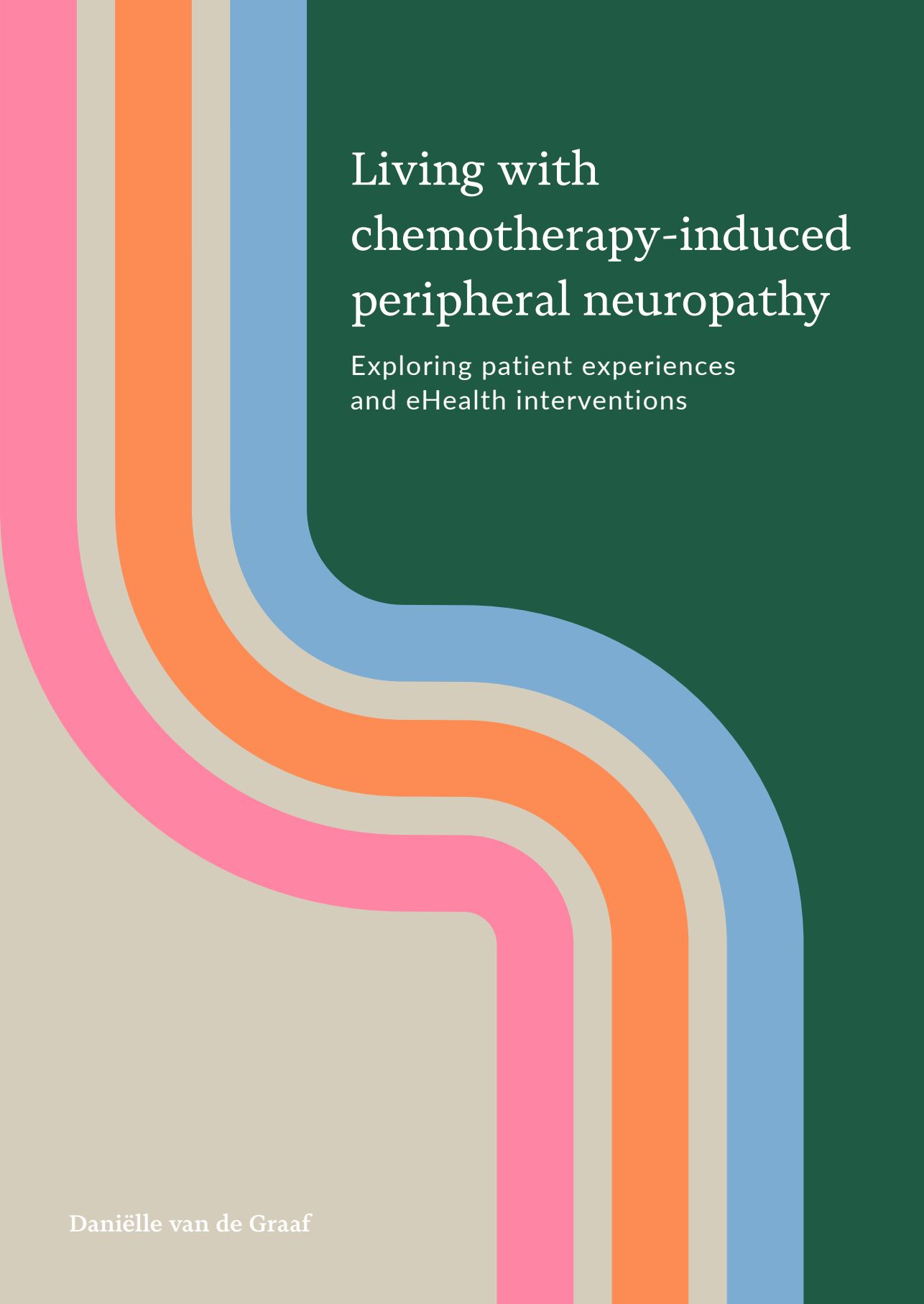


## Living with chemotherapy-induced peripheral neuropathy: Exploring patient experiences and eHealth interventions

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# Living with chemotherapy-induced peripheral neuropathy

Exploring patient experiences  
and eHealth interventions

Daniëlle van de Graaf



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**Living with chemotherapy-induced peripheral neuropathy: Exploring patient experiences and eHealth interventions**

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Exploring patient experiences and eHealth interventions

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# Chapter 1



# General introduction

## **General introduction**

### **Increasing number of cancer survivors**

The number of cancer diagnoses in the Netherlands has increased considerably in recent years. Whereas more than 124,000 diagnoses were made in 2019, this number had risen to nearly 129,000 by 2023 (Integraal Kankercentrum Nederland, n.d.). This increase is expected to continue sharply over the next decade to 156,000 diagnoses per year by 2032 (Integraal Kankercentrum Nederland, 2023). Because diagnostics and treatments have greatly improved in recent years, 5-year survival has increased from 58% for diagnoses made between 2001-2011 to 66% between 2011-2020 (Integraal Kankercentrum Nederland, 2022). This means that the number of cancer survivors is rising and this, consequently, results in more people living with the long-term effects of cancer and its treatments. Many cancer survivors have to deal with physical and psychosocial limitations long after completing treatment and in some individuals, these symptoms do not disappear at all (Foster et al., 2009; Ju et al., 2021; Phillips & Currow, 2010; Rutherford et al., 2020).

## **Part I - Patient experiences**

### **Chemotherapy-induced peripheral neuropathy (CIPN)**

Chemotherapy is an often-used cancer treatment. Its purpose is to stop the growth of cancer cells and induce cell death. However, it cannot differentiate between rapidly dividing malignant and healthy cells, leading to damage to healthy cells (Links & Lewis, 1999). The peripheral nervous system is particularly sensitive to chemotherapy. This can lead to chemotherapy-induced peripheral neuropathy (CIPN), which is a pervasive side effect of chemotherapy. CIPN is caused by chemotherapeutic agents such as taxanes, platinum compounds, and vinca alkaloids (Seretny et al., 2014; Wen, 2007). There is a higher risk of developing CIPN with high cumulative doses of chemotherapy administered (Brewer et al., 2016).

**Prevalence and clinical manifestations**

*“The crazy thing about the chemotherapy period is: I know it [CIPN] was there, but I also strongly felt that it was part of it. I just was not focusing on it at the time. Now, I think, ‘I’m actually suffering a lot from the effects of the disease I have had’. During treatment you don’t think about that. You are exhausted and have pain everywhere. You are anxious. I think that I subconsciously thought ‘Let’s not worry until then. As long as the cancer is gone.’ Now I sometimes wonder if I should have paid more attention to it.*

*It feels like burning. Sometimes I think it is not even pain, but a burning sensation in your feet. It is a feeling of numbness. I always feel like I kind of lose contact with the floor. Then I stand at the stairs and then I have to focus before I go down those stairs.”*

Patient, 50-55 years old, 5-10 years since CIPN onset

Among patients who suffer from CIPN, about 80% of people still have symptoms once treatment is completed (Bao et al., 2016; Bonhof et al., 2018; Eckhoff et al., 2015; Glendenning et al., 2010; Mols et al., 2014; Seretny et al., 2014). Symptoms may also increase in the months after the completion of chemotherapy, a phenomenon known as the *coasting effect* (Staff et al., 2017). This can be particularly confusing for patients, as symptoms are generally expected to stabilize or decrease after treatment completion. About 30% of patients suffer from CIPN 6 months or later after completion of chemotherapy, of which the prevalence differs between cancer types (range 10-60%) (Bao et al., 2016; Bonhof et al., 2018; Eckhoff et al., 2015; Glendenning et al., 2010; Mols et al., 2014; Seretny et al., 2014). This means that while the symptoms eventually disappear in a large proportion of patients, for about one third these symptoms become chronic.

Symptoms of CIPN vary widely because of the influence of chemotherapy type, cumulative dose, patient characteristics, and patient perceptions (Tofthagen, 2010). In general, CIPN symptoms present in the hands and feet and can spread to the arms and legs (Beijers et al., 2012; Farquhar-Smith, 2011; Quasthoff & Hartung, 2002). Sensations that people may experience can be distinguished into non-painful and painful symptoms (Beijers et al., 2012; Bonhof et al., 2020; Farquhar-Smith, 2011; Quasthoff & Hartung,

2002). Non-painful symptoms include sensations such as tingling and numbness, while painful symptoms include, for example, shooting and burning pain, pins-and-needles, and cramps. Additionally, muscle weakness and autonomic dysfunctions may present (Gutiérrez-Gutiérrez et al., 2010).

### ***Diagnosis of CIPN***

The presence, severity, and localization of CIPN symptoms can be identified through both objective measures, such as nerve conduction and tendon reflex, as well as subjective assessments using patient-reported outcome questionnaires (Cavaletti et al., 2010). Previously, assessments of neuropathy often consisted primarily of the observation of neuropathic signs (e.g., search for sensory abnormalities) by health care professionals, while in the last two decades, more attention has been paid to patients' perceptions of symptoms and the limitations that result from these symptoms (Cavaletti et al., 2010). Currently, measurements such as National Institute Common Terminology Criteria (NCI-CTC), Eastern Cooperative Oncology (ECOG), World Health Organization (WHO), and Ajani criteria (Cavaletti et al., 2010; Griffith et al., 2010) are often used to determine symptoms, in which both symptoms and impact on daily functioning are included. However, in these assessments, no distinction in the impact on patients' functioning can be made among individuals who achieve the highest score because this is a crude measure (Griffith et al., 2010). Furthermore, objective measurements are often being perceived as complicated and time-consuming (Cavaletti et al., 2010). The primary benefit of using subjective measurements lies in the ability to assess the actual perceived burden of the patient (Cavaletti et al., 2010). Healthcare professionals often underestimate and underreport the severity of patients' symptoms, resulting in patients not receiving appropriate support and care (Cavaletti et al., 2010). There are several patient-reported outcome measurements available (Jordan et al., 2020), but the most widely-used patient-reported measurement tool is the EORTC QLQ-CIPN20, which enables measuring CIPN symptoms as a supplement to quality of life (QoL) assessment (Postma et al., 2005).

### ***Chronic pain mechanisms***

To comprehensively understand the patients' experience of CIPN, it is essential to examine the chronic pain mechanisms explained by the biopsychosocial model. The biopsychosocial model of chronic pain is the most important and widely-used model to

explain pain mechanisms (Gatchel et al., 2007). It explains that an individual's interpretation of pain and illness results from a complex interplay among biological changes, psychological status, and the sociocultural context. Several contextual factors can either exacerbate or alleviate chronic pain, including anxiety, depression, pain catastrophizing, and pain acceptance (Gatchel et al., 2007; Keefe et al., 2004; Turk & Okifuji, 2002). Over time, this interpretation of pain can impact coping styles and behavior patterns that may result in the exacerbation or alleviation of symptoms (Gatchel et al., 2007). Earlier biopsychosocial research has indeed shown that coping strategies relating to avoidance worsen outcomes such as pain and disability in the long term (Bever et al., 2016; Crombez et al., 2012; Solberg Nes & Segerstrom, 2006; Suls & Fletcher, 1985).

Models related to the behavioral aspect of pain are the Fear-Avoidance model (Crombez et al., 2012; Leeuw et al., 2007; Vlaeyen & Linton, 2000) and the Avoidance-Endurance model (Hasenbring, 1993; Hasenbring & Verbunt, 2010). The Fear-Avoidance model explains that pain-related beliefs and thoughts lead to ruminative, negative, exaggerated thoughts (Crombez et al., 2012; Leeuw et al., 2007; Vlaeyen & Linton, 2000). This results in pain-related fear, which increases avoidance of pain-related activities, creating a cycle of catastrophizing, fear, avoidance, and inactivity. The Avoidance-Endurance model expands on this model, by adding different -response patterns to pain (Hasenbring, 1993; Hasenbring & Verbunt, 2010). This cycle includes distress endurance in which patients suppress distress and experience anxiety and depression but continue with their tasks despite the pain. In doing so, they ignore or minimize the pain, which in the long run can also lead to more limitations.

### **CIPN in daily life**

*"In my feet especially, I have a lot of pain and a lot of cramps. I cannot handle cold, so I always wear socks. For example, cold tiles are hard for me to bear. Then my whole feet cramp up, so I cannot stand. Also, my feet are somewhat numb, so my balance is deteriorated. Because I don't feel well where I walk, I stumble more often. My motor skills are also poor due to numbness in my hands. I can't put a thread through a needle, so unfortunately, I can't knit or crochet anymore. I also don't do crafts and drawing anymore. I can no longer write clearly and I make many typos. I can't open jam jars because I can't put my hand all the way around a jar lid and then also apply force.*

*I must make a lot of adjustments in my week. I have adjusted my life and do things in a different way. My schedule has a different content now. I don't really clean the whole house quickly anymore because I just get too tired. I spread it out more throughout the week. I'm not one hundred percent independent anymore. Sometimes I think 'oh I'm already asking quite a lot and I'm not that old yet'. I find that annoying because I like being independent. It is also stressful for my children because I regularly need their help."*

Patient, 60-65 years old, more than 10 years since CIPN onset

Many patients with CIPN have to deal with several limitations in their daily lives (Bakitas, 2007). Therefore, they experience a lot of interference with their daily lives and the activities they perform (Toftthagen, 2010). Activities such as walking, holding a pen, buttoning a blouse, opening a jar, or riding a car may be difficult or impossible due to CIPN (Beijers et al., 2014; Gutiérrez-Gutiérrez et al., 2010; Park et al., 2013; Toftthagen, 2010). Patients may no longer be able to perform their hobbies, maintain certain relationships, or perform their jobs. As they may have to make adjustments to the roles they have, CIPN can consequently change patients' identities (Jensen et al., 2022).

Multiple studies have shown that CIPN brings about highly limiting consequences as physical, social, and emotional functioning are affected by CIPN, which decreases their QoL (Bakitas, 2007; Bonhof et al., 2020; Ezendam et al., 2014; Mols et al., 2014; Toftthagen, 2010; Toftthagen et al., 2020). This deterioration in QoL is especially seen in patients with painful neuropathy (Bonhof et al., 2020). Furthermore, neuropathic symptoms can also result in other mental issues, such as anxiety and depression (Bao et al., 2016; Bonhof et al., 2019; Hong et al., 2014; Kleckner et al., 2021; Lee et al., 2018; Toftthagen et al., 2013). However, a gap remains in understanding the experiences tied to the consequences of CIPN among patients, wherefore this dissertation focuses on patient experiences relating to CIPN. Currently, there is no comprehensive understanding nor enough recognition of the substantial impact CIPN has on patients' daily lives. This leads to an underestimation of patients' burden, and, consequently, suboptimal medical and psychosocial support.

### ***Treatment options for CIPN***

Current treatment options for CIPN are highly limited, as studies show weak and inconclusive results (Hershman et al., 2014; Jordan et al., 2020; Loprinzi et al., 2020; Mezzanotte et al., 2022). Even though a recent study has provided tentative recommendations for treatments in areas such as psychoeducation, exercise, medication (e.g., duloxetine), and physical therapy (Mezzanotte et al., 2022), and recommendations have been made by the ASCO (American Society of Clinical Oncology) (Loprinzi et al., 2020) and ESMO (European Society for Medical Oncology) (Jordan et al., 2020), it remains challenging to provide recommendations to patients due to the limited strength of the scientific evidence. As no strategies currently exist to prevent CPIN, its development during chemotherapy administration often requires dose reduction to limit excessive symptoms, as CIPN is dose-dependent (Brewer et al., 2016). In some cases, treatment must be temporarily or permanently discontinued, potentially leading to suboptimal treatment, decreased QoL, and morbidity. Currently, dose reduction is the main strategy to manage CIPN (Brewer et al., 2016).

## **Part II - eHealth interventions**

### **Psychological interventions**

In recent years, there has been an increase in research into non-pharmacological treatment options for patients with CIPN (Knoerl et al., 2018; Tanay et al., 2022; Tofthagen et al., 2016), without them currently being part of general recommendations for treating CIPN patients (Jordan et al., 2020; Loprinzi et al., 2020; Mezzanotte et al., 2022).

### ***Acceptance and Commitment Therapy***

As described in the Fear-Avoidance model (Crombez et al., 2012; Leeuw et al., 2007; Vlaeyen & Linton, 2000) and the Avoidance-Endurance model (Hasenbring, 1993; Hasenbring & Verbunt, 2010) (page 6), pain with chronic pain patients often exhibit anxiety and avoidance behavior regarding their pain symptoms (Claes, 2016; Claes et al., 2015; Harvie et al., 2017; Meulders et al., 2015; Vlaeyen et al., 2016). Therefore, psychological interventions, such as Cognitive Behavioral Therapies (CBT) like Acceptance and Commitment Therapy (ACT), can support patients in engaging in helping, adaptive, flexible strategies to overcome fears and avoidance associated with their

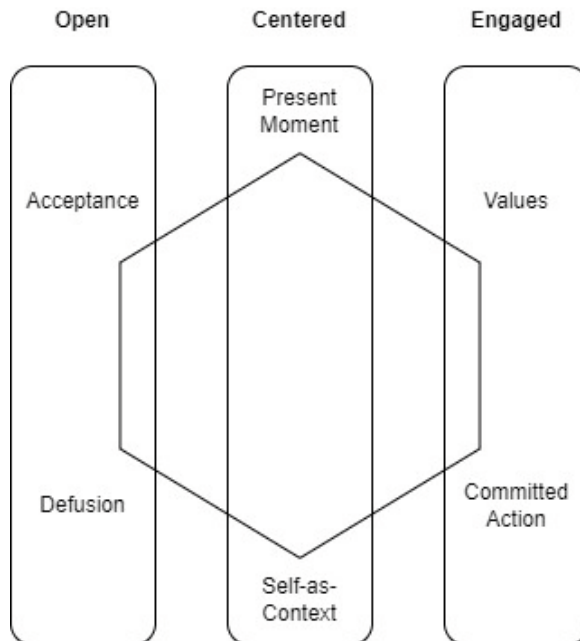
symptoms (Hayes et al., 2006; Scott et al., 2016). ACT is a third generation CBT that guides patients in directing attention toward personally meaningful activities by enhancing pain acceptance, as an alternative to (experiential) avoidance (Hayes et al., 2006). It aims to help patients let go of the struggle with pain and encourage adopting an open and conscious approach towards it. The goal is not mere acceptance, but rather that acceptance may emerge because of making value-oriented decisions in life. This is defined as psychological flexibility.

Psychological flexibility consists of six core processes, which are grouped into three different response styles (Figure 1) (Hayes et al., 2006, 2012): (1) Openness is the first response style, which includes acceptance and cognitive defusion. Defusion entails a disconnection of negative and unwanted thoughts and experiences by looking at this non-judgmentally and from a distance. This allows patients to identify what pain-related avoidance behaviors they exhibit and subsequently change their attitudes. (2) The second response style is engagement, which includes the processes of values and committed action. Engagement is about deciding what is important in several areas of life and formulate concrete reachable steps in doing so. This brings patients closer to value-based living. (3) Centered, or awareness, is the third response style, which includes the processes of present-moment focus and self-as-context. This allows people to be flexible in the here and now (Hayes et al., 2006, 2012). The response style is related to mindfulness, which includes being in the here-and-now without judgment. Mindfulness allows patients to get in touch with bodily sensations, including pain, without trying to change or control them.

ACT has been proven to be effective for other types of chronic pain in two systematic reviews including one meta-analysis (McCracken & Vowles, 2014; Veehof et al., 2011). Furthermore, ACT is increasingly applied in global cancer care (Feros et al., 2013; Hulbert-Williams et al., 2015). However, only one previous study studied CIPN patients specifically, investigating a self-supported online cognitive and behavioral-based pain management intervention for patients with chronic painful CIPN (Knoerl et al., 2018). This intervention included a website to help individuals manage their pain and related symptoms after cancer treatment, such as anxiety, depression, sleep, fatigue, and impaired function. Modules included content regarding, for example, psychoeducation, communication strategies, relaxation techniques, stimulating physical activity, and goal

setting. Results showed positive effects for pain intensity, providing preliminary support for non-pharmacological treatment options (Knoerl et al., 2018). This generates positive expectations regarding ACT for CIPN, especially because ACT seems to better address the mechanisms of chronic pain (e.g., avoidance) compared to CBT, given its focus on psychological flexibility (Hayes et al., 2006, 2012). Furthermore, a recent study has shown that patients with cancer-related pain who exhibit greater psychological flexibility experience lower levels of distress and improved functioning, implying that ACT could be a valuable treatment option for these patients (Duarte et al., 2023). This dissertation therefore concentrates on ACT as a psychological treatment for patients with CIPN.

**Figure 1.** ACT hexaflex including response styles and therapeutic processes (Hayes et al., 2006, 2012)



### Online self-management interventions

Recent years, interventions have been increasingly offered online due to major developments in eHealth (Borosund et al., 2018; Gainsbury & Blaszczynski, 2011; Knoerl et al., 2018), which has created many advantages compared to face-to-face interventions (Borosund et al., 2018; Cuijpers et al., 2008; Knoerl et al., 2018). Online interventions

typically entail lower costs and greater accessibility for patients. Additionally, therapist time and waiting list can decrease as patients can work independently on the management of their symptoms, without the constant need for a therapist. Furthermore, patients do not have to travel to participate, thus reducing both physical and mental burden, which is of considerable benefit, especially in patients with many physical or mental symptoms. In addition, there still is a stigma attached to psychological interventions, which seems less prominent with online psychological interventions. Patients can also be reluctant to participate in a face-to-face intervention because of the overwhelming nature or cause of the symptoms. These multiple benefits may increase the reach of online interventions by attracting people who quit or do not participate at all in conventional forms of treatment because of associated limitations (Cuijpers et al., 2008). Furthermore, in online interventions, patients can often work at their own time and speed, which brings more flexibility (Borosund et al., 2018; Cuijpers et al., 2008; Knoerl et al., 2018). Therefore, online interventions can add great value to current treatments in healthcare.

### ***Online psychological self-management interventions***

Recent research has examined effects of guided online CBT in comparison with traditional face-to-face CBT (Hedman-Lagerlöf et al., 2023). This included a systematic review and meta-analysis focusing on both psychiatric and somatic disorders. The findings indicate that guided online CBT and face-to-face CBT yield comparable outcomes in terms of symptomatic improvement. One of the studies included in this systematic review and meta-analysis is a randomized controlled trial examining online ACT compared to face-to-face ACT for depression (Lappalainen et al., 2014). This study demonstrated that the effects were comparable, suggesting that online ACT might have certain additional advantages given the additional benefits of the online format. Follow-up assessments indicated slightly more favorable outcomes for the online ACT compared to the face-to-face version. The researchers attributed this to the flexibility of the online format, allowing participants to access the therapy at their convenience and revisit components as needed (Lappalainen et al., 2014). Given similar effectiveness and additional benefits compared to traditional interventions, it is interesting to look at opportunities to provide online self-management psychological interventions for patients with CIPN.

Although there has been much research on online interventions for chronic pain or CIPN specifically based on other psychotherapies such as CBT (Bender et al., 2011; Buhrman et al., 2016; Eccleston et al., 2015; Knoerl et al., 2018; Macea et al., 2010), there are also some studies that have looked at the effectiveness of online interventions for chronic pain based on ACT (Buhrman et al., 2013; Trompetter et al., 2015). These studies have shown improvements in depression, pain-related distress, anxiety, pain intensity, psychological flexibility, and pain catastrophizing (Buhrman et al., 2013; Trompetter et al., 2015), which creates positive expectations for such an intervention for patients with CIPN.

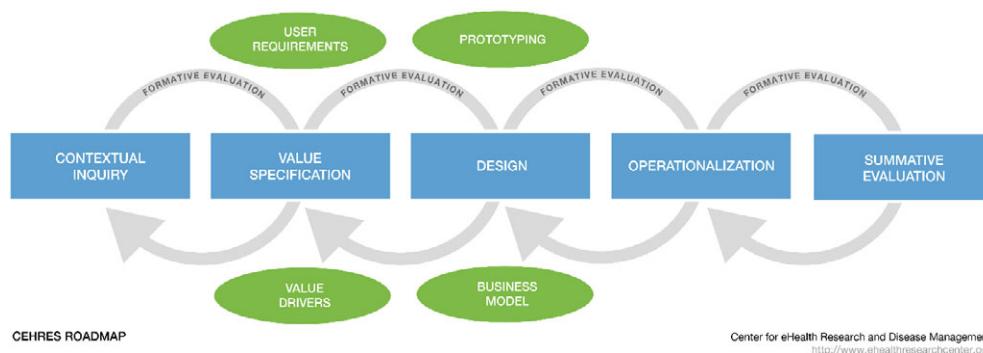
### **Patient-centered development**

To ensure optimal effectiveness in online interventions, it is important to prioritize aspects such as usability in the development. Patient-centered development enables this by involving patients in the choices made in the development process (Demiris et al., 2008). This way of development can be applied using the Centre for eHealth Research (CeHRes) roadmap (Gemert-Pijnen et al., 2011), which is shown in Figure 2. This roadmap provides a holistic framework to develop technology that fits the user and the context of the intervention, by acknowledging healthcare's complexity, as well as patients' and stakeholders' routines and behaviors. It is built on a few principles for eHealth technology development, namely: participatory development, continuous evaluation, integration with implementation, organizational impact, persuasive design techniques, and advanced impact assessment methods. The CeHRes roadmap is a practical guide to properly implement the participatory development process (Gemert-Pijnen et al., 2011). In this dissertation, this roadmap will be used in intervention development.

The framework starts with *contextual inquiry*, which can consist of interviews, for example, to gather information about the users, their requirements, and the context in which the technology will be implemented (Gemert-Pijnen et al., 2011). Personas can be developed from these to inform stakeholders about the users and the context. Next, *value specification* is the step in which to specify the purpose and functional requirements of the technology. After this, *design* refers to developing prototypes based on the previous steps. This may consist of multiple phases with different prototype versions of the technology. This is followed by *operationalization*, which concerns introducing and

applying the technology, allowing it to function. Lastly, *summative evaluation* is the usage of the technology along with an assessment of its impact (i.e., effectiveness) (Gemert-Pijnen et al., 2011). It is important to note that this way of developing technology has a cyclical, iterative evaluation, and development approach. This means that this is not a static linear process, but a flexible process in which forward and backward movement can be made for further development and evaluation.

**Figure 2.** Centre for eHealth Research (CeHRes) roadmap (Gemert-Pijnen et al., 2011)



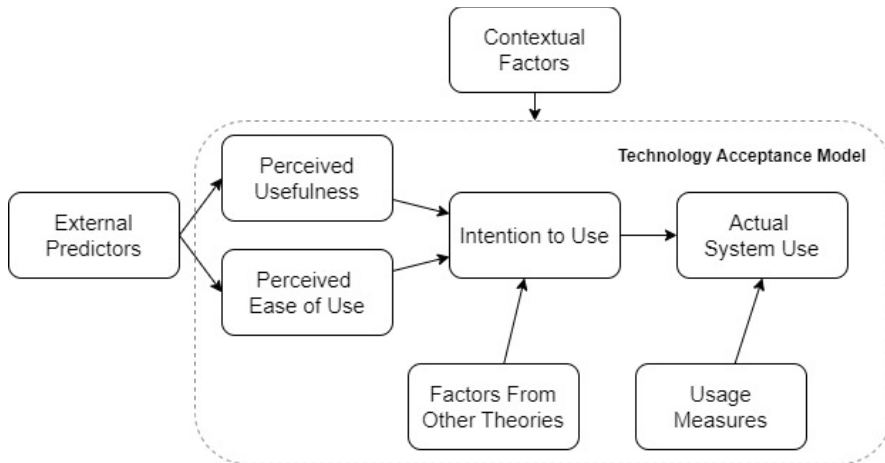
***Theoretical frameworks for technology adoption***

Key theoretical frameworks in online intervention development and implementation include the Technology Acceptance Model (TAM) (Davis, 1989; Marangunić & Granić, 2015) and Task-Technology Fit model (TTF) (Goodhue & Thompson, 1995; Lee et al., 2003). These models illustrate the factors that shape users' adoption of technology and are necessary to understand that traditional interventions cannot be copied from face-to-face variety to an online format without context.

A crucial model that describes user acceptance of technology is the TAM, which is shown in Figure 3 (Davis, 1989; Marangunić & Granić, 2015). The basic model of TAM explains that *perceived usefulness* and *perceived ease of use* influence intentions to use the technology. *Perceived usefulness* refers to the extent to which the user believes the technology helps them perform the task. In addition, *perceived ease of use* includes the extent to which the user believes that using the technology requires little effort. If the perception of at least one of these two factors is poor, it will significantly reduce the

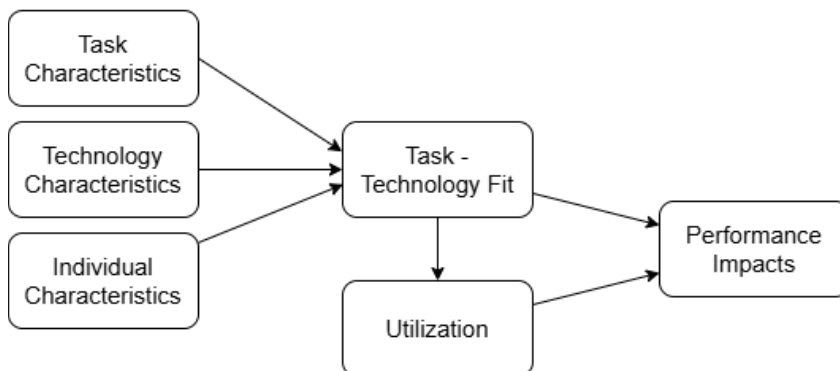
intention to use the technology. This will hinder the ultimate use of the technology (Davis, 1989; Marangunić & Granić, 2015). A recent update to TAM includes some additions, namely *external predictors* (e.g., prior usage and experience), *factors from other theories* (e.g., expectations), *contextual factors* (e.g., gender), and *usage measures* (e.g., attitude towards technology) as factors affecting this process (Marangunić & Granić, 2015).

**Figure 3.** Technology Acceptance Model (TAM) (Davis, 1989; Marangunić & Granić, 2015)



An important complement to TAM is the TTF model (Goodhue & Thompson, 1995; Lee et al., 2003), which is shown in Figure 4. This model explains the connection between technology and individual performance. It explains that a *fit* between task and technology affects *individual performance*, which includes accomplishment of the individual's primary goal. Sometimes, this fit also influences *utilization* (i.e., usage), which also affects individual performance. This *fit* means that task, technology, and individual are aligned together functionally, also: "the degree to which a technology assists an individual in performing his or her portfolio or tasks" (Goodhue & Thompson, 1995). *Technology* here includes the tool the individual uses in performing the task (e.g., software system and computer). *Tasks* include the actions people need to perform in technology (e.g., Acceptance and Commitment Therapy intervention). *Individual* includes the user of the technology to accomplish the tasks, along with any individual characteristics that may affect it (e.g., motivation) (Goodhue & Thompson, 1995; Lee et al., 2003). This model clearly shows how characteristics and context of technology can add value to the use and impact of technology.

**Figure 4.** Task-Technology Fit model (TTF) (Goodhue & Thompson, 1995; Lee et al., 2003)



These models illustrate that choices made in the development process of technology can be of great influence on usage and performance. While these models do not provide generic guidelines for technology development, they explain the significance of thoughtfully aligning user, task, and technology for each specific intervention. Different aspects of technology affect the usage and performance of technology. Achieving an optimal fit between the task, technology, and user affects engagement and effectiveness. Therefore, informed decisions aligned with user needs are crucial in this regard. Therefore, it is crucial to avoid blindly copying a traditional intervention into an online format. Instead, the focus should be on transforming the traditional intervention into a suitable online format tailored to align with the specific needs and habits of the user. This especially applies to self-management interventions targeting chronic pain, given their complexity and necessity for high user motivation (Laugesen, 2013). Following that, this dissertation takes the models TAM and TTF into account.

### ***Engagement with online interventions***

Optimal use is a major challenge for online health interventions, with non-adherence being relatively common (Donkin et al., 2011; Eysenbach, 2002, 2011). *Adherence* includes “the extent to which individuals should experience the content to derive maximum benefit from the intervention, as defined or implied by its creators” (Kelders et al., 2012; Sieverink et al., 2017). It can also be conceptualized as the *intended use* of an intervention, which refers to the degree to which a user is expected to use the

intervention to derive maximum benefit from the intervention, as intended by the developers (Kelders et al., 2012). This is a quantitative approach to the use of an intervention, in which there are multiple ways to measure this. For instance, measures may include frequency of logins, completion of modules, time spent in the system, or number of pages viewed (Donkin et al., 2011). A systematic review was conducted to assess adherence in online therapy, exploring the ways in which adherence can be operationalized (Donkin et al., 2011). The number of logins and modules completed were shown to be the most used operationalizations. However, time spent online and completing activities (e.g., completing a diary) were also common. Regarding the impact on outcomes of online psychological health interventions, the number of completed modules was found to have the strongest effect. With that, it was concluded that patients must interact with the intervention for the content of the intervention to lead to user change, while passive involvement appears to offer fewer benefits (Donkin et al., 2011). Although a quantitative approach to adherence provides many valuable insights into usage, it is not sufficient on its own. Adherence does not provide insights into users' subjective experiences. The aforementioned systematic review on adherence in online therapy also concluded that adherence is an easy way to collect data on use, but it does not include the actual patient experience (Donkin et al., 2011). Here it is mentioned that this particularly applies when users have to work with material themselves, such as homework in-between modules, whereby objective measures may result in an underestimation of use (Donkin et al., 2011). Furthermore, it should be noted that objective measurements are neutral and therefore do not provide information about the user's positive or negative affect towards the intervention.

Subjective experiences of usage in online interventions are, however, captured by the concept of *engagement*. This includes aspects such as dimensions of change, positive affect, endurance, and appeal (Perski et al., 2017). Specifically, engagement is defined as “the extent of usage and a subjective experience characterized by attention, interest and affect” (Perski et al., 2017). Within this context, adherence is an integral component of engagement, yet it is complemented by the highly relevant subjective experiences of the user. Previous research has shown that several illness-related, personal, and psychological factors influence usage, but, on the other hand, factors related to the intervention content and the technology itself also affect usage (Beatty et al., 2017; Beatty & Binnion, 2016;

Compen et al., 2017). Given its substantial influence on effectiveness, the examination of both objective and subjective measures in engagement within online interventions is crucial (Donkin et al., 2011; Perski et al., 2017; Sieverink et al., 2017). Therefore, this approach to engagement is applied in this dissertation.

## **Outline of this dissertation**

This dissertation is divided into two sections. The main objective of this dissertation is to gain insights into (1) the experiences of patients with CIPN and (2) the patient-centered development of an online self-management intervention based on ACT for cancer survivors with chronic painful CIPN.

### **Part I – Patient experiences**

The first section of this dissertation focuses on patients' experiences with CIPN. **Chapter 2** starts with an exploration of the experienced symptoms and daily limitations of cancer survivors with CIPN, to create a clear picture of the issues these patients are facing. Furthermore, the experienced involvement of healthcare professionals and social support provided by their social environment (i.e., the level of empathy as perceived by patients) were examined. This study used data from the Dutch Federation of Cancer Patient Organizations (NFK).

In **Chapter 3**, a study focusing on how patients live with chronic painful CIPN is described. Specifically, this study focuses on coping and self-management strategies that patients apply. Dealing with symptoms and resulting limitations in general falls under coping strategies, while practical actions to reduce symptoms fall under self-management strategies.

Subsequently, **Chapter 4** describes the examination of pre-treatment anxiety and depressive symptoms as predictors of chronic peripheral neuropathy (PN) among colorectal cancer (CRC) patients at one- and two-years post-diagnosis. Here, the focus is on assessing the impact on the severity of PN symptoms.

## Part II – eHealth interventions

The second part of this dissertation focuses on an online self-management intervention for cancer survivors with chronic painful CIPN and its patient centered development. First, a systematic literature review was conducted to provide an evaluation of existing online interventions based on ACT to treat chronic pain in general, which is described in **Chapter 5**. This review focuses on (1) ACT content, (2) design characteristics, (3) design rationales, and (4) adherence, through the lens of TAM and TTF (Davis, 1989; Goodhue & Thompson, 1995). The results of this systematic review provide an important starting point for the subsequent sections of this dissertation.

Next, **Chapter 6** describes the patient-centered development of an online ACT intervention for cancer survivors with chronic painful CIPN. This chapter describes how the online intervention *Embrace Pain* was developed through an iterative development process in collaboration with patients and experts (i.e., CeHRes roadmap (Gemert-Pijnen et al., 2011)). This chapter describes multiple phases of interviews and usability testing, which ultimately led to personas and intervention content.

Furthermore, the protocol of a Randomized Controlled Trial (RCT) examining the effectiveness of the online ACT intervention *Embrace Pain* for cancer survivors with chronic painful CIPN is described in **Chapter 7**. The protocol includes the method of an RCT studying the effectiveness of the online self-help intervention based on ACT compared to waiting list condition (WLC). This protocol also includes the objective of examining baseline demographic, clinical, and psychosocial factors that may moderate its effectiveness, as well as the extent to which effects differ between guided and unguided versions.

**Chapter 8** includes the description of a qualitative exploration of barriers and facilitators to the engagement of an online ACT intervention for cancer survivors with chronic painful CIPN. In this study, engagement with online interventions is defined as the actual usage (i.e., adherence) and subjective experience (e.g., attention, interest and affect) of using the intervention (Perski et al., 2017).

Finally, all results are discussed in the general discussion of this dissertation in **Chapter 9**.

## Setting and background

This dissertation was produced in collaboration with several institutions.

### Dutch Cancer Society (KWF)

This dissertation was made possible by a Young Investigator Grant awarded to dr. Hester Trompetter from the Dutch Cancer Society (KWF) - Alpe d'HuZes (#12181). The title of the grant application was: 'Patient-centered development and effectiveness of online Acceptance and Commitment Therapy for quality of life in cancer survivors with persistent painful chemotherapy-induced neuropathy (QLIPP-CIPN)'.

### PROFILES Registry

**Chapters 2, 4, and 7** are created in collaboration with the PROFILES registry (van de Poll-Franse et al., 2011). PROFILES (Patient Reported Outcomes Following Initial Treatment and Long Term Evaluation of Survivorship) is a registry that examines the physical and psychosocial effects of cancer and cancer treatment in a population-based cohort of cancer survivors (van de Poll-Franse et al., 2011). PROFILES, among others, can provide support in data collection for studies on cancer patients, which was the case in this dissertation.

### Dutch Federation of Cancer Patients Organizations (NFK)

**Chapter 1** was created in collaboration with the Dutch Federation of Cancer Patients Organizations (NFK). The Dutch Federation of Cancer Patients Organizations (*Nederlandse Federatie voor Kankerpatiëntenorganisaties*) is an umbrella organization representing 21 cancer patient organizations. They have a panel of cancer patients in which they perform four online questionnaire studies (*Doneer Je Ervaring*) each year to study the impact of cancer on patients' lives. For this dissertation, the data from 'Pain, numbness or tingling sensation' (April, 2021) was used.

### PROCORE study

**Chapter 4** is based on the PROCORE study, an original PROFILES study. The PROCORE study is a prospective, population-based study aiming to study the longitudinal impact of colorectal cancer, as well as treatment effects on patient-reported outcomes. Details of this study have been published previously (Bonhof et al., 2021).



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# Part I



# Patient experiences

# Chapter 2

The image features a light beige background. On the right side, there is a vertical decorative border consisting of a blue stripe on the left and a pink stripe on the right. A large, white, stylized number '2' is positioned in the upper left quadrant of the page.

# Experiences of cancer survivors with chemotherapy-induced peripheral neuropathy in the Netherlands: symptoms, daily limitations, involvement of healthcare professionals, and social support

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## **Abstract**

**Purpose:** A significant proportion of cancer patients suffer from chemotherapy-induced peripheral neuropathy (CIPN). This descriptive study aimed to examine patients' experience of CIPN symptoms, daily limitations, involvement of healthcare professionals, and social support.

**Methods:** Cross-sectional data have been collected in the Netherlands via a national online questionnaire comprising closed items only (February 2021).

**Results:** Out of 3,752 respondents, 1,975 received chemotherapy only (i.e., without targeted therapy) and were therefore included. The majority (71.2%) reported symptoms in both hands and feet (e.g., tingling and loss of sensation or diminished sensation). Participants reported most limitations in household chores, social activities, hobbies, sports, walking, and sleeping, and least in family/(taking care of) children, cycling, driving, self-care, eating and drinking, and sexuality and intimacy. Many patients indicated that their healthcare professionals informed them about the possibility of CIPN development before treatment (58.4%), and they paid attention to CIPN during and after treatment (53.1%). However, many patients (43%) reported a lack of information on what to do when CIPN develops. Few participants (22%) visited their general practitioner (GP) for CIPN. In general, patients' social environments sometimes to always showed empathy to patients.

**Conclusions:** Symptoms of CIPN are frequently reported and can result in various daily limitations. Support from professionals and peers is crucial in managing CIPN, which is sometimes lacking. Appropriate guidance and support should be provided to patients to decrease the impact of CIPN on daily life. Future research should investigate differences in chemotherapeutic agents and the resulting symptoms and consequences.

## Introduction

In the Netherlands, 123,672 new patients were diagnosed with cancer in 2021 (Integraal Kankercentrum Nederland, 2021). The 5-year survival rate currently is 66% and increases by about 1% each year due to improved diagnostics and treatment (Integraal Kankercentrum Nederland, 2022). The long-term consequences of cancer and its treatment become more prevalent (Mols et al., 2014), which means that after completion of treatment, patients often face several physical and psychosocial limitations in their daily lives (Foster et al., 2009; Ju et al., 2021; Rutherford et al., 2020). Although symptoms usually improve or disappear over time, in some patients the symptoms remain, leaving them with chronic symptoms (Phillips & Currow, 2010).

A common long-term consequence of cancer treatment is chemotherapy-induced peripheral neuropathy (CIPN), which is caused by chemotherapeutic agents like taxanes, platinum compounds, and vinca alkaloids (Seretny et al., 2014; Wen, 2007). Peripheral neuropathy is defined by the National Cancer Institute as: “a nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body” (National Cancer Institute at the National Institutes of Health, 2021), which can be experienced as both painful and nonpainful (C. Tofthagen, 2010). The sensations patients experience can vary greatly depending on patient characteristics and perceptions, as well as chemotherapy type and cumulative dose (C. Tofthagen, 2010). One month after completion of chemotherapy almost 80% of cancer survivors experience CIPN, which decreases to 30% after 6 months or longer (Bao et al., 2016; Bonhof et al., 2018; Eckhoff et al., 2015; Glendenning et al., 2010; Mols et al., 2014; Seretny et al., 2014), showing that it is still present in a significant group of patients until late after chemotherapy.

