cause of the disabled years of life (Vos et al., 2017)

The negative effects of chronic pain manifest themselves as, for example, the inability to perform certain movements, restrictions in daily activities, social isolation, depression and helpless-ness (Breivik, Eisenberg & O'Brien, 2013; Outcalt et al., 2015; Reid et al., 2011). Throughout the world, the under-treatment situation is even worse with a 83% of the global population having either no or inadequate access to treatment for moderate to severe pain (Forest, 2017), which further indicates the severe situation patients with chronic pain are in. The incidence of recurring chronic pain is increased in this group of patients, along with the amount of time spent in the clinical setting (Outcalt et al., 2015; Reid et al., 2011).

From the perspective of pain treatment, the International Association for the Study of Pain (IASP) has described that all clinicians should have certain expertise in pain management, which requires multidisciplinary knowledge and should aim to improve pain and/or pain management in pursuit of a better patient physical, psychological and work and social role functioning (Sutherland, 2020). As a consequence, we see a shift in the desired treatment of chronic pain. Medical treatment, especially the prescription of opiates, which was common for years, is shifting to another direction, as more and more professionals are realizing that pain is a biopsychosocial problem. Guidelines therefore increasingly prescribe pain education and pain-management therapies before moving on to medications. The implementation of these guidelines, however, leaves much to be desired. Many patients report having little or no experience with psychosocial pain interventions. It seems to be time for pain education and management to become available and scalable as medication.

2. Pain Theory & Education

Pain can be a strong emotional and subjective experience – and by influencing related cognitive, emotional and behavioural processes, the pain experience can change. Therefore, the Dutch chronic-pain guideline (Zorgstandaard Chronische Pijn) explicitly mentions that interventions should be administered at the start of treatment, regardless of sources of pain (Vereniging Samenwerkingsverband Pijnpatiënten naar één stem, 2017). In addition, WHO Guidelines (2008) states that the therapeutic regimes for chronic pain need to be combined with psychological support such as Cognitive Behavioural Techniques (CBT) and non-medical therapies, for instance explanation, beliefs and education. Knowledge that forms part of 'Explain Pain' and pain management program has demonstrated its ability to improve functioning and reduce pain scores with a reduction in pain scores that is sustained over a longer period (Moseley & Butler, 2015).

International guidelines (e.g. United States, Germany, Denmark, Norway, Sweden, Finland, Australia, New Zealand and Singapore, etc) prescribe pain education as pain management skills for primary intervention for chronic pain

(Briggs, 2012; Eccleston, Wells, & Morlion, 2018; van Cranenburgh, 2016; Wilgen & Nijs, 2007). Despite this priority and related recommendations, less than 4% of patients receive these interventions during their treatment in the Netherlands (Bala, et al., 2011; Briggs & Mayor, 2013; van Cranenburgh, 2016; Vrolijk, 2016; Wilgen & Nijs, 2007). Let alone those pain-suffering patients in the globe who originally do not have much access to treatment already.

3. Role of Virtual Reality in Pain Treatment

Virtual Reality (VR) as a non-medical intervention for managing pain has been studied for over two decades. This VR technology enables users to fully and harmlessly immerse themselves into a simulated 3D world where users are given multi-sensory stimuli. Whereas other treatment methods of chronic pain are often accompanied by plenty of side-effects.

The VR solution has become more available to this customer-ready market, when the cost-effective VR device *Oculus VR headset* was launched in 2013. As a result of easier accessibility of VR technology, many researchers started looking into the impact of VR technology on pain management. Despite the fact that chronic pain can occur with unknown origin, or it can also be generated from various root problems, such as physical injuries, diseases and drugs, etc (Jensen et al., 2011), the VR solution is proven to be effective depending on three mechanisms (Ahmadpour et al., 2019). Those mechanisms are 1) distraction, the most known attribution of VR which can disrupt the pathways of pain transmission (Pourmand et al., 2018); 2) focus shifting which tells brains that there are more important things to focus on; and 3) skill-building which builds up patients ability to control and regulate their response to their pain.

Such a solution is now considered as a complement to existing treatment methods, which is part of a holistic approach for pain management. There are three types of VR applications available in the market for pain treatment and management:

1) VR recreational games, offering instant distraction;
2) VR scenery videos, helping to relax;
3) VR psychology-based programs, offering long-term effect.

Although all of them can relieve pain, they lay emphasis on different aforementioned mechanisms. The first and second programs provide fun for pain-suffering patients and thus their attention to the pain can be distracted. On top of that, the third solution offers knowledge of pain, which helps patients learn how to confront their pain. Therefore, in the long-term they can gain a stronger mindset to deal with the pain themselves. Such a learning process can also be fun, if in game form.

