Symptom Self-Management Across Settings Emphasizing Virtual Reality

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ABSTRACT

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Symptom management is a cornerstone of nursing practice. Symptoms are of clinical and research importance because they are the most common reason for which individuals seek healthcare. Rapid innovations in technology have made it possible to deliver interventions to alleviate a number of symptoms, providing safe, non-invasive alternatives to traditional pharmacologic treatments. One platform for delivering such interventions is via immersive technologies like virtual reality (**VR**). The purpose of this dissertation is to examine symptom self-management across various settings with an emphasis on virtual reality interventions. A three-paper format was used.

In the first paper, we performed a systematic review of VR for acute pain management that clarified the heterogeneity of available content and need for intentional presentation and pairing of interventions to appropriate populations in order to ensure efficacy. Following this, to better understand factors of symptom self-management, we interviewed inpatient LKDs and found that careful consideration of the

patient population and psychosocial factors that impact patients' symptom experience is required for successful implementation of symptom management interventions. Findings are reported in the second paper Lastly, a feasibility study was performed using VR meditation for fatigue management. This study discovered that remote-based VR deployment is feasible and acceptable to patients, but it is vital to provide clear instructions and parameters for VR content and hardware use to promote participant adherence, especially when using a novel therapeutic technology without direct supervision.

Overall, VR is a viable platform for deployment, but further development of content is currently required. Future research is needed to explore the efficacy of VR interventions for symptom self-management using various therapies over time and across different populations. Due to current limitations in hardware, clinicians should carefully evaluate the context of patient need – and openness to use – prior to utilizing VR and ensure viable matching of content and individual devices to patient needs at home. Research on how VR content and hardware can meet the individual constraints of home environments is needed. Cross-discipline collaboration between researchers with backgrounds in patient care, design, and engineering that is informed by input from patients is key to ensuring development of efficacious and safe VR therapeutics. Additionally, researchers must collaborate with industry partners to ensure translation of these findings into broad clinical use. In the post-COVID-19 world, VR has the capacity to encourage health and healing on a scale previously unimaginable. The scope of VR's impact will largely depend on the level of collaboration between these key stakeholders.

Only by working together can we usher in a new era of healthcare delivery through immersive VR symptom self-management.

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Chapter 1. Introduction

Symptom management is a cornerstone of nursing practice.[1] Defined as the "self-reported perception of an individual's experience of disease or physical distubance",[2,3 (p.500)] symptoms play an essential role in managing disease and injury. Symptoms are of clinical and research importance because they are the most common reason for which individuals seek healthcare.[4] Pharmacologic interventions are essential for managing symptoms such as acute pain and anxiety, yet growing fears regarding harmful side effects and chronic use have increased concerns with using prescription medications as first line therapies. Rapid innovations in technology have made it possible to deliver non-pharmacologic interventions to alleviate a number of symptoms including pain intensity,[5] depression,[6] muscle tension,[7] fatigue[8] and anxiety,[9] among others. These interventions provide safe alternatives to traditional pharmacologic treatments.

Digital delivery of biofeedback,[7] mindfulness,[8] and cognitive behavioral therapy[9] has allowed for streamlined administration of evidence-based treatments and encouraged symptom self-management. Dr. Lauri Linder elegantly defines symptom self-management as the "process by which individuals with chronic illness integrate strategies that allow them to cope with the illness in the context of their day-to-day-life".[10 (p.1)] Often applied in chronic disease populations, most individuals can perform symptom self-management with proper education and training. One platform for delivering such interventions is via immersive technologies like virtual reality (**VR**).[5,6] The purpose of this dissertation is to examine symptom self-management across various settings with an emphasis on virtual reality interventions.

Dissertation Elements

The dissertation purpose is to answer following specific aims:

1) To systematically review the delivery and clinical efficacy of VR therapeutics for acute pain management in adults and identify practical considerations of VR deployment, as well as current gaps in the literature, specifically to ;
    a. Examine the delivery and efficacy of VR therapeutics for clinical acute pain management in adults;
    b. Describe VR's effect on pain-associated metrics (anxiety and physiologic measures);
    c. Explore how included studies utilize VR components;
    d. Determine the duration and kinds of VR content utilized;
    e. Recognize how studies address infection control and training for VR use;
2) Explore living kidney donors' experience of postoperative pain;
    a. Uncover how donors describe their postoperative pain;
    b. Describe what strategies donors use to manage their postoperative pain;
    c. Uncover factors unique to donors' surgical experience that might help mitigate or aggravate their experience of postoperative pain;
3) Examine the feasibility and acceptability of using virtual reality meditation (**VRM**) to manage fatigue in outpatients with rheumatoid arthritis (**RA**);
    a. Examine the feasibility of implementing VRM as an adjunct for managing fatigue
    b. Determine the acceptability of using VRM for fatigue management

c. Explore the experience of using VRM to manage fatigue in outpatients with RA

Each chapter in the dissertation is formatted in the style of its prospective journal. A brief overview of each chapter is as follows:

Chapter 2. A Systematic Review of Virtual Reality Therapeutics for Acute Pain Management

A systematic review was performed in order to examine the delivery and efficacy of VR therapeutics for acute pain management in adults within clinical settings. Additionally, this review identified practical considerations of VR deployment, current gaps in the literature and clearly defined areas for future clinical research.

Chapter 3. Living Kidney Donor Perspectives on Acute Postoperative Pain Management

This paper describes findings from semi-structured interviews to examine living kidney donors' experience of postoperative pain. This study aims to uncover how donors describe their postoperative pain, determine what strategies donors use to manage their postoperative pain, and uncover factors unique to donors' surgical experience that might inform clinical management of donor's postoperative pain.

Chapter 4. Virtual Reality Meditation for Fatigue in Persons with Rheumatoid Arthritis

This paper reports findings from a mixed-methods study that examined the feasibility and acceptability of using a VR meditation therapeutic in a sample of community-dwelling adults with rheumatoid arthritis. The primary symptom of interest was fatigue, with secondary symptoms of depression, anxiety, pain behavior, physical function and mood.

Chapter 5. Conclusion

Successful implementation of symptom management interventions requires careful consideration of the patient population and the psychosocial factors that impact patient's symptom experience. This chapter describes the connotations of the dissertation for clinical practice and research. A discussion of gaps identified in the present work and areas for future research is presented.

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Chapter 2:

A Systematic Review of Virtual Reality Therapeutics for Acute Pain Management

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Abstract

Background: Pain management is a fundamental human right, yet its delivery is a consistently arduous task in clinical settings. Virtual reality (VR) is a non-pharmacologic, virtual platform that can be used for acute pain management.

Aims: The purpose of this systematic review is to examine the delivery and clinical efficacy of VR therapeutics for acute pain management in adults and identify practical considerations of VR deployment, as well as current gaps in the literature.

Methods: A systematic review of all pertinent articles published between January 1st, 2000 and August 1st, 2020 was conducted according the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.

Data Sources: A search of PubMed, CINAHL, PsychINFO, Embase, Compendex, and Inspec was completed using MESH and keyword search terms related to acute pain and VR.

Results: Twenty-three articles met final inclusion criteria and were included in this review. Studies utilized VR in a variety of settings for wound care, procedure-induced pain, physical or occupational therapy, dental treatment or generalized acute pain. The primary means by which included studies promoted analgesia was via distraction. Of the reviewed studies, 19 (83%) reported decreases in pain intensity while using VR compared to no VR use or to a non-VR group.

Conclusions: This systematic review found VR to be an effective tool for acute pain management. Findings from this review also underscore the importance of addressing patient's sense of presence and levels of immersion, interaction and interest when

deploying VR. Future VR studies should consider incorporation of anxiety, presence, and VR side effect measures in addition to acute pain metrics.

A Systematic Review of Virtual Reality Therapeutics for Acute Pain Management

Introduction

Pain management is a fundamental human right, yet its delivery is a consistently arduous task (Brennan et al., 2007; Mitra et al., 2018). Utilizing best practices for pain management helps to minimize its negative effects on healing and quality of life (Chou et al., 2016) and potentially prevents its transition to chronic pain (Meissner et al., 2015). Other factors like anxiety can exacerbate acute pain (**AP**), which usually occurs in the moment and for a short duration (Melzack, 1973; Sternbach, 1968). While pharmacologic management of AP – especially using opioid medications – is highly effective, (Angell, 1982; Bonica, 1966) caution is also required. Numerous side effects (Ricardo Buenaventura et al., 2008), rising rates of chronic opioid use (Brummett et al., 2017) and increased incidence of opioid-related deaths (Calcaterra et al., 2013) have led to greater use of non-pharmacologic alternatives for AP management, such as virtual reality (**VR**). The purpose of this systematic review is to: 1) examine the delivery and efficacy of VR therapeutics for clinical AP management in adults and 2) identify practical considerations of VR deployment, current gaps in the clinical literature and clearly define areas for future clinical research.

Background

As an immersive digital platform, VR utilizes visual and auditory stimuli to give users a sense of physical presence in a virtual space (Slater & Wilbur, 1997; Yumurtacı, 2016). Delivering VR interventions necessitates considering four components: presence, immersion, interaction, and interest (Stark, 1995). For VR interventions that use

distraction as a mechanism of action a higher degree of **presence** (*the more users "feel" they have entered a virtual world*) is linked to greater analgesic efficacy (Gutierrez-Martinez et al., 2010, 2011; Hoffman et al., 2004; Slater & Wilbur, 1997). **Immersion** dictates the degree of presence, via the quality of visual and auditory equipment (hardware) used (Slater & Wilbur, 1997; Yumurtacı, 2016). This is most effectively done using a head-mounted device, linked equipment, and head-tracking that shifts the digital field of view (FOV) – i.e. what they see – as the user looks, and "moves", about the virtual environment (Stark, 1995). Both VR equipment and content (software) determine the level of **interaction** users have with the virtual environment. *Active VR* denotes the ability to interact with, move through, or change the virtual environment, whereas *passive VR* limits interaction and makes the user a reflexive viewer (Stark, 1995). **Interest** in the virtual environment holds these elements together and is positively correlated to presence (Hoffman et al., 2004). Active VR content increases presence and is also more interesting than passive content (Gutierrez-Maldonado et al., 2011; Gutierrez-Martinez et al., 2011; Hoffman et al., 2004, 2006; Wender et al., 2009). Laboratory studies have found that interventions with a high degree of presence, and that use active (*versus passive*) VR modalities, to significantly reduce AP (Gutierrez-Martinez et al., 2010, 2011; Hoffman et al., 2004, 2006; Wender et al., 2009).

Systematic reviews have been performed in order to explore VR's efficacy for burn and procedural pain (Chan et al., 2018; Scapin et al., 2018), among inpatient randomized controlled trials (Dascal et al., 2017), and generally for acute and chronic pain management (Mallari et al., 2019). Given the evolving nature of VR an updated and comprehensive review of clinical studies that use VR for AP management in adults is

needed. Additionally, few address practical considerations for deployment and none have specifically addressed the components of VR interventions that are vital to ensuring an efficacious therapeutic environment (presence, immersion, interaction and interest). The primary aim of this systematic review is to examine the delivery and efficacy of VR therapeutics for clinical acute pain management in adults. As secondary aims, we examine VR's effect on pain-associated metrics (anxiety and physiologic measures), explore how included studies utilize VR components, determine the duration and kinds of VR content utilized, and recognize how studies address infection control and training for VR use.

Methods

Protocol and Eligibility Criteria

This systematic review was completed in accordance with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Moher, 2009; Moher et al., 2015). Articles for review included original research articles in published journal and conference proceedings. Inclusion criteria included articles addressing adults (*18 years and older*), acute pain, procedural pain, surgical pain, postoperative pain, physical pain, measures for pain, pain perception, and virtual reality (**VR**). For purposes of this review, VR was defined as "an immersive 3D display that [excludes] the external (real-world) environment" (Chan et al., 2018, p. 2). If their title or abstract matched the inclusion criteria, articles were reviewed. Articles in a language other than English were translated, using Google Translate, and reviewed against criteria. Exclusion criteria included: 1) articles addressing children and adolescents or containing either in their study in combination with adults, 2) studies focused on chronic pain and chronic pain

syndromes (including chronic diseases with chronic pain elements – such as rheumatoid arthritis, neuropathic pain), 3) those that used augmented reality, and 4) studies that did not include AP metrics or measures. Articles were also excluded that lacked author names or access to full text. A complete list of inclusion criteria based on possible journal filters is included in *Supplementary Materials*.

Search and Study Selection

A search of PubMed, CINAHL, PsychINFO, Embase, Compendex, and Inspec was completed using MeSH and keyword search terms related to AP and VR. Each database required database-specific terminology and terms, a complete list of the individual MESH and keyword terms is listed in *Supplemental Materials*. As the majority of clinical VR research has occurred since 2000, the search included all pertinent articles between January 1, 2000 and August 1, 2020. A database search was performed. Title and abstracts were uploaded to Rayyan, an online tool for managing title and abstracts (Ouzzani et al., 2016); studies were excluded if they failed to meet eligibility criteria. If studies contained titles that were relevant, but lacked abstracts for review, they were included in the final screening. Final screening of studies involved review of complete manuscripts whose title and abstract met the inclusion criteria. Studies were omitted if content failed to meet all stated criteria. Disagreements between reviewers were resolved based on consensus of all authors.

Risk of Bias Assessment

Eligible articles included in the review were assessed for bias using the Cochrane Review's tool for assessing risk in randomized trials (Higgins et al., 2011). Each paper's

bias was rated as “high”, “low”, or “unclear” based on these respective categories. Non-randomized trials were not assessed and instead marked as not applicable (“n/a”). Disagreements at all stages of the selection process were resolved by consensus or in consultation with the senior author (H.T.).

Results

Study Selection and Assessment

Details of the study assessment process are shown in *Figure 1*. The initial search resulted in 3,847 articles, 856 of which were duplicates. The list of 2,991 non-duplicate articles 2,860 articles were excluded based on stated criteria (*vide supra*), leaving 131 articles. Full texts were obtained and 106 of them were subsequently excluded for not meeting inclusion criteria. Two articles were excluded due to duplicate publication. Thus, 23 articles met final inclusion criteria and were included in the review.

Study Characteristics

Among eligible studies, sample sizes ranged from 8 to 182 participants, and 11 studies used a randomized controlled trial design. Studies utilized VR in Inpatient, Outpatient and Procedural Clinics as well as Emergency Room settings for wound care (8), procedure-induced pain (6), physical or occupational therapy (4), dental treatment (3) or generalized acute pain (2). Complete information on study populations, interventions, comparators, primary outcome measures and study designs (PICOS) can be found in *Table 1.*

Components of VR

Just under one third of studies (n=7) used patient-reported measures of presence in the virtual world (*Table 2*). In three of these studies, participants reported a moderate, or greater, sense of presence during VR (Alshatrat et al., 2019; Hoffman et al., 2000; Maani et al., 2011). While individual types of hardware for immersion varied drastically among studies (*Table 2*), the categories of immersive hardware could be divided into several groups. Computer-based VR content was used in 7 studies, one study used both computer- and smartphone-based content (Mosso Vázquez et al., 2019), five used smartphone-based content, 7 used 3D glasses (*or equivalent*), and three studies omitted details on their hardware (Jin C. et al., 2018; Walker et al., 2014; Zschaler, 2010). Over one third of studies (n=9) used active – as opposed to passive – VR, and one study compared active to passive VR (Mosso Vázquez et al., 2019). Interest (*"fun" or another correlate to interest*) was measured in four studies (*Table 2*).