CIPN symptoms can be difficult to deal with and bring significant limitations to patients' daily lives (Bakitas, 2007). Even though patients are often cured of cancer, they might still feel ill due to CIPN as it continuously reminds them of being treated for a life-threatening disease (Jensen et al., 2022). Earlier research has shown that CIPN strongly interferes with daily life activities, such as walking, hobbies, and relationships (C. Tofthagen, 2010). Patients' identities can change due to CIPN, as they have to make changes in their roles because certain activities can no longer be performed (e.g., performing a job or playing an instrument) (Jensen et al., 2022). Furthermore, several studies showed that CIPN

symptoms can negatively affect physical, social, and emotional areas of life (Bakitas, 2007; Bonhof et al., 2020; C. Tofthagen, 2010; C. S. Tofthagen et al., 2020). This shows that CIPN can be a highly relevant limiting side-effect of chemotherapy with major consequences on daily life that affects more than just physical functioning. However, to our knowledge, no earlier study examined the specific daily limitations of a broad patient group (e.g., multiple tumor types) with a large sample size.

It is crucial to be aware of the symptoms and daily consequences these patients experience as well as the attempts they make to control or reduce these symptoms since this knowledge enables healthcare professionals to adequately support patients in their needs (C. Tofthagen, 2010). Healthcare professionals should assess and address the symptoms of CIPN, weigh the impact on the daily lives of their patients and, subsequently, provide appropriate support to try to preserve their quality of life (QoL) (C. Tofthagen, 2010). A Dutch study examined reasons of colorectal cancer patients to visit their GP during the first 5 years of follow-up and concluded that chemotherapy-related symptoms, among which CIPN, was one of the most frequent reasons (Duineveld et al., 2019). However, to the best of our knowledge, no study has assessed how patients perceive support from healthcare professionals regarding CIPN.

In addition to support from healthcare professionals, support from friends, family and significant others (i.e., social support) is important (Zimet et al., 1988). Social support can alleviate several disease aspects, such as coping with cancer and stress (Andreu et al., 2012; Bottaro et al., 2022; Kyngäs et al., 2001; Ozdemir et al., 2018; Parelkar et al., 2013; Zucca et al., 2010), anxiety, depression, and QoL (Parker et al., 2002). A recent study among breast cancer patients examined the effect of perceived social support on chemotherapy-related symptoms, including CIPN symptoms (Oh et al., 2020). Results showed that these symptoms were identified as less severe when patients reported medium to high perceived social support, compared to those with low perceived social support. However, the relevant CIPN symptoms examined in the study were pain and numbness, whereas CIPN involves a much broader spectrum of symptoms. It is important to examine the social support experienced by cancer survivors. In this study, social support is referred to as the degree of empathy shown by the social environment.

This study aimed to report the experiences of cancer survivors who suffer or had suffered from self-reported CIPN in the Netherlands regarding (1) CIPN symptoms, (2) daily limitations, (3) involvement of healthcare professionals, and (4) social support.

## Methods

### Study design

A cross-sectional exploratory national online questionnaire study was performed among adult cancer survivors with CIPN in the Netherlands. The questionnaire was initiated and developed by a patient advocate and a researcher from the Dutch Federation of Cancer Patients Organizations (NFK), which is the Dutch umbrella organization that represents 19 cancer patient organizations. A researcher of the PROFILES Registry with scientific expertise in CIPN was also involved in the development of the questionnaire (van de Poll-Franse et al., 2022). Furthermore, four patient advocates of two patient organizations (the Dutch breast cancer patient organization (*Borstkankervereniging Nederland*) and the Dutch gynaecologic cancer patient support group (*Stichting Olijf*) were involved, three of whom experienced CIPN themselves. These people participated in a workgroup. The workgroup met three times to discuss the content of the questionnaire. In between, the workgroup provided (digital) feedback on draft versions of the questionnaire.

### Data collection

The questionnaire was distributed between February 1 and 15, 2021 via [www.doneerjeervaring.nl](http://www.doneerjeervaring.nl), social media channels and the *Doneer Je Ervaring* (Donate Your Experience) panel. Additionally, patient organizations have spread invitations for the questionnaire among their members and sponsors via email. Finally, partner organizations like the Dutch Cancer Society and Kanker.nl (Dutch web platform with tailored medical information and peer-support targeted at cancer survivors and relatives (Frost et al., 2012)) have spread the invitation.

### Participants

Patients could participate if they currently suffered from CIPN or had suffered from CIPN in the past. Participants were informed about privacy regulations of the NFK, in accordance with the General Data Protection Regulation (EU). The Medical Research Involving Human Subjects Act (WMO) did not apply since the study did not include an

intervention wherefore ethical approval by the Medical Ethical Review Board was not needed. By completing the questionnaire, patients gave implied consent. Participation was completely online and anonymous.

### **Questionnaire**

The questionnaire started with four closed-ended questions regarding demographics. The remaining 29 closed-ended questions included the following topics: CIPN sensations, daily limitations, attention to CIPN by healthcare professionals, and social support. In questioning the daily limitations, cycling was included as a separate category since cycling is one of the most widely used means of transportation in the Netherlands, making it a daily activity for many people and not just a sports activity.

### **Statistical analyses**

No minimum sample size was calculated prior to the study since this study was explorative in nature. Descriptive statistics were reported. Absolute numbers and percentages were provided for nominal variables. Means and standard deviations were provided for continuous variables. For both items related to satisfaction with the supervision of healthcare professionals, the numerical scores 1 to 10 were recoded to the categorical scores insufficient (1-5), satisfactory to good (6-8), and excellent (9-10). IBM SPSS Statistics version 28 was used for all analyses.

### **Results**

In total, 3,752 participants filled in the questionnaire. Participants were included if they had received 'chemotherapy only' as treatment. Excluded were participants that received 'targeted therapy', 'targeted therapy combined with chemotherapy', or neither of those. In total, 1,975 participants who suffered from of had suffered from CIPN remained and were included in this study. Sociodemographic characteristics of participants are shown in Table 1. Participants had a mean age of 58.8 ( $SD=11.3$ ) and 76.1% were female. The most prevalent tumor types were breast (42.8%), blood/lymph (24.2%), colorectal (8.9%), and gynecological cancer (5.8%). In 41% of patients, cancer had been diagnosed more than 5 years ago, followed by 2-5 years ago (34.7%) and less than 2 years ago (23.6%).

**Table 1.** Sociodemographic Characteristics of Participants

Characteristics	<i>n</i>	%	<i>M</i>	<i>SD</i>
Gender				
Male	469	23.7		
Female	1506	76.1		
Other	5	.3		
Age			58.8	11.3
Cancer type				
Breast	848	42.8		
Blood/lymph	480	24.2		
Colorectal	177	8.9		
Gynecological	115	5.8		
Other	90	4.5		
Lung	56	2.8		
Prostate	44	2.2		
Bladder/kidney	37	1.9		
Pancreas	35	1.8		
Testicle	35	1.8		
Stomach/esophageal	31	1.6		
Head/neck	10	.5		
Sarcoma	9	.5		
Brain	9	.5		
Melanoma	4	.2		
Time since diagnosis				
<2 years	468	23.6		
2-5 years	687	34.7		
>5 years	825	41.7		

### CIPN symptoms

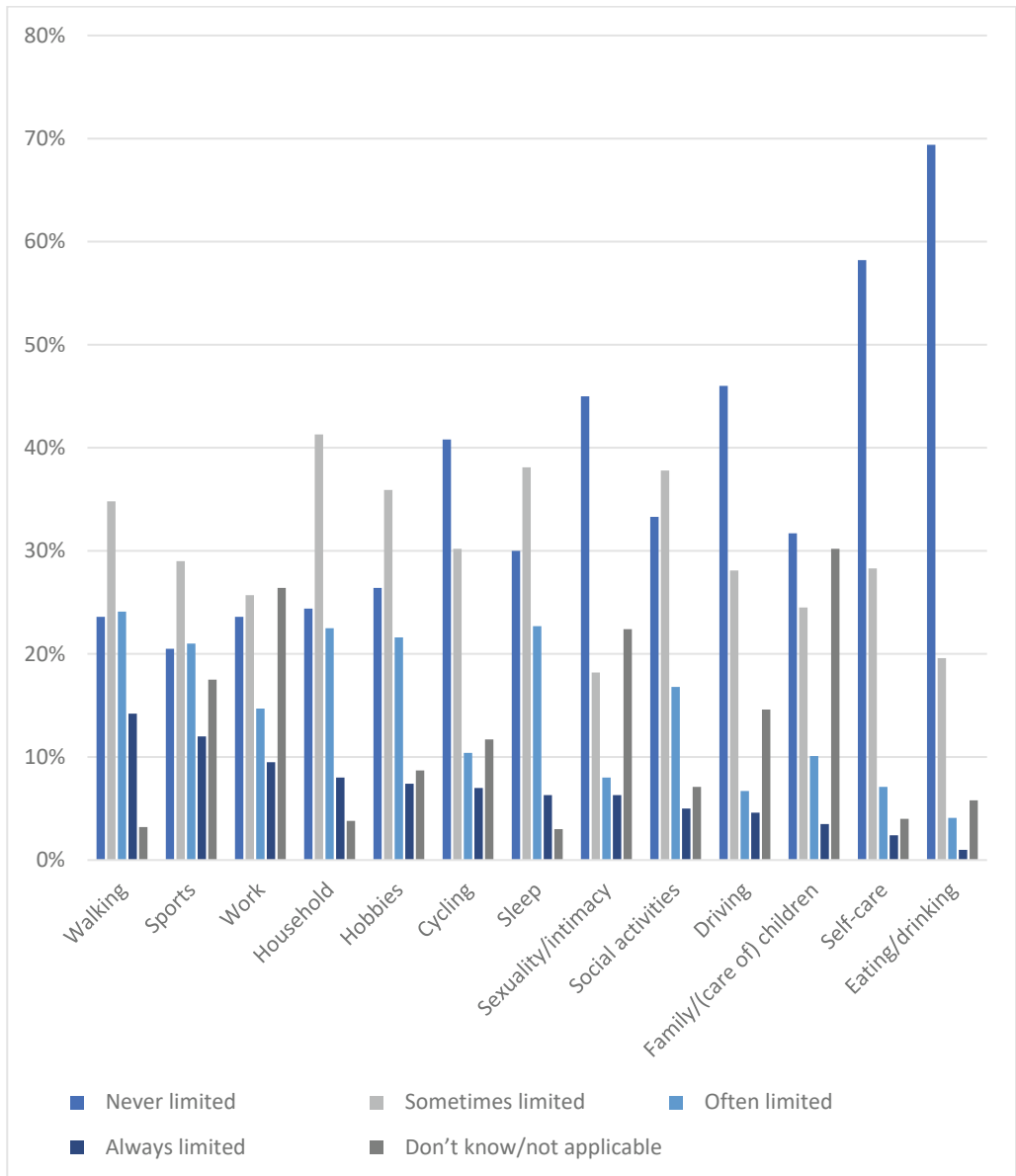
More than half of the participants reported to suffer from CIPN for more than 2 years at the time of the questionnaire (55.1%) (Table 2). In 71.2% of the participants, CIPN was present in both foot/feet and hand(s). The most prevalent symptoms in hands were tingling (59.6%) and loss of sensation or diminished sensation (47.7%). Most participants attempted to reduce or control these symptoms by applying self-management strategies (69.9%).

**Table 2.** Experienced symptoms of CIPN

	n	%
Duration of symptoms		
A few weeks	82	4.1
A few months	195	9.8
About half a year	168	8.5
About 1 year	198	10.0
About 2 years	164	8.3
More than 2 years	1090	55.1
Don't know (anymore)	83	4.2
Location of symptoms		
Foot/feet	423	21.4
Hand(s)	147	7.4
Foot/feet and hand(s)	1410	71.2
Type of symptoms in feet		
Tingling	1327	67.0
Loss of sensation or diminished sensation	1360	68.7
Changed sensation	1043	52.7
Pain	758	38.3
Pain from touch	457	23.1
Pain from temperature changes	669	33.8
Burning or stabbing pain	664	33.5
Balance disorders	592	29.9
Muscle weakness or reduced strength	552	27.9
Muscle cramp	716	36.2
Thinning of muscles	215	10.9
Type of symptoms in hands		
Tingling	1180	59.6
Loss of sensation or diminished sensation	944	47.7
Changed sensation	724	36.6
Pain	486	24.5
Pain from touch	293	14.8
Pain from temperature changes	587	29.6
Burning or stabbing pain	318	16.1
Balance disorders	93	4.7
Muscle weakness or reduced strength	653	33.0
Muscle cramp	334	16.9
Muscle loss	137	6.9
Attempted to reduce or cope with symptoms		
Yes	1384	69.9
No	532	26.9
I don't know/not applicable	64	3.2

### Daily limitations

Figure 1 shows the reported daily limitations due to CIPN. In several types of daily activities, most patients report never experiencing limitations, namely eating and drinking (69.4%), self-care (58.2%), driving (46%), sexuality and intimacy (45%), cycling (40.8%), and family/(taking care of) children (31.7%). In the remaining categories, limitations were more common. Being 'sometimes limited' was most reported by participants for household chores (41.3%), sleep (38.1%), social activities (37.8%), hobbies (35.9%), walking (34.8%), sports (29.0%), and work (25.7%).

**Figure 1.** Daily limitations due to CIPN

### Involvement of healthcare professionals

Table 3 shows an overview of hospital healthcare professionals' and GPs' attention to CIPN. Regarding hospital healthcare professionals, more than half of the participants (58.4%) reported being informed before treatment about the possibility of the development of CIPN. Also, most participants (72.7%) reported that attention was given

to CIPN symptoms during or after treatment. However, many (43%) reported not being informed about what to do when CIPN develops. Satisfaction with attention to CIPN was rated as insufficient by almost a quarter of patients (23%). However, many patients rated it as satisfactory to good (50.3%), or as excellent (26.7%).

Only a small proportion of the participants (22%) reported having visited their GP for CIPN. The majority rated the GPs attention to CIPN as satisfactory to good (53.5%), followed by excellent (25.5%). Few indicated this as insufficient (21.2%).

**Table 3.** Attention to CIPN by healthcare professionals

<b>Hospital healthcare professional</b>	<b>n</b>	<b>%</b>
Before treatment: informed about possibility of CIPN <sup>a</sup> development		
Yes	1157	58.4
No	523	26.4
Don't know (anymore)/not applicable	300	15.2
During or after treatment: attention to CIPN <sup>a</sup>		
Yes	1439	72.7
No	541	27.3
During or after treatment: informed about what to do when CIPN <sup>a</sup> develops		
Yes	716	36.2
No	852	43.0
Don't know (anymore)/not applicable	412	20.8
Satisfaction with attention to CIPN <sup>ab</sup>		
Insufficient (1-5)	417	23.0
Satisfactory-good (6-8)	914	50.3
Excellent (9-10)	485	26.7
<b>General practitioner</b>	<b>n</b>	<b>%</b>
During or after treatment: visited general practitioner for CIPN <sup>a</sup>		
Yes	436	22.0
No	1481	74.8
Don't know (anymore)/not applicable	63	3.2
Satisfaction with attention to CIPN <sup>ab</sup>		
Insufficient (1-5)	89	21.2
Satisfactory-good (6-8)	224	53.3
Excellent (9-10)	107	25.5

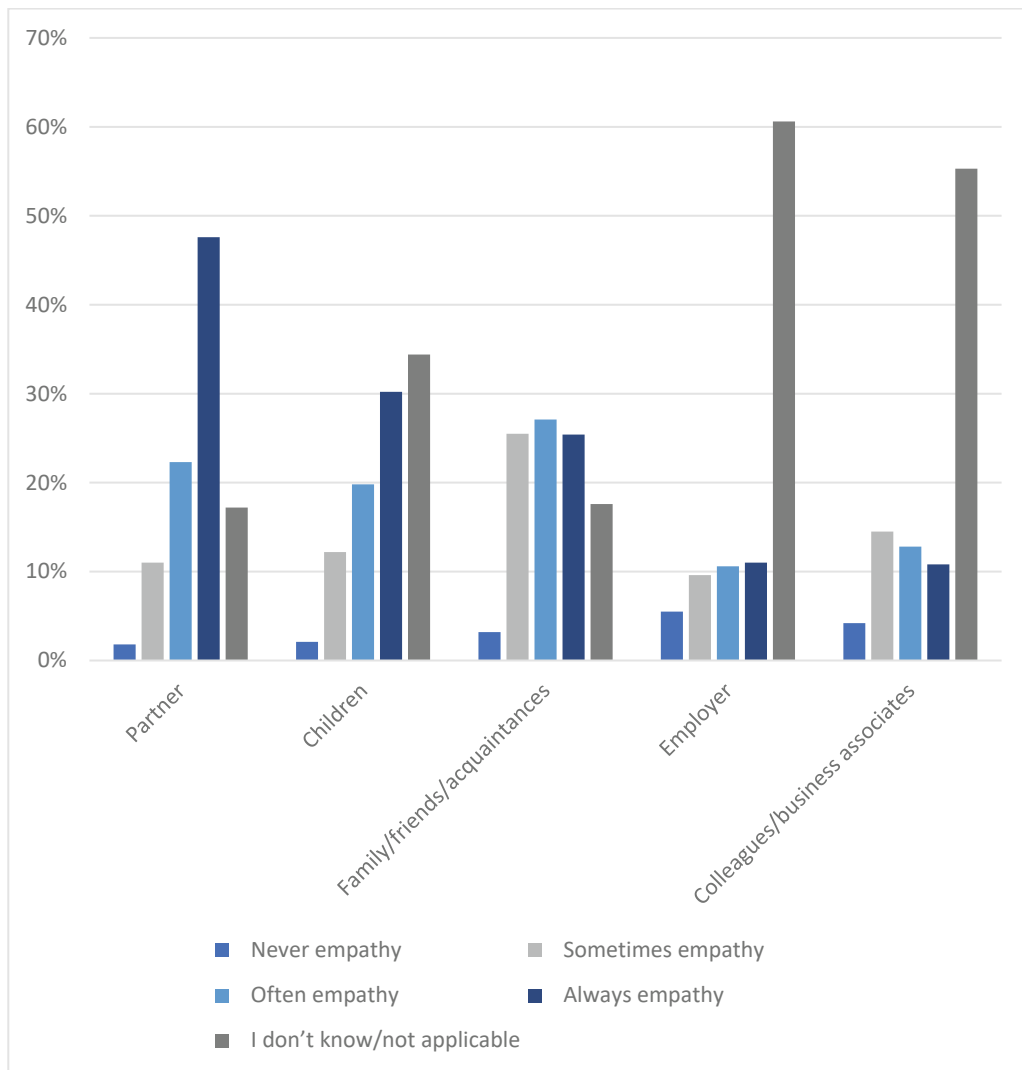
<sup>a</sup> CIPN = chemotherapy-induced peripheral neuropathy

<sup>b</sup> Due to none-obligatory nature of item, valid percentages were reported.

**Social support**

Participants indicated that partners showed empathy regarding CIPN always (47.6%), often (22.3%), and sometimes (11%) respectively (Figure 2). Only a small minority reported that their partner never showed empathy (1.8%). This also applied to children (30.2%; 19.8%; 12.2%; 2.1% respectively). In the case of family, friends, and acquaintances, participants reported that empathy was shown often (27.1%), sometimes (25.5%), and always (25.4%) respectively, followed by a small minority of participants who reported that empathy was never shown (3.2%). Most participants indicated 'I don't know/not applicable' for social support regarding colleagues and business associates (55.3%) as well as for employers (60.6%). However, the remaining participants indicated that empathy was shown never (4.2%), sometimes (14.5%), often (12.8%), and always (10.8%) by colleagues and business associates. In the case of employers, participants reported that empathy was shown never (5.5%), sometimes (9.6%), often (10.6%), and always (11%).

**Figure 2.** Social support and empathy



## Discussion

The aim of this study was to explore patients' experience of CIPN symptoms, daily limitations, involvement of healthcare professionals, and social support. Although symptoms are mostly experienced in both hands and feet and are often non-painful (e.g., tingling and loss of sensation or diminished sensation), a significant part of participants reports painful symptoms. These symptoms can result in a variety of daily limitations, in which most patients are able to perform activities of daily life (ADL) but seem to

experience problems mainly in their roles and social activities. Support and empathy are not always experienced by patients. This mainly applies to support and empathy from healthcare professionals, friends and acquaintances, and work-related peers.

This study has shown that even though most patients with CIPN experience non-painful symptoms, a significant proportion of people (also) experience painful symptoms. Earlier research into colorectal cancer survivors has shown that QoL and physical, role, cognitive, and social functioning are worse in patients with painful CIPN compared with patients with non-painful CIPN (Bonhof et al., 2020). However, the effect of painful versus non-painful CIPN on the daily limitations people experience was not examined in our study. For this reason, and since painful versus non-painful CIPN may involve different impairments and coping mechanisms, research on the difference in daily limitations and appropriate psychosocial interventions between painful and non-painful CIPN is needed.

Results of this study have shown that most patients experience limitations in daily life, which vary in how often people experience them. For example, daily activities such as eating and drinking, self-care, cycling, intimacy and sexuality, and driving, are not limiting for a reasonable group of patients. Therefore, some patients seem able to perform the ADL themselves. However, there are also many ADL in which many patients often experience limitations, such as walking, sleeping, and household chores. Previous research has indeed shown that patients with CIPN might become limited in various aspects of functioning (i.e., physical, social, emotional, role, and cognitive), which in turn deteriorates their QoL (Bakitas, 2007; Bonhof et al., 2018, 2020; Eckhoff et al., 2015; Ezendam et al., 2014). Patients should therefore receive support from healthcare professionals and peers. This may increase the (sense of control over their) ability to perform daily activities independently, contributing to patient empowerment, which can improve QoL (Boveldt et al., 2014; Kaal et al., 2017; McCorkle et al., 2011). However, results should be interpreted with caution as no comparison in daily limitations between patients with CIPN and the general population has been made. Therefore, it is not clear what the CIPN-specific limitations are, as the general population may also experience limitations given the relatively high average age in this sample.

Furthermore, this study showed that patients indicate they were not informed about what to do when CIPN develops. It is not known whether information has not been provided to patients, or whether patients were informed but had different priorities in the process of facing a life-threatening disease. This means that for many patients, a search for symptom self-management begins when CIPN symptoms arise. Research has shown that patients often lack knowledge and self-management skills to properly manage their cancer-related pain (Dalal et al., 2013). Several studies have shown that psychoeducation for cancer-related pain can positively influence patients' knowledge and ability to self-manage their symptoms (Miaskowski et al., 2004; Oldenmenger et al., 2018; Park & Lee, 2022; Thomas & Weiss, 2000; Valenta et al., 2022). Applying symptom self-management must be supported by healthcare professionals (van Dongen et al., 2020), which starts with informing patients appropriately and providing advice, starting before treatment. Furthermore, options and wishes in dose reduction of chemotherapy should be considered during treatment to possibly limit development or worsening of CIPN (Demiris et al., 2008; Hertz et al., 2021; Jordan et al., 2020; Loprinzi et al., 2020; Seretny et al., 2014; Speck et al., 2013). However, no evidence-based treatment recommendations can currently be provided as there are no effective treatments for non-painful CIPN (Jordan et al., 2020; Loprinzi et al., 2020).

In addition, patients should also be supported in self-management by their social environment (van Dongen et al., 2020). Our study showed that most patients often feel empathy by their social environment mainly by partners, family, and friends, in which the degree of empathy varies. Earlier research has shown that such support improves CIPN and coping with cancer (Bottaro et al., 2022; Oh et al., 2020). However, our study showed that empathy by colleagues and employers is often lacking. Work-related social support includes both organizational support from employers (e.g., job security, flexible working hours, and sick pay) and interpersonal support from colleagues (e.g., empathy and positive attitudes) (Amir et al., 2008; Armaou et al., 2018; Tamminga et al., 2012; Wells et al., 2013). Since work-related social support is crucial in achieving work-related goals and returning to work after cancer (Amir et al., 2008; Armaou et al., 2018; Tamminga et al., 2012; Wells et al., 2013), more attention must be paid to social support from colleagues and employers. However, in this study, colleague and employer support was not applicable for most participants since many patients are probably retired given the high

average age of the sample. Therefore, these results should be interpreted cautiously and further research on work-related social support is needed.

Furthermore, even though our research shows that many patients often or always feel empathy with respect to CIPN by family, friends and acquaintances, there is still a significant group of patients who never or only sometimes feel empathy is shown. Earlier research has found that 52% of breast cancer patients experienced to be sometimes avoided or contact is feared by friends and family (Peters-Golden, 1982). Interestingly, this study also examined the perspective of healthy people, which showed that 61% of them would or might avoid people with cancer. Reasons of relatives for not providing social support to cancer patients appear to be diverse and can include, for example, the perception of one's own inability to provide support, as well as not wanting to burden the cancer patient emotionally (Ray et al., 2019). However, it has been shown that patients wish to receive social support, and they experience increased QoL when they receive helpful social support (Arora et al., 2007). However, social support appears to diminish significantly within one year after diagnosis (Arora et al., 2007), which could possibly explain the lack of empathy regarding CIPN experienced by some of the patients in our study, since CIPN can be present for a long time after treatment (Bao et al., 2016; Bonhof et al., 2018; Eckhoff et al., 2015; Glendenning et al., 2010; Mols et al., 2014; Seretny et al., 2014). Another explanation may be that relatives often do not know what CIPN entails and do not understand the symptoms (Tanay et al., 2022). Because of the variety of symptoms, it can be difficult to understand and explain CIPN to family, friends, and acquaintances. Healthcare professionals should provide appropriate information to patients about CIPN even before treatment has started, so that patients can properly explain their symptoms when they arise (Tanay et al., 2022), thus creating more openness and awareness about CIPN.

### **Strengths and limitations**

This study has several strengths. First, this was a nationwide study with a high number of participants. Second, a strength of this study was the variety in the time since diagnosis and the type of cancer of the participants. The distribution of participants in less or more than 2 years after diagnosis is nearly equal. Thus, any coasting effect of CIPN (i.e.,

unexpected decrease or increase in CIPN symptoms in the weeks or months after the last dose of chemotherapy (Staff et al., 2017)) in this sample can be considered less relevant.

Some limitations also need to be discussed. First, the questionnaire was probably mainly filled in by patients that are connected to patient organizations, which might not be representative of all cancer patients. Second, it also appears to be an unrepresentative sample in terms of distribution in tumor types. This applies, for example, to lymphoma, which involves a much lower percentage of patients in the Netherlands than in this sample. It also applies to breast cancer, which explains the high number of women in this sample. As women and men have different coping strategies in general (Tamres et al., 2002) and relating to cancer specifically (Hasan et al., 2022), which may also affect the daily limitations they face, this may have affected the results of daily limitations. Third, the questionnaire was only available in Dutch, which prevented non-Dutch-speaking residents from completing the questionnaire. Fourth, a non-validated questionnaire was used. Fifth, only physical, role and social aspects of functioning were considered in examining daily limitations. Future research should also look at emotional and cognitive functioning. Sixth, fatigue was not taken into account in the assessment of daily limitations, while fatigue is one of the most common side-effects of cancer treatment (Ma et al., 2020). Seventh, the sample is very heterogeneous and no analyses regarding differences between chemotherapeutic agents could be made since no data regarding chemotherapeutic agents was collected. Future research should examine comparisons between chemotherapeutic agents and associated symptom and consequences.

### **Conclusion**

This exploratory study showed that patients with CIPN suffer from various symptoms which may result in daily limitations. The prevalence of these limitations differs, and, as a result, the extent to which patients are able to perform ADL also varies. The degree of attention to, and satisfaction with, this attention from healthcare professionals varies, which also applies to the level of empathy from the social environment. Appropriate guidance from healthcare professionals, starting before treatment, and support from the social environment is crucial in enabling patients to feel empowered in their daily lives despite CIPN.

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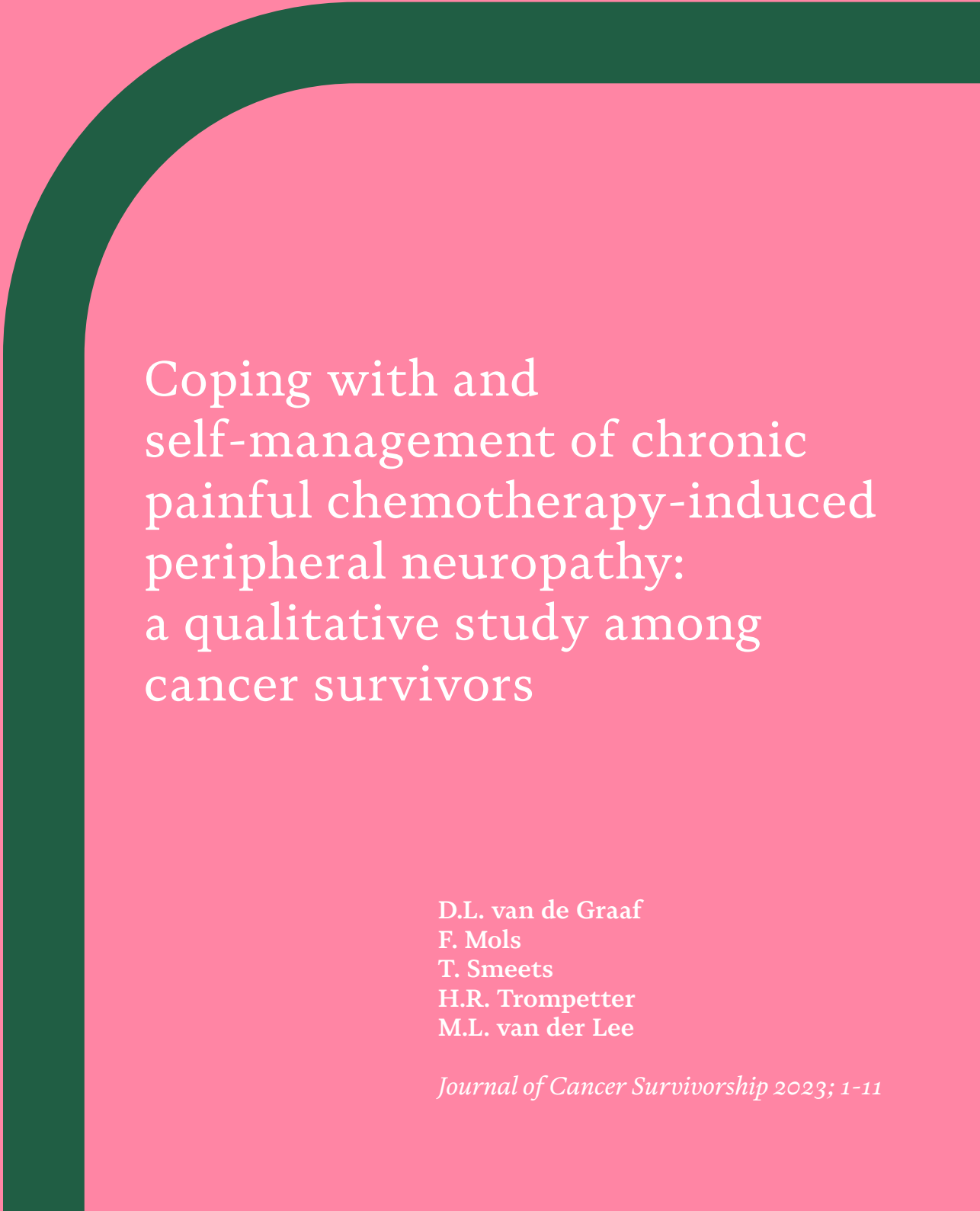
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# Chapter 3

The image features a light beige background. On the right side, there is a vertical decorative border consisting of a blue stripe on the left and a pink stripe on the right. A large, white, stylized number '3' is positioned in the upper right quadrant of the page, partially overlapping the blue stripe.



# Coping with and self-management of chronic painful chemotherapy-induced peripheral neuropathy: a qualitative study among cancer survivors

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## **Abstract**

**Purpose:** Patients with chronic painful chemotherapy-induced peripheral neuropathy (CIPN) may experience a negative impact of CIPN on daily life. They can use various coping (i.e., dealing with symptoms and resulting impairments in general) and self-management (i.e., practical actions to reduce symptoms) strategies to live with their limitations. This paper aimed to examine experienced helpful coping and self-management strategies of patients with chronic painful CIPN.

**Methods:** Semi-structured interviews were conducted with twelve patients with chronic painful CIPN. We applied a hybrid deductive-inductive coding approach. Atlas.ti was used for coding.

**Results:** Generated from the data were two themes and nine codes for coping, and four themes and 31 codes for self-management strategies. Coping of patients often included active strategies like planning, seeking social support, and acceptance. Additionally, patients often used passive strategies such as focusing on and venting emotions and suppressing competing activities. The most common self-management strategies were mostly passive (i.e., medication, deliberate choice of shoes, resting, sitting, and consulting healthcare professionals) but also active (i.e., exercising) strategies.

**Conclusion:** Patients exhibit a great variety of coping and self-management strategies that they perceive as helpful to deal with chronic painful CIPN. However, research has shown that certain strategies are not that helpful or even come with aversive effects. More research into the effectiveness and implementation of psychosocial interventions is needed since it may help patients adopting helping strategies. In addition, healthcare professionals need to refer patients with CIPN in a timely manner to physical therapists, occupational therapists, or rehabilitation teams to reduce or prevent (further) impairments.

**Implications for cancer survivors:** Patients can consult one of their healthcare providers in case of problems in dealing with their symptoms, to get proper guidance and possible referral.

## Introduction

A large proportion of cancer survivors suffer from long-term effects of their diagnosis and treatment, such as chemotherapy-induced peripheral neuropathy (CIPN) (Seretny et al., 2014). This condition is caused by certain chemotherapeutic agents, such as taxanes, platinum compounds, and vinca alkaloids (Argyriou et al., n.d.; Han & Smith, 2013; Wen, 2007). After completion of chemotherapy, around 80% of patients suffer from this, decreasing to around 30% at 6 months or later (Bao et al., 2016; Bonhof et al., 2018; Eckhoff et al., 2015; Glendenning et al., 2010; Mols et al., 2014; Seretny et al., 2014). CIPN presents itself in the hands and feet, but can also spread to arms and legs (Beijers et al., 2012; Farquhar-Smith, 2011; Quasthoff & Hartung, 2002). Symptoms that patients experience greatly vary, which is influenced by chemotherapy type and cumulative dose, as well as patient characteristics and perceptions (C. Tofthagen, 2010). Symptoms may include non-painful symptoms, such as tingling or numbness, as well as painful symptoms, such as shooting or burning pain, pins-and-needles, and cramps (Beijers et al., 2012; Bonhof et al., 2020; Farquhar-Smith, 2011; Quasthoff & Hartung, 2002).

Currently, pharmacological treatment options for CIPN are limited (Mezzanotte et al., 2022). Non-pharmacological treatment options for patients with CIPN are currently increasingly examined in international studies and could be promising (Knoerl et al., 2018; Tanay et al., 2022; C. Tofthagen et al., 2016; van de Graaf et al., 2022). To date, however, there are no general evidence-based non-pharmacological treatment options offered to chronic painful CIPN patients (Jordan et al., 2020; Loprinzi et al., 2020; Mezzanotte et al., 2022). Since the symptoms patients experience strongly vary, the experienced limitations are also diverse. Some patients experience difficulty with even minor daily activities, such as buttoning up a blouse or holding a pen (Beijers et al., 2014). Consequences range from limitations in activities of daily living (ADL), such as walking, sleeping, and intimacy/sexuality, to limitations in social and role activities, such as taking care of (grand)children, working, and sports (Bakitas, 2007; Beijers et al., 2014; van de Graaf et al., 2023), which may complicate or disable participating in daily life. This can eventually result in deteriorated mood, depressive symptoms, performance of regular activities, and quality of life (QoL) (Bonhof et al., 2021; Driessen et al., 2012; Lu et al., 2019; Mols et al., 2013; C. Tofthagen, 2010; C. Tofthagen et al., 2013). Thereby, previous research has

shown that in QoL, patients with painful CIPN present worse outcomes than patients with non-painful CIPN (Bonhof et al., 2020).

Patients with chronic painful CIPN need to learn to live with the symptoms and limitations, and thus how to cope with it. Coping includes performing a response to a perception of stress and relates to cognitive and behavioral actions to manage internal and external stressors (Folkman & Lazarus, 1980; Lazarus & Folkman, 1984). Psychological stress is defined as “a particular relationship between the person and the environment that is appraised by the person as exceeding his or her resources and endangering well-being” (Lazarus & Folkman, 1984, p. 19). Patients with chronic painful CIPN therefore frequently or continuously have a stressor (i.e., painful neuropathic sensations and subsequent limitations) in their daily lives to which they may apply various coping strategies. This involves both active coping, such as planning and acceptance, and passive coping, such as focusing on and venting emotions, restraint coping (i.e., not acting prematurely and taking action only when the stressor occurs), and suppressing competing activities (e.g., setting aside activities to avoid the stressor) (Carver et al., 1989). However, the usefulness of these coping strategies varies widely, as certain strategies (e.g., behavioral disengagement and mental disengagement) are less useful (Carver et al., 1989).

Patients may also take practical actions to be able to perform activities of daily living despite chronic painful CIPN. This is referred to as self-management strategies, where the aim is to relieve symptoms (Blyth et al., 2005). More specifically, it includes patients performing activities or directing others to perform activities to remove or reduce symptoms and associated stress and is also known as symptom management (Fu et al., 2004). Self-management strategies can be divided into two categories (Blyth et al., 2005). Active strategies include activities initiated by the patient to deal with the pain, but do not involve avoidance or escape behavior. This can include both active (e.g., exercise or modified use) and cognitive (e.g., relaxation or distraction) strategies. Passive strategies mean that treatment was offered or provided, without the patient having to actively contribute, or that the patient allows other aspects of their lives to be negatively affected by pain. It may include both passive behavior (e.g., rest or drinking alcohol) and conventional medical strategies (e.g., medication or physiotherapist). Here, avoidance and escape behavior do apply. Passive strategies often have aversive long-term effects, since

these may eventually result in impaired functioning (Reneman et al., 2014). Reduced functioning may relate to emotional, cognitive, social, role, and physical aspects (e.g., emotional distress, pain, sleep problems, loss of purpose) (Bakitas, 2007; Bonhof et al., 2020; C. Tofthagen, 2010; C. S. Tofthagen et al., 2020). Conversely, active self-management strategies contribute to reduced pain-related disability, distress, medication, and pain-related healthcare visits (Blyth et al., 2005).

Knowledge of the helping active, as well as aversive passive strategies that people employ could contribute to the development of appropriate interventions that encourage patients to adopt active coping and self-management strategies, to enhance health-related outcomes. To our knowledge, no previous research studied both coping and self-management strategies of patients with chronic painful CIPN. Since self-management strategies are practical ways of dealing with symptoms and thus part of coping, it is important to look at both within one sample. Therefore, the aim of this paper was to examine coping and self-management strategies that are perceived as helpful by patients with chronic painful CIPN. In this study, we consider coping as dealing with the stressor (i.e., painful neuropathic sensations and resulting impairments) in general, and self-management as a component of coping in which patients take practical actions to reduce symptoms.

## Methods

### Participants

This study was approved by the Ethical Review Board of Tilburg University (School of Social and Behavioral Sciences; #RP284). Participants had to (1) be 18 years or older, (2) experience chronic painful CIPN for at least 3 months, (3) experience self-reported interference of chronic painful CIPN with daily life activities, (4) be in the curative disease phase, and (5) score 3 or higher on an 11-point Numeric Rating Scale (NRS) to assess pain severity. Exclusion criteria were receiving chemotherapy or psychosocial treatment at the time of inclusion. Inclusion and exclusion criteria were based on earlier articles that were conducted in similar research projects (Knoerl et al., 2018; Trompetter et al., 2015).

Participants were recruited via online recruitment flyers via patient organizations and *Kanker.nl* (i.e., Dutch unified web platform delivering tailored medical information and

peer-support for cancer patients and relatives (Frost et al., 2012)). Patients could apply by sending an e-mail to the interviewer (DG). An information letter and informed consent form were sent to interested patients. If the informed consent was filled out and returned, an interview was scheduled. No financial incentives were provided to participants.

### **Data collection and procedures**

Semi-structured interviews were conducted by one of the authors (DG) between September and December 2020. Due to COVID-19, interviews took place via video calling. The interview schedule was mainly based on previous qualitative studies on (cancer) patient experiences (Köhle et al., 2015; Speck et al., 2012; van der Horst et al., 2019). After compiling a first version of the interview schedule, it was discussed with researchers with expertise in painful and non-painful CIPN (FM) and in (coping with) chronic pain (HT) to check whether essential components to assess dealing with chronic painful CIPN were missing. The final semi-structured interview scheme was shown in Table 1. The interviews mainly focused on the helping strategies in patients' perceptions. Interviews were conducted until saturation was reached. This resulted in interviews with twelve patients.

### **Data analysis**

Thematic analysis was used for analyzing the data (Braun & Clarke, 2006). Interviews were audio recorded and afterwards transcribed verbatim by two third-year Psychology bachelor's students and one Psychology master's student from Tilburg University. Transcriptions were re-read by one author (DG) to verify that transcribing had been done correctly and read by a Psychology master's student to become familiar with the data. The first three interviews were coded by DG and one Medical Psychology master's student independently. Differences were discussed afterwards and consensus was reached. The remaining interviews were coded by the Psychology master's student. Difficulties and ambiguities were discussed in weekly meetings between the student and one of the authors (DG).

**Table 1.** Semi-structured interview scheme

Category	Main questions	Optional follow-up questions
Coping	<p>How do you deal with the symptoms daily?</p> <p>Are there any activities that you can no longer perform yourself or modified due to the symptoms? I would like to ask you to imagine yourself in such a situation.</p> <p>Have you recently experienced having many symptoms before or during an activity that was very important to you? For example, the birthday of your (grand)child or an important work appointment.</p>	<p>Are you sometimes afraid to move, to do certain actions or to perform a certain activity, because you think, for example, that the symptoms will worsen? What do you do in such a situation?</p> <p>What kind of emotions do you experience at such a moment?</p> <p>What kind of thoughts do you have at such a moment?</p> <p>What do you do at such a moment?</p> <p>What do you do specifically to solve the 'problem'?</p> <p>What did you do then?</p> <p>Did you make any adjustments?</p> <p>How did you feel before, during, and after the activity?</p>
Self-management	<p>What have you tried to reduce or remedy symptoms yourself?</p>	<p>Did it help in the short term?</p> <p>Did it help in the long term?</p> <p>What does work well for your symptoms?</p> <p>Have you ever used medication (drugstore or pharmacy), exercise, psychotherapy, physical therapy, supplements, etc.?</p> <p>Which healthcare professionals have you visited for these symptoms?</p>

A hybrid deductive-inductive coding approach was applied (Fereday & Muir-Cochrane, 2006). This means that coding was theory-based, but that in addition there was room for new codes to emerge from the data. In this study, coping, which was considered as dealing with the stressor (i.e., painful neuropathic sensations and resulting impairments) in general, was completely coded based on earlier research on coping strategies (Carver et al., 1989). Self-management was defined as a component of coping, in which patients take practical actions to reduce symptoms, for which codes were based on earlier research on self-management strategies for chronic pain patients (Blyth et al., 2005). Self-management coding was mainly theory-based (Blyth et al., 2005), but, novel themes and subthemes were allowed to emerge from the data. Chronic painful CIPN-specific self-management strategies were not covered by the deductive codes based on the study investigating chronic pain. Since there was a partial overlap between the deductive codes of coping and self-management (Blyth et al., 2005; Carver et al., 1989), some codes were eliminated beforehand. Therefore, it was decided that suppression of competing activities and mental disengagement were only coded for coping. Religion and use of alcohol and

smoking were only included in the codes of self-management. Furthermore, coping and self-management strategies were only coded when they were perceived as helpful by patients. Strategies that patients had tried in the past but stopped using because they were perceived as non-helpful were not included in the analyses. Data was only coded when strategies were perceived as helpful by at least one patient, as non-helpful strategies may be not beneficial for anyone. It is important to note that text fragments were sometimes coded as both coping and self-management strategies, as quotes can sometimes be related to both (e.g., asking for a chair at a party is included in the coping strategy 'active coping/planning' and the self-management strategy 'sitting').