More research is required in order to investigate its efficacy in detail, for example its long-run efficacy, efficacy for different pain sources and individual responsiveness, etc. However, VR long after its first introduction has stayed and is ready to serve more people. Another challenge is how to integrate this technology into a really meaningful application by design which is at the heart of the product development (Freeman et al., 2017).

4. Role of Mobile Application in Pain treatment

Mobile application is no longer a novel solution, particularly after a rapid surge of mobile health (mHealth) solutions in recent years. It is valued in four aspects: 1) supporting clinical diagnosis; 2) improving clinical outcome improvements via behaviour changes as well as enhancing patient adherence and compliance with treatment for instance through games; 3) serving as an independent digital therapeutics; and finally 4) primarily delivering disease-related education (Rowland, et al. 2020). WHO also acknowledges mobile applications as a potential smart information and communication technologies to address chronic conditions and issues in healthcare systems (Ryu, 2012). To be specific, when it comes to pain management, mobile applications have become one of the most beneficial solutions for outpatient appointments and home settings. However, the majority of mobile applications lack 1) clinician and patient inputs (Zhao, Yoo & Lancey, 2019; Ledel Solem, et al. 2020); 2) the foundation of scientific evidence; and 3) rigorous (long-term) tests (Salazar, et al. 2018). As a result, what is more important is that the content provided by mobile applications involves stakeholders, is evidence-based and scientifically assessed and reviewed (Thurnheer, et al. 2018).

5. About Reducept

Reducept offers both pain education and pain management skills, which is based, among other things, on the 'Explain Pain' Theory (Moseley & Butler, 2003). To be precise, Reducept teaches patients about pain through virtualization of their own bodies, but to be truly effective, patients use cognitive techniques in a playful way to train the brain themselves.

Our uniqueness lies in the integration of policy guidelines-based education (*Section 2. Pain Theory and Education*) and pain management techniques (*Section 5.2 Working Mechanism*). The aforementioned guidelines in *Section 2. Pain Theory and Education* have been translated into game-based training by which patients learn about pain and about how to apply pain management strategies in their daily lives (Briggs & Mayor, 2013; Elabd, 2012; Moseley & Butler, 2015).

Initiating from VR, in the latter half of the year 2020 Reducept has translated the game into a mobile game to lower the barriers one step further of pain management at patients' own home. Eventually, the aim of Reducept is to enable patients to experience that pain can be influenced and managed in a positive way by changing the way they think about pain.

5.1 Learning experiences

Pain information in Reducept is based on the 'Explain Pain' guidelines (Moseley & Butler, 2015) and on the guidelines by Lauren Heathcade at the IASP World Congress on Pain 2018. In summary, the most important learning experiences in Reducept are that:

- There are many potential factors that contribute to pain
- We are all bioplastic
- Pain is not an accurate marker of tissue damage
- Pain education is a form of treatment
- Pain is a brain expression
- Pain is a protector
- The brain becomes over-excitable/sensitive

5.2 Working mechanism

Reducept offers patients both state of the art pain education and pain management skills. Pain management as a mental skill, have been used since the 1970's and are a fundamental part of modern multidisciplinary pain treatment (Williams, Eccleston, & Morley, 2012; van Dessel et al., 2014).

The pain management techniques used in Reducept are derived from evidence-based psychological treatment techniques. These include techniques from CBT, Acceptance and Commitment Therapy (ACT), Mindfulness and Hypnotherapy (Fennema & Zantema, 2019). Many studies have evaluated and assessed these psychological techniques and among all CBT plays the largest part. On top of the long-proven efficacy of CBT especially for the elderly group aged 65 and above (Ehde, et al. 2014), Veehof et al (2011) suggests an integration of CBT and mindfulness to maximize the therapeutic effectiveness. This treatment effect is seen the strongest in the category of adult chronic pain, if attention is paid to cognitive coping strategies (Eccleston, Morley & Williams, 2013). Traditionally, aforesaid psychotherapies are practiced onset with a psychologist or a medical profession. Nevertheless, adapting and moving them to an online session, the effectiveness is comparable (Knoerl, Lavoie Smith & Weisberg, 2015). This finding justifies the validity of Reducept's exploration on both VR and mobile digital platforms.

In the context of VR, exercises have been redesigned, using the unique features and opportunities that VR has to offer. The immersion of VR gives us the unique ability to better influence the cognitions, attention and emotions of patients with chronic pain (Jin et al., 2016). Being able to direct the patient's experience makes it possible for patients to always achieve success in their training. For patients who have had many painful, ineffective and invasive treatment experiences, this is of great importance for obtaining a positive growth mindset (Fennema & Zantema, 2019). In the form of mobile applications, original Reducept VR game design was translated into a mobile game to fully exploit the possibilities offered by the prevalence of smartphones and easier access to the internet. It means with much lower (upfront) costs, patients can start the training with Reducept and make the most from their training.