Of the included studies, 12 used digitally rendered VR environments, 8 studies used a video or 3D video, one used a computer game (Morris et al., 2010), one study described the environment but not its name (Zschaler, 2010), and one study omitted details on content (Carrougher et al., 2009); see *Table 1*. Of note, one digitally-rendered VR environment (Patterson et al., 2006) and one video (Konstantatos et al., 2009) utilized a specified therapeutic (*hypnosis*); no other studies used content based on evidence-based therapeutics. Though four studies used the same VR environment ("SnowWorld", created by University of Washington HITLab and Harborview Medical Center's Burn Center), all other studies with smartphone or computer-based VR used different environments. Across studies, participants reportedly spent between two and 30+ minutes in virtual environments (*Table 2*).

Effect of VR on Pain Intensity

In all but one study, pain intensity was assessed using a visual analog scale (VAS), graphic rating scale (GRS) or numeric rating scale (NRS; *Table 1*). Of the 23 studies reviewed, 19 reported decreases in pain intensity while actively using VR. Of these 19 studies, 15 studies reported statistically significant decreases in pain intensity ($p<0.05$). Seven were in comparison to a no-VR condition within the same participants (Alshatrat et al., 2019; Furman E et al., 2009; Hoffman et al., 2000; Maani CV et al., 2011; Sikka et al., 2019; Spiegel B. et al., 2019; Tse et al., 2003), and seven to a no-VR group (Ding et al., 2019; Guo et al., 2015; JahaniShoorab et al., 2015; Jin C. et al., 2018; Konstantatos et al., 2009; Pandya et al., 2017; Tanja-Dijkstra et al., 2018). Yet not all studies have shown these positive results. Two studies noted no difference between groups receiving VR for AP and standard of care (Glennon et al., 2018; Walker et al., 2014) and Morris et al. (2010) found that there was no difference in pain intensity when individuals were, or were not, using VR. Lastly, Zschaler et al (2010) found VR to increase pain intensity when paired with patient-controlled analgesia. Further details about study pain measures can be found in *Table 1*.

Secondary Outcomes and Practical Considerations

Anxiety is a correlate of pain, and physiologic measures (*heart rate and blood pressure*) are pain indicators, yet these were rarely assessed in studies. Fewer than half of studies (10 of 23) measured anxiety (*Table 3)*. Virtual reality decreased anxiety, “stress”, or “nervousness” in three of these studies (Tanja-Dijkstra et al., 2018; Hoffman et al., 2000; Patterson et al., 2006), but had no effect on anxiety in others (Glennon et al., 2018; Konstantatos et al., 2009; Morris et al., 2010). In the seven studies that reported

physiologic measures, VR had mixed effects. During some painful events, VR was found to decrease systolic blood pressure (Alshatrat et al., 2019; Mosso Vázquez et al., 2019), yet in the same study by Alsharat and colleagues, no change was seen in diastolic blood pressure or heart rate. Other studies have also reported VR to have little effect on blood pressure (Furman E et al., 2009; Pandya et al., 2017).

Fewer than half of included studies measured, or commented on, VR-related side effects. Of the potential side effects of VR (Cobb et al., 1999), nausea was the only adverse VR symptom reported by articles that were included in this review. Four studies reported no subjects who experienced nausea (Maani et al., 2011; Pandya et al., 2017; Walker et al., 2014; Wright et al., 2005), three studies reported subjects who experienced mild nausea (Carrougher et al., 2009; Furman et al., 2009; Hoffman et al., 2000), and one study reported a small number of subjects with greater than mild nausea after VR use (Alshatrat et al., 2019). Another finding of included studies was that practical considerations – such as infection control and participant training – were seldom mentioned. Only two studies mentioned infection control measures taken during the study (Sikka et al., 2019; Spiegel B. et al., 2019), and 6 studies mentioned training participants in VR use prior to beginning the study. Details on anxiety, physiologic and VR side effect measures used and inclusion of infection control or VR training are found in *Table 3*.

Risk of Bias

Of the studies included in the bias assessment (n=12), one-half clearly utilized random sequence generation, while others omitted how randomization occurred. Only one study reported clear allocation concealment (Tanja-Dijkstra et al., 2018), while three

had high potential for bias (Jin et al., 2018; Spiegel et al., 2019; Walker et al., 2014). The remainder (n=8) failed to address it altogether. The majority of studies suffered from a high degree of bias in blinding of participants and personnel, as well as the outcome assessment (n=9); the remainder failed to mention these details. Only one study noted incomplete data that could have biased the study, and no studies selectively reported on their data. Just under one-half (n=12) of studies were randomized controlled trials and were evaluated using the bias rating tool; other studies were not evaluated but are assumed to contain more bias due to study design. Further details of studies included in the bias tool can be found in *Supplementary Materials*.

Discussion

Pain and Related Outcomes

The results of this systematic review show VR to be an effective tool for AP management. The primary means by which the VR interventions used in these studies promoted analgesia was via distraction. Distraction is a simple but effective approach that has been successfully utilized to assist with AP management (Hudson et al., 2015; Miller et al., 1992; Primack et al., 2012). Distraction leverages elements of the Gate Theory of Pain by directing cognitive attention away from noxious stimuli towards visual and auditory input, or an activity (Melzack & Katz, 2006; Melzack & Wall, 1965). As the brain has limited capacity to process incoming stimuli (Kahneman, 1973), cognitive-related brain areas provide analgesia by inhibiting passage of noxious stimulation to the brain (Melzack & Katz, 2006; Terkelsen et al., 2004). VR for AP utilizes these principles to shift focus away from noxious stimuli and into a computer-generated environment (Gold et al., 2007). This was not the only successful modality for managing AP with VR, as studies by

Konstantatos et al (2009) and Patterson et al (2006) delivered hypnotic suggestions via a virtual environment to reduce AP. However, VR hypnosis in these studies was delivered prior to the pain-inciting event, as opposed to during the painful event as described in other VR distraction studies, which may reduce the ability to compare these kinds of VR interventions. Overall, this review's findings extend the results of laboratory studies showing VR's efficacy for AP analgesia (Boylan et al., 2017; Czub & Piskorz, 2018; Karaman et al., 2019; Sharar et al., 2016) by deploying VR interventions into real-world clinical settings. The implications of this research translation validates using distraction-based VR content for acute-pain analgesia. Distraction-based VR content is best utilized *during* a pain-inciting event, and should be deployed both before commencement and after completion of such procedures for best effect. Hypnosis-based VR content also shows promise as a modality for AP, but further research is needed for clinical validation.

Few studies included measures of anxiety, and those that did varied greatly in the measures used. This made comparison across studies problematic. Even fewer studies utilized physiologic measures, and those that did showed mixed results. This is likely due to the fact that while a majority of physiologic measures have been shown to be valid for AP assessment, it is often necessary to combine them with other AP measures or use interpretive algorithms to ensure accuracy and minimize confounding elements (Cowen et al., 2015; Korving et al., 2020).

Virtual Presence and Null/Negative Outcomes

Four studies showed VR to have little effect, or a negative effect, on AP management. Of these four studies with null or negative outcomes, only Walker et al (2014) utilized VR content and measured presence; participants were found to have a

low sense of presence in the virtual environment. Glennon et al (2018) and Morris et al (2010) both utilized non-VR content (a *nature video and a computer game, respectively*) in their studies, while Zschaler et al (2010) described their content, but omitted further details. While all three used headsets to deliver content and block external stimuli, it is difficult to determine intervention fidelity as none of these studies measured presence.

One reason for neutral or negative outcomes could have also been participant positioning. In the study by Glennon et al (2018), participants were placed in a prone position and then watched a nature video, and Walker et al (2014) placed participants in a supine position prior to immersion in VR. The point of view for most VR environments is from an upright position; these participants were not in upright positions for their procedures, yet these articles make no mention of the VR environment's orientation (or changes in VR content to match these non-upright positions). A mismatched visual-physical experience or poorly matched content (*ex: staring at the ground or up at the sky – unable to see any horizontal content*) could detract from the efficacy of VR. This could have been responsible for the decreased presence found by Walker et al (2014). In addition, when participants used the computer game in the study by Morris et al (2010), it is unknown if participants were immersed in the environment and could look around the virtual world or if their view was fixed, regardless of head position (virtually: playing video games on a television screen in an otherwise dark room). The latter would be an example of using non-VR content with VR hardware – essentially watching a movie at a drive-in. You may feel *present* in that three-dimensional environment, but content (software) limitations do not allow you to actually be *virtually present* in that environment. The capability to be *virtually present* in a digital environment is what sets VR content apart

from other console-, computer- or smartphone-based interventions (ex: personal computer (PC), Playstation®, XBOX®, iOS, Android and other platforms). In the study by Zschaler et al (2010), participants were asked to use a patient-controlled analgesia (PCA) device while in VR. It's unknown if this device was visible in VR or how its use may have impacted users as this study lacked a measure of *presence*. Konstantatos et al (2009) used patient controlled analgesia during the same procedure and in the same population, but as their intervention (VR hypnosis) was delivered prior to the procedure, participants did not have the same issue. These studies underscore the need to measure presence in clinical VR studies and consider how the presentation of content and a participant's positioning might impact the analgesic efficacy of VR interventions. Studies have shown how increasing presence also increases the analgesic efficacy of the virtual environment (Gutierrez-Martinez et al., 2010; Hoffman et al., 2004), but further research is needed to inform deployment of VR in the clinical context.

Considering Elements of Interaction

Active VR and passive VR content varied greatly across included studies. Interaction is another VR component that influences presence and analgesic efficacy. Only Mosso Vasquez et al (2019) compared active VR and passive VR in the clinical context; they found that both kinds of interaction were effective for analgesia, though active (computer-based) VR had greater analgesic efficacy. These findings align with several laboratory studies by Hoffman et al (2004, 2006) and Wender et al (2009) that found active VR to significantly decrease pain intensity, compared to passive VR. This potential for variation in analgesic efficacy based on interaction with the virtual environment could prove problematic in studies with varied kinds of interactive content.

To avoid confounding, it is important for future clinical VR studies to consider the kind of interaction being deployed when designing the study, assigning participants, and performing analyses. Further research comparing the efficacy of active and passive VR content for AP analgesia is needed.

Varying Content and Hardware

While each of the studies included in this review used what they termed “virtual reality”, there was a large variation in the content that was used. Alsharat et al (2019), Guo et al (2015) and Tse et al (2003) utilized non-VR video content that was delivered via a headset (*the equivalent of a seeing a large television screen*). Other studies utilized VR hardware to deliver nature videos (Basak et al., 2020; Ford et al., 2018; Glennon et al., 2018; JahaniShoorab et al., 2015) and digitally-rendered nature content (Furman et al., 2009; Tanja-Dijkstra et al., 2018). VR games were used in several studies (Ding et al., 2019; Hoffman et al., 2000; Jin C. et al., 2018; Maani CV et al., 2011; Walker et al., 2014), while another deployed a non-VR computer game (Morris et al., 2010). Studies by Mosso-Vasquez et al (2019), Pandya et al (2017), Sikka et al (2019) and Spiegel et al (2019) deployed a variety of differing VR content that users could pick from that included 360-degree videos, VR games, and other VR content. Because content differed across the majority of studies and were deployed on a diverse array of devices (with varying levels of screen quality, field of view and some with and others without head-tracking), it is difficult to compare efficacy across studies. That said, laboratory studies have shown that playing non-VR video games and using VR are both effective in decreasing pain intensity compared to a no-VR condition - though VR showed the greatest analgesic efficacy (Boylan et al., 2017). Future clinical studies comparing each of these

interventions – video or television, video games, and VR content – are needed to ascertain which modalities are best deployed to properly address AP analgesic needs and pragmatic constraints across clinical settings. Comparison between types of VR content (360-degree video versus digitally-rendered content) and differing VR modalities (games versus open-world) is also needed to better inform clinical deployment. Lastly, further development of evidence-based therapeutic VR content is needed.

Practical Considerations

While VR is highly effective for AP management, the most immersive and interactive VR content has historically been more expensive and required computer equipment to process the virtual environment (Hoffman et al., 2004, 2006; Wender et al., 2009). In spite of being less interactive, Ford et al (2018) and Mosso Vasquez et al (2019) both note that reduced cost and ease-of-deployment of passive VR content via smartphone-based headsets could allow for more widespread use and should be considered. Additionally, newer VR headsets with greater processing power that do not require a computer are also available on the consumer market at significantly reduced costs. Usability testing of this type of hardware in clinical settings is needed.

Two other barriers to widespread deployment of VR therapeutics are infection control and training in VR use. Few of the included studies mentioned infection control measures, yet this is a vital consideration for clinical deployment. Additionally, infection control procedures – like other technology used in healthcare spaces (Brady et al., 2012; Pratt et al., 2001) – may degrade VR devices' hardware and potentially reduce their performance. Using VR also necessitates training of both clinical staff and participants. Few studies noted taking time to orient and instruct participants in how to use the

headsets and navigate the VR content; failure to do so may have impacted participant's experience. Future studies must consider implementation of infection control measures and assess the time needed to adequately train both staff and participants in VR use. Further research is needed to explore means of maintaining infection control without harming VR equipment, enhance current means of cleaning VR hardware between uses and develop more streamlined approaches to training participants in VR therapeutic use for AP management.

Areas for Future Research

After reviewing the current literature on VR's use for AP management, there are several areas for future research that become clear. While VR has been used extensively in wound care populations, its use in virtually all other healthcare populations for AP management is limited, and in most settings, nonexistent. Use of anxiety, presence, and VR side effects measures in VR studies for AP is limited; future studies should incorporate these measures to provide better insight into VR's efficacy for AP analgesia. The majority of the reviewed VR content lacks firm grounding in evidence-based interventions. Researchers, designers and developers must cultivate collaborations to develop theory-driven and pain-specific content that maximizes VR principles of presence, immersion, interaction, and interest in adult populations. Further research is needed to test distraction- and hypnosis-based VR content over time and across various clinical populations to ensure its safety and maximize its potential efficacy.

Implications for Pain Management Practice

There is a dearth of information currently available for practitioners related to VR content, hardware and deployment. Results from this review are intended to guide translation of VR therapeutics for clinical use, and inform future deployment of VR interventions for AP management. Based on the studies included in this review, there is strong evidence for utilizing VR-based distraction content during pain-inciting events, and promising evidence for utilizing hypnosis-based content prior to pain-inciting events. Providers should be trained on VR deployment prior to use, and utilize infection-control standards in accordance with the population using the intervention and location of deployment.