After all transcripts were coded, the codes were reviewed and, once adjustments were made, finalized. Then axial coding started with a codebook of 36 codes. These codes were written down on paper and were sorted by DG and a Medical Psychology master's student. Sorting was repeated once to ensure that the categories and themes corresponded the data. This resulted in two categories (i.e., coping and self-management) and six overarching themes. Finally, the student created condensed meaning units for each text fragment with codes, to reflect the essence of each participant's quote. After writing the condensed meaning units, the researcher rechecked whether the codes were appropriate to the corresponding text fragments to improve validity.

## Results

Twelve patients with chronic painful CIPN participated in individual interviews. Patient characteristics are presented in Table 2. The interviews lasted about 30 minutes on average.

Results can be divided into two overarching categories: coping strategies and self-management strategies. Two themes (i.e., passive and active) and nine codes for coping strategies emerged from the data. Additionally, four themes (i.e., active behavioral, cognitive (active), passive behavioral, and conventional medical) and 31 codes emerged for self-management strategies. An overview of all strategies is shown in Table 3.

**Table 2.** Participant characteristics

Participant	Gender	Age <sup>a</sup>	Tumor	Time since CIPN onset <sup>a</sup>	Educational level <sup>b</sup>	Marital status
P1	Male	25-30	Hodgkin lymphoma	1-5 years	Middle	Single
P2	Female	50-55	Breast cancer	5-10 years	High	Married/ living together
P3	Female	60-65	Breast cancer	>10 years	High	Divorced
P4	Female	60-65	Breast cancer	5-10 years	High	Divorced
P5	Female	60-65	Breast cancer	5-10 years	High	Divorced
P6	Female	60-65	Lung cancer	1-5 years	High	Divorced
P7	Male	60-65	Hodgkin lymphoma	5-10 years	High	Married/ living together
P8	Female	60-65	Colorectal cancer	6 months-1 year	Middle	Married/ living together
P9	Male	65-70	Leukemia	5-10 years	Middle	Married/ living together
P10	Male	65-70	Multiple myeloma	5-10 years	High	Married/ living together
P11	Female	75-80	Lung and breast cancer	>10 years	High	Single
P12	Female	75-80	Colorectal and skin cancer	5-10 years	High	Divorced

<sup>a</sup> Ranges are shown to ensure anonymity.

<sup>b</sup> Low: primary or secondary pre-vocational; middle: secondary education or vocational education; high: Bachelor's degree or higher.

**Table 3.** Types of coping and self-management strategies used

Category	Theme	Code	No. of times coded	No. of participants	
Coping	Active	Active coping/planning	34	11	
		Seeking social support for emotional and/or instrumental reasons	10	6	
	Passive	Acceptance	15	5	
		Focus on and venting of emotions	23	8	
		Suppression of competing activities	10	5	
		Mental disengagement	7	5	
		Restraint coping	6	5	
		Behavioral disengagement	4	3	
		Denial	3	3	
		Exercise	10	5	
Self-management	Active behavioral	Modified use	5	4	
		Perform actions carefully	2	2	
		Walking	2	2	
		Work	2	1	
		Social activities	1	1	
		Cognitive (active)	Diary writing	1	1
			Mindfulness	1	1
			Passive behavioral	Shoes	11
		Rest		11	7
		Sitting		8	6
	Keeping warm	9		4	
	Bed modifications	5		3	
	Gloves	5		2	
	Feet/legs in certain position	4		3	
	Smoking/alcohol	3		3	
	Socks	3		3	
	Bath/shower	2		2	
	Alternative means of transportation	2	2		
	Conventional medical	Medication	14	9	
		Physiotherapist	7	5	
		Orthotics	2	2	
		Supplements	2	2	
		Psychologist	2	2	
		General practitioner	1	1	
		Physician	1	1	
		Occupational therapist	1	1	
		Osteopath	1	1	
		Life art coach	1	1	
	Coach	1	1		
Rollator walker	1	1			

**Coping: active**

The most common active coping strategy was planning, mentioned by almost all patients. Many patients indicated that they consider their symptoms when planning their week and

make adjustments in advance: *'I plan, of course. I sometimes find that a disadvantage. I have to plan incredibly. I can't go to an exhibition three days in a row.'* (P2). Many patients indicate that they conduct activities in an alternative manner: *'You can say I can't do things anymore. You can also say I can't do things as fast as I used to, but I can do them. ... I just do it more slowly.'* (P8). Furthermore, several patients indicated that they often search for options that will allow them to continue performing certain activities: *'At parties where there are only bar tables ... then I really have a lot of pain. I start wobbling from one leg to the other or I start looking for a chair.'* (P10).

Seeking social support was also mentioned by several patients. They indicated that they reached out to family, friends, and acquaintances for instrumental reasons: *'I have to do it all by myself, but of course: if I need to mop the windows, I sometimes ask my daughter "can you help?"'* (P1). Several patients also indicated that they seek social support for emotional reasons: *'It regularly makes me very sad. ... Surely that's an average of once a week she [wife] says. ... My wife always tries to cheer me up.'* (P11).

Acceptance was also named as helpful by several patients. Many patients report that they cannot change the situation and have learned to live with it: *'I have to learn to live with it, because if I don't, then I have no life.'* (P7). Some patients put the situation into perspective concerning having cancer and sometimes even trivialize the situation: *'Of course it is inconvenient and annoying but well, I think to myself: "if the cancer stays away then I just have to be willing to put up with it." And that is very annoying, but yes, there are actually worse things, I think. And you can live with it.'* (P9). In addition, there were a few patients who indicated they were actively making space for the symptoms and dealing with them: *'Recently, I started walking. First a round through the village. That's 3 kilometers. Then another bit further. ... So now I can walk 10 kilometers, but my feet do hurt all those 10 kilometers. I always feel them but it's not like it hurts so much that I can't walk with them.'* (P10).

### **Coping: passive**

The most common passive coping strategy was focusing on and venting emotions. Some patients experienced fear-related thoughts and feelings prior to an activity: *'We were going to do some tough hikes. At the first one I was like, "I will not be able to do this." And that just gave me way too much stress. I was also like "I want to go home. I'm not going to pull this off.'*

*In the end, I was able to do it easily.*' (P6). However, some patients also regularly experienced anger or irritation when activities cannot be performed as desired: *'Then I couldn't get a thread in the needle of a sewing machine either ... and then you start getting annoyed'* (P3). Some patients regularly experienced sadness when activities cannot be performed as desired: *'With my family we go out once a year. Then they have to think of what we can do and then there are many things I can't do.. .... That gets me very sad on a regular basis.'* (P11).

Several patients mentioned that they regularly suppress competing activities to cope with their symptoms: *'What I do regret is that I used to love going rock and roll dancing with my wife. That's completely gone, and I think that's a shame. ... I can't keep up the pace anymore.'* (P8). Contrary, some patients indicated that they often apply a restraint coping strategy: *'If I want to do something, I'll see how it goes. ... I'm not going to cancel in advance.'* (P4).

Some patients indicated applying behavioral or mental disengagement strategies. An example of behavioral disengagement, which includes reducing attempts to deal with symptoms and possibly giving up on achieving goals, is: *'It's easier to suffer pain than to face it.'* (P8). Mental disengagement includes performing activities to distract from the symptoms: *'I don't want to cancel. I'd rather go somewhere in pain. Distraction is good. ... It distracts from the pain, so when I'm doing other things, working on something, I realize less that I have this pain.'* (P7).

Finally, some patients tend to deny their situation. An example is: *'I always say "I'm not sick". ... Sick people lie in bed, and they have fever. I don't have all that. I have cancer. That's something else. And neuropathy is a result of my treatment, but I'm not sick.'* (P8).

### **Self-management: active**

An active behavioral strategy that was mentioned by many patients is exercise. Low to moderate intensity exercises were specially mentioned, such as walking, cycling, pilates and yoga: *'I take a walk in the evening. I started doing pilates again because that also gives me some space.'* (P3) and *'I have that bike seat and of course that helps. ... You keep your muscles warm and I'm not very stiff because of that.'* (P10). Patients frequently look for other ways to use objects to perform an action: *'I did get some tools from an occupational therapist that make things like cutting and opening bottles easier.'* (P12). Some patients perform actions

cautiously (*'I walk down the stairs very strangely. ... I am so insecure about the ground and my feet. I hold on [to the banister] and always put my foot in. Preferably still at an angle so you can put your whole foot on the step.'* (P4)). Furthermore, some patients mentioned that they use work or social activities to self-manage symptoms: *'Sometimes I get up in the morning and I think "oh, I am so tired" and then I have to go to work. ... If I sit there and I have that distraction then I'm fine.'* (P1).

### **Self-management: cognitive (active)**

Few patients reported using cognitive (active) self-management strategies. One patient indicated keeping a diary: *'Then I started writing diaries. And that helps, too. ... On average, I do that 2-3 times a week. Sometimes the nice things, sometimes the not so nice things.'* (P11). Another patient indicated performing mindfulness exercises: *'I once did mindfulness training provided by the hospital. I still do use that occasionally.'* (P3).

### **Self-management: passive behavioral**

Making conscious choices regarding wearing shoes was a passive behavioral self-management strategy named by many patients, which varied widely from barefoot (*'I always walk barefoot at home now. Then I feel the contact with the ground.'* (P2)) to hiking boots (*'From that moment I had pain in the feet and then I started wearing high shoes. ... Nowadays I always walk on walking shoes.'* (P11)). Furthermore, many patients indicated they need rest to recover: *'Sometimes I say "no I'm not going". I have to cancel. I don't feel well enough. ... Then I usually stay home and sleep or rest a little more.'* (P5). Several patients also indicated that they often sit down during activities to relieve symptoms: *"Taking breaks with cooking is a little more difficult, of course, but then I just sit down with cutting or things like that."* (P4). Some patients also report that keeping their hands or feet warm to relieve their symptoms: *'So if it is very cold outside later, I will have to dress extra for that.'* (P9). In addition, some patients indicated that they benefit from adjustments in bed, wearing gloves, keeping feet/legs in a certain position, wearing socks, and taking a bath or shower. Some patients also reported drinking alcohol to reduce their symptoms: *'If you have very sore feet and you walk on anyway, I sleep badly because then those feet still hurt at night. ... Then I usually have a glass of wine.'* (P1). Furthermore, some patients look for alternatives in transportation (*'I can't drive for long because my feet will protest. ... I go by train or I go on the electric bike.'* (P4)).

### **Self-management: conventional medical**

Many patients use or have used medication to control their symptoms. This differs between over-the-counter medication (*'I take paracetamol very often. ... Still often 3 times 2 a day.'* (P4) and prescription medication (*'If I haven't been able to sleep for a few nights because my leg hurts bad, I take medication, because you do want to sleep. ... Then you take paracetamol or naproxen.'* (P10)). In terms of healthcare professionals, the physical therapist is the most consulted type to control symptoms: *'With the physical therapist, I had to start doing balance exercises. Sometimes you get up and then I couldn't find my balance.'* (P6). Other resources named by a few patients included orthotics, psychologists, supplements, general practitioners, physicians, occupational therapists, osteopaths, life art coaches, coaches, and a rollator walker.

### **Discussion**

This study qualitatively examined coping (i.e., dealing with painful neuropathic sensations and resulting impairments in general) and self-management (i.e., practical actions to reduce symptoms) strategies that were perceived as helpful by patients with chronic painful CIPN. Whereas patients are often told that they simply have to learn to live with CIPN, this study has shown that patients experience it as a difficult road in which they employ various coping and self-management strategies. Strategies that many patients employ are, for example, planning, acceptance, and suppressing competing activities (i.e., coping), as well as practical actions such as medication and sitting (i.e., self-management).

This study has shown that in addition to many patients employing active coping strategies (e.g., planning and acceptance) that are generally considered as effective, a lot of patients also often apply regulation strategies that are generally considered as non-helping and aversive in the long term as has also been shown in research (Aldao et al., 2010; Carver et al., 1989; Webb et al., 2012). Examples of such strategies are focus on and venting of emotions, suppression of competing activities, and mental disengagement. According to the approach-avoidance coping model, these strategies are part of avoidance coping, meaning that patients try to ignore, avoid, or withdraw from the stressor (i.e., painful neuropathic sensations and resulting impairments) (Solberg Nes & Segerstrom, 2006; Suls & Fletcher, 1985). Approach coping, on the other hand, includes patients trying to actively reduce, manage, or eliminate the stressor (Solberg Nes & Segerstrom, 2006; Suls &

Fletcher, 1985). Biopsychosocial research has shown that avoidance strategies can work in the short term but lead to worsened outcomes in the long term (e.g., pain and disability) (Bever et al., 2016; Crombez et al., 2012; Solberg Nes & Segerstrom, 2006; Suls & Fletcher, 1985). Because approach coping strategies are more effective in the long run (Bever et al., 2016; Crombez et al., 2012; S. C. Hayes et al., 2006; Solberg Nes & Segerstrom, 2006; Suls & Fletcher, 1985), patients should be encouraged to adopt associated strategies of which relatively few or no patients in our study indicated they have adopted, such as acceptance, seeking support, and positive reinterpretation. Psychosocial interventions such as Cognitive Behavioral Therapy (CBT) may help patients adopt helping strategies such as improving planning or reducing focusing on and venting emotions (Knoerl et al., 2018). Other psychosocial interventions such as Acceptance and Commitment Therapy (ACT) can help patients counteract experiential avoidance. The mechanism underlying ACT can be explained through Relational Frame Theory (S. Hayes et al., 2001). Because patients have associations and make connections through language, experiencing limitations due to CIPN can cause people to feel less worthy of themselves or to want to avoid associated emotions. This is also due to the association that CIPN has with cancer. ACT focuses on this mechanism and helps patients to become more psychologically flexible (S. C. Hayes et al., 2012) allowing them to better cope with their symptoms. Future directions in research should focus on developing suitable psychosocial interventions for patients with chronic painful CIPN to support them in managing their symptoms.

A wide variety of self-management strategies emerged in this study, with many patients indicating that exercise helped them reducing, managing, or eliminating their neuropathic sensations. Most recent ASCO (American Society of Clinical Oncology) recommendations do not include exercise, but it does indicate that recent preliminary research shows the potential benefits of exercise (Loprinzi et al., 2020). However, recent ESMO (European Society for Medical Oncology) recommendations do include exercise as the amount of evidence is growing (Jordan et al., 2020). Physical exercise and functional training are recommended as these are shown to reduce CIPN symptoms. It improves physical functioning, which can prevent further deterioration of impairments and falls (Jordan et al., 2020). Additionally, a recent systematic review into the treatment of CIPN concluded that some studies reported that exercise shows short-term improvements in CIPN

symptoms, such as pain intensity, physical functioning, and balance, but that statistical and clinical significance varied among studies (D'Souza et al., 2023). Another recent systematic review named that effects appear positive, but studies have low sample sizes and were heterogeneous regarding the used methodology (Park et al., 2022). In conclusion, it seems that exercise is generally recommended for patients with CIPN, but more research on this is needed to demonstrate evident effectiveness (Chung et al., 2022; Jordan et al., 2020; Loprinzi et al., 2020; Park et al., 2022). Possibly improved physical state and interference may also positively affect patients' sense of control in life and therefore the way they deal with their symptoms. Therefore, future research should also examine whether improvements in physical functioning might influence how people cope with their symptoms.

Furthermore, many patients indicated that they approached different healthcare professionals for support in dealing with CIPN. Physical therapy was mostly mentioned by patients in our study in terms of healthcare professionals. There are currently limited recommendations regarding physical therapy (Jordan et al., 2020; Loprinzi et al., 2020). Further referral to physical therapists is included for support in mainly sensory impairment of CIPN (Jordan et al., 2020). Advice is mainly practical, namely in ADL support. Recommendations relate to dressing (e.g., extension loops on zippers for opening zippers) and body hygiene (e.g., electric toothbrush). Advice is also given for housekeeping (e.g., slip-proof handles) and work (e.g., work settings). It is also mentioned that advice can always be discussed with occupational therapists or physical therapists for additional guidance (Jordan et al., 2020). However, little research has been done on broader approaches such as rehabilitation, which often combines the above elements. As patients may experience impaired mobility and therefore an increased risk of falling, appropriate rehabilitation for functional limitations is needed to maintain QoL (Mizrahi et al., 2022). A review that examined the treatment of CIPN and the implementation of physical therapy and rehabilitation has developed recommendations for exercise and rehabilitation protocols (Zhang, 2021). These recommendations include all patients with CIPN following home-based exercise programs, with low-to-moderate intensity progressive walking and resistance exercises, to reduce or eliminate CIPN symptoms. Furthermore, it is recommended that patients with more severe CIPN symptoms, such as impaired balance and coordination, trouble walking, recurrent falls, pain, severe numbness and tingling,

impaired mobility, and durable medical equipment needs, attend an outpatient rehabilitation program. Inpatient rehabilitation is described as crucial when patients have additional rehabilitative, medical, or rehabilitation nursing needs (Zhang, 2021). However, current ASCO and ESMO recommendations do not include rehabilitation (Jordan et al., 2020; Loprinzi et al., 2020). Healthcare professionals should assess individual patients' physical functioning problems and need to refer them on time to healthcare professionals such as physiotherapists, occupational therapists, or rehabilitation teams, to limit problems in physical functioning such as disability and falls (Mizrahi et al., 2022; Winters-Stone et al., 2017).

### Strengths and limitations

Several strengths of this study can be mentioned. As far as we are concerned, where previous studies looked at either coping or self-management strategies, this is the first study that examined both coping and self-management strategies in patients with chronic painful CIPN. Furthermore, interviews were conducted online via video calling. This makes participation in the study more accessible, enabling vulnerable and disabled patients to sign up for participation as well. This might have contributed to a representative sample. Furthermore, this study used a hybrid inductive-deductive thematic analysis. As a result, all patients' coping and self-management strategies were included in the results in a structured way.

This study also has some limitations. First, patients were only recruited through online flyers via patient organizations and *Kanker.nl*, which may have resulted in a biased sample. Second, the sample of this study mainly involves patients who have suffered from CIPN for more than five years. Earlier research on other chronic conditions, such as rheumatoid arthritis, low back pain, and chronic fatigue syndrome, has shown that patients with higher symptom duration report different coping strategies than those with lower symptom duration (Brown et al., 2010; Estlander, 1989; Janiszewska et al., 2020). As a result, this study may provide less insight into patients who have only had CIPN for a shorter period and have yet to learn to live with their symptoms. Third, most patients in this sample are older than 60 years, so young cancer patients are underrepresented. Previous research has shown that younger adults appear to exhibit different coping strategies than older adults due to both the personal development of coping mechanisms and the influence of

environmental factors that vary by age and stage of life (Lachapelle & Hadjistavropoulos, 2005). In addition, older age appears to be associated with fewer coping strategies (Lachapelle & Hadjistavropoulos, 2005). However, since the majority of the population of cancer survivors is over the age of 60, the results can still be considered representative of a large proportion of patients. Fourth, this study described only the self-management strategies that patients found helpful. However, patients also named many non-helpful self-management strategies that they had tried in the past. These were not described in this study as this study focused on the helpful strategies that people use to deal with the symptoms. It is possible that these unmentioned strategies could be valuable to other patients, but they are not represented in this article. Nor have we now gathered insight into the strategies that were ineffective or even counterproductive from the patients' perceptions. Fifth, no intercoder reliability was considered in this study because there was only one coder. This may potentially have affected the validity of the codes and themes that emerged from the data (Kurasaki, 2000).

### **Conclusion**

This study aimed to identify helpful coping and self-management strategies of patients with painful chronic CIPN. Coping and self-management strategies that patients employ diverge greatly. Future directions in research should investigate psychosocial interventions to support patients to adopt helpful coping strategies. Furthermore, healthcare professionals need to monitor symptoms to refer patients to appropriate healthcare promptly when needed to limit the deterioration of physical state and functioning.

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# Chapter 4

# Symptoms of pre-treatment anxiety are associated with the development of chronic peripheral neuropathy among colorectal cancer patients

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## **Abstract**

**Purpose:** Identifying potentially modifiable predictors of chronic (chemotherapy-induced) peripheral neuropathy (PN) is important, especially in light of the limited treatment options. We aimed to examine pre-treatment anxiety and depressive symptoms as predictors of chronic PN symptom severity in colorectal cancer (CRC) patients up to two years after diagnosis.

**Methods:** Newly diagnosed CRC patients from four Dutch hospitals were eligible for participation. Patients (N=336) completed a questionnaire on anxiety and depressive symptoms (HADS) and sensory (SPN) and motor peripheral neuropathy (MPN) (EORTC QLQ-CIPN20) before initial treatment (baseline) and one and two years after diagnosis. Patients were included in the analyses if they either developed some level of SPN or MPN symptoms, or experienced a worsening of pre-treatment SPN or MPN symptoms.

**Results:** At one-year follow-up, 115 patients (34%) reported SPN symptoms and 134 patients (40%) reported MPN symptoms. Of these patients, SPN and MPN symptoms had not returned to baseline level at two-year follow-up in, respectively, 51% and 54% of patients. In multivariable regression analyses, neither pre-treatment anxiety symptoms nor pre-treatment depressive symptoms were associated with SPN or MPN symptom severity at one-year follow-up. At two-year follow-up, pre-treatment anxiety symptoms ( $\beta=0.44$ ,  $p=0.01$ ), but not depressive symptoms, were associated with SPN symptom severity.

**Conclusions:** Pre-treatment anxiety symptoms, but not depressive symptoms, were associated with SPN symptom severity two years after diagnosis. Future studies are needed that assess whether interventions targeted to reduce anxiety before and during treatment can reduce chronic PN severity or even prevent the persistence of PN.

## Introduction

Peripheral neuropathy (PN) is a common problem in cancer patients. In colorectal cancer (CRC), PN is most often caused by the administration of chemotherapy, specifically oxaliplatin. This oxaliplatin-induced PN mainly results in sensory peripheral neuropathy (SPN), with symptoms such as tingling, numbness, and pain in the hands or feet in a stocking-glove distribution, and motor peripheral neuropathy (MPN), with symptoms such as distal weakness, cramps, gait and balance disturbances, and impaired movements (Gutiérrez-Gutiérrez et al., 2010; Seretny et al., 2014). Chemotherapy-induced PN can resolve after chemotherapy, but becomes a chronic condition in approximately 30% of cancer patients, persisting for six months or longer after cessation of chemotherapy (Seretny et al., 2014). While PN most often results from treatment with a chemotherapeutic agent, it has also been found to be present among cancer patients who did not receive chemotherapy (Boyette-Davis et al., 2012), implicating that the disease itself may play a role in the development of PN. Unfortunately, treatment options for PN are limited (Loprinzi et al., 2020), but much needed, as PN has been shown to severely impact health-related quality of life (HRQoL) (Mols et al., 2013).

Previous studies on possible predictors for (chemotherapy-induced) PN mostly focused on acute PN, while a limited number of predictors have been investigated for chronic PN. Older age (Eckhoff et al., 2015), maximum grade of PN during treatment (Eckhoff et al., 2015), cumulative dose (Beijers et al., 2014), and obesity (Bao et al., 2016) were found to be related to chronic (chemotherapy-induced) PN, but few studies focused on psychosocial predictors while these predictors play an important role in other chronic pain-related syndromes (Crombez et al., 2012; Gatchel et al., 2007). According to biopsychosocial models of chronic pain (Gatchel et al., 2007), patient's symptom interpretation will, over time, impact coping styles and behavior patterns such as catastrophizing and repetitious avoidance of activities that may in fact result in the exacerbation of symptoms. Patients who already have a pre-existing vulnerability to develop such non-adaptive coping styles, like those with anxiety and depression, may be at particular risk (Monroe & Simons, 1991; Walker, 2005). Indeed, meta-analyses show that both anxiety and depression are related to chronic pain-related conditions, such as chronic postsurgical pain (Lewis et al., 2015; Theunissen et al., 2012).

Only a small number of studies has been conducted on the association between (chronic) PN and anxiety and depression. While these studies did find a positive association between PN and anxiety and depression (Bao et al., 2016; Cynthia S. Bonhof et al., 2019; Hong et al., 2014; Kleckner et al., 2021; Lee et al., 2018; Tofthagen et al., 2013), only two studies included a pre-treatment assessment of anxiety and depression to explore it as a potential risk factor for (chronic) PN (Kleckner et al., 2021; Lee et al., 2018). A study among women treated with chemotherapy for breast cancer, found that neither anxiety nor depression was associated with chemotherapy-induced PN during active treatment, while pre-treatment anxiety, but not depression, was associated with chemotherapy-induced PN eight months after completion of chemotherapy (Lee et al., 2018). In another study among women with breast cancer, the symptom cluster fatigue, anxiety, and depression was the strongest pre-chemotherapy predictor of numbness and tingling six weeks after chemotherapy (Kleckner et al., 2021).

Especially in light of the limited treatment options for PN, identifying potentially modifiable predictors of chronic PN is important to help find new treatment opportunities. Therefore, the aim of this prospective study among CRC patients is to examine pre-treatment anxiety and depressive symptoms as predictors of chronic PN symptom severity at one and two years after diagnosis. As both anxiety and depression have been found to be related to chronic pain-related conditions (Lewis et al., 2015; Theunissen et al., 2012), we hypothesize that both pre-treatment anxiety and depressive symptoms will be associated with PN symptom severity at one and two years after diagnosis in our sample of CRC patients.

## **Methods**

### **Setting and participants**

This study is based on data from the PROCORE study. This prospective, population-based study aimed to examine the longitudinal impact of CRC and its treatment on patient-reported outcomes. Details of the data collection have previously been described elsewhere (C.S. Bonhof et al., 2021). In brief, data was collected through PROFILES, which is a registry for the physical and psychosocial impact of cancer and its treatment (van de Poll-Franse et al., 2011). PROFILES is directly linked to the Netherlands Cancer Registry

(NCR), which collects data from all newly diagnosed cancer patients in the Netherlands (Nederlandse Kankerregistratie, 2014).

Patients were recruited from four hospitals in the South of the Netherlands: Elisabeth-TweeSteden hospital, Catharina hospital, Elkerliek hospital, and Máxima Medical Centre. All eligible patients newly diagnosed with CRC as a primary tumor between January 2016 and January 2019 were invited to participate. Those previously diagnosed with a different carcinoma, except for basal cell carcinoma of the skin, those with cognitive impairment, and those unable to read or write Dutch, were excluded. All eligible patients were included shortly after diagnosis, before the start of initial treatment. However, in practice, some patients who were previously diagnosed with cancer and those who already started treatment were also included. Therefore, parallel to previous publications based on the PROCORE dataset (Cynthia S. Bonhof et al., 2021), patients were excluded for analysis if (1) they were previously diagnosed with cancer and reported baseline EORTC QLQ-CIPN20 scores  $>0$ , or (2) they already started chemotherapy.

### **Data collection**

Eligible patients received an information package about the study from their nurse or case manager. This information package included an information letter, informed consent form, and baseline questionnaire. Follow-up questionnaires were sent at four weeks after surgery (when applicable), one year after diagnosis, and two years after diagnosis. For the current study, the questionnaire that was sent four weeks after surgery was not included in the analyses, as this questionnaire does not contain a questionnaire on PN. The PROCORE study was approved by the certified Medical Ethic Committee of Medical research Ethics Committees United (registration number: NL51119.060.14).

### **Sociodemographic and clinical characteristics**

Patients' sociodemographic (i.e., age, sex) and clinical (i.e., cancer type, clinical stage, treatment) information was available from the NCR (Nederlandse Kankerregistratie, 2014). Comorbidity was assessed with the adapted Self-administered Comorbidity Questionnaire (SCQ) (Sangha et al., 2003). Questions on partner status and educational level were added to the questionnaire.

### **Peripheral neuropathy**

The sensory and motor scale of the EORTC QLQ-CIPN20 were used to assess chronic SPN and MPN symptom severity (Postma et al., 2005). The items of this questionnaire assess the extent in which the SPN and MPN symptoms were experienced during the past week. Each item is measured on a Likert scale ranging from (1) Not at all to (4) Very much. Scores were transformed to a 0-100 scale, with higher scores representing higher symptom severity (Fayers et al., 2001). As the item on hearing problems has been found unlikely to accurately identify PN (Smith et al., 2018), we calculated the SPN scale excluding this item (Trompetter et al., 2022).

### **Anxiety and depressive symptoms**

Self-reported pre-treatment anxiety and depressive symptoms were measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). The HADS consists of 14 items assessing anxiety and depressive symptoms in the last week. Items are answered on a four-point Likert scale. Total scores for both the anxiety and depressive symptom scale range from 0-21 with higher scores representing more anxiety and depressive symptoms. A clinically relevant level of anxiety or depression is indicated by a cutoff value of  $\geq 8$  (Olsson et al., 2005).

### **Statistical analyses**

NCR data on sociodemographic and clinical characteristics enabled us to compare eligible patients and respondents, using t tests for continuous variables and chi-square (or Fisher's exact) tests for categorical variables. We also compared differences in sociodemographic and clinical characteristics between 1) patients with SPN and those without SPN at one-year follow-up, and 2) patients with MPN and those without MPN at one-year follow-up. Patients were considered as having SPN if they either developed SPN symptoms (i.e. EORTC QLQ-CIPN20 SPN subscale score=0 at baseline and  $>0$  at one-year follow-up) or experienced a worsening of their existing SPN symptoms at one-year follow-up (i.e.  $>0$  difference between EORTC QLQ-CIPN20 SPN subscale score at baseline and one-year follow-up). For MPN, the MPN subscale of the EORTC QLQ-CIPN20 was used. At 1-year follow-up, chemotherapy was completed 7.5 months (range 4-12) prior.

To gain a better understanding of the experienced SPN and MPN symptoms, frequency distributions were calculated in the sample of patients who either developed SPN (or MPN) symptoms or experienced a worsening of their existing SPN (or MPN) at one-year follow-up. Frequency distributions were also calculated for the subsample of patients whose SPN (or MPN) symptoms had not returned to baseline level at two-year follow-up.

Finally, to assess the association between pre-treatment anxiety and depressive symptoms (independent variables) and SPN and MPN symptom severity at one and two-year follow-up (dependent variables), hierarchical regression analyses were conducted. In the first step of the regression analyses pre-treatment anxiety (or depressive) symptoms were included, as well as a priori determined sociodemographic (i.e. age, sex, educational level (high vs. low/medium)) and clinical confounding variables (i.e. tumor type (colon vs. rectum/sigmoid)), cancer stage (III/IV vs. I/II), radiotherapy, oxaliplatin, capecitabine, and pre-treatment SPN/MPN score). In a second step, pre-treatment depressive symptoms (when pre-treatment anxiety symptoms were included in step 1) or pre-treatment anxiety symptoms (when pre-treatment depressive symptoms were included in step 1) was also included in the model.

All analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 24.0 Armonk, NY: IBM Corps USA). A p value <0.05 was considered statistically significant.

## Results

### Patient characteristics

Of the 713 CRC patients who were invited for the study, 68% (n=483) completed the questionnaire at baseline, 52% (n=374) at 1-year follow-up, and 49% (n=347) at 2-year follow-up. A full flow chart of the study has previously been published (C S. Bonhof et al., 2021). Compared with all patients eligible for participation, respondents were younger, more often male, more likely to receive chemotherapy, and less likely to undergo surgery. In addition, they were less often diagnosed with rectosigmoid cancer, they more often had stage III cancer and less often stage IV cancer (data not shown). Of the 374 patients who completed the baseline and 1-year follow-up questionnaires, 32 patients were excluded as they were previously diagnosed with cancer and reported baseline EORTC QLQ-CIPN20 scores >0 and/or had already started chemotherapy at time of baseline. In

addition, six patients had missing data on the EORTC QLQ-CIPN20 and were thus excluded.

Of the remaining 336 patients, 115 patients (34%) developed SPN symptoms or experienced a worsening of existing SPN symptoms at one-year follow-up (Table 1). Patients with SPN symptoms at one-year follow-up were on average younger, less often had stage I or II cancer and more often had stage III cancer compared with patients without SPN symptoms. Additionally, they more often received chemotherapy and specifically oxaliplatin. Regarding MPN, 134 patients (40%) developed MPN symptoms or experienced a worsening of existing MPN symptoms at one-year follow-up (Table 1). These patients were on average younger, more often female, more often had osteoarthritis, and more often received chemotherapy and specifically oxaliplatin compared with patients without MPN symptoms. In addition, they reported more pre-treatment anxiety and depressive symptoms.

### **SPN and MPN symptoms**

Among patients with SPN, the symptoms that patients experienced the most at one-year follow-up were tingling fingers or hands (46%), tingling toes or feet (40%), numbness in toes or feet (38%), and numbness in fingers or hands (32%). At two-year follow-up, SPN symptoms had not returned to baseline level in 59 out of 115 patients (51%; n=18 missing). Patients still most frequently reported numbness in toes or feet (66%), tingling toes or feet (60%), tingling fingers or hands (59%), and numbness in fingers or hands (47%).

Among patients with MPN, the symptoms that patients experienced the most at one-year follow-up were difficulty opening a jar or bottle because of weakness in hands (62%), difficulty manipulating small objects with fingers (50%), difficulty climbing stairs or getting up out of a chair because of weakness in legs (42%), and cramps in hands (35%). At two-year follow-up, MPN symptoms had not returned to baseline in 72 out of 134 patients (54%; n=18 missing). Patients most frequently reported difficulty opening a jar or bottle because of weakness in hands (65%), difficulty manipulating small objects with fingers (50%), cramps in feet (42%), difficulty climbing stairs or getting up out of a chair because of weakness in legs (36%), and cramps in hand (36%).

**Pre-treatment anxiety and depressive symptoms: one-year follow-up**

At one-year follow-up, both pre-treatment anxiety ( $\beta=0.22$ ,  $p=0.009$ ) (Table 2A) and depressive ( $\beta=0.20$ ,  $p=0.02$ ) (Table 3A) symptoms were significantly associated with worse SPN symptom severity in step 1. Explained variance was 4% and 3% for pre-treatment anxiety and depressive symptoms, respectively. In the second model, in which both predictors were included, neither pre-treatment anxiety nor depressive symptoms were significantly associated with SPN symptom severity. In contrast, younger age, low/medium educational level, colon cancer, treatment with oxaliplatin, and worse pre-treatment SPN score were significantly associated with worse SPN severity.

Regarding MPN, pre-treatment anxiety (Table 2A) and depressive symptoms (Table 3A) were both not associated with MPN symptom severity at one-year follow-up in either of the two models. Worse pre-treatment MPN score and treatment with oxaliplatin or capecitabine were associated with worse MPN symptom severity.

*Pre-treatment anxiety and depressive symptoms: two-year follow-up*

At two-year follow-up, both pre-treatment anxiety ( $\beta=0.43$ ,  $p=0.001$ ) (Table 2B) and depressive ( $\beta=0.29$ ,  $p=0.03$ ) (Table 3B) symptoms were significantly associated with worse SPN symptom severity in step 1. Explained variance was 17% for anxiety symptoms and 8% for depressive symptoms, respectively. In the second model, in which pre-treatment anxiety and depressive symptoms were both included, pre-treatment anxiety ( $\beta=0.44$ ,  $p=0.01$ ) remained significantly associated with SPN symptom severity, explaining 10% of its variance, while depressive symptoms were no longer associated with SPN symptom severity. Treatment with oxaliplatin was also associated with worse SPN symptom severity.

Both pre-treatment anxiety ( $\beta=0.30$ ,  $p=0.01$ ) (Table 2B) and depressive symptoms ( $\beta=0.26$ ,  $p=0.03$ ) (Table 3B) were significantly associated with worse MPN symptom severity in step 1, explaining 8% and 6% of its variance. However, these associations disappeared when both predictors were included in the second model, leaving a worse pre-treatment MPN score as the only significant predictor of MPN symptom severity.

## Discussion

This prospective, population-based cohort study first showed that among CRC patients, 34% developed some level of SPN symptoms or experienced a worsening of their existing SPN symptoms at one year after diagnosis. In addition, symptoms did not return to baseline level at two years after diagnosis in 51% of these patients. The development or worsening of existing MPN symptoms were reported by 40% of CRC patients, of which 54% still reported MPN levels above baseline level at two years after diagnosis. The rates are thus somewhat higher than the reported overall chemotherapy-induced PN prevalence of 30% at six months or more after chemotherapy has ended (Seretny et al., 2014). This may be due to differences in method of PN assessment. In contrast to most of the studies included in the meta-analysis (Seretny et al., 2014), we only used the patient-reported EORTC QLQ-CIPN20 (Postma et al., 2005), and patient-reported measures are found to be more sensitive in detecting beginning or mild PN than objective or clinician-rated assessments (Cavaletti & Marmioli, 2010). In addition, in this study, we also included patients with mild PN symptoms, as we included those with any score above 0 on the EORTC QLQ-CIPN20 SPN or MPN subscale.

The main objective of this study was to examine pre-treatment anxiety and depressive symptoms as predictors of chronic PN symptom severity at one and two years after diagnosis. We expected both pre-treatment anxiety and depressive symptoms to be associated with PN symptom severity at both one and two years after diagnosis. The results showed that neither pre-treatment anxiety nor depressive symptoms were significantly associated with SPN or MPN symptom severity at one year after diagnosis. At two-year follow-up, pre-treatment anxiety symptoms, but not depressive symptoms, were significantly associated with SPN symptom severity. These results are in line with a study among breast cancer patients, in which neither pre-treatment anxiety nor depression was found to be associated with chemotherapy-induced PN during active treatment, but that pre-treatment anxiety was associated with chemotherapy-induced PN eight months after completion of chemotherapy (Lee et al., 2018).

The association between pre-treatment anxiety symptoms and SPN symptom severity may be explained through the biopsychosocial model of chronic pain (Gatchel et al., 2007). According to this widely accepted model, pain is a complex and dynamic interplay

between biological, psychological, and social factors. Perceptual and cognitive processes, like catastrophizing, fear-avoidance beliefs, and hypervigilance to negative information may increase PN symptoms and may even cause acute PN to become chronic. For example, acute PN symptoms may cause patients to catastrophize their PN and perceive certain activities, such as physical exercise, as potentially detrimental for their condition. This generally leads to the avoidance of such activities, which may then actually result in the exacerbation of their PN symptoms, leading to increased anxiety and avoidance behavior. Finally, patients may find themselves in a vicious circle of escalating anxiety, avoidance behavior, and exacerbation of PN symptoms (Walker, 2005). At particular risk for chronic PN may be those who have a pre-existing vulnerability to develop such non-adaptive psychological reactions. Within the context of the biopsychosocial model, a diathesis-stress framework proposes that individuals have certain inherent vulnerabilities, or diathesis, to develop certain disorders or difficulties when exposed to stressors such as PN (Monroe & Simons, 1991). Pre-treatment (latent) anxiety can be activated or exacerbated by the stress of PN and the exacerbated anxiety may then cause the PN to develop into a chronic condition.

In line with the biopsychosocial model of chronic pain, it has been hypothesized that acute chemotherapy-induced PN may primarily be caused by the neurotoxic effects of the chemotherapeutic agent, while chronic chemotherapy-induced PN is more likely to be affected by predisposing psychological factors that maintain the chemotherapy-induced PN symptoms (Lee et al., 2018). Chemotherapy-induced PN can be considered chronic when symptoms persist for 6 months or longer after cessation of chemotherapy (Seretny et al., 2014). In our study, chemotherapy was completed four to twelve months prior to one-year follow-up. Therefore, the PN may not yet have turned into a chronic condition for all patients. This may explain why we did find an association between pre-treatment anxiety and SPN symptom severity at two-year follow-up, while no such association was found at one-year follow-up.

An increased production of pro-inflammatory cytokines may also play a role in the persistence of PN among patients with pre-treatment anxiety. Anxiety, as well as (chemotherapy-induced) PN, has been associated with increased pro-inflammatory cytokines, such as IL-6 (O'Donovan et al., 2010; Starkweather, 2010). As pro-

inflammatory cytokines play a crucial role in nerve repair, anxiety might interfere with recovery from the nerve injury in PN.

Interestingly, in our study, pre-treatment anxiety symptoms were not associated with MPN symptom severity at two-year follow-up, but neither was treatment with the chemotherapeutic agents capecitabine or oxaliplatin. Treatment with these chemotherapeutic agents was associated with MPN symptom severity at one-year follow-up, but pre-treatment MPN score was the only significant risk factor for MPN symptom severity at two-year follow-up. In our previous study among the same study population, we examined the course of PN among both patients who received chemotherapy and those who did not (Cynthia S. Bonhof et al., 2021). In both groups, MPN symptoms had increased at one-year follow-up, with those who received chemotherapy reporting significantly more MPN symptoms. At two-year follow-up, symptoms declined among this group and while symptoms did not return to baseline level, there was no longer a significant difference with patients who did not receive chemotherapy, as MPN symptoms further increased among this group. It could be that, at two-year follow-up, MPN symptoms were mostly due to (pre-existing) PN-related comorbidity such as osteoarthritis, diabetes mellitus, and rheumatoid arthritis. We also find it difficult to offer a sensible explanation as to why depressive symptoms were not associated with SPN symptom severity while it has been related to pain intensity in other samples (Lewis et al., 2015), or why pre-treatment anxiety symptoms but not depressive symptoms would be related to SPN symptom severity. Future research aimed to elucidate these findings is necessary.

The findings of our study add to the limited knowledge on potentially modifiable risk factor for chronic PN, especially in light of the limited treatment options. Based on this study, it is too early to make any recommendations for clinical practice. However, as PN negatively impacts the HRQoL of CRC survivors (Cynthia S. Bonhof et al., 2021; Mols et al., 2013; Toftthagen et al., 2013), we would recommend future studies to examine whether interventions targeted to reduce anxiety before and during treatment can reduce the severity of chronic PN or even prevent the persistence of PN.

Some limitations should be acknowledged. First, no information was available on chemotherapy dosage, number of cycles, and possible dose reduction, while these factors are important determinants of chemotherapy-induced PN severity (Seretny et al., 2014). Secondly, it has been advised that self-reported (chemotherapy-induced) PN measures should preferably be combined with clinician-rated neurological assessment tools (Park et al., 2019). Therefore, the use of only the EORTC QLQ-CIPN20 is another limitation. However, due to the subjective nature of PN symptoms and the typical underestimation of PN severity by healthcare professionals (Cavaletti et al., 2010), we feel that patient-reported assessment of PN are of greater importance. In addition, patients lost to follow-up could have stopped participating because of severe PN symptoms in their hands, which could have impacted our findings. Finally, eligible patients and respondents of this study differed in some sociodemographic and clinical characteristics. Therefore, generalization of our findings should be done with caution.