During the design cycle of Reducept a Participatory Design (PD) method was used. To make sure the 'need' of the person suffering from chronic pain to be fulfilled – and to guarantee Reducept would become an easy to use solution for use in clinical and home settings (Heapy et al., 2015a, 2015b; Kuipers, Wartena, Dijkstra, Prins, & Pierie, 2013; Simonsen & Robertson, 2013). Relevant stakeholders-including adults with chronic pain, therapists,

physicians, nurses and game developers-are concurrently involved in the design process. This process includes research, decision-making, development of ideas for the application and for testing of Reducept during and after the development process.

5.3 Research findings

Continuous and anonymous collection of Reducept player data takes place. Each day, hundreds of patients already log on into Reducept. Over more than 10 thousand Reducept sessions, patients report decreases in pain scores 75% of these sessions. In collaboration with the University of Twente, machine learning is applied to our data to discover relevant data patterns.

In collaboration with healthcare centres in the Netherlands, tests were conducted between January 2018 and June 2019. During this testing period, patients with chronic pain could train with Reducept in different care settings such as specialist centres, physiotherapy practices and psychology practices. Patients with chronic pain symptoms (ICD10), in the 18 to 90 age range and of noted minimum average intelligence were enrolled in the study (Supplemental Information 1: WHO ICD10 International Classification of Diseases, n.d.). Exclusion criteria were complex psychiatric problems, visual disorders and patients with impaired reality perception, delusion and/or hallucinations. Training sessions were recorded and processed in the Unity database, after which the data was analysed in Unity and Excel.

The total number of individual training session games played by patients with chronic pain was 4,562. A decrease in pain was noted in 77% of the training sessions. The average decrease in pain score was 8%, corrected for the continuity factor. 180 patients were asked to play the complete training program in chronological order. 104 patients indicated a starting VAS pain score of > 4. The average absolute decrease was 2. Players with a higher pain score noted a greater pain decrease here. User-friendliness of Reducept scored 8 out of 10 (Drew, Falcone, & Baccus, 2018).

In 2020, Lisanne Tilma as a psychosomatic physiotherapist partnered with Reducept and conducted research on Reducept and its application for the physiotherapist. Of various ages and symptoms, 55 patients with chronic pain were recruited (69% were women). These participants were told to 1) play Reducept on an Oculus Go VR headset for one month and 2) to register for training at the practice and had to train with Reducept at least twice a week. The study measured how users experience their quality of life, pain score, as well as the degree to which someone feels annoyed by pain.

In this study, about two third of the participants indicate that Reducept has improved their quality of life, of which 75% of these participants feel an improved quality of life due to less pain. The effects of Reducept on patients vary as well - in some cases all pain disappeared altogether, or pain disappeared for multiple days and others noticed the biggest difference while playing Reducept, in spite of long-term effects yet to be tested. Based on both questionnaires and interviews with patients, Reducept leads to less pain, better sleep, more energy, more relaxation, more capable of dealing with pain and getting mentally stronger.

Currently, a randomized controlled trial (RCT) with the Radboud University Medical Centre and Rijnstate Hospital is taking place (Smits et al., 2021, in progress). In this study, participants with non-specific lower back pain problems have been included. Outcome measures include VAS Scores, quality of life, anxiety and depression scores and daily functioning. Rijnstate and Amsterdam University Medical Centre have submitted several RCT studies for further research.

With Radboud University Medical Centre as sponsor, a work group including six top-clinical hospitals, two Rehabilitation centres and two University Medical Centres is currently applying for a multi-centre RCT.

5.4 Future research directions

At this moment, the research pipeline specifically for Reducept is well fulfilled. The research programs are in collaboration with top university medical centres and health institutions such as Radboud UMC, VUmc, Heidelberg UMC, UMC Brussel, Roessingh Rehabilitation, Rehabilitation Friesland and Maasstad Ziekenhuis Et cetera. Other than the research already pinned on the Reducept roadmap, our future research directions combine data-driven research with clinical studies. Data-driven studies are needed to keep up with the speed of technological development – Reducept, VR and the mobile application. In regard to VR, for example, patients playing Reducept VR can be compared to the SHAM-controlled patients who are the control groups and under a similar procedure omitting a key therapeutic treatment Reducept. As two options - VR and mobile applications are available, a study that compares the effects of Reducept VR, Reducept mobile game and placebo is of vital importance, which can provide more in-depth strategic insight for the company. Moreover, the research questions such as if using Reducept lead to reduced medication intakes and an increase in work participation in the labour markets are interesting topics to investigate. We are open to research collaborations. Science is part of the core of Reducept.

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