Figure 1: Flow Diagram for Study Selection and Inclusion

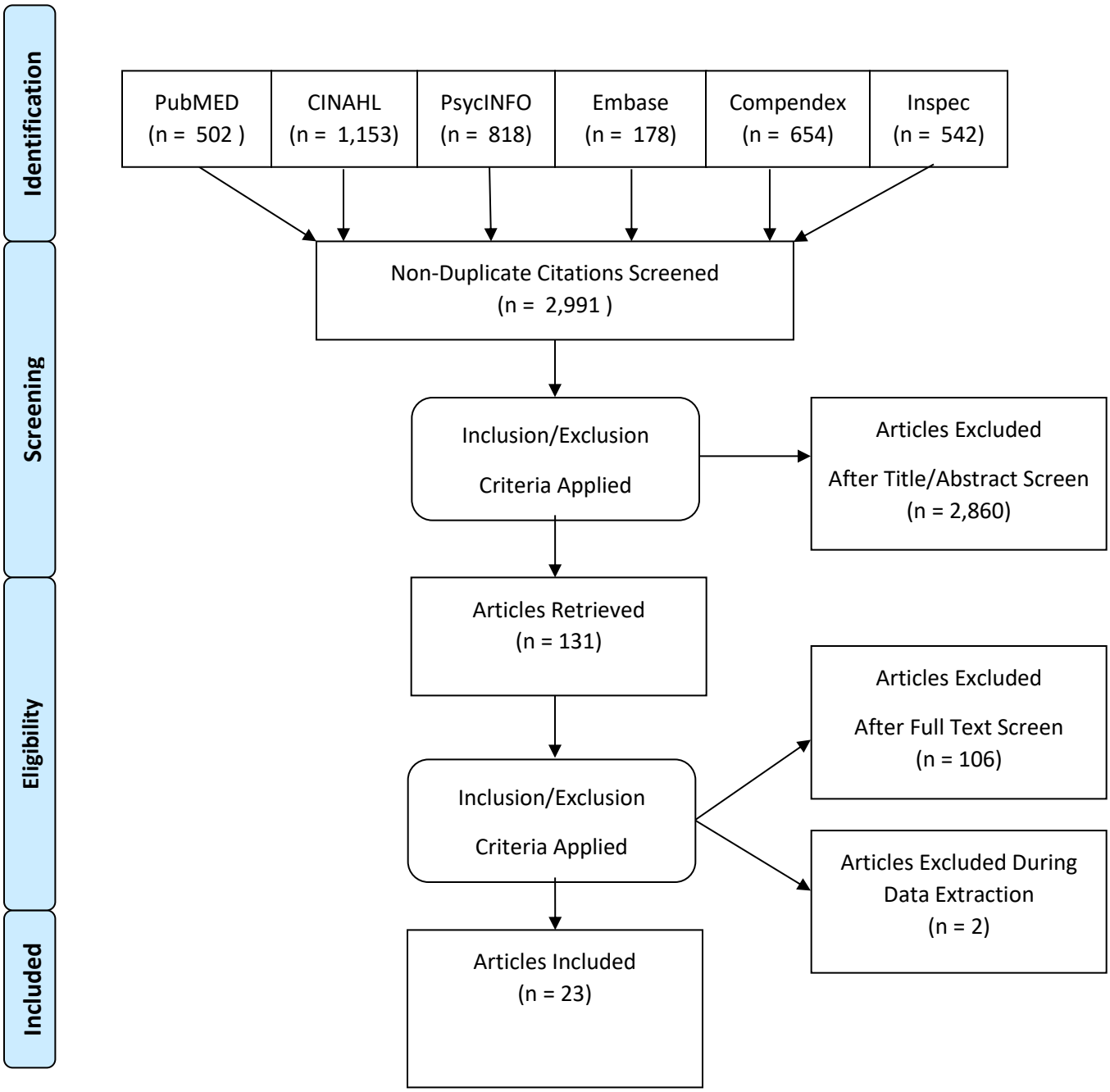

Table 1: Study Populations, Interventions, Comparators, Outcome Measures and Study Designs (PICOS)

Author (year)	Population	Content	Comparators	Origin of Pain	Pain Measure(s)	Study Design
Alshatrat et al (2019)	Patients at Dental Clinic	video [*comedy or documentary*]	VR + standard of care (SOC) vs SOC	Dental procedure	Visual analog scale (VAS) 0-10cm [*5 dimensions: time thinking about pain, pain unpleasantness, how much teeth/gums bothered them, pain intensity, average pain]*	Within-Subjects
Basak, Duman and Demirtas (2020)	Emergency room patients	underwater video	Distraction (VR or Cards) + SOC vs SOC	Peripheral intravenous catheter insertion	VAS 0-10cm [*pain intensity*], 1-10cm [*"satisfaction with procedure"*]	Single-Blind, Randomized, Controlled Clinical Trial
Carrougher et al (2009)	Inpatient burn patients	n/a	VR + SOC vs SOC	Physical or Occupational Therapy	Graphic rating scale (GRS) - 0-100 [*3 dimensions: pain intensity, time spent thinking about pain and pain unpleasantness*]	Within-Subjects
Ding et al (2019)	Hemorrhoidectomy patients	"Snow World"	VR + SOC vs SOC	First hemorrhoid dressing change	VAS 0-10cm [*pain intensity]*	Open-Label, Randomized Clinical Trial
Ford et al (2018)	Outpatient burn patients	VR landscape videos [*8 different to choose from*]	n/a	Burn wound care	4-point Likert-like scale [*provider's impression of patient's pain relief*]	Feasibility and Acceptability Clinical Trial

Furman et al (2009)	Patients at Dental Clinic	"Second Life" [*botanical garden*]	VR + SOC vs movie + SOC vs SOC	Dental procedure	VAS 0-10cm [*5 dimensions - time thinking about pain, pain unpleasantness, how much teeth/gums bothered them, worst pain, and average pain*]	Within-Subjects
Glennon et al (2018)	Patients with hematological diagnosis	Nature scene video [*3 different to choose from*], and "relaxing music"	VR + SOC vs SOC	Bone marrow aspiration and biopsy procedure	Numeric Rating Scale (NRS) 0-10 [*pain intensity*]	Quasi-experimental
Guo et al (2015)	Patients with hand injuries necessitating dressing change	"Afanda"/Avatar [3D film]	VR + SOC vs SOC	Hand wound dressing change	VAS [*pain intensity, unidentified number/type*]	Randomized Clinical Trial
Hoffman et al (2000)	Inpatient burn patients	"SpiderWorld"	VR + SOC vs SOC	Physical or occupational therapy	VAS 0-10cm [*5 dimensions - time thinking about pain, worst pain, average pain, how much wound bothered them, unpleasantness of occupational therapy*]	Within-Subjects

Jahanishoorab et al (2015)	Postpartum primaparous women	IMAX Dolphin and Whales 3D	VR + SOC vs SOC	Episiotomy repair	NRS 0-100	Randomized Clinical Trial
Jin et al (2018)	Patients with osteoarthritis after total knee arthroplasty	VR "Rowing"	VR + SOC vs SOC	Physical therapy	VAS [*pain intensity, unidentified number/type*]	Randomized Clinical Trial
Konstantatos et al (2009)	Inpatient burn wound patients	Virtual Medicine's "Relaxation DVD" [h*ypnotherapy with relaxing visual scenery and audio; further details omitted*]	VR + patient-controlled analgesia (PCA) vs PCA	Burn wound care	VAS 0-10cm [*pain intensity*]	Randomized Clinical Trial
Maani et al (2011)	Inpatient burn wound patients	"SnowWorld"	VR + SOC vs SOC	Burn wound care	GRS 0-10 [*3 dimensions: pain intensity, time spent thinking about pain, unpleasantness of pain*]	Within-Subjects
Morris et al (2010)	Inpatient burn wound patients	"Chicken Little" [PC game]	VR + SOC vs SOC	Physical therapy	NRS [*pain intensity, no metrics listed, referred to as numeric pain rating scale in study*]	Within-Subjects

Mosso Vasquez et al (2019)	Patients during outpatient lipoma removal	"Space coast", "inMind VR", and "Dyno VR games" *[smartphone*], "Enchanted Forest" and "Magic Cliff" [*computer-linked VR*]	Smartphone VR vs Computer-linked VR	Lipoma removal	VAS 0-10cm [*pain intensity*]	Within-Subjects
Pandya et al (2017)	Patients receiving adductor canal catheter placement prior to unilateral primary total knee arthroplasty	"Titans of Space" [interactive with gaze-direction], "Lanterns for Google Cardboard" and "SeaWorld VR2" [both passive] [all had background music]	VR + SOC vs SOC	Ultrasound-guided adductor canal catheter placement [nerve block procedure]	NRS 0-10 [pain *intensity, only measured post-treatment*]	Quasi-experimental
Patterson et al (2006)	Inpatient burn wound patients	"SnowWorld" [no interaction], audio hypnosis	VR + SOC vs SOC	Burn wound care	GRS 0-10 [3 dimensions: pain intensity, time spent thinking about pain, unpleasantness of pain]	Within-Subjects

Sikka et al (2019)	Emergency room patients	24 different environments	VR + SOC vs SOC	Pain score > 3/10; Defined sources of pain	Verbal NRS 0-10 [*pain intensity*]	Within-Subjects
Spiegel et al (2019)	Inpatients in hospital	20 different environments	VR + SOC vs SOC	Pain score > 3/10; Undefined sources of pain	Verbal NRS 0-10, [*pain intensity*]	Randomized Clinical Trial
Tanja-Dijkstra et al (2018)	Study 2: Patients undergoing dental treatment	Virtual coastal path and virtual urban environment	VR Content #1 + SOC vs VR Content #2 + SOC vs SOC	Dental treatment	Immediately post-intervention: NRS 0-10 [*pain intensity*], McGill Pain Questionnaire (SF-MPQ) [*15-item short form*]; At 1-week follow-up: NRS 0-10 [*recall pain intensity, intrusive thoughts of experience, and vividness of memories of experience*]	Randomized Clinical Trial
Tse et al (2003)	Patients with leg ulcers necessitating wound debridement and dressing changes	Opera, cartoons television show, or natural environment	VR + SOC vs SOC	Leg ulcer wound debridement and dressing change	NRS 0-10 [pain intensity]	Within-Subjects

Walker et al (2014)	Men undergoing flexible cystoscopy	"SnowWorld" [game]	VR + SOC vs SOC	Flexible cystoscopy	VAS 0-10cm [4 dimensions - time thinking about pain, pain intensity, average pain, pain unpleasantness]	Randomized Clinical Trial
Zschaler (2010)	Inpatient burn wound care	Cold landscape with snowmen and canyons	VR + PCA vs PCA	Burn wound care	VAS [pain intensity] [no metrics defined]	Randomized Clinical Trial

Table 2: Virtual Reality Components and Considerations

Presence Measures	
Graphic Rating Scale (GRS) 0-10	(Maani CV et al., 2011)
Numeric Rating Scale (NRS) 0-10	(Tanja-Dijkstra et al., 2018)
Visual Analog Scale (VAS) 0-10/0-100	(Alshatrat et al., 2019; Hoffman et al., 2000; Walker et al., 2014)
Other	(Furman E et al., 2009; Guo et al., 2015)
Immersion Method	
3D Glasses	(Alshatrat et al., 2019; Glennon et al., 2018; JahaniShoorab et al., 2015; Konstantatos et al., 2009; Tanja-Dijkstra et al., 2018; Tse et al., 2003)
Computer	(Ding et al., 2019; Furman E et al., 2009; Hoffman et al., 2000; Maani CV et al., 2011; Morris et al., 2010; Patterson DR et al., 2006)
Computer vs Smartphone	(Mosso Vázquez et al., 2019)
Smartphone	(Basak et al., 2020; Ford et al., 2018; Pandya et al., 2017; Sikka et al., 2019; Spiegel B. et al., 2019)
Unknown	(Carrougher et al., 2009; Jin C. et al., 2018; Walker et al., 2014; Zschaler, 2010)
Interaction Type	
Active	(Carrougher et al., 2009; Ding et al., 2019; Furman E et al., 2009; Hoffman et al., 2000; Jin C. et al., 2018; Maani CV et al., 2011; Morris et al., 2010; Tanja-Dijkstra et al., 2018, p.; Walker et al., 2014)
Active + Passive (varying content)	(Pandya et al., 2017; Spiegel B. et al., 2019)
Passive	(Alshatrat et al., 2019; Basak et al., 2020; Ford et al., 2018; Glennon et al., 2018; Guo et al., 2015; JahaniShoorab et al., 2015; Konstantatos et al., 2009; Patterson DR et al., 2006; Sikka et al., 2019; Tanja-Dijkstra et al., 2018; Tse et al., 2003)
Unknown	(Mosso Vázquez et al., 2019; Zschaler, 2010)
Interest Measures	
5-Point Bipolar Adjective Scale ("attractiveness" of VR environment)	(Tanja-Dijkstra et al., 2018)
Numeric Rating Scale (NRS) 0-10 ("enjoyment" in watching video)	(Tse et al., 2003)
Visual Analog Scale (VAS) 0-10 ("fun" in VR)	(Maani CV et al., 2011)
Visual Analog Scale (VAS) 0-10 (how "entertaining" was the virtual world)	(Walker et al., 2014)
Average Time in VR	
0-5 min	(Basak et al., 2020; Guo et al., 2015; Hoffman et al., 2000)
6-10 min	(Carrougher et al., 2009; Ford et al., 2018; Maani CV et al., 2011; Morris et al., 2010; Sikka et al., 2019; Spiegel B. et al., 2019)
11-15 min	(Glennon et al., 2018)
16-20 min	(Furman E et al., 2009; Konstantatos et al., 2009; Patterson DR et al., 2006)
21-25 min	(Ding et al., 2019)
26-30 min	(Jin C. et al., 2018)
>30 min	(Mosso Vázquez et al., 2019)
Unknown	(Alshatrat et al., 2019; Pandya et al., 2017; Tanja-Dijkstra et al., 2018; Tse et al., 2003; Walker et al., 2014; Zschaler, 2010)