In conclusion, this study showed that neither pre-treatment anxiety symptoms nor pre-treatment depressive symptoms were associated with SPN or MPN symptom severity one year after diagnosis, while pre-treatment anxiety symptoms, but not depressive symptoms, were associated with SPN symptom severity two years after diagnosis. These results highlight the importance of future studies that examine the effectiveness of interventions aimed to reduce anxiety before and during treatment in reducing chronic PN severity or even preventing the persistence of PN.

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**Table 1.** Baseline sociodemographic and clinical characteristics of colorectal cancer patients stratified by the presence of sensory and motor peripheral neuropathy at 1-year follow-up

	SPN (n=155)	No SPN (n=221)	MPN (n=134)	No MPN (n=202)
Age (mean, SD)	65.1 (9.0)*	67.3 (8.5)	65.3 (9.5)*	67.3 (8.0)
Female sex	44 (38%)	85 (39%)	62 (46%)*	67 (33%)
Partner (yes)	95 (83%)	191 (86%)	111 (83%)	175 (87%)
Education level <sup>a</sup>				
Low	13 (11%)	17 (8%)	11 (8%)	19 (10%)
Medium	67 (58%)	142 (65%)	84 (63%)	125 (62%)
High	35 (30%)	60 (27%)	38 (29%)	57 (28%)
Tumor location				
Colon	85 (74%)	157 (71%)	93 (69%)	149 (74%)
Rectum/rectumsigmoid	30 (26%)	64 (29%)	41 (31%)	53 (26%)
TNM stage				
I	19 (17%) <sup>‡</sup>	87 (39%)	35 (26%)	71 (35%)
II	22 (19%)	71 (32%)	37 (28%)	56 (28%)
III	70 (61%)	56 (25%)	56 (42%)	70 (35%)
IV	4 (4%)	6 (3%)	6 (5%)	4 (2%)
Unknown	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Tumor differentiation grade				
Well differentiated	93 (81%)	178 (81%)	115 (86%)	156 (77%)
Moderately differentiated	6 (5%)	11 (5%)	3 (2%)	14 (7%)
Poorly differentiated	16 (14%)	30 (14%)	16 (12%)	30 (15%)
Unknown				
Radiotherapy (yes)	21 (18%)	29 (13%)	18 (13%)	32 (16%)
Chemotherapy				
No	51 (44%) <sup>‡</sup>	181 (82%)	83 (62%) <sup>†</sup>	149 (74%)
Capecitabine	10 (9%)	18 (8%)	9 (7%)	19 (9%)
Oxaliplatin	54 (47%) <sup>‡</sup>	22 (10%)	42 (31%) <sup>†</sup>	34 (17%)
Surgery (yes)	112 (97%)	217 (98%)	131 (98%)	198 (98%)
Number of comorbidities				
None	34 (30%)	60 (27%)	33 (25%)	61 (31%)
One	43 (38%)	70 (32%)	47 (35%)	66 (33%)
Two or more	37 (32%)	89 (41%)	54 (40%)	72 (36%)
Comorbidities associated with PN <sup>b</sup>				
Osteoarthritis	26 (23%)	43 (20%)	35 (26%) <sup>†</sup>	34 (17%)
Rheumatoid arthritis	6 (5%)	10 (5%)	7 (5%)	9 (5%)
Diabetes mellitus	13 (11%)	17 (8%)	13 (10%)	17 (9%)
Pre-treatment anxiety symptoms (mean, SD)	5.2 (4.1)	5.1 (3.9)	5.8 (4.3)*	4.7 (3.7)
Pre-treatment depressive symptoms (mean, SD)	4.1 (3.8)	3.5 (3.5)	4.5 (3.9) <sup>†</sup>	3.2 (3.3)

## Chapter 4

Abbreviations: SPN, sensory peripheral neuropathy; MPN, motor peripheral neuropathy; SD, standard deviation

Variables may deviate from 100% due to rounding off.

Significant difference between either patients with SPN and those without SPN at 1-year follow-up, or patients with MPN and those without MPN at 1-year follow-up at \*  $p < 0.05$ ; †  $p < 0.01$ ; ‡  $p < 0.001$ .

<sup>a</sup> Education: Low (no or primary school); medium (lower general secondary education or vocational training); high (pre-university education, high vocational training, university).

<sup>b</sup> Most frequent comorbidities associated with peripheral neuropathy

**Table 2.** Association between pre-treatment anxiety symptoms and SPN and MPN symptom severity at 1-year (A) and 2-year (B) follow-up among CRC patients with chronic peripheral neuropathy

	A. 1-year follow-up				B. 2-year follow-up			
	SPN symptom severity		MPN symptom severity		SPN symptom severity		MPN symptom severity	
	Beta	Adj R <sup>2</sup>	Beta	Adj R <sup>2</sup>	Beta	Adj R <sup>2</sup>	Beta	Adj R <sup>2</sup>
<i>Step 1</i>								
Pre-treatment anxiety symptoms	<b>0.22<sup>†</sup></b>		0.08		<b>0.43<sup>‡</sup></b>		<b>0.30*</b>	
Age	<b>-0.18*</b>		-0.13		-0.20		-0.07	
Sex (female)	-0.03		0.02		0.02		-0.12	
Educational level (high)	-0.17		0.03		-0.11		0.09	
Type tumor (colon)	<b>0.28*</b>		0.03		0.29		-0.11	
Stage (III and IV)	-0.23		-0.15		-		-0.22	
Radiotherapy	-0.18		-0.08		0.02		0.03	
Chemotherapy - Oxaliplatin	<b>0.69<sup>‡</sup></b>		<b>0.43<sup>‡</sup></b>		<b>0.61*</b>		0.31	
Chemotherapy - Capecitabine	0.15		<b>0.21*</b>		0.25		0.18	
Pre-treatment SPN/MPN score	<b>0.22<sup>†</sup></b>		<b>0.59<sup>‡</sup></b>		0.18		<b>0.44<sup>†</sup></b>	
		0.31 <sup>a</sup>		0.33 <sup>a</sup>		0.23 <sup>a</sup>		0.21 <sup>a</sup>
<i>Step 2</i>								
Pre-treatment anxiety symptoms	0.16		0.10		<b>0.44*</b>		0.25	
Age	<b>-0.19*</b>		-0.12		-0.20		-0.08	
Sex (female)	-0.03		0.01		0.03		-0.12	
Educational level (high)	<b>-0.17*</b>		0.03		-0.11		0.09	
Type tumor (colon)	<b>0.29*</b>		0.02		0.29		-0.09	
Stage (III and IV)	-0.23		-0.15		-0.38		0.21	
Radiotherapy	-0.19		-0.07		0.02		0.02	
Chemotherapy - Oxaliplatin	<b>0.70<sup>‡</sup></b>		<b>0.43<sup>‡</sup></b>		<b>0.61*</b>		0.31	
Chemotherapy - Capecitabine	0.14		<b>0.21*</b>		0.25		0.17	
Pre-treatment SPN/MPN score	<b>0.22<sup>†</sup></b>		<b>0.60<sup>‡</sup></b>		0.18		<b>0.34<sup>†</sup></b>	
Pre-treatment depressive symptoms	0.10		-0.03		-0.01		0.06	
		0.31 <sup>a</sup>		0.33 <sup>a</sup>		0.22 <sup>a</sup>		0.20 <sup>a</sup>

Notes: Abbreviations - SPN, Sensory peripheral neuropathy; MPN, motor peripheral neuropathy; CRC, Colorectal Cancer; Adj, adjusted. \* significant at p <0.05; † significant at p<0.01; ‡ significant at p<0.001. <sup>a</sup> Change in adjusted R<sup>2</sup> is significant.

**Table 3.** Association between pre-treatment depressive symptoms and SPN and MPN symptom severity at 1-year (A) and 2-year (B) follow-up among CRC patients with chronic peripheral neuropathy

	A. 1-year follow-up				B. 2-year follow-up			
	SPN symptom severity		MPN symptom severity		SPN symptom severity		MPN symptom severity	
	Beta	Adj R <sup>2</sup>	Beta	Adj R <sup>2</sup>	Beta	Adj R <sup>2</sup>	Beta	Adj R <sup>2</sup>
<i>Step 1</i>								
Pre-treatment depressive symptoms	<b>0.20*</b>		0.04		<b>0.29*</b>		<b>0.26*</b>	
Age	<b>-0.21*</b>		-0.14		-0.25		-0.13	
Sex (female)	-0.03		0.02		0.03		-0.09	
Educational level (high)	<b>-0.18*</b>		0.03		-0.12		0.07	
Type tumor (colon)	<b>0.29*</b>		0.04		0.34		-0.08	
Stage (III and IV)	-0.22		-0.15		-0.29		-0.18	
Radiotherapy	-0.19		-0.08		-0.07		-0.02	
Chemotherapy - Oxaliplatin	<b>0.69‡</b>		<b>0.43‡</b>		<b>0.52*</b>		0.31	
Chemotherapy - Capecitabine	0.13		<b>0.20*</b>		0.16		0.13	
Pre-treatment SPN/MPN score	<b>0.24†</b>		<b>0.59‡</b>		0.15		<b>0.42†</b>	
		0.30 <sup>a</sup>		0.38 <sup>a</sup>		0.11		0.19 <sup>a</sup>
<i>Step 2</i>								
Pre-treatment depressive symptoms	0.10		-0.03		0.01		0.06	
Age	<b>-0.19*</b>		-0.12		-0.20		-0.08	
Sex (female)	-0.03		0.01		0.03		-0.12	
Educational level (high)	<b>-0.17*</b>		0.03		-0.11		0.09	
Type tumor (colon)	<b>0.29*</b>		0.02		0.29		-0.09	
Stage (III and IV)	-0.23		-0.15		-0.38		0.21	
Radiotherapy	-0.19		-0.07		0.02		0.02	
Chemotherapy - Oxaliplatin	<b>0.70‡</b>		<b>0.43‡</b>		<b>0.61*</b>		0.31	
Chemotherapy - Capecitabine	0.14		<b>0.21*</b>		0.25		0.17	
Pre-treatment SPN/MPN score	<b>0.22†</b>		<b>0.60‡</b>		0.18		<b>0.34†</b>	
Pre-treatment anxiety symptoms	0.16		0.10		<b>0.44*</b>		0.25	
		0.31 <sup>a</sup>		0.38 <sup>a</sup>		0.22 <sup>a</sup>		0.20 <sup>a</sup>

Notes: Abbreviations - SPN, Sensory peripheral neuropathy; MPN, motor peripheral neuropathy; CRC, Colorectal Cancer; Adj, adjusted. \* significant at  $p < 0.05$ ; † significant at  $p < 0.01$ ; ‡ significant at  $p < 0.001$ . <sup>a</sup> Change in adjusted R<sup>2</sup> is significant.



# Part II



# eHealth interventions

# Chapter 5

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# Online Acceptance and Commitment Therapy (ACT) interventions for chronic pain: A systematic literature review

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*Internet Interventions* 2021; 26, 100465

## **Abstract**

**Background:** We systematically reviewed all literature concerning online Acceptance and Commitment Therapy (ACT) interventions for chronic pain to evaluate their (1) ACT content, (2) design characteristics, (3) design rationales, and (4) adherence.

**Methods:** A systematic search was performed on July 9<sup>th</sup>, 2020 in; PubMed, PsycINFO, CINAHL, and Web of Science. Search terms related to: Acceptance and Commitment Therapy, chronic pain, and eHealth. Extracted data concerned ACT content, design characteristics, adherence, and design rationales.

**Results:** 20 articles, in which 14 interventions were described, met all inclusion criteria. Adherence and design rationales were described to a limited extent in the included studies. In total, the majority provided an overview of the included ACT processes. In 10 articles it was described that the intervention was delivered via a dedicated website ( $n=10$ ), which was sometimes combined with an app ( $n=3$ ). Guidance was included in most studies ( $n=19$ ). Studies including RCT's ( $n=8$ ) reported online ACT interventions to be effective.

**Conclusion:** Online ACT interventions for chronic pain have been shown to be effective and have generally been constructed in line with ACT theory. However, the majority of studies does not provide information about the choices to optimize the fit between task, technology, and user. Considerations behind the choices for intervention features as well as design rationales could help to optimize future online ACT interventions. Additionally, consistent attention should be paid to measurement and operationalization of adherence, since this is a crucial link between content, design and effectiveness.

## Introduction

Chronic pain is a prevalent, burdensome condition negatively affecting individuals' functioning, as well as socioeconomic factors (Breivik et al., 2006; Breivik et al., 2013). Unfortunately, effectiveness of biomedical treatment options for chronic pain are still not promising (Turk et al., 2011). Much like seen in many mental disorders (e.g., patients with anxiety disorders), chronic pain patients are characterized by high threat sensitivity, unbridled avoidance, and catastrophizing thinking styles (Claes, 2016; Claes et al., 2015; Harvie et al., 2017; Meulders et al., 2015; Vlaeyen et al., 2016). As such, classic psychotherapeutic interventions may aid in helping patients overcome these pain-related fears and avoidance behaviors that would otherwise lead to excessive activity disengagement. Cognitive behavioral therapies (CBT) like Acceptance and Commitment Therapy (ACT) may teach patients to adapt effectively to living with chronic pain (Hayes et al., 2006; Scott et al., 2016). Even more so than traditional CBT, ACT is highly suited to patients with chronic pain through its focus on pain acceptance as an alternative to ongoing, fruitless attempts at pain avoidance. Through this focus ACT can help chronic pain patients to form realistic expectations at pain relief, which are highly necessary given the currently modest effect sizes of existing biomedical and psychological treatment options for pain relief (Vlaeyen et al., 2016). In addition, the appropriateness of ACT has led to the development of many interventions in the last decade. Because it ran parallel to the developments in online interventions, the combination forms a very interesting case for chronic pain to look at in an independent review. ACT helps to shift focus towards performing personally valuable activities in the presence of chronic pain by increasing pain acceptance as an alternative to avoidance (i.e. psychological flexibility) (Hayes et al., 2006). In ACT, psychological flexibility is attained by increasing three different response styles, which are openness (i.e. acceptance and cognitive defusion), awareness (i.e. being present and self-as-context), and engagement (i.e. values and committed action) (Hayes et al., 2012). Earlier reviews described the effectiveness of ACT for chronic pain in improving anxiety, depression, pain intensity, functioning, and quality of life (Graham et al., 2016; Hughes et al., 2017; Simpson et al., 2017; Veehof et al., 2016).

Traditional *face-to-face* psychosocial therapies carry drawbacks, such as costs, accessibility, and psychological burden (e.g. reluctant towards *face-to-face* therapy due to the overwhelming nature of the diagnosis) (Børø Sund et al., 2018; Knoerl et al., 2018).

Additionally, there have been major developments in eHealth recent years (Børøsund et al., 2018; Gainsbury and Blaszczynski, 2011; Knoerl et al., 2018), increasingly more ACT interventions are being offered online (Buhrman et al., 2013). Thereby, patients can perform psychosocial therapy anytime, anywhere (Børøsund et al., 2018; Knoerl et al., 2018). Subsequently, more studies examining the effectiveness of online ACT interventions for chronic pain have been published. Several reviews assessed online interventions' effects. However, these reviews examined other behavioral interventions besides ACT (Bender et al., 2011; Buhrman et al., 2016; Eccleston et al., 2015; Macea et al., 2010) or assessed both offline and online ACT interventions (Graham et al., 2016; Hughes et al., 2017; Simpson et al., 2017; Veehof et al., 2016). Reviews in general included individuals with heterogeneous forms of chronic pain, some excluding headache (Eccleston et al., 2015; Graham et al., 2016; Hughes et al., 2017; Simpson et al., 2017) or malignant pain (Hughes et al., 2017; Simpson et al., 2017). This review focuses on online ACT interventions as it allows us to evaluate the content and design features of the online ACT interventions for chronic pain patients. An additional focus on the content and design characteristics of the intervention is informative when taking models such as the Technology Acceptance Model (TAM) and the Task-Technology Fit (TTF) model into account. TAM and TTF can be a good framework for optimal use of an online intervention. These models can serve as a guideline for research to maximize adherence and effectiveness, especially in the phase of usability testing. TAM shows that user acceptance is influenced by both perceived usefulness and perceived ease of use (Davis, 1989), and has become a crucial model describing users' acceptance of technology (Marangunić and Granić, 2015). However, the perception of technology varies per task, which is included in the TTF model (Lee et al., 2003). More specifically, TTF pictures the relationship between task requirement, individual abilities, and technology functionality (Goodhue and Thompson, 1995). In summary, adherence (i.e. "the extent to which individuals should experience the content to derive maximum benefit from the intervention, as defined or implied by its creators") (Kelders et al., 2012) and effectiveness of online interventions are determined by the ability to reach an optimal combination of task, technology, *and* user (Davis, 1989; Goodhue and Thompson, 1995). Especially in self-management interventions for chronic pain this can be of great importance, since such interventions are complex and require high user motivations (Laugesen, 2013). Although models such as TAM and TTF cannot be used to generate generic, measurable

guidelines for eHealth intervention designs, the models show the importance of considering and substantiating the way in which user, task and technology are brought together for a specific intervention. Given the importance of optimizing TAM and TTF for online interventions for chronic pain, we will evaluate how existing online ACT interventions for chronic pain provided a rationale for, and designed, ACT content as based on the Psychological Flexibility Model (i.e. 'task' in TTF), and design characteristics (i.e. 'technology' in TTF). To our knowledge, this is the first review examining online ACT interventions for chronic pain through the lens of using TAM and TTF, which may provide new insights into the 'fit' of online ACT interventions. TAM and TTF were used here as frameworks or guidelines, rather than testable models. Summarized, the objective of this study is thus to evaluate online ACT interventions in terms of (1) design rationales, (2) ACT content, (3) design characteristics, and (4) adherence.

## Methods

This systematic review was performed using the PRISMA (Preferred Reported Items for Systematic Review and Meta-analysis) guidelines (Moher et al., 2009).

### Search strategy

Databases PubMed, PsycINFO, CINAHL, and Web of Science were systematically searched on July 9, 2020. The main search terms included: Acceptance and Commitment Therapy; chronic pain; pain; Internet; online; telemedicine; telehealth; eHealth; mHealth; mobile health; Internet-based intervention; digital intervention; digital health intervention; web-based; web; mobile applications; mobile application; mobile app; mobile apps; app; apps. Medical Subject Headings (MeSH terms) were used if possible. Complete search strategies for each database are shown in Table 1. Removing duplicates was performed within Mendeley.

**Table 1.** Search strategy

Database	Keywords	Hits
PubMed	((("Acceptance and Commitment Therapy"[MeSH Terms] OR "Acceptance and Commitment Therapy"[Title/Abstract])) AND (("chronic pain"[MeSH Terms] OR "chronic pain"[Title/Abstract] OR ("pain"[MeSH Terms] OR "pain"[Title/Abstract])) AND (("Internet"[Mesh] OR "Internet"[Title/Abstract] OR "Online"[Title/Abstract] OR ("Telemedicine"[MeSH Terms] OR "Telemedicine"[Title/Abstract] OR "Telehealth"[Title/Abstract] OR "eHealth"[Title/Abstract] OR "mHealth"[Title/Abstract] OR "mobile health"[Title/Abstract] OR ("Internet-based intervention"[MeSH Terms] OR internet-based intervention"[Title/Abstract] OR "digital intervention"[Title/Abstract] OR "digital health intervention"[Title/Abstract] OR "web-based"[Title/Abstract] OR "web"[Title/Abstract] OR ("Mobile Applications"[MeSH Terms] OR "Mobile Applications"[Title/Abstract] OR "Mobile Application"[Title/Abstract] OR "Mobile App"[Title/Abstract] OR "Mobile Apps"[Title/Abstract] OR "App"[Title/Abstract] OR "Apps"[Title/Abstract])))	36
PsycINFO	((DE "Acceptance and Commitment Therapy" OR TI "Acceptance and Commitment Therapy" OR AB "Acceptance and Commitment Therapy")) AND ((DE "Chronic Pain" OR TI "Chronic Pain" OR AB "Chronic Pain") OR (DE "Pain" OR TI "Pain" OR AB "Pain")) AND ((DE "Internet" OR TI "Internet" OR AB "Internet" OR TI "Online" OR AB "Online") OR (DE "Telemedicine" OR TI "Telemedicine" OR AB "Telemedicine" OR TI "Telehealth" OR AB "Telehealth" OR TI "eHealth" OR AB "eHealth" OR TI "mHealth" OR AB "mHealth" OR DE "Mobile Health" OR TI "Mobile Health" OR AB "Mobile Health") OR (DE "Digital Interventions" OR TI "Digital Interventions" OR AB "Digital Interventions" OR TI "Digital Health Interventions" OR AB "Digital Health Interventions" OR TI "Internet-based interventions" OR AB "Internet-based interventions" OR TI "web-based" OR AB "web-based" OR TI "web" OR AB "web" OR (DE "Mobile Applications" OR TI "Mobile Applications" OR AB "Mobile Applications" OR TI "Mobile Application" OR AB "Mobile Application" OR TI "Mobile App" OR AB "Mobile App" OR TI "Mobile Apps" OR AB "Mobile Apps" OR TI "App" OR AB "App" OR TI "Apps" OR AB "Apps"))	23
CINAHL	((MH "Acceptance and Commitment Therapy") OR (TI "Acceptance and Commitment Therapy") OR (AB "Acceptance and Commitment Therapy")) AND ((MH "Chronic Pain") OR (TI "Chronic Pain") OR (AB "Chronic Pain") OR (MH "Pain") OR (TI "Pain") OR (AB "Pain")) AND ((MH "Internet") OR (TI "Internet") OR (AB "Internet") OR (TI "Online") OR (AB "Online") OR (MH "Telehealth") OR (TI "Telehealth") OR (AB "Telehealth") OR (TI "Telemedicine") OR (AB "Telemedicine") OR (TI "eHealth") OR (AB "eHealth") OR (TI "mHealth") OR (AB "mHealth") OR (TI "mobile health") OR (AB "mobile health") OR (TI "Internet-based Intervention") OR (AB "Internet-based Intervention") OR (TI "Digital Intervention") OR (AB "Digital Intervention") OR (TI "Digital Health Intervention") OR (AB "Digital Health Intervention") OR (TI "Web-based") OR (AB "Web-based") OR (TI "Web") OR (AB "Web") OR (MH "Mobile Applications") OR (TI "Mobile Applications") OR (AB "Mobile Applications") OR (TI "Mobile Application") OR (AB "Mobile Application") OR (TI "Mobile App") OR (AB "Mobile App") OR (TI "Mobile Apps") OR (AB "Mobile Apps") OR (TI "App") OR (AB "App") OR (TI "Apps") OR (AB "Apps"))	20
Web of Science	((TI="Acceptance and Commitment Therapy") OR (AB="Acceptance and Commitment Therapy")) AND ((TI="Chronic Pain") OR (AB="Chronic Pain") OR (TI="Pain") OR (AB="Pain")) AND ((TI="Internet") OR (AB="Internet") OR (TI="Online") OR (AB="Online") OR (TI="Telemedicine") OR (AB="Telemedicine") OR (TI="Telehealth") OR (AB="Telehealth") OR (TI="eHealth") OR (AB="eHealth") OR (TI="mHealth") OR (AB="mHealth") OR (TI="mobile health") OR (AB="mobile health") OR (TI="Internet-based Intervention") OR (AB="Internet-based Intervention") OR (TI="Digital Intervention") OR (AB="Digital Intervention") OR (TI="Digital Health Intervention") OR (AB="Digital Health Intervention") OR (TI="Web-based") OR (AB="Web-based") OR (TI="Web") OR (AB="Web") OR (TI="Mobile Applications") OR (AB="Mobile Applications") OR (TI="Mobile Application") OR (AB="Mobile Application") OR (TI="Mobile App") OR (AB="Mobile App") OR (TI="Mobile Apps") OR (AB="Mobile Apps") OR (TI="App") OR (AB="App") OR (TI="Apps") OR (AB="Apps"))	35

### **Inclusion and exclusion criteria**

Studies were included if: (1) the publication described an online intervention that was based on ACT (i.e. ACT or acceptance-based) and designed for chronic pain (i.e.  $\geq 3$  months of pain), (2) the publication was an original article (e.g. no poster abstracts, editorials, reviews, letters to editor, etc.), (3) the article was published or in press in a peer-reviewed journal, and (4) the main article was written in English. Furthermore, all research designs were included, as long as it was related to the design or evaluation of an online ACT intervention. Studies were excluded if the intervention included participants under 18 years old or if the intervention concerned therapeutic sessions by telephone or video call only since these do not concern self-management activities. Publications were also excluded when chronic pain included headache (Rickardsson et al., 2020; Sullivan et al., 2018), since this is seen as a different type of pain compared to other chronic pain types and psychological therapies for headache are mainly focused at reducing pain characteristics instead of rehabilitation in the presence of persistent pain (Williams et al., 2019). This does not relate to adherence and design factors. Reference lists of excluded reviews were checked for other relevant publications.

### **Screening**

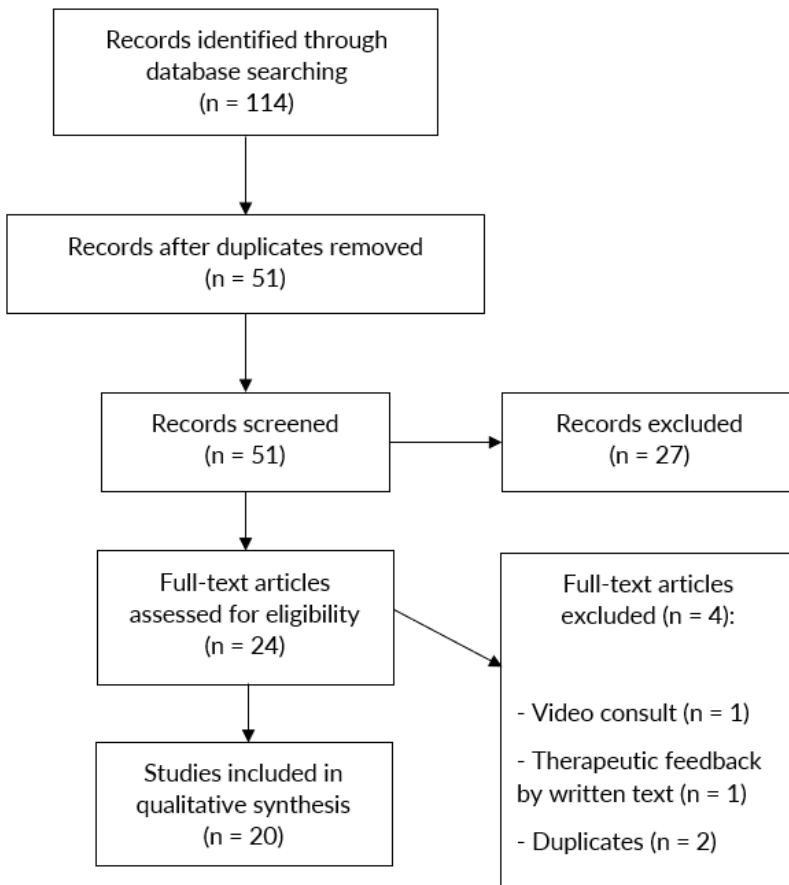
Two authors (DG and FM) screened all titles and abstracts using Covidence. Subsequently, they screened all full texts of the remaining articles. Discrepancies were discussed and resolved in follow-up meetings. While discussing discrepancies, it was decided that therapeutic feedback by written text only did not fit, which is why this type of intervention was also excluded. Furthermore, two additional duplicates were found while screening full texts. Figure 1 shows the flow-chart of the screening procedure.

### **Data extraction**

One of the authors (DG) extracted all data using IBM SPSS Statistics 23 for tabulating the descriptive data out of all included articles. A top-down strategy was used in order to determine which data had to be extracted, based on TAM and TTF models (Davis, 1989; Goodhue and Thompson, 1995). Based on TAM and TTF, it is important to examine both the content of ACT and the design of the online intervention. Additionally, it has to be assessed whether the papers communicate a rationale based on a design theory that is the basis of the development of the online intervention. Information that was extracted

out of the included articles related to: (1) study characteristics (i.e. study title, authors, year of publication, origin of the sample, chronic pain type), (2) design rationales (i.e. rationale that is based on design theory), (3) ACT content (ACT overview, number of modules, duration of modules), (4) design characteristics (i.e. internet delivery type, software, multimedia type, tailoring, guidance, intervention duration, intervention features), and (5) adherence. Adherence was extracted from papers when adherence to the *intervention* was reported, and not adherence to the *study*. Our goal was to report on adherence as “the extent to which individuals should experience the content to derive maximum benefit from the intervention, as defined or implied by its creators” (Sieverink et al., 2017).

**Figure 1.** PRISMA flow diagram



## Results

### Study characteristics

In total, 114 records were identified in the search (PubMed (36), PsycINFO (23), Cinahl (20), and Web of Science (35)), of which 20 were included in this review. Table 2 provides an overview of the relevant interventions and associated studies (Bell et al., 2020; Bendelin et al., 2020, 2018; Buhrman et al., 2013; Fledderus et al., 2015; Gentili et al., 2020; Hayes et al., 2014; Kioskli et al., 2020; Lin et al., 2018, 2017; Paganini et al., 2019; Probst et al., 2018; Scott et al., 2018; Simister et al., 2018; Slattery et al., 2019; Trompetter et al., 2016, 2015b, 2015a; Vilardaga et al., 2020; Yang et al., 2017). Articles were published between 2013 and 2020. Studies originated from Sweden ( $n=4$ ), the Netherlands ( $n=4$ ), Germany ( $n=4$ ), Canada ( $n=2$ ), Ireland ( $n=2$ ), United Kingdom ( $n=2$ ), Singapore ( $n=1$ ), and United States of America ( $n=1$ ). A total of eight studies focused on data of RCT's (Buhrman et al., 2013; Lin et al., 2018, 2017; Probst et al., 2018; Simister et al., 2018; Trompetter et al., 2016, 2015b, 2015a), 3 articles were protocols for (feasibility) RCT's (Bell et al., 2020; Hayes et al., 2014; Slattery et al., 2019), and two articles were development and feasibility studies (Gentili et al., 2020; Yang et al., 2017). Other studies related to development and pilot evaluation (Fledderus et al., 2015), feasibility RCT (Scott et al., 2018), health economic evaluation (Paganini et al., 2019), qualitative study (interviews) (Bendelin et al., 2020), qualitative feasibility study (Bendelin et al., 2018), design and theoretical basis (Vilardaga et al., 2020), and single-arm feasibility trial (Kioskli et al., 2020). Also in Table 2, it is shown that in total, eighteen articles studied general chronic pain (Bell et al., 2020; Bendelin et al., 2020, 2018; Buhrman et al., 2013; Fledderus et al., 2015; Gentili et al., 2020; Hayes et al., 2014; Lin et al., 2018, 2017; Paganini et al., 2019; Probst et al., 2018; Scott et al., 2018; Slattery et al., 2019; Trompetter et al., 2016, 2015b, 2015a; Vilardaga et al., 2020; Yang et al., 2017), one study focused on fibromyalgia (Simister et al., 2018), and one study assessed painful diabetic neuropathy (Kioskli et al., 2020). The twenty included articles described fourteen separate interventions, which are mentioned in Table 2.

### Design rationales

Out of the twenty included papers, only three papers included a description of their design rationale by means of a design theory. One paper mentioned the importance of a user-centered design, which is why their design process was based on the CeHRes

roadmap (Fledderus et al., 2015). This was operationalized by conducting a focus group and several interviews regarding user needs, prototypes, and pilot evaluations. Another paper explained that the development of interventions need an approach including both the academic theory-driven and efficacy approach, as well as the industry's fast development process (Gentili et al., 2020). Therefore, the mHealth Agile Development & Evaluation Lifecycle was followed in this study, which is a framework for mHealth development, evaluation, and implementation. This involved alpha and beta testing, including both patients and expert interviews regarding user needs and experiences. Furthermore, a third study emphasized the importance of a theoretical rationale when designing an online intervention (Vilardaga et al., 2020). Therefore, a formative user-centered design was used, including user interviews and prototype testing.

### **ACT content**

As shown in Table 2, the standard online ACT intervention is a stand-alone online course of 6-8 modules, based on ACT and the full underlying psychological flexibility model with its 6 therapeutic processes. Often, this is a 'fixed format' (i.e. continuing to the next one when a module is completed, or it is released in a fixed order through time) using regular mindfulness exercises and regular experimental exercises of the other ACT processes. This relates to metaphors (e.g. 'passengers on the bus') and exercises to achieve cognitive defusion (e.g. 'milk milk milk') (Bell et al., 2020; Bendelin et al., 2020; Buhrman et al., 2013; Fledderus et al., 2015; Hayes et al., 2014; Kioskli et al., 2020; Lin et al., 2018; Paganini et al., 2019; Probst et al., 2018; Scott et al., 2018; Simister et al., 2018; Slattery et al., 2019; Trompetter et al., 2016, 2015a, 2015b; Yang et al., 2017). The majority of interventions also offer psychoeducation about chronic pain (Bell et al., 2020; Bendelin et al., 2020, 2018; Buhrman et al., 2013; Fledderus et al., 2015; Hayes et al., 2014; Kioskli et al., 2019; Lin et al., 2018; Paganini et al., 2019; Probst et al., 2018; Simister et al., 2018; Slattery et al., 2019; Trompetter et al., 2016, 2015a, 2015b; Yang et al., 2017), but this does not always apply. For most interventions, a detailed table was provided, including an explanation of the content of the intervention for each module (Bell et al., 2020; Bendelin et al., 2018; Hayes et al., 2014; Kioskli et al., 2020; Lin et al., 2018; Scott et al., 2018; Simister et al., 2018; Slattery et al., 2019; Trompetter et al., 2015b; Vilardaga et al., 2020; Yang et al., 2017).

On average, online ACT interventions included 7.47 modules (min=4, max=10). Eleven studies provided information on the duration of modules (Fledderus et al., 2015; Kioskli et al., 2020; Lin et al., 2018, 2017; Paganini et al., 2019; Probst et al., 2018; Scott et al., 2018; Trompetter et al., 2016, 2015b; Vilardaga et al., 2020; Yang et al., 2017), which varied greatly. Four studies described that each module lasted 60 minutes (Lin et al., 2018, 2017; Paganini et al., 2019; Probst et al., 2018). Other studies described daily use ranging from 5 to 45 minutes (Fledderus et al., 2015; Kioskli et al., 2020; Scott et al., 2018; Trompetter et al., 2015a, 2015b; Vilardaga et al., 2020; Yang et al., 2017). While most interventions took seven (Bell et al., 2020; Bendelin et al., 2020; Buhrman et al., 2013; Probst et al., 2018) or eight weeks (Fledderus et al., 2015; Hayes et al., 2014; Lin et al., 2018, 2017; Paganini et al., 2019; Simister et al., 2018; Slattery et al., 2019), the duration of interventions ranged from 5 weeks to 6 months in the overall sample (Bell et al., 2020; Bendelin et al., 2020, 2018; Buhrman et al., 2013; Fledderus et al., 2015; Gentili et al., 2020; Hayes et al., 2014; Kioskli et al., 2020; Lin et al., 2018, 2017; Paganini et al., 2019; Probst et al., 2018; Scott et al., 2018; Simister et al., 2018; Slattery et al., 2019; Trompetter et al., 2016, 2015b, 2015a; Yang et al., 2017). These results were also shown in Table 2.

### Design characteristics

In ten studies, the online intervention was delivered via a website (Table 2) (Bendelin et al., 2020; Buhrman et al., 2013; Hayes et al., 2014; Kioskli et al., 2020; Lin et al., 2018; Simister et al., 2018; Slattery et al., 2019; Trompetter et al., 2015b; Vilardaga et al., 2020; Yang et al., 2017) and in 3 studies it was delivered via both website and mobile application (Bell et al., 2020; Fledderus et al., 2015; Gentili et al., 2020). The remaining studies did not mention anything about the way in which the intervention was delivered (Bendelin et al., 2018; Lin et al., 2017; Paganini et al., 2019; Probst et al., 2018; Scott et al., 2018; Trompetter et al., 2016, 2015a).

Six studies described that only text was used in the online intervention (Bendelin et al., 2018; Fledderus et al., 2015; Slattery et al., 2019; Trompetter et al., 2016, 2015a, 2015b). Four studies explained that the online intervention included text, audio, and video (Kioskli et al., 2020; Lin et al., 2018; Simister et al., 2018; Yang et al., 2017). In two studies text, images, audio, and video were used (Probst et al., 2018; Vilardaga et al., 2020) and in two

studies both text and audio were included (Bendelin et al., 2020; Buhrman et al., 2013). The remaining studies described online interventions that included both text and video (Scott et al., 2018), text, images, animation and audio (Hayes et al., 2014) and text, images, animation, audio and video (Gentili et al., 2020).

Data regarding features of online interventions were also extracted. One study explained that it was possible to chat with a therapist within the online intervention (Gentili et al., 2020); six studies described that it was possible to receive reminders via mobile phone (Buhrman et al., 2013; Fledderus et al., 2015; Gentili et al., 2020; Lin et al., 2017; Paganini et al., 2019; Scott et al., 2018), and five studies via email (Fledderus et al., 2015; Hayes et al., 2014; Probst et al., 2018; Simister et al., 2018; Slattery et al., 2019). Four studies provided information about the possibility to keep a diary in the online intervention (Bell et al., 2020; Fledderus et al., 2015; Trompetter et al., 2016, 2015b). An interactive interface as a feature of the online intervention, like quizzes, was mentioned in two studies (Lin et al., 2018; Vilardaga et al., 2020). One study described the possibility to share tips with other users within the online intervention (Fledderus et al., 2015). Information about software, tailoring, and time spent participating, was not described in the included studies.

All studies, excluding one (Vilardaga et al., 2020), described that the online intervention did include guidance by a therapist, which is shown in Table 2. In three studies, users of the online interventions had the option to choose the way in which they wanted to have contact with the therapist, either between email and mobile phone (Fledderus et al., 2015; Slattery et al., 2019) or between face-to-face and mobile phone (Scott et al., 2018). In most studies, guidance took place via mobile phone (Bell et al., 2020; Bendelin et al., 2020; Buhrman et al., 2013; Gentili et al., 2020; Hayes et al., 2014) or email (Lin et al., 2018, 2017; Trompetter et al., 2015b, 2015a; Yang et al., 2017). Other interfaces used for guidance were chat (Gentili et al., 2020), Internet (Bendelin et al., 2020), and Skype (Kioskli et al., 2020). In 5 studies, no information was provided about the medium that was used for guidance (Bendelin et al., 2018; Paganini et al., 2019; Probst et al., 2018; Simister et al., 2018; Trompetter et al., 2016). Guidance could include weekly contact (Bell et al., 2020; Bendelin et al., 2020; Hayes et al., 2014; Kioskli et al., 2020; Lin et al., 2017; Trompetter et al., 2016, 2015b, 2015a), pre- or mid-intervention contact (Buhrman et al.,

2013; Kioskli et al., 2020; Scott et al., 2018), contact in case of adherence problems only (Slattery et al., 2019), or in the first few weeks of the intervention only (Bendelin et al., 2018). Information regarding contact moments with therapist was unknown in 6 studies (Fledderus et al., 2015; Gentili et al., 2020; Lin et al., 2018; Probst et al., 2018; Simister et al., 2018; Yang et al., 2017). Guidance appears to have the main purpose of motivating users (Bell et al., 2020; Bendelin et al., 2018; Buhrman et al., 2013; Hayes et al., 2014; Kioskli et al., 2020; Lin et al., 2018; Paganini et al., 2019; Probst et al., 2018; Simister et al., 2018; Slattery et al., 2019; Trompetter et al., 2015b, 2015a; Yang et al., 2017) and answering user questions (Bell et al., 2020; Buhrman et al., 2013; Hayes et al., 2014; Simister et al., 2018; Trompetter et al., 2015b, 2015a; Yang et al., 2017).

Also noteworthy is that there are some blended programs that include an aftercare program after a multidisciplinary treatment for chronic pain (Bendelin et al., 2018; Fledderus et al., 2015). In addition, some programs are not completely based on theory of ACT and psychological flexibility, but also on other theory (Bendelin et al., 2018; Vilardaga et al., 2020). These courses, which deviate from the above 'blueprint' (i.e. aftercare or other theoretical models), focus mainly on the engagement process of ACT, and try to achieve long-term behavioral change by adopting value-oriented behavior.

### **Adherence**

As shown in Table 2, most studies ( $n=15$ ) did not include any measure of adherence to the intervention at all (Bell et al., 2020; Bendelin et al., 2020, 2018; Fledderus et al., 2015; Hayes et al., 2014; Kioskli et al., 2020; Lin et al., 2018; Paganini et al., 2019; Probst et al., 2018; Simister et al., 2018; Slattery et al., 2019; Trompetter et al., 2016, 2015a; Vilardaga et al., 2020; Yang et al., 2017). The five remaining studies operationalized adherence in various and sometimes multiple ways, which can be divided into adherence to the intervention (i.e. the percentage of people who adhered to the intended usage of the intervention) and completion of modules. Adherence was reported in four studies, and ranged from 39% to 90.3% (Buhrman et al., 2013; Gentili et al., 2020; Lin et al., 2017; Scott et al., 2018). Completion was reported in five studies, (Buhrman et al., 2013; Gentili et al., 2020; Lin et al., 2017; Scott et al., 2018; Trompetter et al., 2015a). This could include a percentage of completed modules ranging from 84 – 92% (Gentili et al., 2020; Trompetter et al., 2015a) or average number of completed modules varying from 4.2 to

6.9 modules (Buhrman et al., 2013; Lin et al., 2017; Scott et al., 2018). Additionally, one study examined differences in number of modules completed between guidance and non-guidance, which showed that guided online interventions resulted in significantly more completed modules (Lin et al., 2018, 2017). In conclusion, adherence ranged from 39-90.3% in all studies, regardless of operationalization.

## Discussion

This study systematically reviewed all available literature regarding online ACT interventions for chronic pain, and evaluated ACT content, design characteristics, design rationales, and adherence. Most of the articles performed RCT's or studied development of online interventions and/or feasibility trials. A rationale behind the choices regarding the ACT content and design of the online intervention based on design theory was present in only a minority of papers. The majority of interventions were extensively described regarding ACT components using a table. Interventions were extensively described in terms of delivery, the use of multimedia types, as well as other features. Even though adherence is a crucial and problematic aspect in online interventions, it was not reported upon in the large majority of papers. In addition, online ACT interventions have been found to be effective for improving pain interference, acceptance, and fibromyalgia impact as chosen primary outcomes throughout RCTs.