Table 3: Secondary Outcomes and Practical Considerations

Anxiety Measures	
Corah Dental Anxiety Scale	(Furman et al., 2009)
Likert-like scale 0-4	(Glennon et al., 2018)
Visual Analog Scale (VAS) 0-10 ("anxiety")	(Hoffman et al., 2000; Walker et al., 2014)
Modified Dental Anxiety Scale 0-4	(Tanja-Dijkstra et al., 2018)
Patient-Reported Outcome Management Information System (PROMIS) Anxiety Short-Form 8a	(Sikka et al., 2019)
Burn-Specific Anxiety Rating Scale (BSARS)	(Konstantatos et al., 2009; Morris et al., 2010; Patterson et al., 2006)
Physiologic Measures	
Blood Pressure	(Alshatrat et al., 2019; Furman E et al., 2009; Glennon et al., 2018; Mosso Vázquez et al., 2019; Pandya et al., 2017; Walker et al., 2014)
Heart Rate	(Carrougher et al., 2009; Ding et al., 2019; Furman et al., 2009; Glennon et al., 2018; Walker et al., 2014)
Respiratory Rate	(Glennon et al., 2018; Walker et al., 2014)
Oxygen Saturation	(Ding et al., 2019; Glennon et al., 2018)
Temperature	(Glennon et al., 2018; Walker et al., 2014)
Galvanic Skin Response	(Walker et al., 2014)
VR Side Effects Measures	
Visual Analog Scale (VAS) 0-10 ("nausea")	(Alshatrat et al., 2019; Hoffman et al., 2000; Walker et al., 2014)
Graphic Rating Scale (GRS) 0-10 ("nausea")	(Maani et al., 2011)
Unknown	(Carrougher et al., 2009; Furman E et al., 2009)
Practical Considerations	
Mention Infection Control	(Sikka et al., 2019; Spiegel B. et al., 2019)
Train Participants for VR Use	(Ding et al., 2019; Ford et al., 2018; Pandya et al., 2017; Patterson DR et al., 2006; Sikka et al., 2019; Spiegel et al., 2019)

Supplementary Materials

Appendix A: Inclusion Filters by Database

Database	Inclusion Criteria

PubMed	• Article Type
	  ○ Clinical Trial
	  ○ Controlled Clinical Trial
	  ○ Journal Article
	  ○ Observational Study
	  ○ Pragmatic Clinical Trial
	  ○ Randomized Clinical Trial
	  ○ Validation Studies
	• Population
	  ○ Adults (19+ years)

CINAHL	• Article Type
	  ○ Case Study
	  ○ Clinical Trial
	  ○ Doctoral Dissertation
	  ○ Journal Article
	  ○ Randomized Clinical Trial
	• Population
	  ○ Adults (19+ years)

PsychINFO	• Article Type
	  ○ Dissertation
	  ○ Journal Article
	• Age
	  ○ Adulthood (18 years and older)

Embase	• Article Type
	  ○ Article
	  ○ Article in Press
	  ○ Conference Paper
	• Age
	  ○ Young Adult
	  ○ Adult
	  ○ Middle Aged
	  ○ Aged
	  ○ Very Elderly

Compendex	• Article Type
	  ○ Journals
	  ○ Conference Article
	  ○ Conference Proceedings
	  ○ Articles in Press

Inspec	• Article Type
	  ○ Journals
	  ○ Conference Article
	  ○ Conference Proceedings
	  ○ Articles in Press

Appendix B: Database Search Terms

Database	Search Terms
PubMed	("Virtual Reality Exposure Therapy"[Mesh] OR virtual reality OR VR) AND ("Anxiety"[Mesh] OR "Acute Pain"[Mesh] OR "Pain Perception"[Mesh] OR pain perception OR anxiety OR pain)
CINAHL	(((MH “Virtual Reality+”) OR (MH “Virtual Reality Exposure Therapy”) OR TX virtual reality OR TX VR) AND (((MH "Anxiety+") OR (MH "Anxiety (Saba CCC)") OR (MH "Anxiety (NANDA)" OR TX anxiety) OR ((MH "Acute Pain (Saba CCC)") OR TX pain) OR ((TX pain perception))
PsychINFO	((DE "Pain" OR DE "Back Pain" OR DE "Headache" OR DE "Myofascial Pain" OR DE "Neuralgia" OR DE "Neuropathic Pain" OR DE "Somatoform Pain Disorder" OR DE "Pain Perception") OR (TX pain) OR (DE "Anxiety") OR (TX anxiety)) AND (DE "Virtual Reality" OR TX virtual reality OR TX VR))
Embase	('virtual reality'/exp OR 'virtual reality') AND ('pain'/exp OR 'pain' OR 'anxiety'/exp OR 'anxiety')
Compendex	(((virtual reality) WN ALL) AND (((pain) WN ALL) OR ((anxiety) WN ALL)))
Inspec	(((($virtual $reality) WN ALL) OR ({virtual reality} WN CV)) AND ((($pain) WN ALL) OR (($anxiety) WN ALL)))

Appendix C: Article Bias Ratings (Higgins et al., 2011)

Article Info		***Bias Rating: "unclear", "low", or "high"***					
Author(s)	**Year**	**Random Sequence Generation**	**Allocation Concealment**	**Blinding of Participants and Personnel**	**Blinding of Outcome Assessment**	**Incomplete Outcome Data**	**Selective Reporting**
Alshatrat et al	2018	n/a	n/a	n/a	n/a	n/a	n/a
Basak et al	2020	low	unclear	high	high	low	low
Carrougher et al	2009	unclear	unclear	unclear	unclear	low	low
Ding et al	2019	low	unclear	high	high	low	low
Ford et al	2018	n/a	n/a	n/a	n/a	n/a	n/a
Furman et al	2009	n/a	n/a	n/a	n/a	n/a	n/a
Glennon et al	2018	n/a	n/a	n/a	n/a	n/a	n/a
Guo et al	2015	unclear	unclear	unclear	unclear	low	low
Hoffman et al	2000	n/a	n/a	n/a	n/a	n/a	n/a
Jahanishoorab et al	2015	unclear	unclear	high	high	low	low
Jin et al	2018	unclear	high	high	high	low	low
Konstantatos et al	2009	low	unclear	high	high	low	low
Maani et al	2011	n/a	n/a	n/a	n/a	n/a	n/a
Morris et al	2010	n/a	n/a	n/a	n/a	n/a	n/a
Mosso Vasquez et al	2019	unclear	unclear	high	high	high	low
Pandya	2017	n/a	n/a	n/a	n/a	n/a	n/a
Patterson et al	2006	n/a	n/a	n/a	n/a	n/a	n/a
Sikka et al	2019	n/a	n/a	n/a	n/a	n/a	n/a
Spiegel et al	2019	low	high	high	high	low	low
Tanja-Dijkstra et al	2018	low	low	high	high	low	low
Tse et al	2003	n/a	n/a	n/a	n/a	n/a	n/a
Walker et al	2014	low	high	high	high	low	low
Zschaler	2010	unclear	unclear	unclear	unclear	low	low

*Unclear: are randomized clinical trial, but they didn't provide the method they used to generate the random sequence (ex. computer generated), or allocation concealment (ex: envelope).

**N/A: not applicable (not randomized clinical trial

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Chapter 3:

Living Kidney Donor Perspectives on Acute Postoperative Pain Management

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Abstract

Background: Globally, there are over 9.7 million people in need of kidney transplant, and an estimated 2.6 million receiving either a transplant or dialysis every year. Living kidney donation helps to meet the significant need for a kidney transplant. Howeverpostoperative pain can hinder living kidney donor's (LKDs) postoperative recovery and could prevent individuals from considering donation.

Purpose: The purpose of this study is to examine LKD's experience of postoperative pain. Aims include to: 1) Uncover how LKDs describe their postoperative pain; 2) Describe what strategies LKDs use to manage their postoperative pain; and 3) Uncover factors, unique to LKD's surgical experience, that might help mitigate or aggravate their experience of postoperative pain.

Methods: A qualitative descriptive approach with semi-structured interviews was used. Data was analyzed using Atlas.ti (v9.0) and codes were inductively generated. Content analysis was performed and data was reviewed for trends, patterns and insights into LKD's experience of postoperative pain.

Results: Thirteen participants aged 46.5 (+/- 14.4) years participated in this study. LKDs experienced postoperative pain from a variety of sources that hindered postoperative recovery and, in some, created anxiety and fear. Pain management methods employed included opioid and non-opioid medications, social support, and ambulation. LKD's relationships with intended recipients, motivations for donation, social support, past experiences of pain, pain expectations, and meaning of donation all informed their experience of pain and affected pain experience.

Discussion: LKDs comprise a unique population for studying pain. Providers should prioritize pain management when working with this populations and consider coaching and education in addition to pharmacologic interventions for pain. Further study of how LKD's motivation to donate may mediate their postoperative pain experience is needed.

Living Kidney Donor Perspectives on Acute Postoperative Pain Management

The need for kidney donation is significant. Globally, it is estimated that of the over 130,000 solid-organ transplants performed annually, 100,000 of which are kidneys, meet under 10% of transplant needs (WHO, 2021; WHO-ONT, 2019). In the United States alone 90,000 individuals are in need of a kidney transplant (OPTN, 2021). Living kidney transplants are preferred over cadaveric donations due to the enhanced outcomes for recipients (Gjertson & Cecka, 2000), though the cost for donors – both physically and financially – can be quite high (Andersen et al., 2006; Johnson et al., 1999; Kok et al., 2006; Tong et al., 2012).

Due to general good health needed and the screening that one must undergo to be a living kidney donor, surgical complications are rare. As such, pain management becomes the primary focus of the living kidney donor's (hereafter "donors") postoperative care (Mathuram Thiyagarajan et al., 2012; Perry et al., 2003). Most donors discharge from the hospital within a week (Kok et al., 2006; Kuo et al., 2000; Perry et al., 2003; Ratner et al., 1999), but poor pain management (Carr & Goudas, 1999; Gan et al., 2014) and complications from opioid pain medications (Benyamin et al., 2008; Holzer, 2007) may delay discharge.

Pain is a complex experience, and for donors, postoperative pain can be surprising and unexpected (Andersen et al., 2005). Along with physiological components, there are many other factors –genetic, psychological, social, and behavioral – that may impact the postoperative pain experience (Diatchenko et al., 2005; Melzack, 1999, 2005; Melzack & Wall, 1965). Donors represent a unique population with strong motivations for donation, yet their experience of postoperative

pain immediately following donation is profoundly unexplored (Brown et al., 2008; Irving et al., 2012). The purpose of this study is to examine donors' experience of postoperative pain.

Background

Donors are a unique population in which to study pain for severalreasons; while most surgical candidates seek to correct an individual health problem, donors undergo surgery to aid someone else. In short, donors choose to incur side effects in the form of pain and financial costs for another's benefit (Andersen et al., 2006; Johnson et al., 1999; Kok et al., 2006; Tong et al., 2012), and donor's motivation to undergosurgery is often beneficence (Brown et al., 2008; Irving et al., 2012). Furthermore, donors may be a "naïve" pain population. Compared to others who may have experienced multiple surgeries, donors may experience surgical pain for the first time following organ donation (Andersen et al., 2005; Tong et al., 2012). This post-donation pain could even be the donor's worst experience of pain (Andersen et al., 2006, 2007), making them key informants into the experience of postoperative pain. Various pathways contributing to postoperative pain are known (Carr & Goudas, 1999; Melzack, 1990) and strategies for postoperative pain management in both in donors (Andersen et al., 2005, 2006; Mathuram Thiyagarajan et al., 2012; Perry et al., 2003) and other surgical populations (Johansen et al., 2014; McQuay et al., 1988; Pellino et al., 2005; Wall, 1988) are well documented. However, literature about donor's individual experiences of postoperative pain is limited to studies on hospital quality of care (Milutinović et al., 2009; Sherwood et al., 2000), general postoperative recovery (Allvin et al., 2008) and long-term donor outcomes (Meyer et al., 2017). A deeper understanding of donor's experience of

postoperative pain is therefore needed to better inform pain management in this population.

To better examine donor's experience of postoperative pain, this study aims to: 1) uncover how donors describe their postoperative pain, 2) describe what strategies donors use to manage their postoperative pain, and 3) uncover factors unique to donors' surgical experience that might help mitigate or aggravate their experience of postoperative pain.

Methods

Research Design

To gain clear insights into the world of donors and better understand their experience of postoperative pain, this study utilized a qualitative descriptive approach with semi-structured interviews. Furthermore, this approach integrates aspects of phenomenological inquiry in order to better understand donor's experience (Sokolowski, 2000). This methodology is well-suited for this task and has been utilized in other studies focused on donors' experiences (Andersen et al., 2007; Brown et al., 2008). This study was determined to be exempt by the University of Washington's Institutional Review Board.

Sampling

At the study hospital, kidney transplantation usually occurs once a week and includes one donor and one prospective kidney recipient. Donor participants were approached for possible inclusion in the study in a consecutive manner between 2/21/2019 to 6/1/2019 in the hospital on post-operative days two to four. An initial

sample size of five was targeted and then expanded to 13 in order to reach data saturation. This sample size is comparable to other qualitative studies of living kidney donors (Meyer et al., 2017).

To be included in the study, individuals were 18 years of age and older and undergoing kidney donation through the hospital's Living Kidney Donor program. Exclusion criteria included those who had a history of chronic pain, or pain lasting longer than 90 days (McGuirk & Bogduk, 2015; Merskey & Bogduk, 1994), and those with significant communication impairments that might impact audio recording of the interview. To ensure confidentiality, numerical identifiers were assigned to each of the study participants.

Data Collection

Following written informed consent, basic demographic data was collected. Semi-structured interviews were used to capture the patient's experience of pain after surgery and occurred on the same day as enrollment. Questions were informed by the Revised American Pain Society Patient Outcome Questionnaire (Gordon et al., 2010) and a study by Sherwood et al. (2000) related to inpatients' experiences with pain relief and their decision-making related to pain management strategies. Questions included participant's pain experience before and after surgery; how pain was managed; and what factors aided or detracted from their management of pain. All participants were interviewed in their hospital room. Interviews were digitally recorded for later transcription. A complete list of interview questions can be found in *Appendix A*, *Supplementary Materials*.

Data Analysis

All interviews were transcribed using a HIPAA-compliant transcription service. Each transcript was independently reviewed for accuracy by two members of the research team, and patient identifiers were removed from transcripts. ATLAS.ti v9 (ATLAS.ti Scientific Software, Berlin, Germany) was used to manage and support analysis of the data. Data was initially analyzed using a content descriptive approach (Hsieh & Shannon, 2005; Sandelowski, 2000), or "open" coding, from which data codes were inductively generated and keywords identified. A content analysis of the data was performed, and transcript data was coded line-by-line for descriptive (first-level) and theme (pattern) codes and cross-validated by two other members of the research team. Conflicts were resolved by group consensus. A list of major thematic elements was developed through careful study and coding of the transcripts. Data was then grouped and reviewed for trends, patterns, and ideas that gave insight into participant's experience of postoperative pain, needs and expectations, as well as barriers and concerns related to their experience.

Results

Demographics

Thirteen donors agreed to participate in this study. The average age of donors was 46.5 (+/- 14.4) years, and participants were primarily female (n=10). A total of five donors were related (by partnership or genetically) to their intended recipient (**Donors 3, 5, 8, 11, 12**). Of the remaining donors, five more donated directly to a recipient they

were unrelated to (**Donors 1, 2, 9, 10, 13**) while three donated anonymously through a donor-recipient match program (**Donors 4, 6, 7**).