As mentioned earlier, choices in online intervention development are determined by the extent to which these choices aid to optimize task-technology-user fit. There is no uniform answer to the question which choices regarding the design are most appropriate in developing online ACT interventions for chronic pain. In every new development situation, relevant context factors regarding the task (i.e., content), technology, and user must be considered. All factors should be balanced, so that use, acceptance, and adherence are positively influenced. These factors should be the basis during development and should subsequently be checked and improved during usability testing. Rather, it seems important that well-considered choices are made that are appropriate to the relevant TAM and TTF. Remarkably, only three papers used a design rationale for the intervention development (Fledderus et al., 2015; Gentili et al., 2020; Vilardaga et al., 2020). Some studies did explain consideration behind the design, such as Hayes et al. (2014). However, it is recommended to adopt an actual rationale by means of a design

theory, in order to follow a fixed pattern of steps throughout the design process. Interestingly, only one study that adopted a design rationale additionally discussed considerations regarding ACT content (Vilardaga et al., 2020), since a combination like this is most desirable given the TAM and TTF. However, it can be concluded that design and feasibility studies are increasingly published, whereas previously RCT's were published directly, which shows an expansion in attention for the design process.

It is important in online interventions that the content (i.e. three response styles of ACT) is applied in line with the psychological flexibility model that underlies ACT, for example with the use of appropriate exercises and metaphors. It is most common for online ACT interventions to have 7 or 8 modules, and this number seems appropriate to allow the patient to go through all aspects of ACT. Interventions are mostly provided in a fixed-format using the underlying psychological flexibility model, including its therapeutic processes. Additionally, psychoeducation about pain is often provided. In most studies, a detailed overview of intervention content for each module was provided, which is indeed recommended since it informs readers about the content of the intervention and it facilitates replication.

The majority of online ACT interventions uses a combination of text, audio, video, animation and/or images to present information and exercises. Aspects of feedback speed, capacity of sending multiple cues simultaneously, natural language, and personal focus when developing has to be taken into account when deciding which multimedia will be used (Daft and Lengel, 1983). Next to that, in future online ACT interventions for chronic pain, guidance should be included since this positively affects outcomes in the online ACT interventions included in this review (Buhrman et al., 2013; Lin et al., 2018, 2017) as well as other online therapeutic interventions in the psychological domain (Bennett et al., 2019; Heber et al., 2017; Johansson and Andersson, 2012; Richards and Richardson, 2012; Spek et al., 2007; Spijkerman et al., 2016). Different methods can be chosen for delivering guidance (e.g. face-to-face, email, video call, mobile phone), depending on the TAM and TTF in question, which has been applied in the papers included in this review.

Adherence is a crucial aspect in online interventions (Donkin et al., 2011), and was early in the eHealth era recognized as one of the most difficult points in evaluating online interventions (Eysenbach, 2002). Since adherence affects physical and psychological outcomes (Donkin et al., 2011), it should be addressed in research examining online intervention effects. Nevertheless, this review has shown that adherence was scarcely examined in studies, since only five studies examined adherence. However, it is advisable to include adherence in studies because of its crucial link with effectiveness (Han, 2011). It should be measured in an objective and standardized manner (Kelders et al., 2012). Specifically, adherence should be measured on the basis of the intended usage of the intervention. The aim or the working mechanisms of the eHealth intervention must be leading when defining intended usage (Sieverink et al., 2017). This can be standardized, from which adherence percentages can be derived. As an example, actual usage statistics could be used to operationalize intervention adherence when comparing it with the technology's intended usage (e.g. number of logins, completion of module, completion of modules, duration of modules, total duration) (Kelders et al., 2012; Sieverink et al., 2017; Van Den Berg et al., 2013). Subsequently, the percentage of people who adhered to the intervention can be calculated, which shows the overall adherence of the intervention.

Online ACT interventions have been shown to be effective for important primary outcomes in managing chronic pain in 8 articles describing five RCT's. This especially applies to online interventions with guidance and patients with high levels of psychological flexibility at baseline. A positive outcome is that the majority of these RCT's included pain interference as the primary outcome (5 out of 8). This is in line with a recommendation of Veehof et al. (2016), in response to a lack of inclusion of this outcome measure in previous RCT's on online ACT and mindfulness-based interventions for chronic pain.

Several potentially relevant intervention features that could be deliberated in future design of online ACT for chronic pain were not included or considered in the interventions described in the articles included in this review. First of all, an important aspect of online interventions is tailoring the technology. Tailoring is referred to as materials that: "are intended to reach one specific person, are based on characteristics that are unique to that person, are related to the outcome of interest, and have been derived from an individual

assessment" (Wangberg et al., 2008, p. 276). This ties in nicely with TAM and TTF (Davis, 1989; Laugesen, 2013) and has also been shown to stimulate adherence (Kelders et al., 2012; Kerns et al., 2014). Only therapeutic guidance was often described as tailored to the user, by means of tailored feedback. Other examples of tailoring that could be considered include tailoring algorithms based on, for example, demographics by tailoring aspects such as images (e.g. show young female patients pictures of similar young female patients) and language (e.g. language level based on educational level) (Horvath and Bauermeister, 2017). Other examples relate to time investment (e.g., 2 or 4 hours per week) and the extent to which the patient wants to improve his or her situation.

Another feature of online interventions which could be relevant for factors of TAM and TTF is social support (Stinson et al., 2014), which is defined as relationships that meet individuals' needs in daily life (Barker, 2003). It is based on the social learning theory (Bandura and Walters, 1977; Rotter, 1954) and serves patients' empowerment to self-manage their chronic pain and to improve their life (Polomano et al., 2007). Although this may influence effectiveness (Eccleston et al., 2009; Palermo et al., 2010), studies included in this review did not apply any aspect of social support (e.g. monitored discussion board (Stinson et al., 2014)). However, since incorporating social support features in online interventions may bring difficulties regarding privacy and appropriateness of peer feedback (Stinson et al., 2014), and it may thus deteriorate factors of TAM and TTF, it should be carefully considered whether the benefits outweigh the disadvantages.

Finally, no article elaborated on software features, while this could provide useful insights into the possibilities of online ACT interventions. A common and recommended way of delivering eHealth platforms is through the responsive design (Schmidt et al., 2020), in which a cross-platform is created that allows using the intervention on different media devices (e.g. smartphone, laptop, and tablet). This enlarges the TTF, since it is then accessible everywhere, every time, on every platform (Héroux et al., 2017; Schmidt et al., 2020).

Most online ACT interventions have been designed for chronic pain in general. However, neuropathic pain (e.g., chemotherapy-induced peripheral neuropathy) and nociceptive pain (e.g., low back pain) bring different sensations and, therefore, different daily

limitations. This may result in disparate pain related thoughts, beliefs, and (dis)functional coping styles (Daniel et al., 2008; Nicholson, 2006). Neuropathic pain can be 'sharp', for which short-term distraction may be an appropriate strategy, while nociceptive pain is more likely to cause avoidance (Daniel et al., 2008). This should be addressed separately in online ACT interventions, which is why future studies should focus on specific types of chronic pain. In this way, the 'user' aspect of TAM and TTF is appropriately considered.

The main strength of this review is the inclusion of several study designs used in studies into online ACT interventions for chronic pain. In this way, aspects other than effectiveness could be described extensively to inform the future development of online ACT interventions. Unfortunately, it was not possible to use a quality assessment instrument in this review to rate all included studies, since there are no such instruments available that are appropriate to the current study. Next to that, another limitation relates to the inclusion of 20 papers describing only 14 studies. We chose to include all papers since this enabled us to address the research question and models of TAM and TTF appropriately. It may have been concluded that details were missing in some papers, while details may have been mentioned in the original papers. On the other hand, articles should be comprehensible on their own. Therefore, choices (e.g., multimedia, guidance, time investment) should always be explained in a paper, either concisely or comprehensively. Another limitation relates to including studies from a relatively large time span. Technology development and design have changed a lot from 2013 to 2020, which could have an impact on our results. Furthermore, it was only possible to describe whether the type of content was appropriate (e.g., number of lessons and ACT components), as the actual interventions were not publicly available, and we could therefore only use the information regarding the characteristics of the interventions as per how they were described in the papers.

In conclusion, online ACT interventions have been shown to be effective and are overall constructed in line with ACT theory. However, studies provide an insufficient amount of information on choices regarding TAM and TTF and why certain design choices are made. Formulating a rationale about how ACT content is structured and how the match between task, technology and user is expected to be achieved may contribute. Considering and, possibly, applying online intervention features may take online interventions to the next

level, potentially increasing the effectiveness of online ACT interventions for chronic pain patients. It is recommended to uniformly examine and report adherence in studies into online ACT interventions, since this crucial aspect may contribute to achieving optimal effectiveness.

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**Table 2.** Online ACT intervention characteristics and related studies

Title	Chronic pain type	Intervention delivery / multimedia types	Duration / number of modules	Guidance / blended	ACT processes			Study: author(s) and year of publication	Study design	Adherence
					Openness	Awareness	Engagement			
<b>ACT4PAIN</b>	Painful diabetic neuropathy	Website / text, audio, video	12-35 minutes per module / 5 weeks / 8 modules	Guidance	✓	✓	✓	Kioskli et al. (2020)	Single-arm feasibility trial	
<b>ACTonPain</b>	General chronic pain	Website / text, audio, video	60 minutes per module / 7-8 weeks / 7 modules	Guidance	✓	✓	✓	Lin et al. (2017)	RCT	Adherence (based on drop-out rate): guided: 60%, and unguided: 39%. Modules completed: M = 5.94, SD = 2.80 (guided), M = 4.74, SD = 2.89 (unguided)
<b>ACTsmart</b>	General chronic pain	Website, mobile application / text, image, animation, audio, video		Guidance	✓	✓	✓	Lin et al. (2018) Paganini et al. (2019) Gentili et al. (2020)	RCT Health economic evaluation Development and feasibility study	Adherence (during pilot, based on criteria below): 90.3% Average completion of treatment content: 84%. Average of formulated values and reported behavior change: 84%
<b>Get more out of your life</b>	General chronic pain	Website, mobile application / text	5-10 minutes per module (recommended) / 8 weeks / 8 modules	Guidance / blended (aftercare program)			✓	Fledderus et al. (2015)	Development and pilot evaluation	
<b>iACT-CEL</b>	General chronic pain	Website / text, audio, video	45 minutes minimum / 5 weeks / 5 modules	Guidance / (face-to-face sessions at pre and post intervention)	✓	✓	✓	Yang et al. (2017)	Development and feasibility trial	
<b>Living with Pain</b>	General chronic pain	Website / text Text Text	3h per week or 30min per day / 9-12 weeks / 9 modules	Guidance	✓	✓	✓	Trompetter, Bohlmeijer, Fox, et al. (2015)	RCT	
<b>The Pain Tracker Self Manager</b>	General chronic pain	Website / text, image, audio, video	30-40 minutes / 6 months / 4 modules	Blended	✓	✓	✓	Trompetter et al. (2016)	RCT	
								Trompetter, Bohlmeijer, Veehof, et al. (2015)	RCT	Completion of at least 6-9 sessions: 72% completed 6-9 sessions. Of which completion of all sessions: 92%
								Vilardaga et al. (2020)	Design and theoretical basis	

**Table 2.** Online ACT intervention characteristics and related studies (continued)

Title	Chronic pain type	Intervention delivery / multimedia types	Duration / number of modules	Guidance / blended	ACT processes			Study: author(s) and year of publication	Study design	Adherence
					Openness	Awareness	Engagement			
<i>Unknown</i>	General chronic pain	Website / text, image, audio, video	7 weeks / 7 modules	Guidance	✓	✓	✓	Bell et al. (2020)	Protocol for randomized controlled feasibility trial RCT	Completion of all sessions: 39.5%.  Mean completed modules: 4.2 (SD ¼ 2.7).
<i>Unknown</i>	General chronic pain	Website, mobile application / text, audio	7 weeks / 7 modules	Guidance	✓	✓	✓	Buhrman et al. (2013)		
<i>Unknown</i>	General chronic pain	Text	20 weeks / 8 modules	Guidance / blended (aftercare program after multidisciplinary rehabilitation)	✓	✓	✓	Bendelin et al. (2018) Bendelin et al. (2020)	Qualitative feasibility study Qualitative study (interviews)	
<i>Unknown</i>	General chronic pain	Website / text, image, animation, audio	8 weeks / 8 modules	Guidance	✓	✓	✓	S. Hayes et al. (2014)	Protocol for RCT	
<i>Unknown</i>	General chronic pain	Text, video	8-12 minutes per module / 10-12 weeks / 10 modules	Guidance	✓	✓	✓	Scott et al. (2018)	Feasibility RCT	Completion of all sessions: 41.9%. Mean completed modules: 6.90 sessions (SD = 3.49).
<i>Unknown</i>	Fibromyalgia	Website / text, audio, video	8 weeks / 7 modules	Guidance	✓	✓	✓	Simister et al. (2018)	RCT	
<i>Unknown</i>	General chronic pain	Website / text	8 weeks / 8 modules	Guidance	✓	✓	✓	Slattery et al. (2019)	Protocol for RCT	



# Chapter 6

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# Patient-centered development of Embrace Pain: an online Acceptance and Commitment Therapy intervention for cancer survivors with chronic painful chemotherapy-induced peripheral neuropathy

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## Abstract

**Background:** Around 30% of cancer survivors suffer from chemotherapy-induced peripheral neuropathy (CIPN)  $\geq 6$  months after completion of chemotherapy, which comes with limitations in daily functioning and worsened quality of life. Treatment options are scarce. Our aim was to develop an online self-help intervention based on Acceptance and Commitment Therapy (ACT) to reduce pain interference in cancer survivors experiencing painful chronic CIPN.

**Methods:** This paper applied a patient-centered design process using the CeHRes roadmap. User needs were examined using online semi-structured interviews with patients and experts (N=23). Interviews were transcribed verbatim and analyzed using Thematic Analysis. Personas were created based on interviews. Intervention content was based on identified user needs and ACT. Content and design were finalized using low-fidelity prototype testing (N=5), and high-fidelity prototype testing (N=7).

**Results:** Patients appreciated and agreed with the elements of ACT, had varying guidance needs, and wanted to have autonomy (e.g., moment and duration of use). Additionally, it was important to be aware that patients have had a life-threatening disease which directly relates to the symptoms they experience. Patients reported to prefer a user-friendly and accessible intervention. Similar points also emerged in the expert interviews. The final intervention, named *Embrace Pain*, includes 6 sessions. Session content is based on psychoeducation and all ACT processes. Further interpretation of the intervention (such as quotes, guidance and multimedia choices) is based on the interviews.

**Conclusion:** This development demonstrated how a patient-centered design process from a theoretical framework can be applied. Theory-driven content was used as the basis of the intervention. Findings show an online ACT intervention designed for cancer survivors with painful chronic CIPN.

## Introduction

The incidence of cancer unfortunately is still rising, yet treatment options continue to be improved. As such, the long-term consequences of cancer and its treatment become increasingly relevant (Elferink et al., 2010; Heins et al., 2012; Hulvat, 2020; Signaleringscommissie Kanker van KWF Kankerbestrijding, 2011; Sukel et al., 2008; Van Steenberghe et al., 2012). A great amount of cancer patients suffer from chemotherapy-induced peripheral neuropathy (CIPN), which is a long-term consequence (Seretny et al., 2014). Certain chemotherapeutic agents (e.g., taxanes, platinum compounds, vinca alkaloids) can cause CIPN, which includes symptoms such as tingling, numbness, cramps, and aching or burning pain in hands, feet, arms, and legs and feet (T. Beijers et al., 2012; Farquhar-Smith, 2011; Quasthoff & Hartung, 2002; Wen, 2007). One month after chemotherapy CIPN is present in up to 80% of survivors, which decreases to around 30% after 6 months or longer (Bao et al., 2016; Bonhof et al., 2018; Eckhoff et al., 2015; Glendenning et al., 2010; Mols et al., 2014; Seretny et al., 2014; Winters-Stone et al., 2016). CIPN results in decreased quality of life (QoL), specifically in patients with *painful* CIPN (Bonhof et al., 2020). Due to the increasing application of chemotherapy, CIPN is expected to become one of the most prevalent side-effects (A. J. M. M. Beijers et al., 2014). However to date there is only a limited number of treatment options for CIPN (Mezzanotte et al., 2022).

Cognitive Behavioral interventions, like Acceptance and Commitment Therapy (ACT), have been shown to improve cancer patients' QoL (Feros et al., 2013; Hulbert-Williams et al., 2015). ACT helps patients towards acceptance and teaches patients how to perform personally valuable activities (Hayes et al., 2006). It has been shown to be effective in chronic pain patients (McCracken & Vowles, 2014). Interventions are increasingly offered online, bringing benefits regarding costs, accessibility, availability, travelling, stigma, and psychological burden, compared to *face-to-face* interventions (Borosund et al., 2018; Knoerl et al., 2018). Besides, online interventions broaden the scope and diversity of possibilities for different types of interventions for patients, especially for patients who feel more comfortable in an online environment (Barak et al., 2009). A study by Knoerl et al. (Knoerl et al., 2018) has shown that an online CBT intervention positively influenced pain intensity in patients with chronic painful CIPN, suggesting that an online ACT treatment might also be beneficial to CIPN patients. However, since the nature of ACT

(i.e., improving psychological flexibility) appears to better fit the mechanisms of chronic pain compared to CGT, and the intervention by Knoerl et al. (Knoerl et al., 2018) was not developed for and with CIPN patients specifically, further research is needed. To the best of our knowledge, development of online ACT interventions for patients with chronic painful CIPN has not yet been undertaken.

When developing online (asynchronous) interventions, several considerations need to be taken into account regarding the main components of the online intervention: program content, multimedia use/choices, interactive online activities, and feedback support provision (Barak et al., 2009). These components need to be chosen in a way that they fit the task and serve the end user. To make sure that the technology comes with high usability and utility, a patient-centered design process, a form of user centered design whereby patients are involved in the choices made in the development process, is advised (Demiris et al., 2008). In this process, it is crucial to focus on matching the user, task, and technology of the intervention, in which the Technology Acceptance Model (TAM) (F. D. Davis, 1989; Marangunić & Granić, 2015) and Task-Technology Fit model (TTF) (Lee et al., 2003) could serve as appropriate theoretical frameworks. More specifically, TAM shows that use is determined by perceived usefulness and perceived ease of use (F. D. Davis, 1989). The TTF model serves as an appropriate complement, showing that the relationship of task, user and technology determine the task-technology fit, which ultimately determines usage (Lee et al., 2003). Both theories show the importance of involving the user in development to align task and technology with them.

The aim of this study is therefore to develop an online asynchronous ACT intervention to improve pain interference in cancer survivors with painful chronic CIPN using a patient-centered design process. In addition, this study specifically focusses on matching the user, task, and technology of the intervention, based on TAM (F. D. Davis, 1989; Marangunić & Granić, 2015) and TTF (Lee et al., 2003). We expect the patient-centered design process to allow for the best possible patients' needs assessment, which will result in optimal development of the online asynchronous ACT.

## Methods

### Overview

In this study, the Centre for eHealth Research (CeHRes) roadmap, which is a framework for how to develop technology that fits the user and context, has been used to apply a patient-centered design process (Gemert-Pijnen et al., 2011). As this practical roadmap aligns well with the theoretical reasoning of TTF and TAM, it was considered an appropriate method for this study, guiding the steps to be taken when developing an eHealth solution. Steps to be taken are described in the following paragraphs. This study was approved by the Ethical Review Board of Tilburg University (School of Social and Behavioral Sciences; #RP284).

### User needs exploration

Semi-structured interviews with patients were conducted to assess online intervention needs. Inclusion criteria were: (1) 18 years or older, (2) having CIPN for at least 3 months, (3) experiencing self-reported interference of CIPN with daily life activities, (4) curative disease phase, and (5) score of 3 or higher on an 11-point Numeric Rating Scale (NRS) to assess pain severity. Patients were recruited by distribution of digital recruitment flyers via patient organizations and *Kanker.nl* (i.e., Dutch unified web platform delivering tailored medical information and peer-support for cancer patients and relatives (Frost et al., 2012)). Patients did not receive financial remuneration incentives for participating. Interviews took place via video calling due to COVID-19. The interview scheme was divided into different topics, including perceptions of and experience with online interventions, attitude towards ACT elements, user needs (i.e., amount of time, design, content, requirements), need for guidance, and importance of comorbidities.

Additionally, semi-structured interviews were conducted with experts from several relevant fields (i.e., oncology, oncology nursing, psychology, and eHealth). This included assessment of experts' perceptions of patients' online intervention needs. Experts were recruited based on their relatedness to the topic. People were considered experts in this context if they had been working in oncology, oncology nursing, psychology, or eHealth for several years. Experts did not receive financial incentives for participating. Interviews took place via video calling due to COVID-19. Several topics were included in the interview scheme, including user needs (i.e., amount of time, content, requirements), need

for guidance, and importance of comorbidities. Interviews with psychologists also included questions about patients' willingness to engage in ACT as well. Interviews with eHealth experts were complemented with adherence and engagement questions.

Interviews were transcribed verbatim and analyzed using Thematic Analysis (Braun & Clarke, 2006). Analyses have been performed in Atlas.ti. Interviews were coded, after which themes were created. Also, condensed meaningful units were created for each quote of all code, which reflected the main point of a participant's quote.

Insights from the exploratory interviews were used to create personas. Persona development includes representations of the patient user group, including demographics, behavior, preferences, thoughts, feelings of a fictitious person to enhance an optimal fit between task, technology and user to improve use (LeRouge et al., 2013; van Velsen et al., 2012). Personas were developed for IT developers and psychologist involved in the development, to inform them about the user group.

## **Development**

### ***Intervention content development and low-fidelity prototype testing***

Structure and content of the intervention sessions were created by 2 psychologists specialized in ACT (HT and ABS) and final content edited by a communication and information scientist (DG).

Low-fidelity prototype testing (i.e., iterative evaluation) was applied to evaluate the content of the intervention. Evaluation interviews with patients and experts took place via video calling due to COVID-19. The interview structure was created based on items of the Website User Satisfaction Questionnaire (WUSQ) (Muylle et al., 2004), of which the information (e.g., 'The information in the web site is easy to understand') and language customizations (e.g., 'The information is provided in a desired language') subscales were incorporated. Patients were given a plain text version of one of the sessions to review. After this, they were asked their opinion about the session. This resulted in content adjustments on the particular session and on the other sessions for which the feedback was also relevant.

### Software development and high-fidelity prototype testing

Subsequently, high-fidelity prototype testing (i.e., formative evaluation) was applied to evaluate the online environment of the intervention. Evaluation interviews with patients and experts also took place via video calling due to COVID-19 using the entire WUSQ. Participants were provided with access to the online intervention and were asked to work through one of the sessions before providing feedback. Adjustments in the online intervention were then made based on participants' suggestions.

## Results

### User needs exploration

#### Interviews (patients)

Patients with chronic painful CIPN (N=12) participated in individual interviews (Figure 1). Comprehensive patient characteristics are presented in Table 2. Participants included Caucasian patients only. Interviews lasted between 60 to 90 minutes. Patients had varying ages, cancer diagnoses and time since CIPN onset. In total, 45 codes and 10 themes were defined in the patient interviews; psychosocial aspects, overall intervention need, exercises, content, intervention development, usability, guidance, peer support, comorbidities, and implementation.

**Figure 1.** Patient-centered development process and interview participants

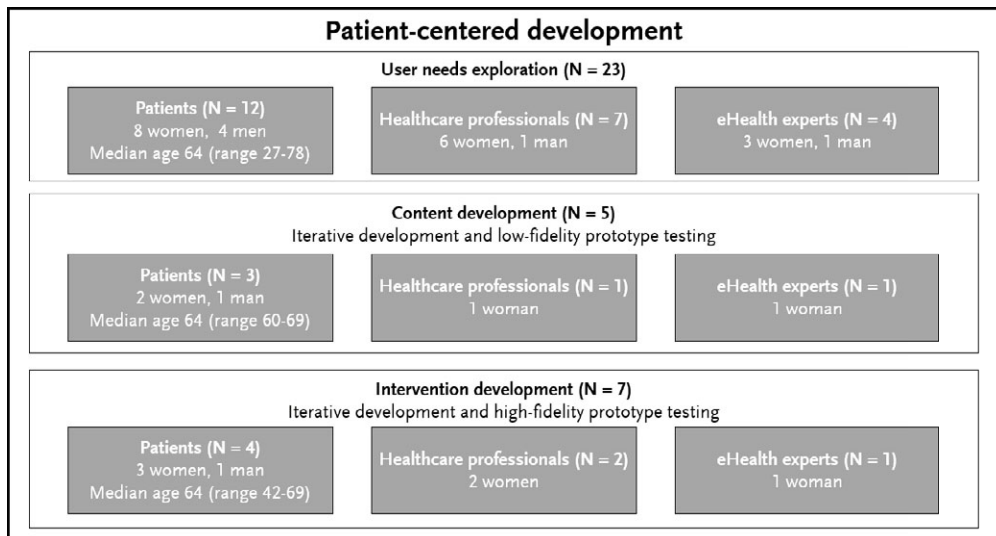


Table 1 shows the main results of the interviews, including patients' needs and quotes. Patients supported the development of an online ACT intervention for CIPN, ranging from "strong need" to "no need" and appreciated the elements of ACT. Attitudes towards ACT's mindfulness component varied from no interest to high interest. Communication with social environment and psychoeducation were topics that were also strongly encouraged, while opinions about peer support differed, varying from highly interested to not interested. Patients demanded having autonomy in usage (e.g., moment and duration of use). There were many differences in need for guidance or the intensity thereof. Patients reported appreciating doing exercises, and indicated that exercises should be short. Patients preferred a user-friendly and accessible intervention. This specifically applied to this patient group as many experience a 'chemo brain' which comes with self-perceived difficulties regarding thinking and memory due to chemotherapy (Hermelink, 2015). Preferences regarding type of device to use for the online intervention differed. Patients agreed that recognizing that patients have had a life-threatening illness is important. Finally, patients described it was important that the intervention is eventually implemented at hospitals or external parties (e.g., patient websites), given findability and reliability.

### ***Interviews (experts)***

Experts (N=11) included oncologists (N=2), oncology nurses (N=2), psychologists (N=3), and eHealth experts (N=4) (Figure 1). Interviews varied from 15 to 45 minutes in 36 codes and 10 themes; psychosocial aspects, overall intervention need, exercises, content, intervention development, usability, guidance, peer support, comorbidities, and implementation.

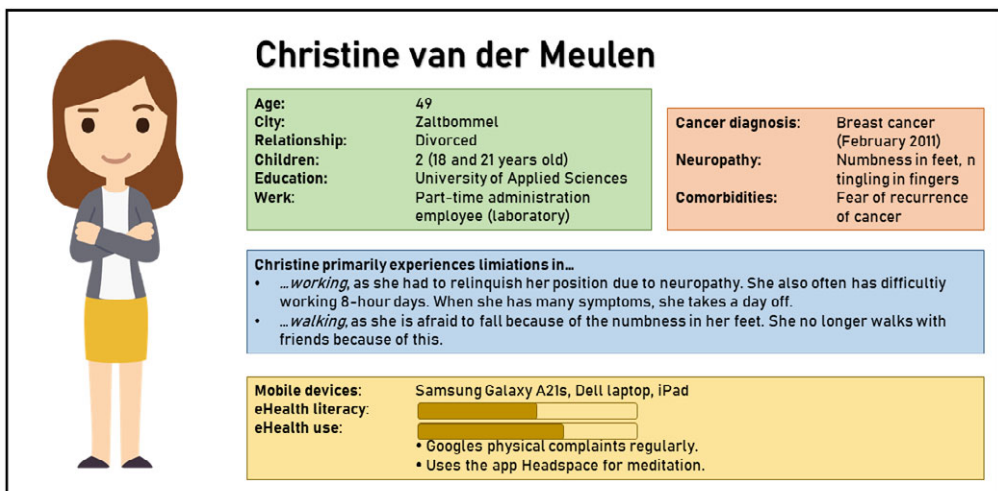
Table 1 shows the main results of the interviews, including experts' perceptions of patients' needs and experts' quotes. Experts described being pleased with the development of the intervention, stating that it can provide a helpful resource for patients. They also acknowledged the importance of acceptance of pain and limitations. Furthermore, mindfulness was indicated as important. Experts pointed to a potential stigma on mindfulness and highlighted a need for explanation about application of mindfulness. Repetitive exercises were perceived as crucial for practice and attaining knowledge. Furthermore, psychoeducation, communication to social environment, and

paying attention to the patient's voice were indicated as important topics by multiple experts. Furthermore, experts acknowledged the importance of patients' autonomy. Experts indicated the importance of explaining that the intervention is also applicable for other comorbidities besides neuropathy. Guidance from a therapist was indicated as highly important, but it was also acknowledged that needs would vary between patients. Peer support was suggested by some experts as relevant. Experts mentioned the importance of user-friendliness and accessibility as health literacy and digital literacy may vary between patients. In terms of multimedia, experts indicated that variety is important, noting that texts, videos, and audio files should be short and easy to understand. It was also acknowledged that adherence is a major pitfall in online interventions, and that meeting patients' needs is crucial to prevent non-adherence. Finally, experts emphasized the importance of implementation at hospitals or external parties (e.g., patient websites).

### Personas

Based on the patient interviews, three personas were developed. These personas represent different target groups within users. They included Caucasian patients from different user groups: gender (1 male, 2 female), age (one AYA (i.e., adolescent and young adult), one middle-aged, and one elderly), social status (1 student, 1 parttime employee, 1 pensioner), and daily limitations (1 study-related, 1 work-related, 1 daily task related). One example of a persona is shown in Figure 2.

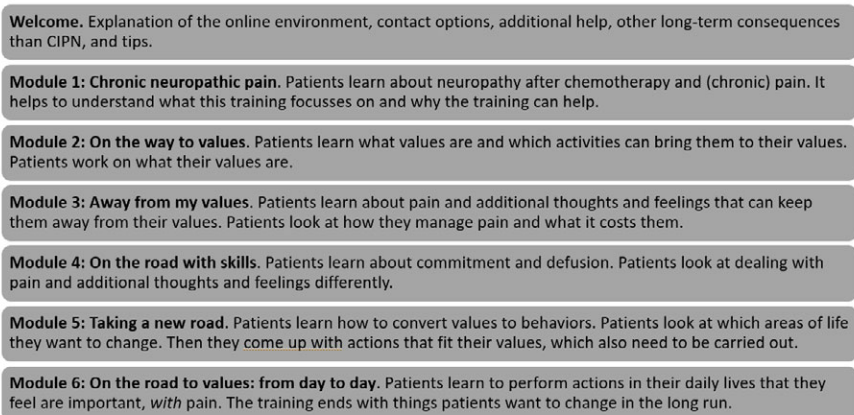
Figure 2. Example of persona



### Intervention content development and low-fidelity prototype testing

The online intervention was called *Embrace Pain* (in Dutch: *Omarm Pijn*) and includes an 8-week asynchronous intervention with 6 sessions. Sessions contain sub-session with experiential information, exercises, metaphors, mindfulness audio files, and quotes. A complete overview of all exercises can be found in Van de Graaf et al. (2022). Quotes and personas to supplement the session information and exercises were incorporated in an attempt to humanize the intervention (Lankton et al., 2015; Parker et al., 1978). An overview of all session is shown in Figure 3.

**Figure 3.** Overview of *Embrace Pain* sessions and content



In total, 3 patients and 2 experts evaluated session 2 in the content development phase (Figure 1), which resulted in adjustments to the content of all sessions. These adjustments included: 1) shortening texts to improve readability, leaving only essential information and no jargon; 2) rewriting some texts to better explain ACT processes; 3) removing several text sections that may have elicited negative emotions in patients; 4) removing references to other sessions to avoid confusing patients; and 5) rendering some exercises optional.

### Software development and high-fidelity prototype testing

The online intervention was built within an existing eHealth platform, named Karify. Privacy and security issues are covered by this organization. Karify is ISO 27001 and NEN 7510 certified. For programming the online environment, a standard format was used in which adjustments were made based on the needs of patients conducted from the exploratory interviews. The platform is available on smartphones, tablets, and computers.

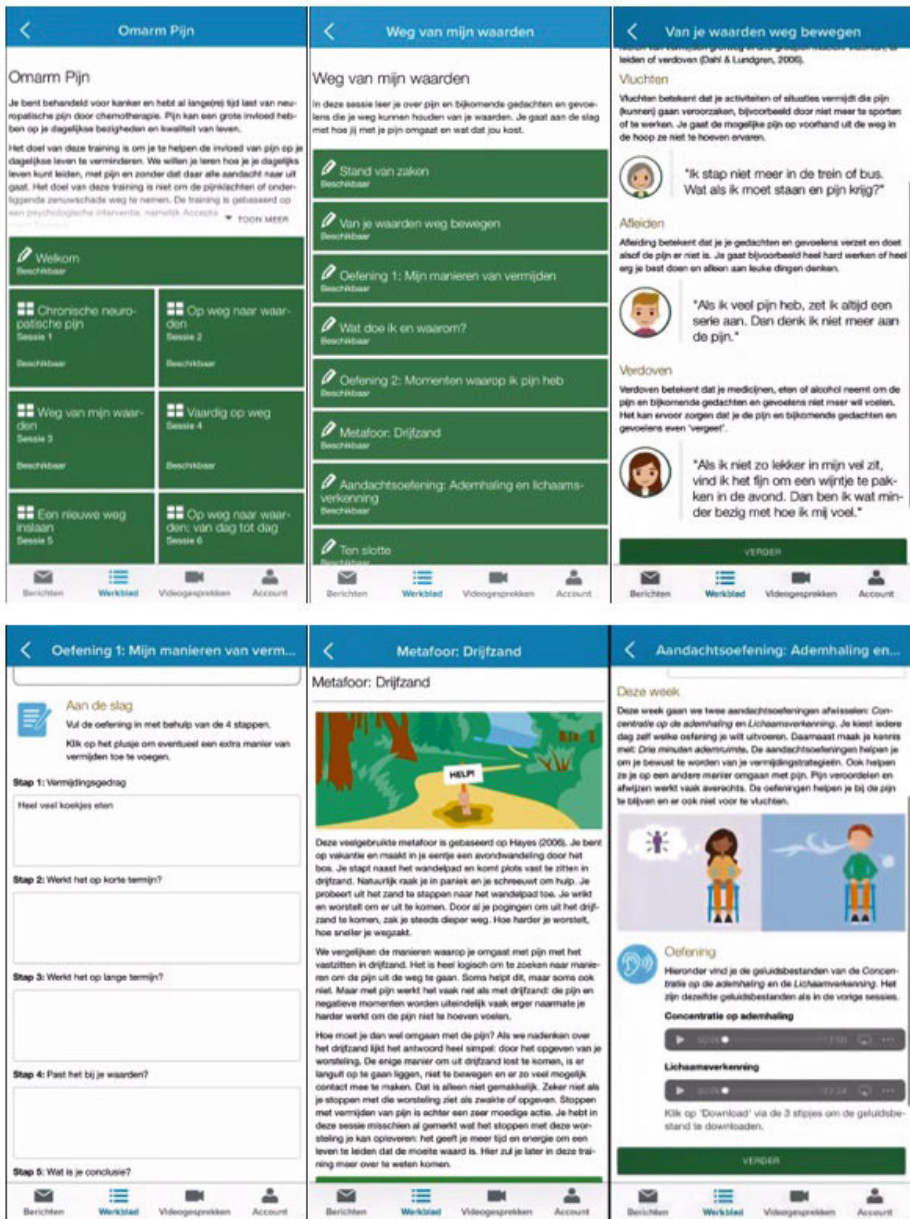
Participants receive an invitation to access the platform via an e-mail link to create an account.

Evaluations by 3 patients and 3 experts were performed within the online environment. Changes mostly involved textual corrections. In addition, some nuances were made to prevent misinterpretation (e.g., “dangerous” and “alarming” were removed). Furthermore, some exercises were removed or merged to decrease the number of exercises, leading to some adjustment of the order of sub-sessions. Additional quotes were added after positive evaluations.

Exploratory interviews showed that mindfulness should receive particular attention, as it comes with social stigmas, which has also been shown in earlier research (Harrison et al., 2017). To lower the barrier and promote practice, nuances have been made in the delivery of mindfulness. Mindfulness exercises are called ‘focus exercises’ which might prevent scaring off people, with an explanatory text that the exercise concerns mindfulness. How mindfulness should be practiced (e.g., it is about practicing and not about the result) and how it relates to chronic pain was also clarified.

Finally, all sessions were reviewed by 2 researchers for final textual corrections. Figure 4 shows an overview of the final version of the online intervention in Dutch. Translations of the screenshots are provided in Appendix A. All parts of the intervention are mandatory, with a new session opening when the previous session has been completed. Patients are expected to spend 2 hours per week to complete the intervention.

Figure 4. Embrace Pain application screenshots (Omarm Pijn; Dutch text)



To ensure that patients did not experience any problems using the intervention, clear instructions regarding usage were presented in the 'Welcome' session. Furthermore, a support page was available. Additionally, the online intervention enabled asynchronous guidance through a chat feature for content-related questions and motivation.

## Discussion

### Principal findings

This study described the development of an online ACT intervention for cancer survivors with painful chronic CIPN using a patient-centered design process following the CeHRes roadmap (Gemert-Pijnen et al., 2011). This roadmap was considered to be an appropriate method to properly reflect the reasoning of TAM (F. D. Davis, 1989; Marangunić & Granić, 2015) and TTF (Lee et al., 2003) in the development. Interviews with both patients and experts were conducted to determine intervention needs. Overall, patients mainly indicated a need for a user-friendly and accessible intervention with a high level of autonomy. Furthermore, they valued and agreed with the elements of ACT. The interviews also showed the importance of realizing that patients have had a life-threatening illness and that is directly relates to the symptoms patients experience. These results also emerged in the expert interviews. Content was created based on patient needs and ACT-theory. During the development, adaptations have been made based on both low-fidelity and high-fidelity prototype testing. Feedback and findings resulted in an 8-week online intervention named *Embrace Pain*, which includes 6 sessions consisting of texts, illustrations, quotes, and audio clips. Besides all processes of ACT, psychoeducation was included.

Regarding patients' needs regarding the online intervention, the interviews showed some interesting results. Needs regarding guidance for the online intervention varied widely. For example, some patients reported having no need for guidance, while others indicated to want extensive contact via video calling. In the final online intervention, only guidance via chat was implemented. Knoerl et al. (Knoerl et al., 2018) suggested further improvements of their online CBT intervention for patients with CIPN, including interaction with a health care professional, which could contribute to usage. Earlier studies have indeed shown that guided online interventions show better outcomes regarding satisfaction, usage and adherence compared to non-guided versions (Baumeister et al., 2014; Lin et al., 2017; Musiat et al., 2022). As guidance involves high costs and is less appropriate for reaching large groups of people (Musiat et al., 2022), it seemed appropriate to only implement low-threshold email guidance in this online intervention.

Furthermore, some interview findings were not directly incorporated into the development. First, this relates to peer support, which could be perceived as pleasant as indicated by some patients. Peer support includes helping fellows who are suffering from the same condition (Dennis, 2003) and a systematic review has shown effectiveness in improving QoL and distress (Hu et al., 2019). However, this only applied to interventions including peer training. Avoiding or cautiousness use of online peer support without peer group training has been recommended due to risk of misinformation (Hu et al., 2019; Salzer et al., 2010). Implementation of peer support was beyond the scope of this online intervention and future research should assess integration of supervised peer support. Second, no decisions were made regarding future implementation. Patients and experts indicated that implementation should be performed with healthcare professionals and external partners. Previous studies studying online interventions emphasized that is indeed important to consider external parties such as healthcare professionals and organizations (Christie et al., 2018; Drozd et al., 2016). However, implementation was not within the scope of the current study, and should be considered by future research in accordance with findings from a randomized controlled trial (RCT) (van de Graaf et al., 2022). However, an already existing online platform (i.e., Karify) that is widely used by healthcare institutions was chosen, which facilitates implementation.

Although this study included participants with varying backgrounds (e.g., age, educational, tumor type), patients with low health literacy (i.e., patients who have difficulties obtaining, processing, understanding and communicating about health-related information (Berkman et al., 2010)) were not specifically involved. Nowadays, eHealth literacy, which relates to the ability to search, find, and appropriately use online health environments (Norman & Skinner, 2006) is relevant as well. Based on prototype testing, texts were shortened in the current development, without compromising the content. Nevertheless, as text rather than audiovisual content is the basis of the intervention, this is less suitable for patients with low health literacy (Mackert et al., 2009). Mackert et al. (2009) suggest developing an intervention in which audio and video are the basis, with more in-depth texts for users with high health literacy. This could be considered when optimizing the intervention for possible implementation after effectiveness has been studied.

## Strengths and limitations

This paper has several strengths. First, patients have been involved in all development phases, in accordance with the CeHReS roadmap (Gemert-Pijnen et al., 2011). This may eventually positively influence adaptation and future implementation (Gemert-Pijnen et al., 2011). Second, multiple experts with various backgrounds (i.e., healthcare professionals and eHealth experts) have also been able to contribute to the development throughout the development process. Third, this study was designed and conducted by a multidisciplinary team, including psychologists working in clinical and scientific settings, as well as a communication and information scientist. This multidisciplinary approach helped to develop a user-friendly evidence-based intervention.

There are also several limitations. The first limitation related to the low-fidelity and high-fidelity prototype testing. We aimed to use the think-aloud method that includes a usability evaluation method in which participants perform tasks in the prototype, while being encouraged to express their thoughts and feelings for optimizing technology (R. Davis et al., 2020; Jaspers, 2009; Yen & Bakken, 2012). As prototype testing had to take place via video calls due to COVID-19, properly using the think-aloud protocol was difficult. Therefore, online interviews using the WUSQ were conducted. This may have resulted in less concrete feedback compared to an observational method such as the think-aloud method (Bolle et al., 2016) and may specifically apply to the current patient group who often experience memory-problems due to older age and so-called 'chemo brain'. It may have limited optimization of the intervention. Future research could evaluate the upcoming RCT results and conduct think-aloud usability tests to create an optimized version of *Embrace Pain*. Second, not all individual sessions have been evaluated by patients and experts. However, all sessions have been written by the same authors. Thereby, all sessions consist of the same structure and are based on the same concept (i.e., psychological flexibility). Furthermore, all sessions will be evaluated in an RCT (van de Graaf et al., 2022). Third, recruitment via digital flyers only may have resulted in a limited representation of patients who may have been less technology competent.

## Conclusion

This study showed how a patient-centered development process could be applied in the development of an online self-management intervention based on ACT for patients with

chronic painful CIPN. The development resulted in an 8-week online intervention called *Embrace Pain*, which was based on user needs and ACT. Next, we will perform an RCT to study the effectiveness of the online intervention (van de Graaf et al., 2022). Usage and adaptation also need to be assessed, as this may optimize the online intervention to enhance effectiveness.