Donor's Experience of Postoperative Pain

Though each donor described their pain to be nominal at the time of interview ("…*tolerable, just more sore and uncomfortable*"; **Donor 9**), 70% of donors noted moments of extreme pain during their postoperative course ("*It hurt. It was painful… because it's in your core area… [which] is fundamental to movement, and so no matter which way you moved, it hurt";* **Donor 11**). Though initially felt at the surgical site, donors described postoperative pain exacerbations as a whole-body experience ("…*what I noticed yesterday was that I knew that it was localized to my torso, but because it felt so bad, it was like all of me felt bad*"; **Donor 10**).

Most donors (77%) reported feeling "bloated", "distended", or having "gas" pain. ("*But the gas pain is so bad, um, because it just comes bubbling up, and then just pushes on everything, and it hurts so much";* **Donor 8**) This was a serious issue for several donors ("*Um. I think right now my biggest pain is just coming from, I'm just extremely bloated";* **Donor 9**) but not for others. Some donors expected bloating-type pain ahead of time (*"I even looked on YouTube for people that went through it, and they were talking about, 'Oh the gas is just terrible, and that's the worst part, get Gas-X…' ";* **Donor 1**), while others required more preparation ("*It was very painful actually, I've never had --I haven't had surgery so I didn't really know what to expect*"; **Donor 4**). A lack of prior painful experiences also impacted donor's self-evaluation and communication regarding their pain ("*So before this, I've never broken a bone, never*

had surgery…, I've never had any major pain.... They asked, "Okay, well how's it feel compared to a Charley horse?" I've never had a Charley horse….”; **Donor 8)**. Regardless of how they experienced pain in the past, donors were anxious and fearful about pain prior to surgery (“*Oh, the pain, yeah, all this, that was my biggest fear*”; **Donor 1**). This fear of pain also influenced how donors managed their pain after surgery: “*I hit [the pain button] and I don't think I needed to. I think it was just my fear of pain*”; **Donor 13**).

Donors also noted the duration of their pain as a component that differentiated it from other acutely painful events (“*Um, it's- its kind of a different kind of pain, cause I knew [the needle pain] was gonna be over. And uh, I don't know. This is… is probably worse. Just cause it's more prolonged”;* **Donor 6**). Many donors found their postoperative pain to be “*surprising*”.

> *Because it didn't feel bad. I just took [pain medication] before I tried to get up. So, I wasn't feeling bad at the time. Oh, fine. I mean it hurt, but not, I mean, it was a two [out of ten], maybe a 4 [out of ten]…. Manageable, but surprising to me….* (**Donor 13**)

Even low-intensity pain could be surprising to donors. In the hours and days following surgery, many noted extreme pain intensity– for five donors (**Donors 4, 6, 8, 9, 10**) it was the worst pain they had experienced (“*It might have been yesterday. I'd be hard pressed to think of feeling worse than I did yesterday…. Sitting up…, I thought, ‘my insides are going to tear out and spill all over the floor’…, it just…felt like something has to be tearing right now*”; **Donor 10**). This lack of prior pain experience was not the case for the remaining donors.

Five donors reported childbirth to have been their worst experience of pain ("*I have had kids. Yeah, that hurt*"; **Donor 2.** Complications from migraines ("…*the migraine is a whole-body experience…, it… feels awful everywhere*…"; **Donor 13**) or prior surgeries *("I had appendicitis, I was coming out [of surgery], I was crying for mother, I was hunched over, I didn't want to move, I thought that nurses were evil for making me move, and it was just like pain all over";* **Participant 1**), as well as medical or traumatic emergencies (*"I banged up my neck in a horse accident…, that was pretty bad";* **Donor 9**) were detailed as more intensely painful experiences than the donation surgery.

Strategies for Postoperative Pain Management

To minimize the effects of postoperative pain, donors utilized a variety of means for pain management. Pharmacologic management using opioid and non-opioid medications was highly effective and the primary means donors used for their postoperative pain management. Even so, the donor's journey was not always smooth:

> *"So the first like 24 hours was okay, I mean that hurt, it's very painful. They did [numbing medication]…and then actually it kind of got worse after that wore off and it wasn't -- people kind of talked about that, but I wasn't really ready for that. So the first 24 hours I managed okay and then yesterday was my 24-hour mark…, and that was kind of miserable for a couple of hours. …Basically yeah we just… had to like "up" my pain medication quite a bit right then. But now we changed some things up, the last 12 has been good, incredible."* (**Donor 4**)

Bowel medications helped with alleviating bloating pain, but aggressive management lead to other issues:

> *"Sorry I got the burps... which I guess is another one, yeah, the- the gas moving around is, it's frustrating…, they had to give me a suppository to get things moving. Once I did have a bowel movement, it became confusing as to what was gonna be gas, and what was gonna be solid. So that was another, that was a more surprising frustration, because, you know, then I'd have to, I'd go to the bathroom, get up, "Okay, I feel better," lay down, that would shift all the bubbles, immediately it'd feel like I have to go to the bathroom and get back up, go to the bathroom, I did that three times, uh, at 4:00 AM this morning."* (**Donor 8**)

Some donors used movement as a means of coping (*"…I mean I can't stay in the bed forever… [and] I have to get out of bed.… Not just medical, but yeah, I mean yeah just being here, lying here, drives me crazy"*; **Donor 4**), while others thought walking was generally beneficial ("*Being up and walking felt pretty decent. I mean, it felt like it actually maybe was, uh, it was good for me*"; **Donor 7**). Donors also recognized the ability to encourage bowel motility by walking ("*yeah, walking, walking helps. It's good, gets things moving*"; **Donor 9**). This message was reinforced by providers: ("*Yeah the [doctors and nurses] - they want me to get up, because that encourages my bowels to move";* **Donor 8**). Unfortunately, movement also incited pain *("..as I walk, my pain fluctuates";* **Donor 8**) Donors balanced the pain they felt from walking with the benefits they expected walking to have ("*Pain does increase with walking, naturally, but you need to walk to do it because you are going to have retention";* **Donor 1)**. Attention to

proper movement techniques was a successful non-pharmacologic pain management strategy, but it required much more effort and energy from donors.

> *…being able to know how to roll out of bed, know the tuck and roll type of position, not like a diver or anything, but tuck and roll seemed to work pretty well and slow, move slowly so that, like any other system, when you just let it equilibrate a little, let yourself equilibrate a little bit so that you're not forcing the issue…* (**Donor 11**)

Movement could be beneficial for symptom management or impeded by those same symptoms when they became too extreme.

> *"Yeah, but actually I- I kind of think because I have been um, a little more, um, woozy, dizzy when I stand up, today. Um, although that does help with the dizziness. Standing up and walking around. It's just kind of general soreness, but I think again, with the- with the nausea and the um, um, dizziness, it made me not want to move."* (**Donor 6*)***

In addition to moving, donors also employed other measures for non-pharmacologic pain management including mindfulness and relaxation ("*I suppose breathing techniques, how to try to relax, similar relaxation techniques…. At night and just kind of just relax between people coming in and trying to just try to relax, because when you relax, your muscles relax*" **Donor 11**) as well as "bracing" with a pillow ("[it hurt] a little bit less when I had a pillow on my tummy"; **Donor 7**). These strategies often helped alleviate donor's pain, but they also noted other issues while trying to address their pain.

Adverse Symptoms and Pain Management Results

Many donors noted adverse symptoms following surgery. Six noted dizziness, attributing it to low blood pressure at rest or standing, or side effects from opioid medications. Eleven donors (85%) reported nausea during their postoperative course:

> *"I think it's really hard for me, maybe for other people too, having nausea just because I feel like it's harder to think clearly understand what would make you feel better because you just want to… just make it go away…. Also just being confused about… [why] my stomach feels weird, …is that… the gas pressure from surgery? Is that pain or is that nausea, [it is] just all working together. So I think… getting rid of nausea… helps me distinguish more easily what's going on [in my body] and how it felt."* (**Donor 5**)

Dizziness and nausea often occurred together, and their combination could be unbearable ("*The Dilaudid making me dizzy, and the nausea, I would rather be in pain than have those*"; **Donor 8**). Feeling these symptoms also interrupted participant's capacity to address their own pain management.

> *"I think something that like kind of confuses me surrounding the pain is feeling nauseated, it's like I just know I don't feel good somewhere inside, it's not the same as pain, but I think when I'm nauseated it feels harder to address the pain because… [all I can] think about… [is] feeling sick. Does that make sense?"* (**Donor 5**)

Concurrently addressing nausea and postoperative pain proved challenging, yet despite difficulties encountered during their hospital stay, donors expressed overall satisfaction

with their postoperative pain management. *“My pain was controlled. I was getting a 1,000 milligrams of Tylenol again…, and…I feel like since that point, it's been okay”* (**Donor 9**). Though the changing nature of postoperative pain and symptom management complicated their experience, donors worked with healthcare providers and staff to achieve their pain management goals.

> *“Right up front. It has been... bad? Not real bad. Definitely that night and then most of yesterday, it really just felt like I'd done a ton of sit-ups. Like eighteen thousand too many. I mean my lats and right here really were sore. Or maybe I'd been kicked by a bull. That has been the extent of it. The pain has not been super bad. For me, the worst was I get, a lot of people do, but I get nauseous a lot from the anesthesia. And so, getting that under control, so far, has been a little bit more of a thing. The feeling nauseous makes me feel bad all over. Just kind of feels gross. And once they got a couple of different nausea medications in and we figured that out, the pain is more easily dealt with than the feeling [of] grossness….”* (**Donor 7**)

Unique Considerations for Donors

Donors are a highly-motivated surgical population who drew inspiration to donate from a variety of sources including family, close friends, spiritual communities, biographies and social media. Family members and close friends were especially driven to donate, and many donors prioritized the needs of their intended recipient, regardless of the impacts on themselves.

> "*It's my best friend's [child]. [They] had been sick since [they were] about two, so we always knew [they] would need a kidney, and that day came about a year ago. So, we all signed up…. Mostly it was just the connection…. I mean, …I don't even think I asked them at first. I just kind of told [my partner], "The day's here, [my best friend's child] needs a kidney. So, are we good?" And then, I mean, really the only emotion or thought about was just getting [them] healthy."* (**Donor 2**)

Support from family and friends empowered donors to weather adverse side effects and intense bouts of postoperative pain: *"I've had really good social support like more than what I would have thought, …the only thing that's been like… harder than I thought was the pain";* **Donor 4**. Yet even with support, donors still wrestled with understanding the physiological and psychological impacts of their donation surgery:

> *"They're taking an organ out of me, …I at least feel like it should be normal to be anxious. …I don't know, I- I didn't have a specific anxiety, I was just anxious about the whole thing because I'd never had surgery, I'd never had anything painful like this, so I just, maybe it was just the unknown, but I think it was just... scary."* (**Donor 8**)

While donors may have been educated regarding what to expect after their surgery, those without prior postoperative pain experience were still at a severe disadvantage. Of the five donors who noted postoperative pain as the worst pain they had experienced, 60% had never had surgery, and 40% had little experience with intense pain. This dearth of prior experience with pain gave these donors unclear

expectations and left them vulnerable to anxiety and fear about their pain. This created the conditions necessary for an intense and surprising postoperative pain experience.

> "*I haven't had a lot of previous experience with incisions and surgery and that kind of thing, I don't think I really knew what to expect. I heard there would be a lot of pain, but I didn't really know what that meant. And so, I think yesterday, I was really surprised by the, by the amount of pain"* (**Donor 10**)

Ultimately, donors were motivated by feelings of altruism ("*Just having friends and family and seeing their responses and it's kind of a good feeling to say, "Hey, you know I was able to make somebody's life better*"; **Donor 11**) and beneficence (*"You know, here I am getting to witness the benefit, I think, of, of this surgery… watching [the recipient] walk the halls and hearing about… [their improved kidney] numbers"*; **Donor 9**). For some, these positive motivations allowed donors to find meaning in their pain.

> *"Well, yeah, you know you love your family members, and you will do anything to make their life better, more livable. That was a primary consideration that I had…. I knew it was going to hurt. It was kind of like a loving hurt…, …because you're donating a kidney to a loved one in your family and so that kind of overrides a lot of other, what was "me"-type of things…."* (**Donor 11**)

Instead of reacting, these donors re-framed postoperative pain as a necessary sacrifice in order to aid their loved one *("You are saving a life… and you will never get this opportunity again. And the pain is minuscule, it is well managed*"; **Donor 1**). As the pain became purposeful, donors were less anxious and fearful ("*I'd never had surgery and so it was just this idea that [the pain] was going to be horrible, and it's really not*";

Participant 13), which gave donors the capacity to be more present in their donation experience ("…*it's kind of like, I guess I gave this gift to [the recipient] but, the whole process has been kind of a gift to me too";* **Donor 10**).

Discussion

The purpose of this study was to examine living kidney donor's experience of postoperative pain. Donors predominantly felt pain at the surgery site, but likely due to pain's propensity for drawing attention (Melzack, 1990; Melzack & Wall, 1965) and individual adaptations to pain (Brennan, 2011), many donor's pain became a "whole body" experience when it became extreme. While described as "sharp" or "tearing" at the incision site, donors also noted "bloating" pain in their abdomen as well. Most donors experienced dizziness, nausea, or a combination of these symptoms in the days following surgery, a common finding after surgery. Though tempered through provider intervention, these experiences detracted from donor's recovery. Andersen et al. (2005) noted that donors often found their postoperative pain surprising. This study builds on these findings by noting that many donors were surprised by their postoperative pain, regardless of its intensity. Individual expectations – especially when rooted in fear and anxiety – play prominent roles in modifying individuals' experience of pain (Melzack & Katz, 2006). Many donors reported fear and anxiety about their pain prior to surgery, though it was most notable in the three donors whom experienced surgery for the first time – a phenomenon also noted in studies by Andersen et al. (2006) and Tong et al. (2012). Consequently, the vast majority of donors in this study had histories of painful experiences that informed their expectations of pain after surgery; these donors were not a naïve pain population. Many donors differentiated their postoperative pain from

other forms of acute pain they had experienced by its duration – specifically that it lasted “longer”. While normally attributed to persistent postoperative pain (Wu & Raja, 2011), this aspect likely contributed to the surprising nature of donor’s pain experience.

As pain management is a key priority for donor’s postoperative care (Mathuram Thiyagarajan et al., 2012; Perry et al., 2003), each donor worked closely with their providers to achieve their analgesic goals. In the hospital setting, opioid pain medication constitutes first-line therapy for managing postoperative pain (Angell, 1982; Bonica, 1966; Raffa, 2001; Schug & Goddard, 2014). This was also true for participants in this study, yet donors’ individual experiences of pain management varied. While some participants reported their pain management plan of care to be effective, others had more difficulty and often required transitions from one medication to another, adjustments in dosing, or the addition of other medications to manage side-effects such as nausea. These findings are common in pain management of donors (Mathuram Thiyagarajan et al., 2012; Perry et al., 2003) and other surgical populations (Chandrakantan & Glass, 2011; Lerman, 1992). Abdominal “bloating” pain was another issue donors noted. Post-laparoscopic abdominal pain is common following intra-operative pneumoperitoneum for organ visualization during laparoscopy and decreased bowel motility from opioid pain medications (Gurusamy et al., 2009; Ricardo Buenaventura et al., 2008). Bloating pain was a concern for many donors as the latter cause can lead to opioid-induced bowel dysfunction (or “opioid-induced constipation”) which can both slow patient’s postoperative recovery and negatively impact their pain management (Bell et al., 2009; Dorn et al., 2014). Ambulation has long been known to help increase bowel motility and potentially prevent or correct constipation (Derby &

Portenoy, 1997; Palumbo et al., 1953) and providers supported donors' efforts to get moving. Donors balanced this need to move with the pain it caused, and they utilized non-pharmacologic means such as bracing with a pillow and meditation to help.

Hearing from donors also elucidated several specific considerations regarding their care. As noted elsewhere (Andersen et al., 2005, 2006; Tong et al., 2012), social support was a driving factor in the donation experience. Donors noted how support from family, providers and clinical staff was vital to their postoperative course. Additionally, this study found donors' motivations to be primarily altruistic and beneficent, which corroborates findings by Andersen et al. (2005, 2006), Tong et al. (2012), Brown et al. (2008) and Irving et al. (2012). More than donors' motivation itself is how they harnessed this motivation within the context of managing their pain; while all donors had postoperative pain, some recognized it as a necessary sacrifice to get through while others, viewing it with fear and anxiety, seemed to inadvertently dwell on it. Those who were able to reframe their experience of pain did not necessarily have less pain, but rather seemed more able to cope with the pain they experienced.

Limitations

There are several potential limitations to this study. Donors were interviewed on postoperative days two to four due to pain management or complication concerns in the 24-hours following surgery. Thus, a donor's picture of their postoperative course and description of pain may have changed depending on the day of their interview, and this may have introduced some variability into interview data and reported experiences but was likely mitigated through saturation of themes found in the data. Additionally, because this study took place while participants were still in the hospital, participants

may have been reluctant to criticize the health care team's performance as it relates to pain and symptom management.

Clinical Considerations and Areas for Future Research

Living kidney donors comprise a unique population for studying pain. Providers should prioritize pain management when working with this populations as it is a key factor in determining readiness for discharge (Mathuram Thiyagarajan et al., 2012; Perry et al., 2003). While pharmacologic interventions are often necessary, providers should also consider participant's surgical history (or lack thereof) and degree of social support as potential factors that can vastly impact donor's postoperative pain experience. Primarily used for cancer or chronic pain management (Kravitz et al., 2011; Sullivan et al., 2018), a combination of coaching and education are effective non-pharmacologic tools for assisting with pain management. Providers should emphasize educating donors about their pain prior to surgery and consider coaching them through painful experiences in the postoperative period. This should include integration of prior pain exposures and experiences. Given that bloating pain and nausea are common side effects from surgery and opioid use and often experienced by donors post-operatively, providers should also encourage non-pharmacologic means of promoting motility and be prepared to administer antiemetics as needed. Further study of how LKD's motivation to donate may impact their postoperative pain is needed. Gaining key insights into how these disparate concepts may be related could increase clinician's ability to proactively manage LKD's postoperative pain and provide space for conversation and education about postoperative pain before it becomes a chronic issue.

While much is known about the pathophysiology of postoperative pain (Brennan, 2011), understanding of participant's experience, especially donor's experience in the immediate postoperative period, is still understudied. Donor's experiences have often been catalogued, but focus is placed on psychosocial elements and interviews often occur long after the initial postoperative period (Andersen et al., 2006, 2007; Tong et al., 2012). Future research is needed to better understand how discrete biopsychosocial elements of participant's experience impact donor's postoperative pain management. Specifically, deeper understanding of how the interplay between non-pharmacologic interventions and individual behavior (i.e. motivation for surgery) might ameliorate donor's pain and minimize pharmacologic intervention is needed.

Supplementary Materials

Appendix A: Interview Guide Used to Explore the Acute Post-Operative Experience of Living Kidney Donors

1. First and foremost, **can you tell me the story of how you decided to donate your kidney**?
2. **What role did pain play in your first few days after surgery?**
3. **Tell me about the worst pain you've ever had.**
4. After surgery, **have you had any other symptoms that have impacted your recovery?**
5. **What expectations did you have related to your surgery?**
6. **Picture going home – what will your recovery look like?**
7. **Have you learned anything about yourself through this experience?**
8. If you were contacted by someone who was about to donate their kidney – **what would you tell them about your experience?**

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Chapter 4:

Virtual Reality Meditation for Fatigue in Persons with Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis (RA), a debilitating chronic disease that affects over 1.28 million people in the United States and nearly 20 million people worldwide. Recent pharmacologic advances in the management of RA have led to a decrease in inflammatory symptoms, such as chronic pain or even disease remission, yet up to 70% of patients with RA still suffer from fatigue. The most effective interventions for RA symptom management are behavioral therapies (such as mindfulness) or movement-based approaches. While VR-delivered meditation shows promise for pain and anxiety management in other rheumatic diseases, there is little information on VR meditation (VRM) use for fatigue management in those with RA

Aims: The specific aims of this convergent mixed-methods study include: 1) examining the feasibility of implementing VRM as an adjunct for managing fatigue; 2) determining the acceptability of using VRM for fatigue management; and 3) exploring the experience of using VRM to manage fatigue in outpatients with RA.

Methods: This study utilized a convergent, mixed-methods study design. Quantitative study data were collected and managed using electronic data capture (REDCap) tools hosted at the University of Washington's Institute for Translational Health Services (ITHS), and a qualitative descriptive approach was taken to formulating questions and performing semi-structured interviews with participants.

Results: Thirteen participants who were 18 years and older with a diagnosis of RA completed this study. On average, participants saw decreases in PROMIS Fatigue *(-6.4 +/-5.1*), Depression (*-5.6 +/- 5.7*), Anxiety (*-4.5 +/- 6*), and Pain Behavior *(-3.8 +/- 5.4*) scores, and improvements in PROMIS Physical Function (*1.4 +/- 2.7)* and BMIS mood

scores (*5.6 +/-7*) over the course of this 4-week study. Eleven of these participants (84%) completed all study measures, while two (16%) failed to complete one or more weekly surveys. Overall, participants used VRM an average of 8.9 (+/- 8.5) times for an average duration of 8.9 (+/- 2.4) minutes/session. Many participants found VRM relaxing and most found VRM acceptable for use; barriers to use were identified and contextual factors also impacted participant's abiltiy to use VRM. During post-hoc analysis and creation of the mixed-methods matrix, PROMIS and BMIS measures were categorized according to use counts of *High*-, *Moderate*- and *Minimal*-use groups Post-hoc categorization revealed decreases in fatigue, depression, anxiety and pain behavior and increases in physical function and mood across all 3 use groups.

Conclusions: The results of this study have shown that VRM is a feasible and acceptable intervention for managing fatigue and associated symptoms in outpatients with RA. In alignment with prior findings of the efficacy of VR for managing anxiety, depression, fatigue and pain,[24] as well as mood disturbance,[11] our study found that VRM decreased fatigue, depression, anxiety and pain behavior, while increasing physical function and positive mood. This study adds to current VR literature by providing key insights into outpatient VRM use.

Virtual Reality Meditation for Fatigue in Persons with Rheumatoid Arthritis

Introduction

Outpatient healthcare has seen sweeping changes over the past decade as immersive, stand-alone and wearable technologies like virtual reality (VR) have become available.[1] The possibilities of VR within healthcare are seemingly endless. However, further development is needed to bring this technology to a mature level where it can consistently deliver accurate, remote and safe non-pharmacologic therapies that employ focused, disease-specific treatment strategies (e.g., arachnophobia treatment[2]) as well as general wellness (e.g., mindfulness[3]) content. One condition that could potentially benefit from VR is Rheumatoid arthritis (RA), a debilitating chronic disease that affects over 1.28 million people in the United States and nearly 20 million people worldwide.[4] Recent pharmacologic advances in the management of RA have led to a decrease in inflammatory symptoms, such as chronic pain or even disease remission,[5,6] yet up to 70% of patients with RA still suffer from fatigue.[7,8] For those with RA, fatigue and pain management are closely tied together;[9] the most effective interventions for symptom management are behavioral therapies (such as mindfulness) or movement-based approaches.[10] While VR-delivered meditation shows promise for pain and anxiety management in rheumatic diseases (e.g.: RA, Lupus, Fibromyalgia, etc.),[3,11] there is little information on VR meditation (VRM) use for fatigue management in those with RA.

The **goal** of this research study is to examine the feasibility and acceptability of using VRM to manage fatigue in outpatients with RA. The specific **aims** of this **convergent mixed-methods study** include: 1) examining the **feasibility** of implementing VRM as an adjunct for managing fatigue; 2) determining the **acceptability** of using VRM for fatigue management; and 3) exploring the **experience** of using VRM to manage fatigue in outpatients with RA.

Materials and Methods

Design and Approach

This study utilized a **convergent, mixed-methods study design** which is detailed in ***Figure 1***. Quantitative study data were collected and managed using electronic data capture (REDCap) tools hosted at the University of Washington's Institute for Translational Health Services (ITHS).[12,13] A **qualitative descriptive approach** was taken to formulating questions and performing semi-structured interviews with participants. This study was approved by the University of Washington's Human Subjects' Division.

Population and Recruitment

Eligible participants were 18 years and older with a diagnosis of RA. Exclusion criteria included: 1) past medical history of uncorrectable visual or auditory impairment that would interfere with a full experience of VR, 2) history of seizure disorder or seizure caused by technology use, 3) extensive motion sickness or vestibular dysfunction that could cause motion sickness, or 4) excessive face or scalp sensitivity to pressure that

could inhibit use of a VR headset. Recruitment occurred face-to-face at an outpatient rheumatology clinic prior to the COVID-19 pandemic, after which participants were recruited via posted flyers in the same clinic during the ongoing pandemic. All interested and eligible participants were enrolled between 11/1/2019 to 1/14/2021. Electronic or written informed consent was provided by all subjects prior to commencement of study procedures.

Patient-Reported Outcome Measures

PROMIS. This study used Patient-Reported Outcome Measurement Information System (PROMIS) measures banks for fatigue (v1.0), depression (v1.0), anxiety (v1.0), pain behavior (v1.0) and physical function (v1.2). The primary measure, fatigue, was chosen as it often persists even when RA is medically well-managed.[7,8] Secondary measures of depression, anxiety, pain behavior and physical function were selected based their connection to fatigue and RA.[9,10,14] PROMIS scores rage from 0-100, and use a T-score metric in which "50" is the mean of a relevant reference population and 10 is the standard deviation (SD) of that population (e.g., a score of 40 is one SD lower than the mean of the reference population).[15] Higher scores mean more of the concept being measured. All PROMIS measures were deployed using their respective computer-adaptive test (CAT) forms. This method was chosen to ease subject burden and because PROMIS fatigue, pain interference and physical function CAT measures have been successfully validated in persons with RA.[16]

BMIS. Following PROMIS measures, participants completed the Brief Mood Introspection Scale (BMIS). The BMIS consists of 16 mood-adjectives that range across

predominantly positive or negative mood states; this study scored participants along the pleasant-unpleasant mood domain.[17]

VRM Use Data

The date, time and duration of VRM use was electronically recorded for each participant. Use data was stored on headsets during use and extracted following completion of the study. Time stamps and counts were corroborated with de-identified interview transcripts regarding VRM use to validate data and ensure accuracy.

Semi-Structured Interviews

Semi-structured interview questions focused on feedback about participants' experiences with RA, prior experience of fatigue, and strategies participants use for fatigue management. The questions also addressed participant's experience using VRM and recommendations for future use at the completion of the study. Interviews were digitally recorded and transcribed.

Procedures

Demographic and Baseline Data. Following enrollment , participants were emailed a survey link to complete demographic data – including age, sex, highest level of educational achievement, marital status and employment status – and baseline PROMIS and BMIS measures.

Procedures prior to the COVID-19 pandemic. Following completion of baseline questionnaires, participants were interviewed and digitally audio recorded in-person prior to and following their first VR session (which was observed but not recorded). VR headsets were then sent home with participants following their first session.

Procedures during the COVID-19 pandemic. Due to protocol changes required during the pandemic, participants were instead interviewed over-the-phone or via video chat and conversations were digitally audio recorded. Following completion of their initial semi-structured interview, headsets preloaded with VRM content and instructions for set-up, maintenance and use were mailed to participants.

Virtual Reality Meditation. To maintain safety and minimize the potential for VR side effects while using VRM, participants were given a training packet regarding VRM software and headset use. For their safety, participants were instructed to sit in a fixed chair with arm rests (without wheels or rollers). VRM content (Virtual Therapeutics, Kirkland, WA, USA) was self-administered by participants. A free-standing and wireless Oculus Go was loaded with VR software content and used to deliver the intervention. VRM uses “passive” VR content wherein users are immersed into a realistic 360-degree landscape and guided through a meditative session via an audible voice. Participants could turn their head to look about the environment, but their “virtual selves” were fixed in position and could not move through the virtual space. Participants chose from several realistic natural environments and session lengths (up to 15 minutes). There was no “masking” or “blinding” due to the obvious nature of wearing a VR headset. VRM duration was limited based on the programmed content, which aligns with recommendations to keep individual VR sessions to less than 30 minutes to decrease potential for VR side effects.[18,19] To better understand VRM use, participants were allowed to use VRM as frequently as desired, though they were instructed to have one-hour “rests” between individual sessions to decrease the potential for VR side effects.

Weekly Measures and Post-intervention Interview. All participants were emailed links to complete PROMIS and BMIS measures on a weekly basis for a total of four weeks from the date they received their VR headsets. After completion of these questionnaires, a final semi-structured interview was scheduled with participants in-person (pre-COVID) or via phone or video chat (during COVID). VR headsets were collected during this final in-person meeting or mailed back to the study staff via a prepaid box and return label. Study completion was defined, a priori, as: 1) receiving the VR headset, using it at least once and returning it to the study staff, 2) completing at least one week's worth of PROMIS and BMIS data in addition to the baseline measure and 3) completion of semi-structured interviews before and after the intervention period (twice). Missing data was addressed by using the last value carried forward, and all PROMIS, BMIS, use and interview data were stored on a secure server at the University of Washington.

Analyses and Mixed-Methods Matrix

Descriptive statistics (mean and standard deviation) were calculated for participant's age, gender, highest degree completed, employment status, and marital status; see ***Table 1***. Average change scores for PROMIS and BMIS data were calculated for each participant who completed the study by subtracting the baseline score from the average treatment period score (across 4 weeks of VRM use). As with PROMIS measures, average change scores were calculated for each participant who completed the study by subtracting the baseline score from the average treatment period score. Transcriptions were reviewed for accuracy against recordings, and then coded by two different investigators and a list of major thematic elements was created through careful study of the transcripts; conflicts were resolved by group consensus.