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**Table 1.** Main results of patient and expert interviews

Category	Theme	Code	Condensed meaning unit	Meaning unit
Patients	Overall intervention need	Overall intervention need	Many patients were supportive of the development of an online ACT intervention for CIPN Some patients did not think it was necessary but would use it to improve their situation regarding CIPN	"I've also used another app, so I'm familiar with it. I definitely see positives in it." "I'm always up for ways to minimize my pain and to have minimal discomfort, but I think I'm already doing a lot of that myself."
			Some patients felt no need because they did not experience any problems in dealing with CIPN	"I think I just already do that myself. ... I know very well what I want and don't want and what I consider important and what I consider less important. Things I consider less important have no priority for me at all." "Accepting that those symptoms are there, and they won't go away but you can learn to live with them." "Not only accepting thoughts and learning to live with, but also looking at possibilities and limitations."
	Psychosocial aspects	ACT	All patients appreciated and agreed with the elements of ACTC	"I'm not meditative every day either, but sometimes you have one of those days when you think 'oh yes nice rest'. Yes, I like that. ... Yes. It can be very helpful to take some distance from the thoughts you have about your complaints." "I participated in a study on mindfulness. I found it very confronting."
		Mindfulness	Some patients enjoyed doing mindfulness.	"That people really say the most terrible things to you ... That's often quite difficult too I think. ... And also accept that people who don't have that don't understand it either. Because you can't blame them. That, I didn't understand it before either. But they can so say things to you that would almost get you into an argument." "Well I've missed a lot of information. ... I also like a piece of information. ... What it is and what it does to you and that it is not strange. And that it is actually quite normal because I think that already helps a bit with acceptance."
	Content	Communication social environment	Some patients had difficulty with (the concept of) mindfulness. Many patients experienced difficulties with communicating to social environment in daily life	"That people really say the most terrible things to you ... That's often quite difficult too I think. ... And also accept that people who don't have that don't understand it either. Because you can't blame them. That, I didn't understand it before either. But they can so say things to you that would almost get you into an argument."
		Psychoeducation	Many patients perceived psychoeducation as useful	"Well I've missed a lot of information. ... I also like a piece of information. ... What it is and what it does to you and that it is not strange. And that it is actually quite normal because I think that already helps a bit with acceptance."
	Peer support	Peer support need	Some patients had a strong need for peer support Some patients had no need for peer support	"I do like it. I also always really enjoy talking to fellow sufferers." "No. ... Then you're going to put energy into something that will only annoy you."
	Exercises	Intensity	All patients liked doing exercises	"By doing assignments or things like that, you also become much more aware of it and then it sticks much more in your mind than if you just read or listen to something and don't do anything with it."
All patients wanted to have autonomy in the moment and duration of use Many patients indicated that exercises should be short			"I think 2-3 times a week half an hour would work for me. And then you can arrange that yourself in that week." "As long as it's not half an hour or three quarters of an hour, because people obviously have to have the time. But 15 or 20 minutes, should be quite doable."	

**Table 1.** Main results of patient and expert interviews (continued)

Category	Theme	Code	Condensed meaning unit	Meaning unit
	Guidance	Guidance need	Some patients had guidance needs	"I want to fill out 2 things but then I want to talk to you online."
			Some patients had no guidance needs	"I talk easily and if I want to talk about something I can share it with my social environment like friends or colleagues."
	Usability	Ease of use	Many patients preferred a user-friendly and accessible intervention	"Yeah, user-friendly. ... Well, when you start, a bright homepage with really clear imagery. ... So, a good layout and divided into good chapters that can also be found again. So that when you start that you don't have to search through everything but that you can go straight to where you left off."
			Chemo-brain	Many patients experience chemo-brain
Intervention development	Multimedia		Many patients indicated that variety in multimedia is important	"It has to be something very concrete. Something catchy. That makes you think 'oh yeah' ... Yes, it's the combination of it all."
			Many patients indicated that multimedia (e.g., text) should not take too long	"If you're going to offer a text about neuropathy and it's somewhat scientific or medical, it shouldn't be too long because, then people will drop out."
	Device		Some patients preferred using a laptop or computer	"I think anyway, you might take a little more time to actually sit down and open that website for that than if you get a notification and you're on the train and you just quickly fill it out before the stop."
			Some patients preferred using a tablet	"I would do it on the tablet, because I find it easier to work with."
	Design		Some patients preferred using a smartphone	"I just find it easiest on my phone."
			Many patients preferred a calm design, especially regarding colors	"Yes, personally I'm not into those very wild colors because it's distracting. ... Yes, should be a little quiet in color, yes."
Comorbidities	Fatigue		Some patients acknowledged that it is crucial to include information about comorbidities	"I would do it, because the pain always gives fatigue. ... Yes, that, um, that yes, illnesses are always linked to fatigue, I think. So, I would definitely include that, yes."
	Fear of recurrence		Some patients acknowledged that it is crucial to recognize that patients had a life-threatening disease	"Well, I think you can explain that it's normal for people to be afraid that the cancer will recur."
Implementation	Healthcare professionals		Some patients indicated that it was important to involve healthcare professionals and hospitals in implementation	"In principle, I would always like it if at least health care providers knew about it. ... Being able to offer it and that if you do something with it that they also know what you're talking about."

**Table 1.** Main results of patient and expert interviews (continued)

Category	Theme	Code	Condensed meaning unit	Meaning unit
		External parties	Some patients indicated that it was important to involve external parties in implementation	"That's why I also said of see if you can experience a combination with a foundation, whichever one that is. Then you also don't have to constantly chase an app like that yourself."
Experts	Overall intervention need	Overall intervention need	Some experts acknowledged the importance of patients' motivation	"Well I think people are definitely motivated. ... I think people there are willing to invest per week in that."
	Psychosocial aspects	ACT	Many experts acknowledged the importance of acceptance of pain and limitations	"A person can only accept if he feels that there is an alternative. ... And that alternative is picking up activities that are worthwhile for you. ... I don't think you can make that switch overnight. You need a number of exercises."
		Mindfulness	Few experts perceived mindfulness as an important aspect of ACT Few experts recognized mindfulness as an element that needs specific attention	"Yes, you will have to move toward mindfulness." "You have to be careful about how I bring that for example, because many people already switch off when you use the word mindfulness. They find that spiritual very quickly." "You want to get them to practice anyway, so you have to explain; hey you have trouble concentrating so what's going to happen when you do this exercise is you're going to keep thinking 'oh I can't do this, I can't do this.' But, the good news is you can't do it wrong because you're practicing."
	Exercises	Intensity	Many experts perceived repetition of exercises as crucial	"Behavior change, I think, is more easily achieved by spending a little time with it every day than a few very long sessions."
			Some experts perceived autonomy in when and how long to practice as important	"Maybe it's best if they can choose. I want five or 10 minutes every day or I want 15 minutes to half an hour twice a week."
	Content	Psychoeducation	Few experts indicated psychoeducation as important	"After that I think you have to increase knowledge of what exactly is going on. ... Patients sometimes don't know exactly what caused it. ... It helps to in being able to accept and deal with this."
		Communication to social environment	Few experts indicated communication to social environment as an important topic	"How to talk about it with your partner? ... So, the social environment. How do you talk about it?"
		Patient's voice	Some experts indicated the patient speaking as an important topic	"People really enjoy watching those videos. ... People do find it very nice to know that they are not the only ones struggling with something."
	Comorbidities	Integration in intervention	Many experts indicated that the intervention could be applied to other complaints, but that it should mainly focus on CIPN	"It quickly becomes very diffuse and large when you also include all these other issues and people often just suffer from one thing most prominently. And you actually start with one thing and of course they end up with the other things, because that feeds into each other."

**Table 1.** Main results of patient and expert interviews (continued)

Category	Theme	Code	Condensed meaning unit	Meaning unit
	Guidance	Guidance need	Many experts indicated that guidance was highly important, but needs would vary between patients	"I myself always found the option that there is a possibility on patient initiative so to speak. ... I think it's nice that you can get some kind of extra help with self-help. But some people also choose very explicitly for just something unguided."
	Peer support	Peer support need	Some experts suggested peer support as a relevant component	"What you always hear, but I don't know if you can facilitate that, is that they sometimes can learn a lot from each other."
	Usability	Adherence	Many experts suggested to take adherence into account	"I don't think dropout is necessarily a problem at all. ... It can also just be an early positive."
		Ease of use	Few experts mentioned ease of use is important.	"Why does Google work? Because it is simple."
		Information	Many experts acknowledged that information should be comprehensive and easy to understand.	"That you don't have too much information thrust upon you."
		User-characteristics	Many experts mentioned the importance of considering different user-characteristics such as health literacy and digital literacy	"You have people with low health skills and people with average health skills and people with high health skills."
	Intervention development	Multimedia	Many experts indicated variety in multimedia is advisable	"A mix of, because some people like to read things, some people learn more when they see a video, some people do better when they see some pictures. So, if you can get a balanced mix in there .... Then I think everyone gets the most out of that."
			Many experts acknowledged that texts, videos and audio should not be too long and too difficult	"As a result, you have to watch the language, but length and formatting are also super important. You don't want it to be a Word document."
		Design	Some experts indicated a calm design, especially regarding colors, would be necessary.	"We had a very simple first page that didn't have too much on it and they all appreciated that. ... So, basically it should be quiet, and it shouldn't have too many bells and whistles and not too many bold colors. ... It shouldn't have too many stimuli."
	Implementation	Healthcare professionals	Few experts indicated that it was important to involve healthcare professionals and hospitals in implementation	"So I think you just need to find some places and have health care providers refer to them."
		External parties	Few experts indicated that it was important to involve external parties in implementation	"In that sense, you have to use and the entry points of the existing environments where patients already come. <i>Thuisarts.nl</i> could be one place. <i>Kanker.nl</i> , <i>de Verwijsgids Kanker IKNL</i> , the Dutch Federation of Cancer Patients Organisations, the patient associations. Those are places where patients come and that's where you need to offer it."

**Table 2.** Participant characteristics

Participant	Gender	Age <sup>a</sup>	Educational level <sup>b</sup>	Marital status	Tumor	Daily Internet use	Self-perceived Internet expertise	eHealth literacy (1-10)
P1	Male	25-30	Middle	Single	Hodgkin lymphoma	3-5 hours	Expert	5.86
P2	Female	50-55	High	Married/living together	Breast cancer	2-3 hours	Average	
P3	Female	60-65	High	Divorced	Breast cancer	> 5 hours	Average	6.57
P4	Female	60-65	High	Divorced	Breast cancer		Average	7.71
P5	Female	60-65	High	Divorced	Breast cancer	1-2 hours	Average	
P6	Female	60-65	High	Divorced	Lung cancer	2-3 hours	Average	
P7	Male	60-65	High	Married/living together	Hodgkin lymphoma	3-5 hours	Expert	6.43
P8	Female	60-65	Middle	Married/living together	Colorectal and colon cancer	3-5 hours		7.43
P9	Male	65-70	Middle	Married/living together	Leukemia and acute lymphoblastic leukemia	1-2 hours	Expert	5.71
P10	Male	65-70	High	Married/living together	Multiple myeloma	2-3 hours	Average	9.86
P11	Female	75-80	High	Single	Lung and breast cancer	2-3 hours	Average	7.86
P12	Female	75-80	High	Divorced	Colorectal, colon, rectal and skin cancer	< 1 hour	Average	9.57

<sup>a</sup> Age ranges are shown to ensure anonymity.

<sup>b</sup> Low: primary or secondary pre-vocational; middle: secondary education or vocational education; high: Bachelor's degree or higher

## **Appendix A.** Translations of Dutch screenshots

### **Screenshot 1**

Header: Embrace Pain

Title: Embrace Pain

You have been treated for cancer and have been experiencing neuropathic pain caused by chemotherapy for long(er) period. Pain can greatly influence daily activities and quality of life.

The goal of this training is to help you reduce the impact of pain on your daily life. We want to teach you how to live your daily life, with pain and without focusing all your attention on it. The goal of this training is not to eliminate the pain symptoms or underlying nerve damage. The training is based on a psychological intervention, namely Acceptance and Commitment Therapy.

[Welcome

Available]

[Chronic neuropathic pain

Module 1 (Available)]

[On the way to values

Module 2 (Available)]

[Away from my values

Module 3 (Available)]

[On the road with skills

Module 4 (Available)]

[Taking a new road

Module 5 (Available)]

[On the road to values: from day to day

Module 6 (Available)]

### **Screenshot 2**

Header: Away from my values

Title: Away from my values

In this session, you will learn about pain and additional thoughts and feelings that can keep you away from your values. You will work on how you deal with your pain and what it costs you.

[Current situation (Available)]

[Moving away from your values (Available)]

[Exercise 1: My ways of avoiding (Available)]

[What do I do and why? (Available)]

[Exercise 2: Moments when I am in pain (Available)]

[Metaphor: Quicksand (Available)]

[Attention exercise: Breathing and body exploration (Available)]

[Finally (Available)]

### **Screenshot 3**

Header: Moving away from your values

These different ways of getting rid of pain and additional thoughts and feelings are called avoidance. You can roughly categorize ways of avoidance into three groups: escape, distraction or numbing (Dahl & Lundgren, 2006).

#### Escaping

Escaping means that you avoid activities or situations that will (or may) cause pain, for example, by not exercising or working out. You avoid the potential pain in advance in hopes of not having to experience it.

"I no longer get on the train or bus. What if I have to stand and get pain?"

#### Distraction

Distraction means that you resist your thoughts and feelings and pretend that the pain is not there. For example, you start working really hard or trying really hard and thinking only about nice things.

"When I have a lot of pain, I always watch TV-series. Then I don't think about the pain anymore."

## Numbing

Numbing means taking medicine, food or alcohol to stop feeling the pain and additional thoughts and feelings. It can make you "forget" the pain and additional thoughts and feelings for a while.

"When I'm not feeling so good, I like to grab a glass of wine in the evening. Then I'm a little less concerned with how I'm feeling."

[Futher]

### **Screenshot 4**

Header: Exercise 1: My ways of avoiding

Title: Getting Started

Complete the exercise using the 4 steps.

Click on the plus sign to add an additional way of avoiding if necessary.

Step 1: Avoidance behaviors

[Eating a lot of cookies]

Step 2: Does it work in the short term?

Step 3: Does it work in the long term?

Step 4: Does it fit your values?

Step 5: What is your conclusion?

### **Screenshot 5**

Header: Metaphor: Quicksand

Title: Metaphor: Quicksand

This commonly used metaphor is based on Hayes (2006). You are on vacation and take an evening walk through the woods by yourself. You step off the hiking trail and suddenly find yourself stuck in quicksand. Naturally, you panic and scream for help. You try to step out of the sand toward the hiking trail. You wriggle and struggle to get out. Through all your attempts to get out of the quicksand, you sink deeper and deeper. The harder you struggle, the faster you sink.

We compare the ways you deal with pain to being stuck in quicksand. It makes perfect sense to look for ways to get out of pain. Sometimes this helps, but sometimes it doesn't.

But with pain, it often works just like quicksand: the pain and negative moments often end up getting worse the harder you work to avoid feeling the pain.

So how should you deal with the pain? When we think about quicksand, the answer seems very simple: by giving up your struggle. The only way to get unstuck from quicksand is to lie stretched out on it, not move and make as much contact with it as possible. That's just not easy. Especially if you see quitting that struggle as weakness or giving up. Stopping avoiding pain, however, is a very courageous action. You may have noticed in this session what quitting this struggle can give you: it gives you more time and energy to live a life worth living. You will learn more about this later in this training.

### ***Screenshot 6***

Header: Attention exercise: Breathing and body exploration

Title: This week

This week we will alternate between two attention exercises: Concentration on breathing and Body exploration. Each day you will choose which exercise to perform. In addition, you will be introduced to: Three minutes of breathing. The attention exercises help you become aware of your avoidance strategies. They also help you deal with pain in a different way. Condemning and rejecting pain is often counterproductive. The exercises help you to stay with the pain and not flee from it.

Title: Exercise

Below are the sound files of the Concentration on breathing and Body exploration. They are the same sound files as in the previous sessions.

Title: Concentration on breathing

Title: Body exploration

Click on 'Download' via the 3 dots to download the sound file.



# Chapter 7

The page features a light beige background. A thick orange line starts from the left edge, curves upwards and then rightwards, ending near the top right corner. A vertical pink bar runs along the right edge of the page.

# Effectiveness of the online Acceptance and Commitment Therapy intervention Embrace Pain for cancer survivors with chronic painful chemotherapy-induced peripheral neuropathy: study protocol for a randomized controlled trial

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## **Abstract**

**Background:** About 30% of cancer survivors suffer from chemotherapy-induced peripheral neuropathy (CIPN)  $\geq 6$  months after completion of chemotherapy. This condition, for which treatment options are scarce, comes with limitations in daily life functioning and decreased quality of life. The current study examines the effectiveness of an online self-help intervention based on Acceptance and Commitment Therapy (ACT) in comparison to a waiting list condition (WLC) to deal with CIPN. In addition, it examines which factors moderate effects and to what extent the effects differ between guided and unguided ACT intervention.

**Methods:** A two parallel, non-blinded randomized controlled trial (RCT) will be carried out. Adult cancer survivors who experience painful CIPN for at least 3 months and completed chemotherapy at least 6 months ago will be recruited ( $n=146$ ). In the intervention condition, participants will follow an 8-week self-management course containing 6 modules regarding psychoeducation and ACT-processes, including therapeutic email guidance. By means of text and experiential exercises, supplemented with illustrations, metaphors, and audio files, people will learn to carry out value-oriented activities in their daily life with pain. Participants will learn new ways of coping with pain, including reducing pain avoidance and increasing pain acceptance. Participants in the WLC will be invited to follow the intervention without therapeutic guidance 5 months after start. Pain interference is the primary outcome, while psychological distress, quality of life, CIPN symptom severity, pain intensity, psychological flexibility, mindfulness skills, values-based living, and pain catastrophizing will serve as secondary outcomes. All outcome measures will be evaluated at inclusion and baseline, early-intervention, mid-intervention, post-treatment, and 3- and 6-months post-treatment. Qualitative interviews will be conducted post-treatment regarding experiences, usage, usability, content fit, and satisfaction with the intervention.

**Discussion:** This study will provide valuable information on the effectiveness of an online self-help intervention based on ACT versus WLC for chronic painful CIPN patients.

## Introduction

The number of cancer survivors continues to grow (Elferink et al., 2010; Heins et al., 2012; Hulvat, 2020; Sukel et al., 2008; Van Steenberghe et al., 2012) as the population ages, early detection through screening rises, and cancer survival rates improve (Signaleringscommissie Kanker van KWF Kankerbestrijding, 2011). Many of these survivors face long-term side effects of cancer and its treatment, whereby their quality of life (QoL) is strongly affected (Heins et al., 2012; Mols et al., 2014). Chemotherapy can cause multiple disabling long-term side effects like chemotherapy-induced peripheral neuropathy (CIPN) (Seretny et al., 2014). CIPN can occur due to the use of certain chemotherapeutic agents, such as taxanes, platinum compounds, and vinca alkaloids (Wen, 2007). CIPN presents itself with symptoms such as tingling, numbness, cramps, and aching or burning pain in hands and feet, which can also spread to arms and legs (T. Beijers et al., 2012; Farquhar-Smith, 2011; Quasthoff & Hartung, 2002). Up to 80% of cancer survivors suffers from CIPN one month after chemotherapy, which stabilizes to around 30% at 6 months or longer after chemotherapy (Bao et al., 2016; Bonhof et al., 2018; Eckhoff et al., 2015; Glendenning et al., 2010; Mols et al., 2014; Seretny et al., 2014). This prevalence differs between cancer types (range 10 – 60%). As the application of chemotherapy in cancer treatment is rising, CIPN is likely to become one of the most common long-term side effects for cancer survivors (A. J. M. M. Beijers et al., 2014). CIPN is a very limiting condition, as a systematic review has shown that CIPN negatively influences QoL in adult cancer survivors (Mols et al., 2014). Patients can experience impaired QoL due to CIPN up to 11 years after chemotherapy, caused by decreased performance of regular activities, depressive symptoms, and poor sleep quality (Bonhof et al., 2021; Mols et al., 2013; Tofthagen, 2010; Tofthagen et al., 2013). In addition, it has been shown that specifically *painful* CIPN is associated with lower QoL compared to non-painful CIPN (Bonhof et al., 2020).

In order to improve patients' QoL, Cognitive Behavioral Therapies (CBT), like third generation CBTs as Acceptance & Commitment Therapy (ACT), are increasingly used in global cancer care (Feros et al., 2013; Hulbert-Williams et al., 2015). ACT helps patients to shift focus towards engaging in personally valuable activities by increasing pain acceptance (S. C. Hayes et al., 2006) and has been shown to be effective for other types of chronic pain (McCracken & Vowles, 2014). Although the effectiveness of online ACT

interventions have not yet been investigated for chronic painful CIPN patients, a previous study found that treatment with online CBT positively affected pain intensity in this patient group, creating positive expectations for treatment with online ACT as well (Knoerl et al., 2018). Traditional *face-to-face* psychological therapies have some drawbacks, such as high costs, not being accessible or hardly available, having to travel to the therapist, negative stigma, and high psychological burden (Borosund et al., 2018; Knoerl et al., 2018). Due to developments in the field of eHealth, these obstacles can be mitigated (Borosund et al., 2018; Gainsbury & Blaszczynski, 2011; Knoerl et al., 2018). That is, with the use of online self-management interventions, patients are able to receive psychological therapy whenever and wherever they would like to, without having to travel to a therapist (Borosund et al., 2018; Knoerl et al., 2018). Online self-management interventions offer the additional benefit of augmented protection of patients' anonymity and privacy (Gainsbury & Blaszczynski, 2011).

Even though online interventions are relatively new, several such interventions have demonstrable effectivity in improving QoL in cancer patients and survivors (Borosund et al., 2018; Kuijpers et al., 2016; McAlpine et al., 2015; Slev et al., 2016). A randomized controlled trial (RCT) has shown that the use of an online CBT intervention significantly improved CIPN pain intensity and may be effective (Knoerl et al., 2018). Furthermore, research has shown that online interventions based on ACT are capable of improving pain intensity, pain-interference, pain catastrophizing, disability, depression, anxiety, psychological inflexibility, and QoL in chronic pain patients with a variety of pain diagnoses (e.g., fibromyalgia, rheumatoid arthritis, and back complaints) (Trompetter et al., 2015; Veehof et al., 2016). These findings suggest that an online self-help intervention based on ACT might be effective for adult cancer survivors with chronic painful CIPN as well. However, effects may differ between patients, since previous research has shown factors such as pain intensity, depressive and anxiety symptoms, and emotional well-being to predict the effectiveness of online ACT for chronic pain (Trompetter et al., 2016), and the extent to which patients benefit from the online intervention may hence vary. Furthermore, there may also be differences in effectiveness with different types of the online intervention, namely with or without guidance. Earlier research has shown that guidance, including feedback, explanations, motivations and reminders, improves treatment effects compared to unguided interventions (Baumeister et al., 2014; Lin et al.,

2017). The primary aim of this study researching the online intervention named *Embrace Pain* is to reduce pain interference in cancer survivors with chronic painful CIPN. To study this, three objectives have been formulated:

*Objective 1:* To examine the effectiveness of an online self-help intervention based on ACT for reducing pain interference in cancer survivors with chronic painful CIPN in a randomized controlled trial (RCT) and compare this to a waiting list condition (WLC).

*Objective 2:* To examine which baseline demographic, clinical, and psychosocial factors may moderate the effectiveness of an online self-help intervention based on ACT.

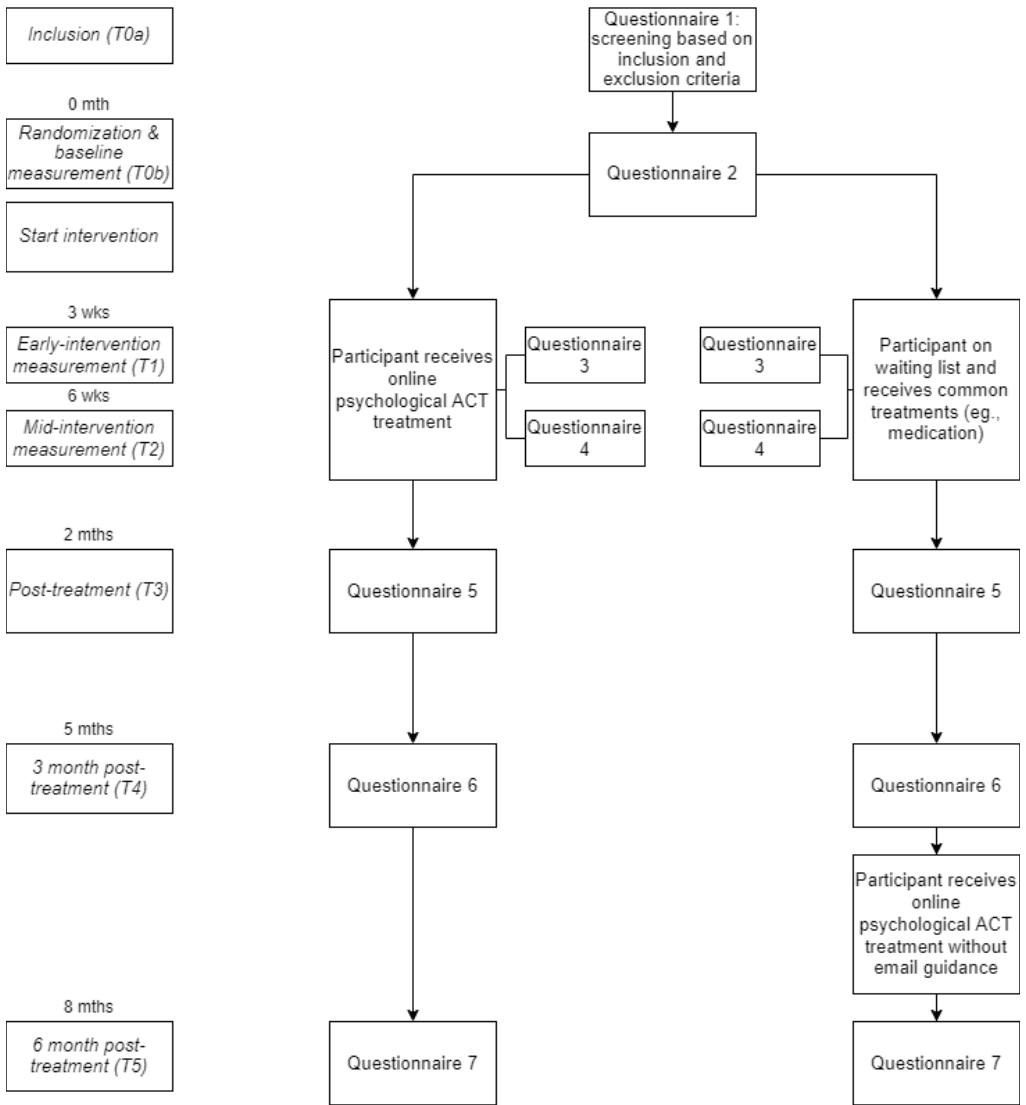
*Objective 3:* To examine the extent to which effects differ between guided and unguided versions of the online self-help intervention based on ACT.

## Methods

### Study design

An RCT will be carried out with two parallel, non-blinded groups. Participants will be involved in the study for a duration of 8 months from first to last measurement. Outcome measures will be collected at baseline (T0), early-intervention (T1; 3 weeks after baseline), mid-intervention (T2; 6 weeks after baseline), directly at the end of intervention (T3; 2 months after baseline), and through two follow-up measurements (T4; 3 months after intervention, T5; 6 months after intervention). A flowchart of the study is shown in Figure 1.

**Figure 1.** Flowchart



**Study population**

Inclusion criteria consist of: a) age of 18 years or older, and b) identified by a clinician or self as having painful sensations (i.e., aching, burning, “pins-and-needles”, shock-like, painful tingling, numbness, cramps) bilaterally in the feet/legs and/or hands/arms for at least 3 months. Furthermore, c) a score of 3 or higher on an 11-point pain intensity scale

(Numeric Rating Scale), d) the pain was not present prior to receiving chemotherapy, e) chemotherapy ended at least 6 months ago, and f) a score of 1 or higher on EORTC QLQ-CIPN20. Exclusion criteria are: a) enrollment in psychological treatment related to cancer, pain, or psychological disorders upon entry, b) new chemotherapy scheduled during study participation, c) no access to the Internet/no email address, d) not enough time to follow the intervention (2 hours per week), and e) according to patient's own perception no problems with the Dutch language.

### **Recruitment**

Patients will be recruited through a flyer with QR code and a link to a website. These flyers will be distributed in various ways (in the Netherlands): online media (e.g., Kanker.nl, Facebook groups for neuropathy, patient associations), hospital waiting rooms (e.g., oncology departments, AYA centers, pain clinics), and through other healthcare providers (e.g., oncological foot care providers). Interested patients can visit the recruitment website where they can read more information and sign up if interested.

When a patient is interested in participation, the patient will receive an information letter and an informed consent form by mail, sent by a research assistant. The informed consent also includes information regarding collection and use of participant data in follow-up studies. Afterwards, the participant will receive a questionnaire (T0a) regarding inclusion criteria, to examine whether the participant is eligible to participate. Additionally, patients must achieve certain scores on several questionnaires, namely Numeric Rating Scale  $\geq 2$  and EORTC QLQ-CIPN20  $\geq 1$ . If the questionnaire from T0a shows that respondents are not suitable for participation, they will be notified with a rejection and along with it the reason for rejection based on the relevant inclusion or exclusion criterion.

### **Randomization**

When the patient is admitted to the study, the patient will receive confirmation of participation, the result of randomization, and the baseline questionnaire (T0b). Patients will be randomized to receive either ACT or WLC. The study will stratify by age and sex by means of block wise randomization. An online generator will be used for this. Randomization will be performed by a research associate.

## **Intervention**

The experimental condition includes an online psychological intervention with therapist email guidance based on ACT. The intervention can be worked through by the patient from home or at another location of choice, in webpage or app by logging in with email and self-created password. Participants receive a welcome letter from the supervisor. It consists of 6 modules which can be worked through in 8 weeks. The intervention primarily consists of text and experiential exercises, complemented with illustrations, metaphors, and audio (mp3) files. Before starting the module, participants read an introduction about the training. The first module includes psychoeducation on neuropathic pain and CIPN (Table 1). Participants will be provided with information to familiarize themselves with intervention goals and mindfulness exercises central to ACT. In subsequent modules, participants will learn about the aversive effects of pain avoidance, gain insight into their personal values, and work on pain acceptance. Throughout the intervention, participants will exercise to recognize unhelpful thoughts about their pain and learn the difference between the subjective (judging) and objective self, create activities that align with values, and think about concrete actions to prevent relapse. When access to the online environment is terminated, participants can no longer view the online environment or communicate with the supervisor. However, participants can always continue to view the session they submitted.

Participants in the experimental condition will receive guidance from Psychology master's students from Tilburg University, who will be first trained and then supervised by a licensed healthcare psychologist. In addition, they receive supervision in the first weeks of providing guidance. Also, they will always have the possibility to ask advice from a licensed clinical psychologist during the intervention. There will also be a backup in case of possible psychological problems that require more help. In that case, the licensed clinical psychologist will be informed and asked for advice. Guidance of participants will occur via email. Contact will be without obligation. It is possible to send an email every week in the protected environment of the online intervention, which complies with all privacy conditions as stated by the GDPR. Guidance is mainly intended for feedback related to the exercises made, answering questions about the content, and maintaining motivation to continue with the intervention. Here the choice lies with the participant, but facilitators will continue to encourage questions throughout the training.

**Table 1.** Schematic overview of modules of ACT intervention

Module	Therapeutic processes	Information	Assignments	Audio files (mindfulness)
Welcome		Online environment, contact, additional help, other long-term consequences, and tips.		
1: Chronic neuropathic pain	Psychoeducation	CIPN and chronic pain		A: Concentration on breathing
2: On the way to values	Values	Values and valued-based activities	I: Explore your values II: My values III (optional): My values in pictures	A: Body exploration
3: Away from my values	Pain avoidance	Avoidance and managing pain	I: My ways of avoiding II: Moment when I am in pain	A: Concentration on breathing B: Body exploration C: Three-minute breathing space
4: On the road with skills	Commitment and Defusion	Learning how to deal with pain differently	I: Acceptance in action II: Your recurring thoughts of pain III: Is the thought useful? IX (optional): Struggle or open up	A: Allowing what is
5: Taking a new road	Committed action	Converting values to behaviors in different life areas and devising valued-based activities	I: My ACT matrix	A: Concentration on breathing B: Body exploration C: Three-minute breathing space D: Allowing what is
6: On the road to values: from day to day	Social context	Perform actions in daily life and long-term changes	I: Your communication about pain II: Self-care	A: Three-minute breathing space B: Notice five things C: Brushing your teeth with attention

### Waiting list condition

The control condition includes a WLC. At 5 months after start (i.e., T4) participants in the WLC receive the opportunity to follow the intervention without email guidance by a

therapist. They neither receive a welcome letter at the start, which means that they only read the introduction about the training before starting.

### **Outcomes**

Questionnaires will be completed online via the PROFILES Registry (van de Poll-Franse LV, Horevoorts N, Schoormans D, Beijer S, Ezendam NPM, Husson O, 2022). Patients will receive reminders via email to promote participant retention and complete follow-up. A complete overview of enrolment, interventions, and outcome measurements is shown in Table 2.

#### ***Primary outcome***

*Pain interference* will be measured using the Multidimensional Pain Inventory, Dutch language version (MPI-DLV) – subscale Interference (Kerns et al., 1985; Lousberg et al., 1999). The MPI consists of statements rated on a 7-point Likert scale ranging from 0 (no change) to 6 (a lot of change). The subscale Interference focuses on psychosocial aspects of chronic pain, such as functioning in work, homework, recreational and social activities. The scale consists of 11 items and has been translated/validated into Dutch (Lousberg et al., 1999).

#### ***Secondary outcomes***

*Quality of life* will be measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core-30 item (EORTC QLQ-C30) (Aaronson et al., 1993). This is a validated 30-item self-report screening scale for QoL in cancer patients including a 4-point Likert scale ranging from 1 (not at all) to 4 (very much) including five subscales (i.e., physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning) (Aaronson et al., 1993).

**Table 2.** Schedule of enrolment, interventions, and assessments.

TIMEPOINT**	STUDY PERIOD						
	Enrolment	Baseline	Treatment		Post-treatment		
	T0a	T0b	T1	T2	T3	T4	T5
<b>ENROLMENT:</b>							
Informed consent	X						
Eligibility screen	X						
Informing general practitioner and/or medical specialist	X						
Allocation		X					
<b>INTERVENTIONS:</b>							
ACT: direct start intervention <i>with</i> therapist guidance			—————				
WLC: waiting list intervention <i>without</i> therapist guidance						X	
<b>ASSESSMENTS</b>							
Demographics	X	X					
Multidimensional Pain Inventory (MPI) – subscale Interference		X	X	X	X	X	X
Numeric Rating Scale (NRS)	X				X	X	X
Hospital Anxiety and Depression Scale (HADS)		X	X	X	X	X	X
EORTC QLQ-C30		X			X	X	X
EORTC QLQ – CIPN20	X				X	X	X
Psychological Inflexibility in Pain Scale (PIPS)	X		X	X	X	X	
Freiburg Mindfulness Inventory FMI-NL		X	X	X	X	X	X
Engaged Living Scale (ELS)		X	X	X	X	X	X
Pain Catastrophizing Scale (PCS)		X	X	X	X	X	X
Intervention evaluation					X (ACT)		X (WLC)

*CIPN symptom severity* will be measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN20 (EORTC QLQ-CIPN20) (Postma et al., 2005). This questionnaire is intended to be used as a supplement to the EORTC QLQ-C30. It assesses CIPN-related symptoms as well as functional limitations related to CIPN. The questionnaire has been validated and includes 20 items on a 4-point Likert scale ranging from 1 (not at all) to 4 (very much) including three subscales (i.e., sensory, motor, and autonomic symptoms) (Smith et al., 2013).

*Pain intensity* will be measured with the Numeric Rating Scale (NRS-11) (R. R. H. Dworkin et al., 2005). This is based on International Association for the Study of Pain (IASP) recommendations for measures in clinical trials on chronic pain (R. R. H. Dworkin et al., 2005). This questionnaire has been validated and includes 2 items on a 11-point Likert scale ranging from 0 (no pain) to 10 (the worst pain possible) (Hjermstad et al., 2011).

*Psychological distress* will be measured using the Hospital Anxiety and Depression Scale (HADS) (Spinhoven et al., 1997; Zigmond & Snaith, 1983). This is based on IASP recommendations for measures in clinical trials on chronic pain (R. R. H. Dworkin et al., 2005). The HADS is a validated 14-item self-report screening scale (ranging from 0 to 3) including two subscales (i.e., anxiety and depression symptoms) (Spinhoven et al., 1997; Zigmond & Snaith, 1983).

*Pain catastrophizing* will be measured using the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995). This questionnaire includes three subscales (i.e., rumination, magnification, and helplessness). It consists of 13 items on a 5-point Likert scale ranging from 0 (not at all) to 4 (always) and has been validated (Sullivan et al., 1995).

*Psychological flexibility* will be measured with the Psychological Inflexibility in Pain Scale (PIPS) (Wicksell, Lekander, et al., 2010; Wicksell, Olsson, et al., 2010). This is a validated 12-item measurement, including two subscales (i.e., avoidance and cognitive fusion) (Trompetter et al., 2014). It consists of a 7-point Likert scale, ranging from 0 (never true) to 6 (always true).

*Mindfulness* will be measured using the Freiburg Mindfulness Inventory (FMI) (Bruggeman-Everts et al., 2017). This validated measurement consists of 14-items with two subscales (i.e., presence and acceptance) (Bruggeman-Everts et al., 2017). It includes a 4-point Likert scale, ranging from 0 (rarely) to 3 (almost always).

*Values-based living* will be measured with the Engaged Living Scale (ELS) (Trompetter et al., 2013). This is a validated 16-item measurement, consisting of two subscales (i.e., valued living and life fulfillment) (Trompetter et al., 2013). It includes a 5-point Likert scale, ranging from 0 (completely disagree) to 4 (completely agree).

*Intervention evaluation* includes 15 questions regarding the evaluation of the intervention. It includes questions regarding amount of use and overall satisfaction with the content and guidance, which was based on an earlier RCT studying an online ACT intervention (Trompetter et al., 2015). Overall satisfaction will be measured using the Client Satisfaction Questionnaire (CSQ-8) (Attkisson & Zwick, 1982). Also, participants will grade the intervention on a scale from 1 (extremely poor) to 10 (excellent).

### **Process outcomes**

Technical data regarding usage of the intervention will be gathered, namely moment when session was first viewed, moment when session was finished, moment of message sent to supervisor, and moment of feedback given by supervisor. This enables evaluation of adherence to the intervention and information about the use of guidance. Once all participants have completed the online training, Karify will make this data available. Karify is the eHealth platform in which the online intervention was build (ISO 27001 and NEN 7510 certified).

### **Other outcomes**

Qualitative data on intervention experiences and satisfaction will be collected by means of interviews with some participants after completion of the intervention. In this way, it will be possible to examine experiences, usage, usability, content fit of intervention with complaints, and satisfaction. Specifically, both participants who adhered and did not adhere to the intervention will be interviewed. Patients adhered to the intervention if all sessions were completed (i.e., based on data retrieved from Karify) and a minimum of

2 hours per week was spent on the intervention (i.e., self-reported). Participants are informed about this by the information letter and informed consent form. As a starting point, 4 patients in each group (i.e., adherent and non-adherent) will be interviewed. New interviews will be done until saturation is reached.

### ***Participant characteristics***

Socio-demographic factors are assessed, including sex, marital status, having children, educational level, and work. Clinical information will be examined as well, including year of diagnosis, tumor type, other cancer treatments besides chemotherapy, CIPN characteristics (i.e., days per week, medication used to treat CIPN), long-term consequences of cancer (other than CIPN), and psychological problems. Comorbidities in the last 12 months will be examined using the Self-administered Comorbidity Questionnaire (SCQ) (Sangha et al., 2003).

### ***Sample size calculation***

Per group, 51 participants during follow-up measurements are necessary to detect minimal effect sizes of interest ( $d = .50$ ) on the primary outcome. This is based on earlier findings on effectiveness of online and face-to-face ACT intervention for chronic pain (Trompetter et al., 2015; Veehof et al., 2016). The power will be high enough ( $p = 1 - \beta = .80$ ) to find significant effects in a two-sided test at  $\alpha = .05$ . As found in previous online ACT interventions, a drop-out rate of 30% needs to be considered. G\*Power calculations revealed that 73 participants per group are needed at baseline, which means that 146 participants are needed in total.

### **Statistical analysis**

#### ***Primary analyses***

Significant differences at baseline between the conditions will be checked by performing one-way ANOVA's and Chi-square tests. Effects of the intervention on all outcomes will be assessed by performing intention-to-treat analyses using general linear mixed models. Baseline to post-intervention and 3- and 6-month follow-up differences will be used as repeated measures, with treatment (2 levels), time (3 levels) and their first-order interactions as fixed factors. Confidence intervals of 95% will be calculated for all outcomes. Drop-out and non-adherence are relatively common in online interventions

(Eysenbach, 2011). Therefore, secondary analyses will be performed to examine effects on outcome variables for participants who adhered to the intervention (i.e., all session completed and self-reported minimum of 2 hours per week spent on intervention). At post-intervention and follow-up, effect sizes (Cohen's *d*) will be calculated using means and standard deviations. Effect sizes of 0.80 are considered large, effect sizes of 0.50 are evaluated as moderate, and effect sizes of 0.20 are considered small (Cohen, 1988).

Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations will be followed to evaluate the proportion of participants showing clinically significant change (R. H. Dworkin et al., 2008). Clinical improvement will be assessed with missing values imputed by the Expectation Maximization-algorithm. Proportions of clinically improved participants and Chi-square tests will assess statistically significant differences in the proportions for the two conditions. It will be calculated for: a) pain interference (MPI – Interference), b) pain intensity (NRS), c) CIPN symptom severity (EORTC QLQ – CIPN 20). A decrease of at least 0.6 standard deviation will be assessed as evidence of clinically significant change for the MPI – Interference scale, based on the IMMPACT guidelines (R. H. Dworkin et al., 2008). Decreases of 20% or higher in pain intensity (NRS) will be assessed as minimum and moderate changes. No specific IMMPACT guidelines exist for the HADS. Therefore, a distribution-based decrease of at least 1 standard error of the mean is recommended (R. H. Dworkin et al., 2008).

### ***Secondary analyses***

To assess predictors of effects, steps of a study on predictors of change during CBT for chronic pain will be followed (Turner et al., 2007). Pain interference at 3-month follow-up will be used as indicator of treatment effect. Using the PROCESS macro for SPSS (A. Hayes, 2013), linear regression models will be applied (two-tailed). Predictor variables may include sex, age, educational level, number of comorbidities, time since CIPN onset, CIPN symptom severity (EORTC QLQ – CIPN20), quality of life (EORTC QLQ-C30), pain intensity (NRS), psychological distress (HADS), psychological inflexibility (PIPS), mindfulness (FMI-NL), valued based living (ELS), and pain catastrophizing (PCS). They will be selected based on theoretical and empirical considerations.