Coding was supported through use of Atlas.ti v9 software (ATLAS.ti Scientific Software, Berlin, Germany). Following analysis of PROMIS, BMIS and VRM use data, and transcription and coding of semi structured interviews, data was then integrated to create a mixed-methods matrix.[20] This matrix allowed for easier comparison of quantitative data with quantified, qualitative results of feedback from participant's interviews.[21–23] Details on mixed methods analysis can be found in **Figure 1**.

Results

Demographics

Seventeen participants enrolled in the study, with 13 (76%) completing study procedures. Consolidated Standards of Reporting Trials (CONSORT) study details are noted in ***Figure 2***. The average age of participants was 52 (+/- 16) years. They were primarily female (*n=10*), had received post-secondary education (bachelor's, master's, or professional degree*; n=10*), and were currently employed (*n=10*). Further demographic details can be found in ***Table 1***. Based on interview data, one participant had a history of VRM use and just under half (46%) had a history of using meditation. All participants noted ongoing symptoms of both fatigue and pain during their interviews.

Patient-Reported Outcome Measures

On average, participants saw decreases in PROMIS Fatigue *(-6.4 +/-5.1*), Depression (*-5.6 +/- 5.7*), Anxiety (*-4.5 +/- 6*), and Pain Behavior *(-3.8 +/- 5.4*) scores, and improvements in PROMIS Physical Function (*1.4 +/- 2.7)* and BMIS mood scores (*5.6 +/-7*) over the course of this 4-week study. Further detail on PROMIS and BMIS scores can be found in **Table 2**.

Aim 1: Feasibility

Thirteen participants (76%) completed this feasibility and acceptability study (***Table 2***). Eleven of these participants (84%) completed all study measures, while two (16%) failed to complete one or more weekly surveys. Overall, participants used VRM an average of 8.9 (+/- 8.5) times for an average duration of 8.9 (+/- 2.4) minutes/session. Three participants used VRM 14 or more times, three participants used VRM seven or more times and six participants used VRM six or less times. Only one participant noted adverse effects from VRM use, ("I actually found myself getting a little motion sick, trying to use it"; **Participant 24**).

Aim 2: Acceptability

Many participants found VRM relaxing and most found VRM acceptable for use ("*in the evening, it defnintely helped better with turning some of that stress off and releasing some of the pressure that helps cause the fatigue*"; **Participant 21**). Patients appreciated having VRM to use in the moments that they needed symptom relief ("*I really enjoyed VRM to tell you the truth…, because with [RA] it's cyclical…; some days are harder than others. And on a hard day actually having a meditation, like a VR meditation, would be really, really helpful";* (**Participant 9**), and most felt relaxed – or even energized – after using VRM ("*It was relaxing enough to recoup. The batteries would recharge a little bit…, and it kind of invigorated [me]…, it woke me up. Yeah, it took me out of whatever funk I was in";* **Particpant 3**). One outcome participants reported after using VRM was better sleep ("*It was wonderful…. [VRM] made me relax and… sleep better at night*"; **Participant 6**). One participant with prior experience using meditation noted that VRM assisted them to maintain their mindful focus:

> *I like the fact that [it's] visual… [and there are] a lot of different ways they sort of [keep you] engaged with it…. Meditating in a quiet room…, your mind goes off in one direction [and]…. you got to remind yourself to come back to why you're sitting here…. That [VRM] system [makes it] …a little easier to stay on track*. (**Participant 4**)

Another participant noted that VRM allowed them to achieve "*more general relaxation… than I feel I would have found through, just, you know, standard meditation without the VR*" (**Participant 21**). Creating a conducive enviornment was essential to utilizing VRM for symptom mansagement, but a variety of barriers prevented participants from constently using VRM.

Barriers to Use. Over half of participants (62%) noted barriers to consistent use of VRM ("*I try to do it every… night before I [go] to bed. Sometimes I wasn't able to…, it slipped my mind or [I] forgot…*"; **Participant 27**). Though VRM's purpose was symptom management, sometimes these symptoms (e.g., pain and fatigue) prevented VRM use.

> "…*They're trying to change my… big biologic [medication] because it's not working very well anymore…. When I started with the VR headset, I was not feeling as bad as I am now. So for the first couple of weeks, it was really interesting and I enjoyed it…. But within two weeks, my hands really started hurting. And I couldn't use the trigger as well. But beyond that, when I'm in pain…, I found… I can't still my mind."* (**Participant 23**)

In addition to physical barriers, most participants were "*not able to form any sort of daily habit of meditation."* (**Participant 27**). Reasons for this included hardware and software

issues ("*I never paid attention to the types of errors… I just press the button on the side of the VR [headset] and turn it off and then start it again. And sometimes the little handheld [controller]… was a little screwy too"*; **Participant 4**), issues with VR headset fit ("*…[VRM] can be fun, but I didn't really like the style of the headset and the fit and the comfort, so I didn't use it very much"*; **Participant 26**) and headset weight ("*I had to look up a lot because of the heaviness of the headset"; **Participant 26***). Participants also noted having trouble finding time for VRM ("*It was hard finding times to do it, so I didn't do it all a whole lot, unfortunately. I wish I could have done it more, but I also didn't find myself like gravitating toward it…"; **Participant 2***), and difficulty finding personal space to meditate ("*I think part of what interrupted my usage is if I had other people around… [and] it just kind of felt awkward saying, 'Excuse me, I'm going to go [meditate]'*"; **Participant 1**). Overuse was also an issue in this study. Two particpants noted repeatedly using the headset for more than the recommended time in one sitting ("*30 minutes minimum"*; **Particpant 26**), which proved too long for initial use ("*I can see why you said no more than a half hour or whatever at a time…. [I would do] about two of…the longer [sessions]…. It went quickly, but it was, 'when is this going to end?*'"; **Participant 3)**. Both participants curtailed VRM use to a total of 4 times each during the study, and both noted significant barriers – dislike for elements of the VR environment and weight of the VR headset – that may be byproducts of extending sessions beyond the recommended duration. Thus, by engaging too quickly with longer VRM sessions, participants may have inadvertantly created barriers to use.

Contextual Factors. Interviews uncovered contextual factors that may have impacted patient-reported outcome scores (PROMIS and BMIS) as well as VRM use.

Participants noted issues with unclear, changing, and additional diagnoses ("*So… vasculitis, RA, CHF and here I am";* **Participant 3**), inadequate symptom management ("*I just finally hit the wall…. You stop, you have to. You can't go on anymore because you can't walk and every joint in your body hurts*"; **Participant 6**), diffuse symptom sources ("*I think it's just [infuriating] not being able to understand that the source of where… my fatigue mainly stems from*"; **Participant 24**), poor education about their health ("*I still feel very unaware of all of the effects [of RA on] the day to day living, even though it's been two or three years now";* **Participant 1**), and frustration around uncertainty in their diagnosis ("*It's extremely frustrating, extremely frustrating…. There are so many factors in here…[that] it's basically [the providers are] never sure what they're exactly dealing with"*; **Participant 21**). Socioeconomic status and living in a rural area heavily impacted participants access to care:

> *"Out here is the physical location to services is horrible because even paratransit, trying to get, they won't… help pay for gas to go [to the clinic] because they said there's other rheumatologists that are closer. Well, the other rheumatologists that are closer were not accepting new patients that were on state medical. Things like that are huge barriers."* (**Participant 1**)

Participants had mixed feelings about the chronic care their RA required ("…*when you have [a] disability you fight for [a] living*"; **Participant 11**), and often placed a lot of pressure on themselves to manage their illness ("*Yeah, I'm not very good at managing my [RA]. I mean having any sort of… illness is a commitment to take care of and I already have a lot of commitments in my life. So it's kind of just on the backburner a lot of the time"*; **Participant 2)** Some participants noted concerns about using VR ("…*will I*

know what is reality and not, or will I want the virtual more than reality? So I guess that yeah, the line between reality and not, is what scares me"; **Participant 24**), yet others we drawn to the novely of VR use, and some found a new tool for symptom management (*"I do need to work on [meditation] becoming a habit";* **Participant 1**).

Aim 3: Experience using VRM

Mixed-Methods Matrix. During post-hoc analysis and creation of the mixed-methods matrix, PROMIS and BMIS measures were categorized according to use counts of *High*- (>/=14 times), *Moderate*- (7-13 times) and *Minimal*-use (1-6 times) groups (see **Table 3**). Post-hoc categorization revealed decreases in fatigue, depression, anxiety and pain behavior and increases in physical function and mood across all 3 use groups. Participants in *High, Moderate* and *Minimal* groups used their headsets an average of 22, 7 and 3 times, respectively, over this four-week study. While there was little difference in total average use time between *Minimal*- and *Moderate*-use groups, the *High*-use group used VRM for nearly twice the duration of time. Additionally, during interviews, one (33%), two (66%), and three (50%) of the *High*, *Moderate* and *Minimal*-use participants (respectively) reported active sleep issues related to RA, fatigue and chronic pain. It should be noted that the one *High*-use participant who reported sleep issues prior to VRM use also reported improvements after VRM use (*I always did it…before I went to bed and then by sleeping all night I wasn't as tired during the day. …When I don't use it I'm really tired* "; **Participant 6**).

Discussion

The results of this study have shown that VRM is a feasible and acceptable intervention for managing fatigue and associated symptoms in outpatients with RA. In alignment with prior findings of the efficacy of VR for managing anxiety, depression, fatigue and pain,[24] as well as mood disturbance,[11] our study found that VRM decreased fatigue, depression, anxiety and pain behavior, while increasing physical function and positive mood. While this data is compelling, it should be interpreted cautiously as the sample size is small, standard deviations are large and the vast majority of participants did not use the device consistently throughout the study. The high survey and measure completion percentages (84% and 100%, respectively) indicate clear protocol feasibility (**Aim 1**). Most participants enjoyed using VRM and found it acceptable for fatigue management (**Aim 2**). Both of these findings extend initial results from Venturupalli et al[3] by providing evidence for the feasibility of VRM, beyond pain and anxiety management, for addressing symptoms of fatigue in RA. However, participant experience using VRM (**Aim 3**) varied greatly, and many individuals experienced barriers to consistent use. These barriers included issues with hardware and software, VR headset fit and weight, hand immobility (due to pain), as well as issues finding time and space for VRM. These problems are also reflected in studies by Glegg and Levac[25] and Evenson and Fleury[26] that explore barriers to VR intervention use and outpatient adherence (respectively). These barriers were compounded by the stressors participants faced daily in managing their disease. The biopsychosocial impacts of fatigue and pain, paired with potential socio-economic status and accessibility issues (e.g., rural living) often left participants feeling exhausted. VRM provided a remote

platform for participants to experience and practice meditation, yet it is vital to consider these barriers prior to VRM deployment.

Within the context of RA management these results are promising. A variety of non-pharmacologic interventions have been shown to assist with RA symptom management including nutrition changes to limit “flare-ups”,[27] psychological interventions for mental health,[28,29] and web-based education to encourage symptom self-mangement.[30] Specifically for fatigue, physical activity and psychological programs have been shown to be most effective.[31] VR provides a novel medium for non-pharmacologic interventions that remotely immerse users in a therapeutic environment. VRM has the potential to meet psychological needs of fatigue management, but other kinds of VR content that incorporate movement-based approaches are still needed. While VR physical activity programs have shown potential in other rheumatic populations,[32] further testing in populations with RA is needed. VR has enormous potential as an immersive platform that can be deployed remotely, but further development of efficacious content is needed to meet the vast need of urban and rural patient populations.

Limitations

Limitations to this study relate primarily to the occurrence of the COVID-19 pandemic after study commencement and its feasibility and acceptability design. All aspects of this study engagement with participants required change due to the COVID-19 pandemic, and recruitment was particularly impacted. Also, as this was a feasibility and acceptability study there was no control group, increasing the potential for bias. As

noted above, the small sample size diminishes the generalizability of this study, but does not detract from achievement of this study's aims.

Recommendations and Areas for Future Research

This study adds to current VR literature by providing key insights into outpatient VRM use. Coaching regarding consistent, daily use of the VRM, as well as education regarding VRM timing and duration of use, are recommended for successful intervention deployment. Improved instructions on the adjustment, application and fit of VRM hardware are recommended for future studies. Additionally, due to the reliance on medications for disease management in RA, future intervention studies in this population should account for medication use and disease course (noting "flare-ups") during the study. Areas for future research include determining the efficacy of VRM for fatigue management, extending the duration of VRM use beyond 4 weeks, expanding VRM use to other rheumatic populations, and exploring how different kinds of VR-delivered meditation might impact symptom management including fatigue in these populations.

Figure 1: Convergent Mixed-Methods Design and Analysis

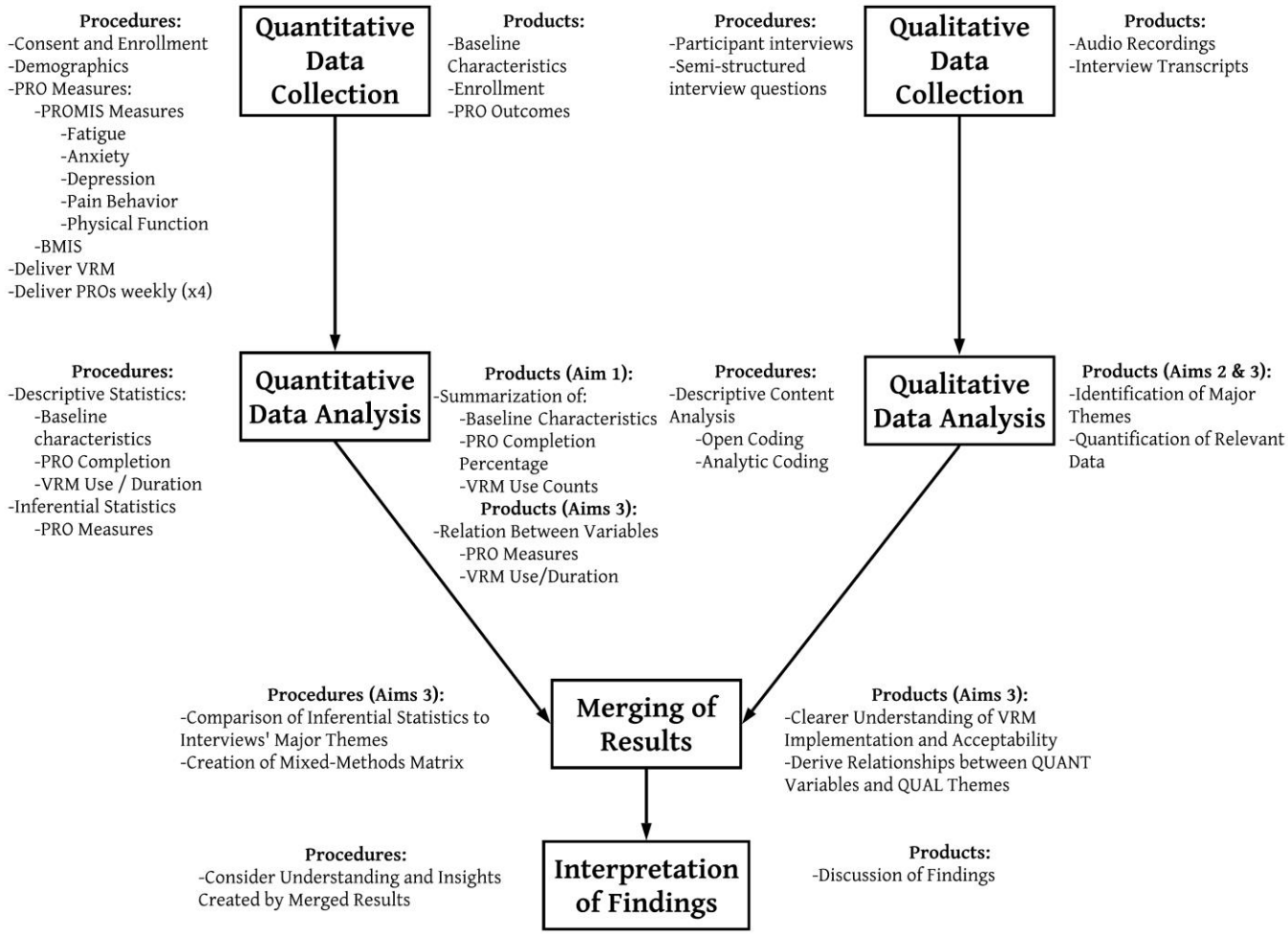

Figure 2: Consort 2010 Diagram for Virtual Reality Meditation for Fatigue in Persons with Rheumatoid Arthritis