To assess differences in effects between the guided and unguided version of the intervention, independent samples t-tests and a two-stage hierarchical multiple regression analysis for each primary and secondary outcome will be conducted. Baseline to 3-month follow-up change will be used as the dependent variable. The independent variable will be an intervention dummy variable. Baseline score on the respective outcome measure will be used as control variable. Effect sizes for both conditions will be computed to indicate differences in the magnitude of the effects of online ACT with and without email counselling.

### ***Interview analyses***

Qualitative data will be used to gain further insight in the intervention effects, usage, usability, content fit of intervention with complaints, and satisfaction. All interviews will be recorded and transcribed verbatim. Thematic analysis in Atlas Ti 8.0 will be used to analyze the data. Following transcription, two researchers will independently (re)read a set of 3-4 interviews and perform inductive coding followed by a discussion of disparities. One researcher will further code the rest of the interviews using a codebook that will be generated from the first round of coding, adding new codes along the way, and discussing outcomes of coding with the second researcher.

### ***Ethical considerations***

This study protocol has been reviewed and approved by the Medical Research Ethics Committee Brabant, the Netherlands (reference number: NL78436.028.21). If there are protocol modifications, all relevant parties will be informed. Tilburg University has insurance for participants for compensation in the unlikely event that participants are harmed from trial participation.

### ***Data security***

Each participant will be assigned a study number, which guarantees confidentiality and anonymity. Only the research assistant will be able to connect the study numbers to the participants. Data will be stored in a secure location (PROFILES registry) for 15 years. PROFILES data is freely available (FAIR principles) for non-commercial scientific research through [www.profilesregistry.nl](http://www.profilesregistry.nl) (van de Poll-Franse LV, Horevoorts N, Schoormans D, Beijer S, Ezendam NPM, Husson O, 2022).

### **Output**

Trial results will be published in (inter)national peer reviewed scientific journals and will be communicated to the stakeholder group, the Dutch Cancer Society, and Netherlands Comprehensive Cancer Organisation (IKNL). Presentations will be held at (inter)national conferences.

### **Discussion**

Chronic painful CIPN is a very limiting long-term consequence of chemotherapy that many adult cancer survivors suffer from, resulting in a greatly reduced QoL. Since treatment options are limited, online self-help therapy could offer support to these patients. This study aims to evaluate effectiveness of an online self-help intervention based on ACT. It could provide an entry point for the development of psychological treatment for cancer patients suffering from other forms of cancer pain, which is a major, growing cancer survivorship issue that is highly under recognized.

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# Chapter 8

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# Exploring barriers and facilitators to engagement of an online Acceptance and Commitment Therapy intervention for cancer survivors with chronic painful chemotherapy-induced peripheral neuropathy

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## **Abstract**

**Background:** Online self-management interventions for cancer survivors are increasingly being used, but engagement is often difficult for patients. Gaining an understanding of barriers and facilitators that patients experience to such interventions can play a crucial role in enhancing engagement. The aim of this study was therefore to qualitatively examine barriers and facilitators to engagement to an online self-management intervention for cancer survivors with chronic painful chemotherapy-induced peripheral neuropathy (CIPN) with and without guidance.

**Methods:** Patients who had participated in the Randomized Controlled Trial (RCT) of this project were asked to participate in this study. The RCT involved studying an online self-management Acceptance and Commitment Therapy intervention for pain interference in daily life. Thereafter, twelve patients experiencing chronic painful CIPN participated in semi-structured interviews. An inductive coping approach was applied and Atlas.ti was used for coding.

**Results:** In total, two themes and seventeen codes emerged from the data, namely seven codes for barriers and ten codes for facilitators. Barriers related mostly to an unfavorable program schedule, burden, lack of guidance, and irrelevance of content. In addition, patients experienced different facilitators mainly related to usability, being engaged in positive self-management and symptom management, and a favorable program schedule.

**Discussion:** Facilitating and impeding factors varied greatly and depended on personal situations. Suggestions for future researchers and developers could be provided relating to recognition, program schedule, burden, and guidance.

## Introduction

Online interventions for cancer patients are increasingly being used because of benefits regarding costs, accessibility, availability, traveling, stigma, and psychological burden (Borosund et al., 2018; Knoerl et al., 2018). Earlier studies into online interventions have often shown positive patient outcomes (McAlpine et al., 2015; Skrabal Ross et al., 2020), which also applies to patient groups with long-term consequences of cancer and treatment, such as cancer patients with chemotherapy-induced peripheral neuropathy (CIPN) (Knoerl et al., 2018). However, online health interventions raise significant issues regarding adherence (Donkin et al., 2011; Eysenbach, 2002), which includes “the extent to which individuals should experience the content to derive maximum benefit from the intervention, as defined or implied by its creators” (Kelders et al., 2012). Adherence is often defined by module completion, and positively affects mental health outcomes in psychological health interventions (Donkin et al., 2011). Despite being very valuable, quantitative operationalizations of adherence provide limited insights. Subjective experiences such as aspects of challenges, feelings of positivity, endurance, and appeals, belong within the concept of engagement (Perski et al., 2017). Engagement with digital behavior change interventions is defined as “the extent of usage and a subjective experience characterized by attention, interest and affect” (Perski et al., 2017). In this, adherence is part of the definition of engagement. Considering engagement in online interventions is crucial, given its significant impact on the effectiveness (Donkin et al., 2011; Perski et al., 2017; Sieverink et al., 2017).

The adoption of online interventions by users is explained in several studies. A systematic review examined engagement and proposed an integrative conceptualization of engagement in digital behavior change interventions (Perski et al., 2017). The authors argue that engagement is determined by (1) intervention (i.e., content and delivery), (2) context (i.e., setting and population), and (3) targeted behavior. While this conceptualization has not yet been studied, the authors emphasize the significance of considering factors that could impact the use of online interventions. This is in line with the Task-Technology Fit model (TTF) that depicts the relationship between task (e.g., complexity), technology (e.g., functionality), and user (e.g., motivation), which determines adherence and effectiveness (Davis, 1989; Goodhue & Thompson, 1995; Kelders et al., 2012; Lee et al., 2003). This especially applies to online self-management interventions

for patients with long-term or chronic symptoms, such as CIPN, because self-management of these symptoms involves ongoing time-consuming complex tasks (Laugesen, 2013).

In recent years, research on patients' experiences of online self-management interventions has grown. A systematic review examined quantitative and qualitative literature studying predictors and participant-reported reasons for adherence to online self-management psychological interventions (Beatty & Binnion, 2016). It was concluded that personal and psychological factors influence adherence (e.g., guidance and sufficient time to complete). Intervention- and computer-related factors were also found to negatively influence adherence (i.e., impersonal content and technical problems) (Beatty & Binnion, 2016). Other qualitative studies also show that several factors promote or reduce adherence. A qualitative study assessing experiences of neck cancer and lung cancer patients in a guided self-management intervention for psychological distress reported multiple negative (e.g., low motivation and discipline levels) and positive experiences (e.g., coaching and working on assignments) (Krebber et al., 2017). However, the intervention was available both in book form and via the Internet. As a result, no experiences related to technology use were reported in the study. However, another study qualitatively examined an online self-management intervention for cancer-related distress (Beatty et al., 2017). Five overarching factors related to adherence were identified: illness, psychological, personal, intervention, and computer. Another study has qualitatively explored barriers and facilitators of an online Mindfulness-Based Cognitive Therapy for cancer patients, finding factors of treatment setting, format, therapist, and patient characteristics (Compen et al., 2017). In conclusion, these studies have shown that there are specific factors that affect patients' experience with online interventions.

It is unclear whether previously studied influencing factors to engagement in online self-management interventions are generic. Evaluating individual interventions is crucial for optimal effectiveness. Therefore, this qualitative study aims to examine barriers and facilitators to engagement to an online self-management intervention for cancer survivors with chronic painful CIPN, called *Embrace Pain* (van de Graaf et al., 2023). This analysis is part of a larger randomized controlled trial (RCT), assessing the effectiveness of the intervention, which is based on Acceptance and Commitment Therapy (ACT) compared

to a waiting list condition (WLC) on pain interference in daily life (van de Graaf et al., 2022).

## Methods

### Context and intervention

The online self-management intervention *Embrace Pain* is an 8-week course containing 6 modules in which patients receive psychoeducation and ACT processes, including asynchronous therapeutic email guidance. Patients learn to perform value-oriented activities in daily life with pain, provided by text and experiential exercises, supplemented with illustrations, metaphors, and audio files to reduce pain avoidance and increase pain acceptance. The indicated time investment per week was 2 hours. In the WLC, participants were able to follow the interventions five months after inclusion without therapeutic email guidance. The only distinction between the guided and unguided groups was the provision of guidance through therapeutic email communication. Despite this, the content of the intervention administered to both groups was identical, which is why both groups were examined in this study. The RCT's method, including an overview of the intervention, was previously published in a protocol paper (van de Graaf et al., 2022) along with a qualitative paper describing the patient-centered development (van de Graaf et al., 2023). Effects of the RCT are currently unknown and are expected in the fall of 2024.

### Participants

Participants were selected from the group of participants in the RCT of this project (van de Graaf et al., 2022). Inclusion criteria are described in the protocol paper previously published (van de Graaf et al., 2022). Patients who indicated that they would like to participate in an interview were approached and they were contacted as soon as possible after completion of the intervention. They provided informed consent for an interview before enrolment in the RCT. An equal distribution between the intervention group and the WLC group was attempted, which also applies to the gender distribution. Efforts were also made to include participants with different levels of engagement. This was estimated by one of the researchers (DG) who was aware of the patients' usage by accessing user data in the intervention's online system. Excluded were patients who had not activated their account of the intervention *Embrace Pain* and who were unable or unwilling to participate in an online video call via Teams.

This study was approved by the Medical Research Ethics Committee Brabant, the Netherlands (#NL78436.028.21) and the Ethical Review Board of Tilburg University, the Netherlands (School of Social and Behavioral Sciences; #TSB\_RP70).

### **Data collection and procedures**

Interviews were semi-structured and were conducted by one of the authors (DG) between September 21<sup>st</sup>, 2022, and December 19<sup>th</sup>, 2023. Interviews took place via video calling through Teams. The interview scheme was based on two qualitative studies into cancer subjective patients' experiences of online self-management interventions (Beatty et al., 2017; Krebber et al., 2017) and the TTF model (Davis, 1989; Goodhue & Thompson, 1995; Kelders et al., 2012; Lee et al., 2003), combined with input from previous patient interviews in the context and content of the intervention (van de Graaf et al., 2023). The final semi-structured interview scheme is shown in Table 1. Recruitment for interviews stopped when saturation was reached, indicating that additional interviews yielded no novel information, with recurring topics consistently emerging in the last few interviews.

### **Data analysis**

Thematic analysis was used for analyzing the data (Braun & Clarke, 2006). Audio of the interviews was recorded and transcribed verbatim by one author (DG) and by a Psychology master's student from Tilburg University. DG reviewed the transcriptions to confirm accuracy.

Interviews were coded in Atlas.ti 23. One transcript was coded by DG and FM independently. Subsequently, differences were deliberated upon, and consensus was reached. DG coded the remaining transcripts. Transcripts were inductively coded, deriving themes directly from the data. Text fragments were coded when they involved barriers or facilitators in the use of the online training *Embrace Pain* from the patient's perception. When patients discussed potential barriers and facilitators relevant to other patients but not applicable to their situation, these were not coded.

**Table 1.** Semi-structured interview scheme

Category	Questions
Motivation to participate	Why did you decide to participate? Did you have any doubts about participating? Why (not)?
Reason of non-usage	Were you able to complete the training? If not, why did you quit the training? What influenced you to quit training?
Experiences with intervention content	To what extent did you find the training relevant and of decent quality? How was your experience with the... ... information sections? ... exercises? ... quotes? ... audio fragments? ... time investment? ... mental workload? Were there components that made you want to put more or less time and energy into the training? If so, which ones? Which parts did you find difficult and why?
Experiences with intervention technology	What do you think of the online format of the training? To what extent did you experience problems using a computer, tablet, or phone? To what extent did you experience problems using the online environment?
Experiences with supervisor (if applicable)	What was your experience with the guidance you received during the training?
Personal circumstances	What personal circumstances may have increased your use of the training? Were there any circumstances in your personal life that made it difficult to attend the training? How did you deal with these?
Experiences of intervention effects	Do you feel the training was worthwhile? Why yes/no? How did the training change your thoughts and behaviors? Did the training help you to cope better with the neuropathy? Why (not)?

Once all transcripts were coded, codes were reviewed and adjusted if necessary. Subsequently, axial coding started using a codebook comprising 20 codes. Codes were written down and categorized into themes. This process was repeated once for verification. Ultimately, condensed meaning units were generated for every text fragment that was coded, capturing the core message of each quote. This provided a comprehensive overview of all coded data.

## Results

In total, thirteen patients participated. However, one participant was excluded because of cognitive problems. This eventually resulted in twelve participants, of which the participant characteristics are provided in Table 2. In total, 10% of all participants from the RCT (N=111) took part in this qualitative study. Interviews lasted 20 to 30 minutes.

**Table 2.** Participant characteristics

Participant	Gender	Age <sup>a</sup>	Educational level <sup>b</sup>	Time since end of intervention	Indicated average time spent on intervention per week	Guidance <sup>c</sup>	Indicated intervention completion (modules completed)
P1	Male	70-75	High	16 weeks	14 hours	Yes	Yes
P2	Female	55-60	High	<1 week	2 hours	No	Yes
P3	Female	60-65	High	7 weeks	8 hours	Yes	Yes
P4	Male	60-65	High	11 weeks	<1 hour	Yes	Yes
P5	Female	50-55	Middle	20 weeks	2 hours	No	Yes
P6	Female	70-75	High	6 weeks	1 hour	Yes	Yes
P7	Male	60-65	High	10 weeks	1 hour	Yes	Yes
P8	Male	65-70	Middle	8 weeks	2 hours	Yes	Yes
P9	Female	70-75	Middle	10 weeks	3 hours	Yes	Yes
P10	Female	55-60	High	3 weeks	N/A	No	Yes
P11	Female	60-65	High	4 weeks	2 hours	No	Yes
P12	Female	55-60	High	4 weeks	1 hours	No	No (5/6)

<sup>a</sup> Ranges are shown to ensure anonymity.

<sup>b</sup> Middle: secondary education or vocational education; high: Bachelor's degree or higher.

<sup>c</sup> Participants who received guidance were in the intervention group. Participants who did not receive guidance were in the WLC group.

Results can be divided into two overarching themes: barriers and facilitators to engagement. Seven codes emerged from the data for barriers and ten codes for facilitators. An overview of all strategies is presented in Table 3.

**Table 3.** Barriers and facilitators to engagement

Theme	Code	No. of times coded	No. of participants
Barriers	Program schedule	19	7
	Burden	11	7
	(Lack of) guidance	9	6
	Irrelevance	7	6
	Mindfulness exercises	6	4
	Usability	4	4
	Missing content	2	2
Facilitators	Usability	14	12
	Recognition	15	10
	Positive self-management	18	9
	Program schedule	14	8
	Symptom management	10	8
	Relevance	9	7
	Guidance	9	6
	Experiential exercises	7	6
	Mindfulness exercises	7	5
	Value-based living	5	5

### Barriers

The most common barrier identified was the program schedule. Many patients indicated having insufficient time for completion: *"I did find 8 weeks of training too tight. ... Especially with the effects of cancer, you do have days when you feel bad. And now you had to keep going because of the time frame."* (P2). Furthermore, many patients indicated that the timing was unfavorable due to personal schedule (*"I suddenly had to start, but you have to be able to plan ahead. By then a week had passed. That made me feel rushed."* (P3)) or holidays (*"We spent about three weeks on vacation during that period. That also takes you out of it and makes it harder to get going again."*).

Another barrier mentioned by several patients was the overall burden of the intervention. Some patients indicated that it was confronting to work on the training: *"You do also get into a deeper layer. I had a bit of a problem with that, too. ... I became aware of something of which I thought 'oh I left that behind me a long time ago'."* (P3). Also, some patients indicated physical limitations or cognitive limitations due to chemo brain: *"Because I have some cognitive impairments, processing is difficult. I understand it, but I also forget it very quickly, so I have to go back often."* (P10). Burden also related to remembering to attend the training during the intervention period as indicated by some patients: *"At the end I ran out of time, also a little bit due to my chemo brain. Then I forget I'm doing that training."* (P11).

Many patients indicated barriers related to guidance. Several patients who did not receive guidance expressed a need for some form of guidance, to be able to ask questions: *"Sometimes I had questions and then I couldn't ask those questions. ... Sometimes I found that quite difficult."* (P5). Some other patients indicated that they would have preferred guidance for motivation or reminders: *"It would have helped if once a week or so there was an email with: 'Is it all working out? Do you have any questions? This is the end date when you should be finished.'" (P11).* Furthermore, one patient who did receive guidance indicated that the delivery of guidance (i.e., by email) was not as required: *"I enjoy talking [verbal communication] to someone and then you also get more motivation from them. Like: the coach comes into play and I have to do well."* (P6).

Furthermore, several patients indicated that irrelevant content was a barrier. This meant that some patients experienced no connection to their own situation: *"What I always find difficult is when it comes to your partner. I am a mother with adult children who is divorced and who lives alone. I can't do anything with examples related to partners."* (P2). In addition, some patients indicated that they were already familiar with the content: *"Well I have found that I do a lot of things already. A lot of things were not new to me."* (P5).

Several patients reported experiencing barriers related to the included mindfulness exercises. This related to the length (*"All those mindfulness exercises, I did that occasionally but most of it I didn't do. Certainly not the longer exercises."* (P7)) or quantity (*"I think the training is put together well, but that meditation thing maybe there shouldn't be too much emphasis on that. It does make sense, but not two of those assignments."* (P9)) of mindfulness exercises.

Some patients reported experiencing barriers regarding usability. Some patients indicated difficulties navigating through the training: *"At one point it said 'look back at how that went'. Then I think 'yeah I'm not going to look back'."* (P9). Also, one patient indicated that the lack of face to face communication was a barrier: *"The emotion in the communication is not there."* (P1). Furthermore, one patient indicated problems logging in: *"There were a few email addresses and then I didn't know exactly how to get to the right address to log in."* (P7).

Finally, barriers were reported by a few patients due to missing content. One patient indicated that the exercises contained insufficient explanation and examples: *"I found the exercise about the areas of life difficult. ... Maybe it would be good to mention in the first exercise 'if you don't get there, you can still do the alternative exercise.'"* (P3). Another patient indicated that they missed the opportunity for peer contact: *"I would like to hear other people's response. ... I think if you are in a group where you also hear what the others are saying, you can have a lot of support from that."* (P5).

### Facilitators

One facilitator that many patients mentioned was usability. Several patients indicated benefiting from the flexibility of the training, allowing them to use it at their convenience, pausing when needed: *"It was nice. Sometimes on the tablet, sometimes briefly on the phone. You can put it away again for a while."* (P12). Several patients also indicated that the freedom in the training facilitated their use: *"I could look back. I did that regularly. Then I looked back a few sessions to continue."* (P8). Also, a few patients indicated that the training was easy to use: *"I found the course very doable online. It was clear and straightforward. The structure was consistent, and I could find everything very easily."* (P2).

Furthermore, many patients indicated recognition as a facilitator. Several patients indicated that they found recognition in the fictitious personas: *"I am reminded of the example given in training of a tennis player who had back pain. If he played tennis hard, he would forget the pain. I feel the same way."* (P1). Several patients also indicated that the examples and personas clarified the information and theory that was provided: *"When you see practical examples like this, it also indicates how differently you can deal with it. That supports the theory. I really liked that combination."* (P11).

Additionally, many patients indicated facilitators related to positive self-management. For several patients, the training was a way to find reflection: *"Well, for me, the most important thing was the insight that I put a lot of limitations on myself. I knew that, but it went much further than I actually realized."* (P10). Also, several patients indicated that they appreciated being able to further develop themselves through the training: *"Here you learned about negative thoughts and what can help you turn that around. I also found that helpful."* (P3). Furthermore, some patients indicated that they received confirmation of their coping

through the training: *"A lot of things I was already doing. ... It was often just confirmation for me."* (P5).

Many patients indicated the program schedule as a facilitator, which mainly related to the flexibility of the program schedule. This mainly related to being able to work on the training whenever and wherever the patient wanted: *"You can grab it at your own time when you have time for it. You just sit down for it and you don't have to leave the house."* (P4). Some patients appreciated the option to pause or request extensions for the training, particularly during personal circumstances that temporarily hindered use: *"During the training I found out that the cancer is back. Then I took a break from it."* (P10). There were also some patients who indicated that they valued being able to make their own choices about completing the exercises: *"In the mindfulness part, you got these 20-minute sessions, and you got a shorter one. Actually, you were supposed to apply both, but then I backed off. ...Then I chose to do the shorter one."* (P9).

Several patients indicated symptom management as a facilitator. Several patients felt that participation in training might improve their symptoms: *"I've tried quite a bit to combat neuropathy and anything I come across is welcome to me."* (P1). Furthermore, some patients indicated that they liked getting tips: *"I had gotten tips from you guys that I could just apply to that as well. That generally works pretty well I must say."* (P12). There were also some patients who experienced psychoeducation as a facilitator: *"I often really enjoyed reading about the theory about mechanism of a human being of why we do things and what the effect is if you choose to avoid the pain. I found that very useful to read."* (P11).

Finally, certain elements in the training were identified as facilitators by several patients. Several patients indicated that the relevance of the training was a facilitator because this made it possible to apply the training to one's own situation: *"It was relevant because I do have the symptoms. Regardless of where they come from. ... The complaints are there and you only refer to them."* (P10). Furthermore, several patients found the option for guidance a facilitator for various reasons, such as motivation, clarification of information, and feedback: *"I really liked that I had that online guidance. ... That does keep it going. I knew she [guide] would respond every Friday and I would fill in some things in advance."* (P3). Additionally, several patients indicated that they experienced both experiential exercises

“Yes, I liked those because then you get to know yourself better and you see what you are doing.” (P5)) and mindfulness exercises (“Especially that 4-minute breathing exercise where you focus on breathing in and out and where the air goes. I sometimes did it in bed at night after completion of the training, because the neuropathy is more pronounced then.” (P8)) as facilitators. Content related to value-based living was also perceived by several patients as a facilitator: “You never think about that so much. You get sucked into all the things that maybe you don’t feel like doing. This made you look at: ‘What are your values? What do you like to do? What are the things that are important to you?’ That impressed me.” (P9).

## Discussion

This study qualitatively examined barriers and facilitators to engagement of an online self-management intervention for cancer survivors with chronic painful CIPN. A variety of factors emerged from this analysis, with patients tending to report facilitators more than barriers. Facilitators most frequently mentioned were mostly associated with usability, recognition, being involved in positive self-management and symptom management, and a favorable program schedule. Barriers, on the other hand, most frequently mentioned were related to unfavorable program schedule, overall burden, (lack of) guidance, and irrelevance of content. Some factors (e.g., program schedule) were identified as both facilitators and barriers, indicating that it depends on personal preferences and situations. In summary, the barriers and facilitators identified in this study refer to the intervention content, technological aspects, and individual user characteristics. These findings align with prior research on barriers and facilitators (Beatty et al., 2017; Compen et al., 2017), as well as theoretical frameworks like the conceptualization of engagement in digital behavior change interventions and TTF model (Davis, 1989; Goodhue & Thompson, 1995; Kelders et al., 2012; Lee et al., 2003; Perski et al., 2017).

This study has found that many patients found recognition in the online intervention, especially through the quotes used based on patient experiences. Quotes and personas were incorporated into the current online intervention to humanize the technology (Lankton et al., 2015; Parker et al., 1978; van de Graaf et al., 2023). These patient experiences, depicted in a first-person narrative, can contribute to the feeling of social support which can help alleviate feelings of isolation for patients in coping with symptoms (Barabasch et al., 2021; Newhouse et al., 2016; Ziebland & Wyke, 2012). However,

patient experiences may contain unbalanced information or misinformation (Drewniak et al., 2020). In the current online intervention, therefore, researcher-written narratives based on experiences shared by patients were incorporated. This can be seen as an accessible and controlled way of incorporating patient experiences in online interventions to increase the sense of social support.

Furthermore, this study has shown that many patients perceived participating in the online intervention as a pleasant way of engaging in positive self-management. Self-management empowers cancer survivors to enhance their health and well-being (Cuthbert et al., 2019). Previous research has shown that theoretically based self-management interventions for various types of chronic diseases, including cancer, can positively influence outcomes such as quality of life, coping, health goals, self-regulatory skills, and self-efficacy (Bandura, 2004; Chodosh et al., 2005; Cuthbert et al., 2019; Lorig & Holman, 2003). Self-efficacy for symptom management in cancer patients is defined as “the ability to implement behaviors to prevent, recognize, and relieve symptoms” and is a vital component in enabling patients to effectively self-manage their cancer-related symptoms (White et al., 2017, 2019). Self-efficacy empowers patients to change their self-management behaviors and helps patients set realistic goals in coping with the symptoms (Merluzzi et al., 2001; White et al., 2019). This aligns strongly to embrace symptoms and pursue a value-based life, given the ACT approach to the online intervention in the current study. This alignment could possibly explain why being involved in positive self-management and symptom management was a frequently reported facilitator observed in this study.

While for many patients the flexibility of the training program was a facilitator, many patients experienced the training program as a barrier. In this case, this is related to both unfavorable start time and insufficient time to complete the training due to personal situations, in the context of the study. This aligns with previous studies regarding adherence in online psychological interventions which have shown that time-related factors (e.g., not having enough time or being too busy) deteriorate adherence and engagement (Beatty et al., 2017; Beatty & Binnion, 2016; Donkin & Glozier, 2012). It is important to mention that in the current study, the start of the training was not aligned with the participants in advance. In the study, participants received an invitation at the

time of start and had 8 weeks for completion, which was only extended upon request. Based on this study's results, it is recommended to initiate online interventions in coordination with participants. Additionally, it is suggested that the intervention's total duration is sufficiently long, incorporating several weeks of flexibility in scheduling (e.g., 9 weeks for an online intervention with 6 components). It can also be considered to allow unlimited access to the intervention. We also recommend that participants are encouraged to contact the contact person or supervisor of the online intervention if they encounter problems so that it can be assessed when an extension of access is needed to avoid dropout.

Furthermore, barriers identified in this review included the burden and chemo-brain that patients may suffer from. Chemo-brain is known to be a consequence of chemotherapy which is characterized by self-perceived thinking and memory problems (Hermelink, 2015). In this study, for example, patients reported that the training was too stressful or that they had concentration problems. Therefore, a low cognitive effort of the online intervention is necessary for proper understanding of the content and effective use (Rotondi et al., 2017). This can be achieved by dividing the intervention into short manageable sections to reduce the complexity on the pages, and to provide simple navigation between pages and sections (Rotondi et al., 2017). Patients also indicated that they valued the ability to schedule the use of the intervention within the provided timeframe of the training themselves, as well as the ability to pause when needed, which has also been shown in previous qualitative research on adherence in computerized cognitive behavioral therapy for depression (Gerhards et al., 2011). This way, patients can consider their physical and mental limitations in their use, which will contribute to adherence and effectiveness.

In terms of guidance, patients who had access to guidance indicated that they experienced it as valuable, despite not all of them using it (equally). Among those without access to guidance, some expressed a need for it. For example, these patients would have appreciated being able to ask questions to clarify information or exercises, as well as to discuss private situations that made use of the online intervention difficult. Previous research has shown that online interventions with guidance compared to non-guided versions result in better outcomes in satisfaction, usage, and adherence (Baumeister et

al., 2014; Lin et al., 2017; Musiat et al., 2022). Also, an earlier study examining a self-guided online Cognitive Behavioral Therapy intervention for patients with CIPN suggests that counseling could be a useful addition (Knoerl et al., 2018). However, a systematic review assessing adherence to online psychological interventions reported that preferences regarding guidance varied widely from the need for intensive guidance because of engagement, to no need for guidance because of anonymity and freedom (Beatty & Binnion, 2016). Therefore, it seems recommendable to offer guidance without obligation to patients.

### **Limitations and strengths**

Some limitations of this study should be mentioned. First, no results were available from patients with very low engagement levels, since these people were reluctant to participate in interviews. The current sample is therefore not representative of the entire user group. Barriers that might exist with low engaged patients, such as lack of time and low levels of motivation (Beatty et al., 2017; Beatty & Binnion, 2016), were therefore not completely reflected in this study. Furthermore, non-adherers might also comprise patients who realized they were already proficient in managing their symptoms and consequently discontinued the intervention. Unfortunately, obtaining insights into this matter was not possible because these patients did not participate in the interviews. Second, there was much difference in the time between intervention completion and the interview. Possibly, patients with a longer period between the intervention and interview may have remembered fewer details of their experience with the intervention. Third, the results of this study may be less applicable to other self-management interventions. Each intervention has its characteristics in terms of tasks, technology, and users, all of which affect adherence (Davis, 1989; Goodhue & Thompson, 1995; Kelders et al., 2012; Lee et al., 2003). Consequently, the experiences encountered by patients also vary. Fourth, the study sample included highly educated and highly motivated patients, who experienced little or no difficulty with language and the use of technology. Therefore, the generalizability of the results to groups with lower education levels and lower technology literacy levels might be limited.

Some strengths should also be emphasized. First, interviews were semi-structured, enabling patients to freely express their individual experiences without being constrained

by the interview's format. The core questions were addressed in all interviews, leading to a consistent structure across all interviews. Second, interviews were conducted with patients from all conditions, including both those who received therapeutic email guidance and those who did not. This enabled the assessment of the experienced barriers and facilitators associated with the availability or unavailability of guidance. Third, interviews took place via video call, enabling vulnerable and disabled cancer patients to participate without being hindered by, for example, physical limitations.

### **Conclusions**

This study qualitatively identified facilitators and barriers to engagement to an online self-management intervention for cancer survivors with chronic painful CIPN. Facilitators and barriers varied greatly and were dependent on personal situations. Recommendations could be given in terms of recognition, program schedule, burden, and guidance. Consideration of such recommendations following qualitative evaluations is imperative to ensure careful implementation in practice.

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# Chapter 9



## General discussion

This dissertation on patients with chemotherapy-induced peripheral neuropathy (CIPN) was divided into two sections. The first section included gaining insights into the experiences of patients with CIPN, which was described in **Chapters 2, 3, and 4**. The second objective included studying an online psychological intervention for patients with CIPN and its patient-centered development in **Chapters 5, 6, 7, and 8**.

In this general discussion, the main findings will be summarized first. Subsequently, several relevant topics that relate to patient experiences with CIPN will be discussed, as well as topics that relate to online psychological interventions and patient-centered development. Implications for future research are provided as well. The general discussion ends with an outline of the strengths and limitations of this dissertation.

## Summary of the main findings

### Part I - Patient experiences

To provide a clear picture of the problems of those living with CIPN, an exploratory quantitative study of the experiences of patients with CIPN in terms of symptoms and daily limitations was conducted in **Chapter 2**. This showed that patients mainly experience complaints in both hands and feet, such as tingling and loss of or diminished sensation. Patients are often able to perform activities of daily life (ADL), but they experience many limitations in performing activities in their social and work-related roles. An exploration of perceived support from healthcare professionals showed that patients often feel they are not informed about what they can do when CIPN occurs. The degree of social support, measured as the degree of empathy patients experienced from the direct environment, varies considerably. Although it varies, most patients experience at least some empathy from the direct environment.

In **Chapter 3**, a qualitative exploration of how patients deal with the symptoms associated with CIPN, categorized as coping and self-management strategies, was described. Only strategies perceived by patients as helpful were explored. Coping was defined as strategies patients use to deal with symptoms and associated limitations in general. Many patients reported using active strategies, such as planning and seeking social support. Additionally, many patients used passive strategies, such as avoiding burdensome

activities. Furthermore, self-management strategies were assessed, which were defined as practical actions to reduce symptoms. It was shown that there is a wide variety of self-management strategies that patients employ. In this, a lot of patients indicated to apply passive strategies, such as medication and rest. However, some patients indicated that active strategies were helpful, such as exercising.

**Chapter 4** describes peripheral neuropathy in colorectal cancer patients and the extent to which pre-treatment anxiety and depression predict symptom severity after treatment. Patients in whom peripheral neuropathy symptoms arose or worsened during chemotherapy were included. Multivariable regression analyses showed no associations for pre-treatment depressive symptoms and neuropathy symptom severity at one- or two-year follow-up, nor for pre-treatment anxiety symptoms at one-year follow-up. However, pre-treatment anxiety was shown to be a predictor of symptom severity at two-year follow-up.

## Part II - eHealth interventions

**Chapter 5** describes a systematic review of online Acceptance and Commitment Therapy (ACT) interventions for chronic pain in general. This systematic review assessed a total of 20 articles, encompassing fourteen distinct individual interventions. It was found that most studies provided insight into the ACT processes that were incorporated into the eHealth intervention, but considerations regarding technology choices were rarely explained. It also showed that measures of adherence were highly inconsistent. This chapter can be used as input into the essential factors that researchers and developers should consider when developing or evaluating an online psychological intervention.

In **Chapter 6**, the patient-centered development of an online ACT intervention for patients with chronic painful CIPN is described. This chapter followed the CeHRes roadmap for an iterative development process, which involved semi-structured interviews with patients and experts to ascertain needs and context as well as low-fidelity and high-fidelity prototype testing. Key outcomes included having autonomy and varying needs relative to guidance. Furthermore, patients indicated positive attitudes toward ACT. It resulted in a theory-driven online intervention called *Embrace Pain* consisting of 6

components based on ACT and psychoeducation. Choices regarding quotes, guidance, and multimedia were also based on the interviews and prototype testing.

A protocol for a randomized controlled trial (RCT) was described in **Chapter 7**. The protocol included studying the effectiveness of an online self-help intervention based on ACT compared to a waiting list condition (WLC) to deal with CIPN, as well as factors moderating the effects and the extent to which effects differ between a guided and unguided version of the intervention. The protocol included a two-parallel, non-blinded RCT. Patients in the intervention condition were offered six modules including psychoeducation and ACT processes, with therapeutic email guidance. Five months after enrolling, participants in the WLC were offered the intervention without guidance. The main outcome of this study protocol is pain interference. Besides quantitative measures regarding psychological outcomes and adherence, qualitative interviews regarding user experiences are also part of the study protocol.

To qualitatively examine the use of *Embrace Pain*, the barriers and facilitators of engagement were studied, of which the results were described in **Chapter 8**. Engagement was defined as a combination of adherence and the subjective experience reported by the user. In general, it can be concluded that barriers were mainly related to unfavorable program schedules, burden, lack of guidance, and irrelevance of content. In contrast, patients identified facilitators as the usefulness of the program, engaging in positive self-management and symptom management, and favorable program schedule. Factors varied widely between users and are likely dependent on personal situations. This variability may explain why certain factors, like program scheduling, were perceived as barriers by some individuals while being viewed as facilitators by others.

## **Discussion of the main findings**

### **Part I - Patient experiences**

#### ***Searching for a way to deal with symptoms and limitations***

A recurring note in the qualitative studies within this dissertation was that patients experience CIPN as a challenging and lonely quest. Before and during the treatment process, patients have different priorities. Patients often indicated that they wanted to survive, considering any subsequent concerns following treatment to be of secondary

importance. Besides, the severity and burden of CIPN are likely underestimated by patients because it is difficult to accurately imagine a physical sensation that people without this condition have never experienced. As a result, often no or insufficient attention has been paid by patients to the (possible) development of CIPN during treatment, which patients often regret afterward. This has led to highly limiting symptoms in many patients (**Chapter 2**), resulting in a variety of coping and self-management strategies that they employ to limit symptoms (**Chapter 3**). It is recommended that patients are thoroughly informed about the potential development of CIPN before and during chemotherapy treatment. Individual values and boundaries relating to possible consequences of CIPN should be discussed with patients by attending medical specialists or nurse practitioner. Based on these discussions, decisions such as dose reduction can be made when necessary.

Additionally, it is advised to provide both emotional and instrumental support to patients during and after treatment. Emotional support may include psychological support from a social worker or medical psychologist to address the challenges and problems arising from CIPN. Based on ESMO and ASCO recommendations, some practical advice can also be given to healthcare professionals (Jordan et al., 2020; Loprinzi et al., 2020). Encouraging physical activity is generally recommended for patients with CIPN because it contributes to improving overall physical condition as well as CIPN symptoms (Jordan et al., 2020). Also, healthcare professionals can refer patients to a physical or occupational therapist for additional support for physical limitations and problems in performing general daily activities due to CIPN (Jordan et al., 2020; Loprinzi et al., 2020). Besides supporting the patients themselves, it is advisable to involve their social environment, such as a partner, family, and close friends, in the process where possible (**Chapter 2**). Through psychoeducation about the development and symptoms of CIPN, understanding among relatives can be fostered, potentially leading to increased support for patients in their daily lives. Furthermore, future research should explore ways in which patients would like to be supported in the context of CIPN so that the support provided meets the needs of patients as best as possible. On top of that, the current absence of effective treatments underscores the critical importance of ongoing research into both the prevention of and treatment options for CIPN.

***Guidance even before treatment starts***

In **Chapter 4** it was discussed that pre-treatment anxiety is a predictor of symptom severity at two years follow-up in colorectal cancer patients with peripheral neuropathy. Patients who experience chronic pain can fall into a vicious circle in which they end up experiencing more pain and strain, which is described in the Fear-Avoidance Model (Crombez et al., 2012; Vlaeyen et al., 2016). This describes the phenomenon where individuals experiencing severe or 'threatening' pain engage in catastrophizing thoughts. These thoughts lead to pain-related fears, resulting in pain-hyperfocus (i.e., hypervigilance) and increased pain-avoidance behaviors. Consequently, this increases inactivity, which might result in negative emotions and loneliness, as well as a deteriorated physical state. Ultimately, this lowers the threshold for experiencing pain, meaning that pain perception increases in the long term. In this regard, it seems reasonable that people who are naturally more anxious, experience more intense pain than people who are naturally less anxious. It is also known that anxiety and catastrophizing are predictors of pain severity and disability in various types of chronic pain, such as chronic postsurgical pain and musculoskeletal pain (Leeuw et al., 2007; Theunissen et al., 2012). Additionally, neuroticism, a personality trait characterized by emotions such as anxiety, is shown to be a moderator in the effect of pain catastrophizing on pain severity (Goubert et al., 2004). People who score high on negative affect are more likely to notice physical sensations because of their hypervigilance, which means that they are more likely to attentionally scan both the external and internal environment for negative stimuli (e.g., pain), which is driven by anxiety and uncertainty (Watson & Pennebaker, 1989).

It is important to consider strategies to support patients who are naturally more anxious and consequently more likely to experience higher symptom severity of peripheral neuropathy. The Fear-Avoidance model demonstrates that various psychological factors influence pain perception (Crombez et al., 2012; Vlaeyen et al., 2016), implying that psychological interventions could be valuable in improving pain intensity. Therefore, being vigilant for patients' anxiety levels prior to initiating treatment is recommended. This can be done by attentively monitoring patient behavior, including verbal and nonverbal cues, that may indicate heightened levels of anxiety or asking the patient directly. When high anxiety levels are identified, asking what the patient needs for more comfort, or offering interventions such as psychoeducation on treatment and side effects

may be valuable, before, during or after treatment. Important to note here is that these interventions are low threshold, to minimize the burden on patients during an intense period of diagnosis and treatment.

### ***Coping and pain-related factors***

Due to the limited treatment options for CIPN, healthcare professionals are often unable to provide medical treatment to patients, whereby patients are often told to 'just deal with it'. However, this seems like an oversimplified message, and it does not seem to contribute to the coping and self-management strategies that patients ultimately employ. **Chapter 3** described that patients use a variety of self-management (e.g., medication, resting, and exercising) and coping strategies (e.g., planning, seeking social support, and avoiding competing activities) to deal with their symptoms. However, the qualitative interviews in **Chapter 3** indicated that there is still a tendency of uncertainty among patients about their management of symptoms and impairments. Patients thereby experience a lonely and challenging quest for ways to manage their symptoms and daily limitations. Therefore, healthcare professionals must consider factors beyond medical interventions.

The importance of coping and self-management strategies does not seem to be widely recognized in healthcare, while it is highly desirable to support patients in adopting these strategies. This support is crucial as the adoption of helpful coping strategies contributes to a reduction in several pain-related factors. Earlier research has shown that active coping strategies, in which patients try to control their pain themselves, contribute to reduced disability, while passive coping strategies, in which patients leave control of their pain to others, worsen impairments in breast cancer patients with chronic pain (Bishop & Warr, 2003). Other research has also shown that passive strategies can eventually lead to impaired functioning (Reneman et al., 2014) which can lead to long-term impaired functioning in emotional, cognitive, social, role, and physical areas (Bakitas, 2007; Bonhof et al., 2020; Tofthagen, 2010; Tofthagen et al., 2020). Furthermore, pain coping flexibility, meaning that patients are able to apply multiple coping strategies to deal with their painful symptoms, appears to positively affect a perceived sense of control over pain (Haythornthwaite et al., 1998), where it seems primarily important that patients adapt these multiple strategies to the situation in which they find themselves. With this, patients

feel that they are able to reduce pain and accurately predict fluctuations in pain intensity, giving them a greater sense of control over their lives (Haythornthwaite et al., 1998). Other factors related to well-being such as satisfaction with life have also been demonstrated to improve through the use of helping coping strategies (Walker & Esterhuysen, 2013). *Approach coping*, which includes attempts to actively manage pain, (e.g., using available social and professional support) appears to have a moderating effect on the influence of pain severity on satisfaction with life. This moderating effect is not present for *avoidance coping*, which includes people's attempts to avoid coping with the pain (e.g., withdrawal from social activities). Patients applying *approach coping* strategies thus experience less deterioration in their satisfaction with life (Walker & Esterhuysen, 2013). The beneficial effects on psychological and pain-related outcomes show the importance of addressing coping mechanisms in patients. It might even ensure that by supporting patients in adopting more helpful coping strategies, patients need to rely less on the limited medical treatment options available, such as duloxetine. Duloxetine, an antidepressant and analgesic that can also be used to treat CIPN, is associated with several side effects including drowsiness, headache, and dizziness (Lunn et al., 2015). Many patients experience at least one of these adverse effects, which can further negatively impact their daily lives (Lunn et al., 2015). Consequently, minimizing the need for such medication is often preferable for enhancing patient well-being. Interventions aimed at enhancing patients' coping strategies, such as ACT in which patients are encouraged to refrain from using avoidance strategies (Hayes et al., 2006; Scott et al., 2016), are thus recommended.