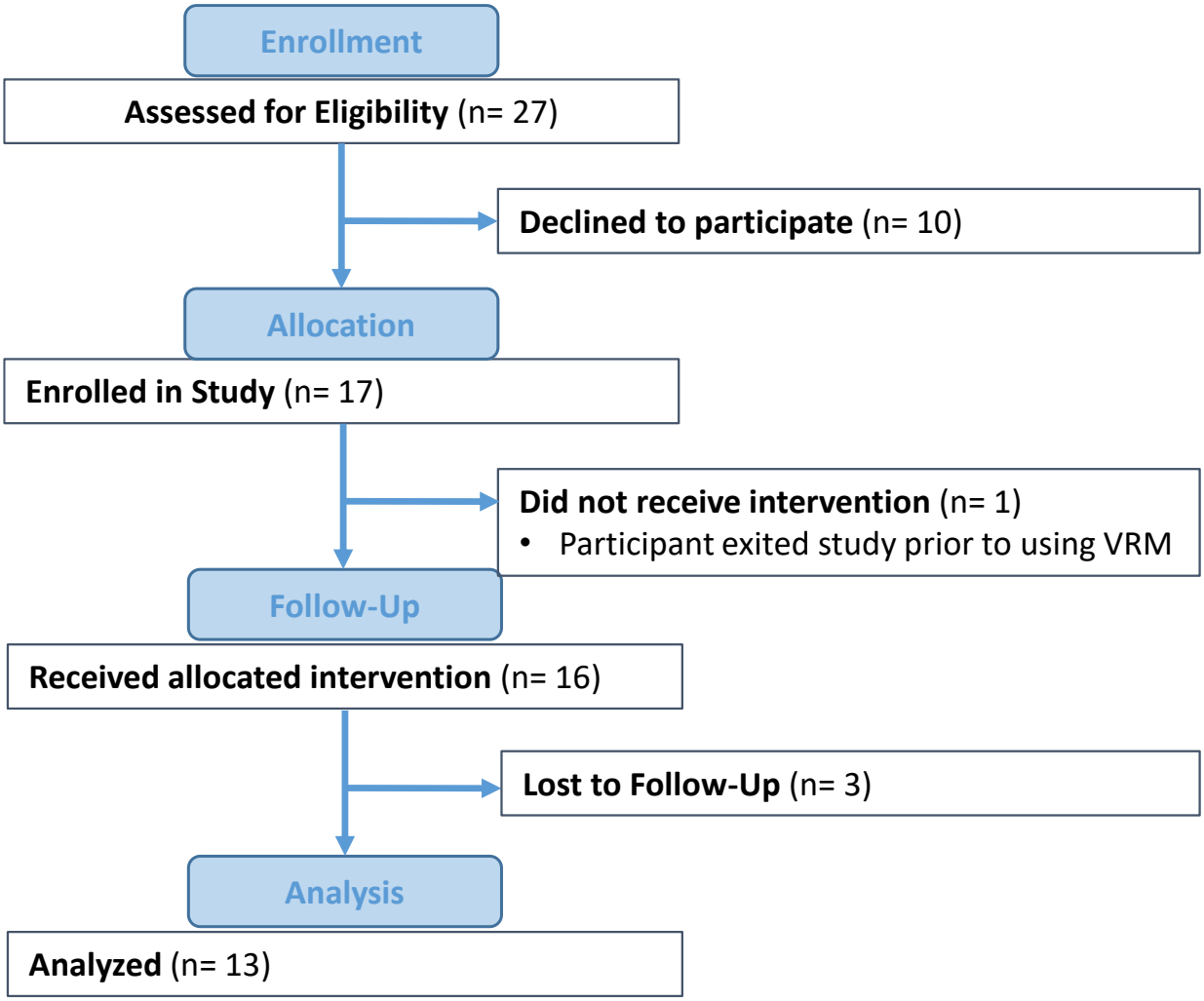

Table 1: Demographics

Age	**Mean (SD)**
	52 (+/-16)
Gender	**N (%)**
Female	10 (77%)
Male	3 (23%)
Education	**N (%)**
Completed High School/GED	1 (8%)
Some College	1 (8%)
Bachelor's Degree	3 (23%)
Master's Degree	5 (38%)
Professional Degree	2 (15%)
Omitted	1 (8%)
Employment	**N (%)**
Employed	9 (69%)
Unable to Work	2 (15%)
Retired	1 (8%)
Self-Employed	1 (8%)
Marital Status	**N (%)**
Single or Never Married	2 (15%)
Married or Domestic Partnership	5 (38%)
Divorced	4 (31%)
Separated	1 (8%)
Widowed	1 (8%)

Table 2: Patient Reported Outcome Measures and Use Data

	PROMIS Measures					BMIS	Use Data	
Participant	**Fatigue***	**Depression ***	**Anxiety***	**Pain Behavior***	**Physical Function***	**Mood***	**Overall Use****	**Average Use Time*****
P001	-9.1	-4.5	-8	-4.1	0.1	14.8	*7*	*7.4*
P002	-8.1	-7.2	-0.7	-6.2	2.1	-6	*3*	*6.8*
P003	1.9	-1.7	2.6	-1.4	-2.6	5.5	*4*	*9.6*
P004	2.4	1	2.2	-2.4	0.3	-8	*28*	*13.1*
P005	-3.9	-8	-4.7	-0.5	0.5	0.3	*8*	*9.0*
P006	-2.3	-4.6	-6	-1.7	0	10.8	*23*	*11.9*
P009	-9.7	-1.4	-7.6	-2.8	7.6	7	*7*	*7.6*
P011	-14.9	-20.1	-21.2	-20.5	5.3	15.8	*2*	*6.8*
P021	-4.4	-13.28	-3.4	-5.7	1.5	7	*14*	*12.9*
P023	-5.6	-6.3	-5	-0.4	-0.6	3.3	*6*	*8.8*
P024	-11.8	-1.3	-1.9	-2.7	0.6	5.5	*1*	*6.8*
P026	-8.4	-3.5	-4.2	-1.4	3.5	3.3	*4$^{\phi}$*	*na*
P027	-9.5	-1.7	-0.2	-0.3	0.36	1.3	*4*	*6.9*
Avg (SD)	**-6.4 (+/-5.1)**	**-5.6 (+/-5.7)**	**-4.5 (+/-6)**	**-3.8 (+/-5.3)**	**1.4 (+/-2.7)**	**4.6 (+/-7)**	**8.9 (+/-8.5)**	**8.9 (+/-2.4)**

*average change scores ** counts ***minutes $^{\phi}$ based on patient report

Table 3: Mixed Methods Matrix

Use Categories	**High** (>/=14 times)	**Moderate** (7-13 times	**Minimal** (1-6 times)
Fatigue*	-1.4 (+/-3.5)	-7.6 (+/-3.2)	-8 (+/-5.8)
Depression*	-5.6 (+/-7.1)	-4.6 (+/-3.3)	-6.4 (+/-7.2)
Anxiety*	-2.4 (+/-4.2)	-6.7 (+/-1.8)	-4.4 (+/-8.6)
Pain Behavior*	-3.2 (+/-2.1)	-2.5 (+/-1.8)	-5.2 (+/-7.8)
Physical Function*	0.6 (+/-0.8)	2.7 (+/-4.2)	0.9 (+/-2.7)
Mood*	3.3 (+/-9.9)	7.3 (+/-7.2)	4.2 (+/-7.1)
Average Use**	22	7.3	3.3
Average Use Time***	12.6	8	7.6
Barriers to Use******	0	66.6	99.9
Prior VR Therapy Use******	33.3	0	0
Prior Meditation Use******	66.6	66.6	33.3
Fatigue******	99.9	99.9	99.9
Pain******	99.9	99.9	99.9
Sleep Issues******	33.3	66.6	49.9
*average change scores	** counts	****minutes	****percentage of participants

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Chapter 5. Conclusion

Symptom management is essential to health maintenance. While pharmacologic treatments are often necessary, non-pharmacologic treatments are a vital treatment component. Virtual reality (VR) is a non-pharmacologic healthcare delivery platform for symptom self-management on which a variety of treatment options can be deployed remotely. The purpose of this dissertation was to explore symptom self-management across various settings with an emphasis on VR interventions.

In chapter 2 of this dissertation, a systematic review of on VR for acute pain was conducted according the PRISMA guidelines in order to examine the delivery and efficacy of VR therapeutics for acute pain management in adults within clinical settings. All pertinent articles published between January 1st, 2000 and August 1st, 2020 were included. A search of PubMed, CINAHL, PsychINFO, Embase, Compendex, and Inspec was completed using MESH and keyword search terms related to acute pain and VR. Twenty-three articles met final inclusion criteria and were included in this review. Studies utilized VR in a variety of settings for wound care, procedure-induced pain, physical or occupational therapy, dental treatment or generalized acute pain. The primary means by which included studies promoted analgesia was via distraction. Of the reviewed studies, 19 (83%) reported decreases in pain intensity while using VR compared to no VR use or to a non-VR group.

In chapter 3 of this dissertation a qualitative descriptive approach with semi-structured interviews was used examine living kidney donors' experience of postoperative pain. Interview transcripts were reviewed for trends, patterns and insights into living kidney donors' (LKDs') experiences of postoperative pain. Content analysis of

the interview data was performed using Atlas.ti (v9.0) and codes were inductively generated. Thirteen LKDs whose average age was 46.5 (+/- 14.4) years participated in this study. LKDs experienced postoperative pain from a variety of sources that hindered postoperative recovery and, in some, created anxiety and fear. Pain management included opioid and non-opioid medications, social support, beautiful scenery, and ambulation among others. LKD's relationships with intended recipients, motivations for donation, social support, past experiences of pain, pain expectations, and meaning of donation all informed their experience of pain, and affected their pain management.

In chapter 4, a convergent, mixed-methods study was performed to explore the feasibility and acceptability of VR medication (VRM) for addressing fatigue in persons with RA. A qualitative descriptive approach was taken to formulating questions and performing semi-structured interviews with participants. This study utilized the Patient-Reported Outcome Measurement Information System (PROMIS) measures banks for fatigue (v1.0), depression (v1.0), anxiety (v1.0), pain behavior (v1.0) and physical function (v1.2), as well as the the Brief Mood Introspection Scale (BMIS). On average, participants saw decreases in fatigue *(-6.4 +/-5.1*), depression (*-5.6 +/- 5.7*), anxiety (*-4.5 +/- 6*), and pain behavior *(-3.8 +/- 5.4*), and improvements in physical function (*1.4 +/- 2.7)* and mood (*5.6 +/-7*) over the course of this 4-week study. The high survey and measure completion percentages (84% and 100%, respectively) indicate clear protocol feasibility. Most participants enjoyed using VRM and found it acceptable for fatigue management. However, participant's experience using VRM varied greatly, and many participants experienced barriers to consistent use.

Key barriers included symptom “flare-ups”, issues finding time and space for VRM use, and difficulties with VR headset fit and weight. These barriers were compounded by the daily stressors participants faced, daily, in managing their chronic disease. The biopsychosocial impacts of fatigue and pain, paired with potential socio-economic status and accessibility issues (ex: *rural living*) often left participants feeling exhausted and stuck. VRM provided a remote platform for participants to experience and practice meditation, yet it is vital to consider these barriers prior to VRM deployment.

As a whole, this dissertation adds to the state of the science regarding therapeutic deployment of VR in three ways. First, the systematic review of VR for acute pain management showed the heterogeneity of available content and need for intentional presentation and pairing of intervention content to appropriate populations. Second, by interviewing inpatient LKDs it became clear that careful consideration of the patient population and psychosocial factors that impact patients’ symptom experience is required for successful implementation of symptom management interventions. Finally, the feasibility study using VRM for fatigue management makes clear that remote-based VR deployment is feasible and acceptable to patients, but clear instructions and parameters for VR content and hardware use are vital to patient adherence, especially when using a novel therapeutic technology without direct supervision.

Currently, there are a vast array of content options on the market, and many different types of hardware on which to deploy them. Expense does not equal quality. Due to current limitations in hardware, clinicians should carefully evaluate the context of patient need – and openness to use – prior to utilizing VR. Great strides are being made

to design content and headsets that better meet user needs. Unfortunately, much of this is being done outside the clinical context, without consideration of infection control measures and heavy (multi-person) use. Thus, currently, clinicians considering VR therapeutics for their patient populations should be matching content and individual devices to patient needs at home.

Overall, VR is a viable platform for deployment, but further development of content is currently required. Future research is needed to explore the efficacy of VR interventions for symptom self-management using various therapies over time and across various populations. While there are a number of different content offerings available, and many efficacious non-pharmacologic therapies used in clinical practice, there is a dearth of symptom-targeting, evidence-based VR content. Paired with biologic and pharmacologic interventions, creation of this kind of VR content is vital to enhance current standards of precision medicine by extending the therapeutic capacity of providers beyond the clinic and into spaces more conducive to healing – patient's own homes. Research on how VR content and hardware can meet the individual constraints of home environments is needed. Cross-discipline collaboration between researchers with backgrounds in patient care, design, and engineering that is informed by input from patients is key to ensuring development of efficacious and safe VR therapeutics. Additionally, researchers must collaborate with industry partners to ensure translation of these findings into broad clinical use. In the post-COVID-19 world, VR has the capacity to encourage health and healing on a scale previously unimaginable. The scope of VR's impact will largely depend on the level of collaboration between these key stakeholders.

Only by working together can we usher-in a new era of healthcare delivery through immersive VR symptom self-management.