## **Part II - eHealth interventions**

### ***Theory-driven interventions with informed technology choices***

To provide a theory-driven foundation for the intervention development in this dissertation, a systematic review of online ACT interventions for chronic pain was conducted in **Chapter 5**. Previous research pointed out the importance of theory-driven content in online ACT interventions for chronic pain, but also indicated that it is often lacking (Gentili et al., 2020). On the contrary, in the current dissertation it was found that information about the theory behind the intervention and related content (e.g., aspects of psychological flexibility) were often mentioned. It is reassuring that intervention developers and researchers seem to understand the need for this. Although, **Chapter 5**

also highlighted that the explanations of the theoretical considerations were quite limited. Explanations of content choices may include, for example, the creation of text fragments on ACT theory, choices for ACT metaphors, and the development of mindfulness exercises. Deliberate selection of theory-driven content is crucial for optimal development, as well as for study replication and evaluation of the intervention.

This same sentiment applies to the choices being made regarding opportunities in technology. Especially for technology choices, **Chapter 5** found that considerations were barely explained, making it unclear what the reasoning behind the choices of developers and researchers were. Since choices regarding technology depend on the particular user group and context (e.g., cognitive problems due to treatment), it is crucial that considerations are explained and that it is clear what led the developers and researchers to their final choices. In contrast to theory-driven content, where a theoretical framework underpins the intervention and largely defines its structure, choices regarding technology are not determined by a singular guiding theory, allowing for a broad spectrum of possibilities. However, theories such as the Technology Acceptance Model (TAM) (Davis, 1989; Marangunić & Granić, 2015) and Task-Technology Fit model (TTF) (Goodhue & Thompson, 1995; Lee et al., 2003) may serve as valuable frameworks for guiding technology-related decisions. These models can assist developers and researchers in identifying and considering the key factors that influence technology choices. Furthermore, scientific practical roadmaps are developed for developers and researchers to utilize in iterative development of online interventions in collaboration with patients and other experts, also known as patient centered design or human centered design (Demiris et al., 2008; Gould & Lewis, 1985; Gulliksen et al., 2003). This enables them to make decisions during the development process that are aligned with user needs and contextual factors. An example is the Centre for eHealth Research (CeHRes) roadmap, which was followed in **Chapter 6** of this dissertation (Gemert-Pijnen et al., 2011). In addition to this roadmap, there are several other practical frameworks that can be followed for developing eHealth interventions, which are described in a systematic scoping review and concept mapping study (Bonten et al., 2020). It is important to choose a roadmap that matches the objectives of the specific research project with respect to quality, safety and implementation (Bonten et al., 2020; Kip et al., 2022). However, these roadmaps are not a precise step-by-step plan for carrying out an eHealth development

process, but provide tools for setting up such a process in line with the goals of the research project (Kip et al., 2022). Within these frameworks, as in the CeHRes roadmap, all kinds of methods (e.g. focus groups and usability testing) and products (e.g. prototypes and personas) can be used to apply the iterative development process (Kip et al., 2022). The complexity of eHealth development necessitates the integration of multiple strategies. Furthermore, it is crucial that the selection of these methods and products again aligns with the objectives of the research project (Kip et al., 2022).

### ***The need of multidisciplinary work in intervention development***

During the first phases of the development process (**Chapter 6**), it has been noticed that there often is an underestimation of the complexity of an online intervention development process. From conversations with stakeholders, it still seems to be common for traditional conventional interventions to be 'copied and pasted' into an online format by healthcare professionals, psychologists, and researchers. This completely misses the point in the context of patient-centered design. Since developing eHealth is very complex and different disciplines are continuously needed (Kip et al., 2022; Rooij & Marsh, 2016), it is very important that development projects are conducted by multidisciplinary teams. Each expert contributes specialized knowledge and experience pertinent to their field: for example, a psychologist offers expertise in therapeutic objectives and content, a medical specialist provides insights into the patient's medical context, a software developer contributes knowledge on platform development, an eHealth specialist ensures alignment of platform features with user requirements, etc. This must be accompanied by intensive involvement of the patients themselves. Only by using a multidisciplinary team, patient-centered development can reasonably be carried out (Velsen et al., 2013). This way of working has also been adopted in **Chapter 6**.

This multidisciplinary way of working does bring certain challenges. For example, team members likely have different methodologies and jargon due to their diverse backgrounds, as well as different levels of involvement, power, and interest, which may all affect their goals and expectations in the project. (Latuapon et al., 2023; Pagliari, 2007). Previous research examined the challenges of multidisciplinary collaboration within an eHealth project, based on a project conducted by Uppsala University (Grönqvist et al., 2017). In this examination, general challenges as well as eHealth program specific

challenges were identified. Regarding eHealth programs, there are two challenges that are striking and that were also recognizable in the development of this dissertation. First, it relates to the openness regarding to others' discipline. People are often used to collaborate within their own field, in which they experience similarities with respect to science, jargon, and culture. When working within a multidisciplinary team, these factors will differ from each other. It can be challenging for team members to be open to and adapt to the beliefs and expectations of others. Second, while it is known that the diverse theoretical perspectives among experts provide substantive added value, this diversity can also be a great challenge for team members as it can hinder communication. In this case study, the authors emphasized the critical role of coordinating multidisciplinary teams to overcome these challenges effectively (Grönqvist et al., 2017). The eHealth intervention in the current dissertation was developed by a multidisciplinary team that consistently openly discussed personal attitudes, beliefs and goals, to maintain alignment during the project. This responsibility was overseen by one of the team members. Through this approach, miscommunications could be recognized and resolved promptly, ensuring that the team functioned as optimally as possible.

### ***Challenges in usability regarding patient characteristics***

In response to the qualitative user needs exploration in **Chapter 6**, it was discussed that experts indicated that health literacy and digital literacy vary between patients and that it should be considered in the development of the online intervention because of usability. Health literacy and digital literacy are both highly relevant to eHealth use and are more comprehensively encompassed by the concept of *digital health literacy*. It is defined as “the ability to seek, find, understand, and appraise health information from electronic sources and apply the knowledge gained to addressing or solving a health problem” (Norman & Skinner, 2006) and this concept relies on individuals' competencies in all facets of both health literacy and digital literacy. Currently, it is considered to be one of the greatest predictors of health (van Kessel et al., 2022).

Several factors influence digital health literacy in cancer patients, which was recently described in a scoping review (Zhang et al., 2023). This review concluded that cancer patients of older age, with a low education level, of male gender, and living in rural places, have lower digital health literacy levels. In addition, this review has also shown that high

education levels, more information-seeking behavior, and more social support contribute to digital health literacy (Zhang et al., 2023). This shows that there is a variety of factors that determine a patient's ability to use, understand, and apply the online intervention. Earlier research has also qualitatively examined digital health literacy in digital health technologies in cancer patients (Kemp et al., 2021). In the study, several factors were identified that were seen by stakeholders (e.g., patients, caregivers, healthcare professionals, digital health and/or oncology researchers, and developers) as detrimental to the level of digital health literacy. High levels of digital health literacy were generally seen as beneficial for engagement in digital health technologies. In addition, it was concluded that stakeholders perceive that digital health literacy is more difficult for older patients because of technology, but also for younger patients because of lower motivation levels. Stakeholders also indicated that people in lower socioeconomic classes might have more problems in terms of digital health literacy because of limited accessibility to digital systems (Kemp et al., 2021). This was also reflected in the recruitment for the interviews described in **Chapters 3, 6, 7, and 8** of this dissertation. It was more difficult to include older patients due to the digital aspect of the study and we mainly included patients with above-average socioeconomic status. Furthermore, the earlier mentioned qualitative study also concluded that geographical locations with poor internet connectivity are associated with lower digital health literacy (Kemp et al., 2021), which seems to be less relevant in the Netherlands where we recruited our samples. However, it is crucial but difficult to recognize and account for diversity in digital health literacy in the development process of online interventions. Therefore, it is recommended to consider the factors relevant to the intervention, context, and patient group in question.

In addition to digital health literacy, cognitive problems caused by the so-called chemo brain (Hermelink, 2015) were also taken into account in the development of the online intervention (**Chapter 6**), because this is present in a substantial part of the current patient group. These factors were considered by providing concise information sections, providing varying multimedia (e.g., images as supporting material, and audio files for mindfulness exercises), dividing modules into multiple sections, and pausing the intervention when desired. Language level was selected to be highly accessible for patients with low digital health literacy and engaging for those with high digital health literacy. Close monitoring was also conducted during patient participation in the online

intervention to identify when patients experienced problems using the system or when misperceptions of the content were observed. In this case, guidance to the patient was intensified (e.g., increase the frequency of asking the patient if they have any questions or unclarities). This method of tailoring is highly recommended, as it allows misperceptions to be corrected promptly and potentially limits problems related to use.

### ***Engagement to gain a deeper understanding of usage***

During the development of this dissertation, it was observed that the terms *engagement* and *adherence* are frequently used interchangeably, despite their distinct meanings. In **Chapter 8** it was discussed that adherence is a quantitative approach to study usage to which it aligns to the developer's intention. Engagement on the other hand is a broader approach that includes both adherence as well as subjective user experiences (Kelders et al., 2012; Perski et al., 2017). Previous studies indicated that terms such as engagement, (non-)adherence, (non-)attrition, patient engagement and patient participation are often used interchangeably (Barello et al., 2016; Sieverink et al., 2017). However, these terms often measure distinct concepts (Barello et al., 2016; Sieverink et al., 2017) and relate to different facets of the actual definition of patient engagement (Barello et al., 2016). A systematic review evaluating patient engagement in eHealth stated that this implies that studies evaluating patient engagement often fail to account for the complexity of the concept of patient engagement (Barello et al., 2016).

Engagement with eHealth interventions is shown to be crucial for their effectiveness (Donkin et al., 2011; Perski et al., 2017; Sieverink et al., 2017). Patient engagement in eHealth is a complex and multifaced concept (Barello et al., 2016). It includes three distinct dimensions: behavioral, cognitive, and emotional. The behavioral dimension of patient engagement relates to the actions that patients perform regarding coping with the disease and treatment. Patients' knowledge and understanding of the disease and treatment are part of the cognitive dimension of patient engagement. The emotional dimension of patient engagement relates to patients' psychological and emotional responses to the adjustments in daily life that have to be made due to the condition. When eHealth evaluations involve all these dimensions, they enable a comprehensive assessment of the patient's subjective experience. If only part of the concept of patient

engagement is included, some of the experiences may be overlooked, potentially hindering the effective implementation of the intervention (Barello et al., 2016).

Within eHealth research, there is still regularly a tendency to focus on quantitative measurements in evaluating usage (i.e., adherence), which includes only the behavioral aspect of engagement. Because of the complexity of engagement, merely examining the quantitative nature of adherence is not sufficiently comprehensive (Barello et al., 2016). It is crucial to focus on examining patient engagement so that patient experiences can be assessed as broadly as possible and thus interventions can be optimally aligned to patients' actual needs. A systematic review examining engagement in digital behavior change interventions has constructed a conceptual framework emphasizing that engagement is affected by the technology itself (i.e., content and delivery mechanisms), the contextual elements (i.e., context and patient population), and the specific behaviors being targeted (Perski et al., 2017), which aligns with theoretical frameworks such as TAM and TTF (Davis, 1989; Goodhue & Thompson, 1995; Lee et al., 2003; Marangunić & Granić, 2015). This demonstrates that engagement is a highly suitable method for comprehensively evaluating the usage of online interventions. Therefore, future research should examine engagement to build consensus on how engagement should be assessed, allowing for more reliable comparisons of study outcomes.

### ***eHealth as an integral part of healthcare***

In the conversations with patients as part of the qualitative research interviews in this dissertation (**Chapters 3 and 8**), it became clear that patients experienced learning to deal with the CIPN as a lonely quest. In their perception, little or no support was offered to them after treatment, leaving patients to rely on themselves. When proven effective, online psychological interventions such as *Embrace Pain* (**Chapter 6**) could offer patients support in an accessible way to learn how to deal with their symptoms and limitations. This would allow patients to receive guidance at an early stage, something that many patients indicated that they had missed during or shortly after their treatment. For example, nurse specialists in hospitals could offer online psychological interventions to patients, since psychological, informational, and educational support are crucial facets of their responsibilities (Kerr et al., 2021). Providing this in a timely manner may possibly help prevent any worsening of (mental or physical) complaints.

It is important to emphasize that online psychological interventions should in principle not be seen as a replacement for traditional psychological interventions. Online interventions broaden the range of treatments available, mainly for patients who have a positive attitude towards online environments (Barak et al., 2009). If patients have more intense psychological problems in dealing with cancer-related problems, for example, they must be referred to specialized mental health professionals, preferably specialized in psychological care for cancer patients. In the online intervention *Embrace Pain*, guidance was not provided by a BIG registered psychologist. Consequently, patients with severe mental health issues were unable to receive appropriate professional guidance. When substantial psychological issues were identified by either the researcher or the supervisor, patients were advised to contact a healthcare professional (e.g., general practitioner). Furthermore, it was clarified that patients who were already undergoing psychological treatment should not engage in *Embrace Pain*. In such cases, the researcher emphasized the importance of the ongoing psychological treatment, and access to the online intervention was either not provided or was terminated. This approach was adopted because the online self-management intervention was perceived as suitable exclusively for individuals exhibiting moderate to mild symptoms.

The recent introduction of the *Kanker.nl Appstore* in the Netherlands represents an advancement towards enhancing accessibility to digital healthcare (Kanker.nl, n.d.). In this tool, which was funded by the Dutch Cancer Society (KWF), patients receive a credit of €100 that they can freely spend for purchasing psychosocial oncology apps. The *Kanker.nl Appstore* contains a large variety of apps, including both paid and free options, offering decision aid tools and modules designed for several cancer-related issues such as fatigue and panic disorder. The apps that are available in the Appstore have been tested by the Netherlands Comprehensive Cancer Organisation (IKNL) and the Public Health Authorities (GGD) and are considered reliable and safe. This allows patients to use reliable and secure digital healthcare in an accessible way. Patients are thereby relieved from the burden of seeking digital healthcare themselves, which is often challenging for patients because of the difficulty of assessing which apps are suitable from the large available range (Hyzy et al., 2024). Previous research has demonstrated that user ratings and download numbers do not reflect the quality of app, despite being commonly relied upon by users when selecting health apps (Hyzy et al., 2024). A systematic review of pain

management apps has also shown that many apps have not been scientifically developed and evaluated and that, for example, the content was not based on scientific theory (MacPherson et al., 2022). The *Kanker.nl Appstore* therefore seems an appropriate place to offer Dutch online interventions such as the one developed in this dissertation, if proven effective.

eHealth development and implementation should not be driven solely by feasibility but rather by its contextual appropriateness and ability to address specific healthcare challenges for healthcare professionals and patients. The National Institute for Public Health and the Environment (RIVM) in the Netherlands carried out an eHealth monitor in 2021 into the availability and use of eHealth, commissioned by the Ministry of Health, Welfare and Sport (National Institute for Public Health and the Environment, 2022). This report has shown that there was an increase in eHealth applications, but that they were not always effective. It also emphasized that eHealth solutions can place an additional burden on healthcare professionals and that eHealth is often not yet used optimally by patients because they are often not aware of the possibilities. Currently, eHealth options are often seen as 'extra', while it should be an integral part of healthcare (National Institute for Public Health and the Environment, 2022). This indicates that numerous eHealth tools are being developed without clear objectives and appropriate implementation strategies, resulting in suboptimal utilization. It is therefore essential that a patient-centered development approach is used in the development of online interventions to optimize alignment with user needs and context and integrate implementation considerations from the early stages of the process (Demiris et al., 2008; Gould & Lewis, 1985; Gulliksen et al., 2003).

## **Strengths and limitations**

### ***Holistic approach to CIPN***

Determining whether patients have CIPN is often approached objectively: patient symptoms are measured, and scores are used to determine whether they have CIPN. This is assessed either by the patient through a self-administered questionnaire or by a medical specialist using a standardized objective measurement instrument (Cavaletti et al., 2010; Griffith et al., 2010; Postma et al., 2005). In this dissertation, the EORTC QLQ-CIPN20 has been used to measure CIPN symptoms (Postma et al., 2005). Potential participants

were asked if these symptoms had developed since or after chemotherapy treatment and were allowed to participate if so. The advantage of subjective experience measuring patients' complaints, is that it identifies patients' actual burden (Cavaletti et al., 2010). In the psychological approach to physical conditions like CIPN, the critical factor is the extent of experienced burden induced by the symptoms. A patient may experience many CIPN symptoms, but if they do not experience it as a burden, they will not want or need to use psychological support. In contrast, a person with only mild CIPN symptoms may experience severe impairment in daily functioning and be very willing to apply self-management techniques to improve symptoms. It also depends on the extent to which the symptoms a patient experiences impede the performance of value-based activities (Hayes et al., 2012). For example, a piano teacher who experiences numbness in his fingers will likely perceive this as highly limiting. Furthermore, earlier research examining psychosocial support for distress during cancer treatment has shown that a crucial aspect in the decision to search for psychosocial support is the patients' willingness (Parmet et al., 2023). Thus, there must be a sufficient willingness to want to take on psychological support and invest time and energy in it. The biopsychosocial model of chronic pain (Gatchel et al., 2007) also emphasizes the subjective experience of pain and thus the variability in the perceived burden of CIPN.

### ***Semantics of the word pain in the context of neuropathy***

During the recruitment of participants for **Chapters 3, 6, and 8** it was noticed that a lot of patients do *not* describe the CIPN symptoms they have as *pain*, while the sensations they experience do belong to *painful* CIPN. This implies that many patients find it difficult to recognize nerve pain and therefore do not label it as pain. This may have resulted from patients experiencing no or little nerve pain in their childhood: children learn that stubbing your toe hurts and that a stabbing feeling in your stomach is also painful, but nerve pain seems uncommon. It is assumed that the capacity for pain-related language develops early in childhood, as children may experience pain from birth and the ability to communicate about pain is a crucial function (Stanford et al., 2005). The limited occurrence of nerve pain in childhood could explain why adult patients also find it difficult to recognize neuropathic pain. In part, pain can be derived from objective anatomical, physiological, and behavioral measurements, but the vast majority of the patient's definition of pain is determined by the patient's verbal communication about the pain (Borelli et al., 2018;

Main, 2016). Besides, earlier research has shown that communicating about pain is extremely difficult (Rowbotham et al., 2012). Pain is not visible and only present internally, so no external confirmation can be given. Therefore, it is also impossible to know whether the same sensation experienced also receives the same verbal description in another person (Rowbotham et al., 2012). Because of this, many patients may experience a certain insecurity when communicating about their pain, which may also have influenced patients' description of *painful* neuropathy.

Part of this dissertation was related to *painful* CIPN specifically (**Chapters 3, 6, 7, and 8**), which was also mentioned in the recruitment of patients. There were probably a reasonable number of patients who did not register to participate in the study because they did not consider their symptoms relevant to the study because of the word *pain*, even though the symptoms would be characterized as *pain* within the operationalization of *painful* CIPN. This occurred multiple times during telephone communications with potential participants. In these conversations, it was possible to clarify which symptoms were encompassed by the operational definition of *painful* CIPN. Consequently, some patients decided to enroll in the study after receiving this explanation. However, it is conceivable that a subset of patients did not express their concerns about *painful* CIPN to the researchers, which made it impossible to engage in conversation with them about this.

#### ***Developed within the framework of the current project***

In this dissertation, the patient-centered development of an online ACT intervention for patients with CIPN has been described (**Chapter 6**). However, the choices regarding program content, multimedia use/choices, interactive online activities, and feedback support provision (Barak et al., 2009) in this development process were somewhat limited, since an existing platform, Karify/Avinty, was chosen because of future implementation possibilities. This platform had certain capabilities and limitations within which the development had to take place. There were also time and budget constraints within this project, which made opportunities about, for example, video material development impossible. This is especially a limitation because of the current patient group with cognitive impairments (i.e., chemo-brain) due to treatment (Hermelink, 2015). These limitations are likely prevalent in numerous eHealth development research projects.

### ***Effectiveness of Embrace Pain***

The effectiveness of *Embrace Pain* is currently unknown and therefore unfortunately not described in this dissertation. The protocol of the RCT is described in **Chapter 7**. The results of the RCT will later be published in a scientific journal, which is expected in the winter of 2024. Results will also be fed back to clinical practice. However, patients' experiences were evaluated in a qualitative manner in this dissertation (**Chapter 8**). Experiences with *Embrace Pain* varied strongly among patients. Several patients reported positive experiences, highlighting the program's relevance, user-friendliness, self-management features, and flexibility. Conversely, some patients perceived less benefit from *Embrace Pain*, which may primarily include those who were already effectively managing their symptoms prior to the program. Additionally, it is important to note that the qualitative evaluation failed to include patients who discontinued participation, complicating the ability to draw comprehensive conclusions. Reliable conclusions about the effectiveness can only be drawn after analysing the results of the RCT.

### **Conclusion**

This dissertation studied two different topics in the context of patients with CIPN. First, this dissertation focused on patients' experiences with CIPN. It can be concluded that CIPN is a long-term consequence of chemotherapy that can cause many symptoms, which can subsequently result in many limitations in daily life. Patients' roles and identities may be negatively affected by CIPN. From this follows a long search for dealing with the symptoms and limitations, in which patients may feel lost. Future research should look at ways in which patients would like to be supported in this quest. A recommendation for practice includes ongoing discussion with patients of (possible) development of CIPN symptoms and offering psychoeducational, emotional, and instrumental support once symptoms have developed. In the second section of this dissertation, online psychosocial intervention and patient-centered development were investigated. From this, it can be concluded that online ACT interventions should be developed with a patient-centered approach. In this approach, contextual factors, user characteristics, and choices regarding technology, as well as the interactions between these elements, must thoroughly be considered. Crucially, the content of these interventions is anchored in theory to achieve therapeutic goals. Future research is recommended to evaluate online interventions using a broad approach through engagement to gain a comprehensive understanding of the

users' actual use and affect. In summary, it can be concluded that patient-centered developed online psychological interventions, such as ACT-based, have considerable potential for transforming the care of patients with CIPN.

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# Appendix



## Summary

As the number of cancer diagnoses has increased and continues to increase, along with improved treatment options and therefore survival rates, the number of cancer survivors is increasing. Therefore, more patients have to live with the long-term consequences of cancer and its treatment, which often involves substantial physical and psychosocial limitations in their daily lives. One of these consequences is chemotherapy-induced peripheral neuropathy (CIPN), which is one of the main side effects of chemotherapy. After completion of chemotherapy, around 80% suffers from CIPN, which decreases to 30% at six months after completion of chemotherapy, meaning that a substantial number of patients suffer chronically from this side effect. Symptoms can include, for example, tingling, numbness, shooting and burning pain, and cramps, in hands, feet, arms and legs. Unfortunately, treatment options are limited. The main objective of this dissertation was to gain insights into (1) the experiences of patients with CIPN and (2) the patient-centered development of an online self-management intervention based on Acceptance and Commitment Therapy (ACT) for cancer survivors with chronic painful CIPN.

### Part I – Patient experiences

In **Chapter 2**, experiences regarding symptoms, daily limitations, involvement of healthcare professionals, and social support of patients with CIPN were quantitatively explored. Cross-sectional data were collected. Results showed that most patients (71.2%) experienced symptoms in both hands and feet, such as tingling and loss of or diminished sensation. In general, patients seem to experience mainly limitations in social and role activities (e.g., hobbies and household), but seem able to perform their activities of daily life (e.g., self-care and taking care of children). Patients further reported that while they were informed about CIPN, they were not provided enough information about what to do if CIPN developed. Furthermore, support from the social environment varies. This indicates that support from healthcare professionals and peers is sometimes not sufficient.

A qualitative exploration of how patients deal with CIPN was performed in **Chapter 3**. Coping was defined as dealing with symptoms and resulting impairments in general, while self-management strategies were defined as practical actions to reduce symptoms. Twelve semi-structured interviews were conducted with patients with chronic painful

CIPN, which were coded following a hybrid deductive-inductive approach. For coping, two themes and nine codes were generated, while for self-management, four themes and 31 codes were identified. Results showed that coping often included active coping, such as planning, seeking social support, and acceptance. However, passive coping was also often applied, which includes only acting when the pain occurs, but not prematurely, such as focusing on and venting emotions, as well as suppressing competing activities. Furthermore, self-management was mostly applied using passive strategies (i.e., in which the patient does not actively contribute, or allowing negative impacts on other areas of life due to the pain), such as medication or resting. Active self-management strategies (e.g., exercising) was also regularly applied. It is particularly important for healthcare professionals to encourage patients to adopt adaptive strategies, as some strategies may also have aversive effects.

**Chapter 4** assessed the extent to which pre-treatment anxiety and depression predict post-treatment symptom severity in colorectal cancer patients with peripheral neuropathy. Questionnaires assessing anxiety and depressive symptoms (HADS) and sensory (SPN) and motor peripheral neuropathy (MPN) (EORTC QLQ-CIPN20) were completed prior to initial cancer treatment (baseline) and at one- and two-years post-diagnosis. Hierarchical regression analyses showed that pre-treatment anxiety and depressive symptoms were not associated with SPN or MPN symptom severity at one-year follow up. However, pre-treatment anxiety symptoms, but not depressive symptoms, were associated with SPN symptom severity at two-year follow up.

## **Part II - eHealth interventions**

A systematic literature review of online ACT interventions for chronic pain in general is described in **Chapter 5**. It was aimed to describe their (1) ACT content, (2) design characteristics, (3) design rationales, and (4) adherence. A total of 20 articles were assessed, comprising 14 distinct individual interventions. The results showed that most articles described the included ACT processes by providing an overview. However, adherence and design reasons (e.g., technology choices) were described only to a limited extent. Most interventions were delivered via a website (n=10), which was sometimes combined with an app (n=3). Guidance (e.g., therapist contact via face-to-face, email, video call, or mobile phone) was often included (n=19). Measures of adherence varied

substantially across studies, with many studies not assessing adherence at all. Among the few studies that did evaluate adherence, methods of measurement were inconsistent (e.g., percentage of participants who completed the intended use or average number of modules completed). Furthermore, among the studies that included randomized controlled trials (RCTs) (n=8), online ACT interventions were reported to be effective.

**Chapter 6** describes the patient-centered development of an online ACT intervention for patients with chronic painful CIPN. An iterative development process was applied following the CeHRes roadmap. This included conducting semi-structured interviews with both patients and experts (e.g., psychologists, oncologists, and eHealth experts) to identify needs and contextual factors, along with low-fidelity and high-fidelity prototype testing. Patients indicated to have a positive attitude towards ACT, besides prioritizing having autonomy in the use of the intervention. It was shown that patients preferred a user-friendly and accessible intervention. Needs regarding guidance varied between patients. Comparable implications were observed in the expert interviews. Assessments resulted in a theory-driven online intervention, which was called *Embrace Pain* (in Dutch: *Omarm Pijn*), which was accessible both via the web and through a mobile application. It included six parts based on ACT and psychoeducation. Specific decisions were made concerning the inclusion of quotes, the options for guidance, and the types of multimedia, aligned with the findings from the interviews and prototype testing.

In **Chapter 7** a protocol for a RCT was described, which included studying the effectiveness of an online self-help intervention based on ACT compared to waiting list condition (WLC) to deal with CIPN. Moderating effects and the extent to which a guided and unguided version of the intervention differ were also included in the protocol. It included a two-parallel, non-blinded RCT. The intervention included six modules including psychoeducation and ACT processes, in which therapeutic email guidance was also offered. Participants learned new coping strategies for managing pain, which include reducing pain avoidance behaviors and enhancing pain acceptance. Patients in the WLC were offered the intervention without guidance after five months. Pain interference was the main outcome of this study protocol, which includes the psychosocial aspect of chronic pain (e.g., functioning in work and social activities). Other quantitative somatic (e.g., CIPN symptom severity) and psychological outcomes (e.g., psychological flexibility

and pain catastrophizing), as well as adherence measures were included. Additionally, qualitative examinations using interviews assessing user experiences were also involved in the protocol.

**Chapter 8** qualitatively examined the use of *Embrace Pain*, with and without guidance, regarding barriers and facilitators of engagement, as engagement is often difficult for users. In this chapter, engagement was defined as a combination of adherence and the subjective experiences of the user. Twelve semi-structured interviews were conducted with patients experiencing chronic painful CIPN who participated in the RCT. An inductive coping approach was used. Seven codes for barriers and ten codes for facilitators emerged from the data. Barriers mostly included unfavorable program schedule, burden, lack of guidance, and irrelevance of content. In contrast, facilitators were experienced in terms of usability, being engaged in positive self-management and symptom management, and a favorable program schedule. It can be concluded that the factors greatly vary between users, likely influenced by individual circumstances and contexts. This variability may account for why certain factors, such as program scheduling, are perceived as barriers by some individuals while being viewed as facilitators by others.

Finally, in **Chapter 9** the main findings of this dissertation were discussed. Relevant topics that relate to the findings were discussed, as well as implications for future research. Strengths and limitations of this dissertation were also explained. In conclusion, this dissertation studied experiences of patients with CIPN, as well as eHealth interventions. In the first area of focus, patient experiences, it was concluded that CIPN is a long-term consequence of chemotherapy, resulting in a range of symptoms that can substantially impair daily functioning. These symptoms may affect roles and identities that patients employ, often leading to a long search for dealing with symptoms and associated impairments in which patients may feel lost. Future research should explore patients' support wishes in this search. Besides, healthcare professionals should be encouraged to ongoingly discuss the potential development of symptoms, along with providing psychoeducational, emotional, and instrumental support once symptoms emerge. The second section of this dissertation explored online psychosocial intervention and patient-centered development. It was concluded that developing online ACT interventions requires a patient-centered approach that considers contextual factors, user

characteristics, technology choices, and the interplay between these elements. Furthermore, intervention content should be grounded in theory to achieve therapeutic goals. Future research should evaluate online interventions following a broad approach of engagement to better understand users' actual use and affect. Concluding, it can be stated that patient-centered theory-based online psychological interventions, such as those employing ACT, show substantial potential for enhancing care for patients with CIPN.



## **Nederlandse samenvatting (Dutch summary)**

Doordat het aantal kanker diagnoses is toegenomen en blijft toenemen, samen met verbeterde behandelopties en daardoor overlevingskansen, neemt het aantal mensen dat leeft met of na kanker toe. Daardoor moeten meer mensen leven met de lang termijn gevolgen van kanker en de behandeling daarvan, wat vaak aanzienlijke fysieke en psychosociale gevolgen in het dagelijks leven met zich meebrengt. Een van deze consequenties is chemotherapie-geïnduceerde perifere neuropathie (CIPN), wat één van de belangrijkste bijwerkingen van chemotherapie is. Na afronding van chemotherapie heeft ongeveer 80% van de patiënten last van CIPN, wat afneemt naar 30% bij zes maanden na afronding van chemotherapie. Dit betekent dat deze bijwerking bij een aanzienlijk deel van de patiënten chronisch wordt. Symptomen kunnen bijvoorbeeld tintelingen, gevoelloosheid, pijscheuten, brandende pijn en krampen in handen, voeten, armen en benen inhouden. Helaas zijn de behandelopties beperkt. Het belangrijkste doel van dit proefschrift was inzicht verkrijgen in (1) de ervaringen van patiënten met CIPN en (2) de patiëntgerichte ontwikkeling van een online zelfmanagement interventie gebaseerd op Acceptance en Commitment Therapie (ACT) voor mensen die leven met en na kanker met chronische pijnlijke CIPN.

### **Deel I – Patiëntenervaringen**

In **Hoofdstuk 2** werden ervaringen van patiënten met CIPN met betrekking tot symptomen, dagelijkse beperkingen, betrokkenheid van zorgverleners, en sociale steun kwalitatief onderzocht. Cross-sectionele data werden verzameld. Resultaten lieten zien dat de meeste patiënten (71.2%) symptomen ervoeren in zowel handen als voeten, zoals tintelingen en verlies of vermindering van gevoel. Over het algemeen lijken patiënten voornamelijk beperkingen te ervaren in sociale en rol activiteiten (zoals hobby's en huishouden), maar lijken zij in staat te zijn om algemene dagelijkse levensverrichtingen (zoals zelfzorg en het zorgen voor kinderen) uit te voeren. Patiënten gaven verder aan dat ondanks dat zij geïnformeerd waren over CIPN, zij niet voldoende informatie hadden gekregen over wat te doen wanneer CIPN ontstaat. Verder bleek de ervaren steun uit de sociale omgeving te variëren. Dit laat zien dat steun en begeleiding van zorgverleners en de sociale omgeving soms als onvoldoende wordt ervaren.

Een kwalitatieve exploratie van hoe patiënten omgaan met CIPN werd uitgevoerd in **Hoofdstuk 3**. Coping werd gedefinieerd als het omgaan met symptomen en bijbehorende beperkingen in het algemeen, terwijl zelfmanagement strategieën werden gedefinieerd als praktische acties om symptomen te doen verminderen. Twaalf semigestructureerd interviews werden afgenomen met patiënten met chronische pijnlijke CIPN, die werden gecodeerd volgens een hybride deductieve-inductieve benadering. Voor coping werden twee thema's en negen codes gegenereerd, terwijl voor zelfmanagement vier thema's en 31 codes werden geïdentificeerd. Resultaten lieten zien dat coping vaak actieve coping inhield, zoals plannen, het zoeken van sociale steun en acceptatie. Passieve coping werd echter ook vaak toegepast, wat inhoudt dat je enkel handelt wanneer de pijn optreedt (en niet voortijdig), zoals het focussen op en afreageren van emoties en het vermijden van activiteiten. Verder werd zelfmanagement het meest toegepast door middel van passieve strategieën (d.w.z. waarin patiënten niet actief bijdragen), zoals medicatie of rusten. Actieve zelfmanagement strategieën (zoals sporten) werd ook regelmatig toegepast. Het is met name belangrijk dat zorgverleners patiënten aanmoedigen om helpende adaptieve strategieën toe te passen, aangezien sommige strategieën ook nadelige effecten kunnen hebben.

**Hoofdstuk 4** bestudeerde in hoeverre angst en depressie vóór de behandeling voorspellen hoe ernstig de symptomen na de behandeling zijn bij patiënten met darmkanker die lijden aan perifere neuropathie. Vragenlijsten met betrekking tot angst en depressieve symptomen (HADS) en sensorische (SPN) en motorische perifere neuropathie (MPN) (EORTC QLQ-CIPN20) werden afgenomen voorafgaand aan de initiële kankerbehandeling (baseline) en bij één- en twee-jaar na diagnose. Hiërarchische regressieanalyses toonden aan dat angst en depressieve symptomen voor de behandeling niet geassocieerd waren met de ernst van SPN of MPN symptomen bij één-jaar follow-up. Angst symptomen voor de behandeling (maar niet depressieve symptomen) waren echter wel geassocieerd met de ernst van SPN symptomen bij twee-jaar follow-up.

## Deel II - eHealth interventies

Een systematische literatuur review van online ACT interventies voor chronische pijn in het algemeen is beschreven in **Hoofdstuk 5**. Het doel was om de volgende aspecten te beschrijven: (1) ACT inhoud, (2) ontwerpeigenschappen, (3) ontwerp overwegingen, en (4)

adherentie (d.w.z. therapietrouw). In totaal werden 20 artikelen beoordeeld, die veertien afzonderlijke interventies omvatten. Resultaten toonden aan dat de meeste artikelen de opgenomen ACT-processen beschreven door een overzicht te geven. Adherentie en ontwerp overwegingen (zoals technologie keuzes) werden slechts in beperkte mate beschreven. De meeste interventies werden aangeboden via een website (n=10), wat soms werd gecombineerd met een app (n=3). Begeleiding (zoals contact met de therapeut via face-to-face, email, videogesprek of mobiele telefoon) was vaak opgenomen in de interventies. Metingen van adherentie varieerden aanzienlijk tussen studies, waarbij veel studies adherentie helemaal niet bestudeerden. Onder de weinige studies die adherentie evalueerden, waren de meetmethoden inconsistent (bijv. percentage deelnemers dat het beoogde gebruik voltooidde of gemiddelde van het aantal voltooidde modules). Verder toonden de onderzoeken met een randomized controlled trial (d.w.z. gerandomiseerd onderzoek met controlegroep) (RCT) (n=8) aan dat online ACT interventies effectief waren.

**Hoofdstuk 6** beschrijft de patiëntgerichte ontwikkeling van een online ACT interventie voor patiënten met chronische pijnlijke CIPN. Een iteratief ontwikkelproces werd toegepast volgens de CeHRes roadmap. Dit omvatte het afnemen van semigestructureerde interviews met zowel patiënten als experts (bijv. psychologen, oncologen en eHealth experts) om behoeften en contextuele factoren te identificeren, als ook het testen van *low-fidelity* en *high-fidelity* prototypes. Patiënten gaven aan een positieve houding te hebben ten opzichte van ACT, naast het prioriteren van autonomie in het gebruik van de interventie. Ook gaven zij aan dat het belangrijk is dat de interventie gebruiksvriendelijk en toegankelijk is. Vergelijkbare implicaties werden gevonden in de expertinterviews. Resultaten leidden tot een theorie gedreven online interventie, genaamd *Omarm Pijn*, die zowel via het web als via een mobiele applicatie toegankelijk was. De interventie bestond uit zes onderdelen gebaseerd op ACT en psycho-educatie. Specifieke keuzes werden gemaakt wat betreft het invoegen van quotes, mogelijkheden voor begeleiding en type multimedia, in lijn met de resultaten van de interviews en het prototype testen.

In **Hoofdstuk 7** werd een protocol voor een RCT beschreven, waarbij de effectiviteit van een online zelfhulpinterventie gebaseerd op ACT vergeleken werd met een

wachtlIJstconditie (WLC) om met CIPN om te gaan. Modererende effecten en de mate waarin een begeleide en onbegeleide versie van de interventie van elkaar verschillen, zijn ook opgenomen in het protocol. Het protocol omvat een twee-parallele, niet-geblindeerde RCT. De interventie bevat zes modules waaronder psycho-educatie en ACT processen, waarin therapeutische begeleiding werd aangeboden. Participanten leerden nieuwe coping strategieën voor het omgaan met pijn, waaronder het verminderen van pijnvermijgend gedrag en het verbeteren van pijnacceptatie. Na vijf maanden wordt de interventie aan patiënten in de WLC aangeboden zonder begeleiding. De hoofduitkomstmaat van het studieprotocol was pijn interferentie, die het psychosociale aspect van chronische pijn omvat (zoals functioneren in werk en sociale activiteiten). Andere kwantitatieve somatische (bijv. ernst van CIPN symptomen) en psychologische uitkomstmaten (bijv. psychologische flexibiliteit en pijn catastroferen), als ook adherentie, werden opgenomen. Het protocol omvatte ook kwalitatieve onderzoeken door middel van interviews waarin gebruikerservaringen werden geëvalueerd.

**Hoofdstuk 8** bestudeerde het gebruik van *Omarm Pijn* op kwalitatieve wijze. Hierbij werd de interventie met en zonder begeleiding geëvalueerd met betrekking tot barrières en facilitatoren van betrokkenheid bestudeerd, omdat betrokkenheid voor veel gebruikers moeilijk is. In dit hoofdstuk werd betrokkenheid gedefinieerd als een combinatie van adherentie en de subjectieve ervaringen van de gebruikers. Twaalf semigestructureerde interviews werden afgenomen met patiënten met chronische pijnlijke CIPN (die eerder hadden deelgenomen aan de RCT). Data werd geanalyseerd middels inductief coderen. Zeven codes voor barrières en tien codes voor facilitatoren resulteerden uit de data. Barrières hadden voornamelijk betrekking op een ongunstig opbouw en planning van het programma, belasting, gebrek aan begeleiding en irrelevantie van de inhoud. Daarentegen werden facilitatoren voornamelijk ervaren op het gebied van gebruiksvriendelijkheid, betrokken zijn bij positief zelfmanagement en symptoom management en een gunstige opbouw en planning van het programma. Er kan geconcludeerd worden dat de factoren sterk verschillen tussen gebruikers, wat waarschijnlijk beïnvloed wordt door individuele omstandigheden en contexten. Deze variatie kan verklaren waarom bepaalde factoren, zoals opbouw en planning van het programma, door sommige gebruikers als barrières worden ervaren, terwijl ze door anderen als bevorderend worden gezien.

Ten slotte werden in **Hoofdstuk 9** de belangrijkste bevindingen van het proefschrift gesproken. Relevante onderwerpen die gerelateerd waren aan de resultaten werden bediscussieerd, als ook implicaties voor toekomstig onderzoek. Sterke punten en beperkingen van dit proefschrift werden ook toegelicht. Concluderend beschrijft dit proefschrift onderzoek naar de ervaringen van patiënten met CIPN, als ook naar mogelijkheden met betrekking tot eHealth interventies. In het eerste deel van dit proefschrift met betrekking tot patiëntenervaringen werd geconcludeerd dat CIPN een langetermijneffect van chemotherapie is en dat dit resulteert in een range aan symptomen die tot aanzienlijke beperkingen in het dagelijks leven kunnen leiden. Deze symptomen kunnen de rollen en identiteiten die patiënten hebben beïnvloeden, waardoor vaak een lange zoektocht naar het omgaan met symptomen en bijbehorende beperkingen volgt waarin patiënten zich verloren kunnen voelen. Vervolgonderzoek zou de behoeften van patiënten op het gebied van ondersteuning hierin moeten bestuderen. Bovendien dienen zorgverleners te worden aangemoedigd om doorlopend mogelijke symptoomontwikkeling te bespreken en, zodra symptomen zich voordoen, psycho-educatieve, emotionele en instrumentele ondersteuning te bieden. Het tweede deel van dit proefschrift exploreerde online psychosociale interventies en patiëntgerichte ontwikkeling. Geconcludeerd werd dat het ontwikkelen van online ACT interventies een patiëntgerichte benadering vereist, waarin contextuele factoren, gebruikerskarakteristieken, technologiekeuzes en het samenspel hiertussen worden overwogen. Verder is het belangrijk dat de inhoud van interventies gebaseerd worden op theorie, om therapeutische doelen te bereiken. Vervolgonderzoek zou online interventies moeten evalueren gebaseerd op een brede benadering van betrokkenheid om beter begrip te krijgen van het daadwerkelijke gebruik en de emoties van gebruikers. Concluderend kan gezegd worden dat patiëntgerichte op theorie gebaseerde online psychologische interventies, zoals die gebaseerd op ACT, een aanzienlijk potentieel hebben voor het verbeteren van zorg voor patiënten met CIPN.



## List of publications

- van de Graaf, D. L.**, Schoonman, G. G., Habibović, M., & Pauws, S. C. (2021). Towards eHealth to support the health journey of headache patients: a scoping review. *Journal of Neurology*, 268(10), 3646-3665.
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## **About the author**

Daniëlle van de Graaf was born on October 31<sup>st</sup>, 1995, in Rotterdam, the Netherlands. After finishing secondary education at CSG Willem van Oranje in Oud-Beijerland, she earned her propaedeutic diploma in Communication at Rotterdam University of Applied Sciences (Hogeschool Rotterdam) in 2014. She received her bachelor's and master's degrees in Communication and Information Sciences at Tilburg University in 2020. Afterwards, she started her PhD at the department of Medical and Clinical Psychology at Tilburg University. Currently, she works as a postdoctoral researcher at Tranzo, Tilburg University. Her research focuses on the intrinsic evaluation of a digital self-management platform for severe mentally ill people.



