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Developing Rehabilitation Treatment Decision Aid for People Living with Complex Regional Pain Syndrome (CRPS)

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Health and Rehabilitation Sciences

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Abstract

This Ph.D. dissertation aimed to develop a treatment decision aid for people with Complex Regional Pain Syndrome (CRPS) using the Ottawa Decision Support Framework (ODSF). The decision aid was developed throughout a two-phase process.

The first phase involved understanding the existing evidence and the factors influencing decision-making in CRPS rehabilitation: priorities and preferences of patients and therapists were considered. This phase encompassed the integration of diverse sources of evidence, including systematic reviews, overview of systematic reviews, critical appraisal of guidelines, and a survey exploring patients' and therapists' priorities and preferences for CRPS rehabilitation interventions. All forms of evidence were used to inform a draft decision aid. The second phase involved evaluating the content validity of the developed decision aid through cognitive interviews conducted with patients and therapists. These findings were presented in separate chapters.

The evidence suggested that specific interventions, including mirror therapy and the graded motor imagery program can significantly improve pain and disability for patients with CRPS. However, the most evidence is available in the post-stroke CRPS population, and these interventions showed promising outcomes when used as additions to conventional stroke rehabilitation interventions compared to common rehabilitation approaches. The effectiveness of other targeted interventions compared to conventional physical therapy or sham treatments remains to be determined due to limited evidence. Furthermore, the appraisal of guidelines highlighted that clinical practice guidelines for CRPS management rely mostly on expert opinion and clinical experience rather than robust empirical evidence. Based on the findings of evidence, clinical guidelines, and the patients' and therapists' opinion, recommendations for conservative management primarily focus on pain management, functional restoration, and inter/multidisciplinary care. Both patients and therapists emphasized the importance of reducing pain and improving overall function as critical outcomes. Shared decision-making emerged as the preferred approach for selecting a rehabilitation intervention among most patients and therapists.

The developed decision aid consists of two sections: an educational section and a decision aid section. The educational section provides patients with the concept of decision aid, the definition and diagnosis of CRPS, and a simple explanation of the available rehabilitation interventions. The decision aid section addresses key topics across seven subsections: 1. identifying important outcomes, 2. evaluating the effectiveness of interventions on specific outcomes, 3. weighing the pros and cons of each rehabilitation intervention, 4. highlighting key points to remember, 5. reflecting on priorities and preferences, 6. fact-checking information about CRPS, and 7. determining the patients' leaning towards making a final decision.

The development of this treatment decision aid represents a significant step forward in addressing the complexities of decision-making in CRPS rehabilitation. By incorporating evidence-based recommendations and the perspectives of patients and therapists, the decision aid aims to improve patient outcomes and facilitate collaborative decision-making processes. Implementing this decision aid in clinical settings is expected to empower patients, enhance their engagement in their care, and ultimately lead to more personalized and effective treatment approaches for individuals with CRPS.

Keywords

Complex Regional Pain Syndrome, CRPS, Treatment Decision Aid, Conservative treatment, Rehabilitation

Summary for Lay Audience

The goal of this Ph.D. thesis was to create a helpful tool for people with Complex Regional Pain Syndrome (CRPS) to make decisions about their treatment. The tool was developed in two stages. In the first stage, we gathered information from different sources to understand what factors influence decision-making in CRPS rehabilitation. We looked at existing studies, treatment guidelines, and we surveyed both patients and therapists to learn about their priorities, goals, and needs.

In the second stage, we tested the tool by talking to patients and therapists and getting their feedback. This helped us make sure the tool was useful and relevant to their needs. We presented our findings in separate chapters of the research. Based on the evidence we gathered, we found that certain treatments, like mirror therapy and the graded motor imagery program, can help reduce pain and improve function for people with CRPS. These treatments worked best when used alongside traditional rehabilitation approaches. Other treatments, like pain exposure therapy and adding aerobic exercises to physical therapy, also showed promise in reducing pain. However, there are still many other treatments that need more research before we can be confident they help more than usual care. Our research also shows that clinical guidelines for CRPS management rely heavily on expert opinions and clinical experience, rather than strong scientific evidence. We recommend a conservative management approach that focuses on pain management, functional restoration, and interdisciplinary care based on the evidence we gathered and the opinions of patients and therapists.

By using multiple sources of evidence, our project was able to provide a comprehensive overview of the available evidence for CRPS rehabilitation, while the survey added valuable insights from the perspectives of patients and therapists.

The decision aid we developed has two parts: an educational section and a decision support section. The educational section provides information on what a decision aid is, the definition and diagnosis of CRPS, and a simple explanation of the available rehabilitation options. The decision support section helps patients identify important outcomes, evaluate the effectiveness of different interventions, consider the pros and cons, reflect on their priorities and preferences, fact-check information about CRPS, and make a final decision.

Creating this decision aid was necessary because it helps people with CRPS make informed choices about their treatment. We used information from research and talked to patients and therapists to create the tool. The goal was to improve how patients make decision and make sure everyone is involved in the decision-making process. We want patients to feel more in control of their care and have treatments that work better for them. We hope therapists, clinicians, and clinics will use this tool to help patients and make their treatments more personalized and effective.

Co-Authorship Statement

The core idea of the research question and the design of the studies were developed by Erfan Shafiee and his supervisor, Dr. Joy C MacDermid. The committee members were then provided their feedback on the main idea, the details of each milestone, and their expectations.

Co-authors were invited when additional help and expertise were required. The specific contributions of each co-author are presented below:

Chapter 1: Introduction

Erfan Shafiee – Sole Author

Chapter 2: The effectiveness of rehabilitation interventions on pain and disability for Complex Regional Pain Syndrome; A systematic review and meta-analysis

Erfan Shafiee: Primary author, study design, running search strategy, study selection, data extraction, quality appraisal, data analysis, writing manuscript, preparing the manuscript for submission.

Joy MacDermid: Co-author, conception of study idea and study design, revising the manuscript for important intellectual content, final approval of the manuscript before submission.

David Walton: Co-author, manuscript reviewer

Tara Packham: Co-author, manuscript reviewer

Ruby Grewal: Co-author, manuscript reviewer

Maryam Farzad: Co-author, second reviewer for quality appraisal, second data extractor, manuscript reviewer

Chapter 3: Rehabilitation interventions for Complex Regional Pain Syndrome; an overview of systematic reviews

Erfan Shafiee: Primary author, study design, running search strategy, study selection, data extraction, quality appraisal, data analysis, writing manuscript, preparing the manuscript for submission.

Joy MacDermid: Co-author, conception of study idea and study design, revising the manuscript for important intellectual content, final approval of the manuscript before submission.

David Walton: Co-author, manuscript reviewer

Tara Packham: Co-author, manuscript reviewer

Ruby Grewal: Co-author, manuscript reviewer

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Maryam Farzad: Co-author, second reviewer for quality appraisal, second data extractor, manuscript reviewer

Chapter 4: A Systematic Critical Appraisal of Clinical Practice Guidelines for Non-pharmacological Conservative Management of Complex Regional Pain Syndrome (CRPS) Using the AGREE-II Instrument

Erfan Shafiee: Primary author, study design, running search strategy, study selection, data extraction, quality appraisal, data analysis, writing manuscript, preparing the manuscript for submission.

Joy MacDermid: Co-author, conception of study idea and study design, revising the manuscript for important intellectual content, final approval of the manuscript before submission.

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Chapter 5: A survey of patient/therapist preferences and priorities for conservative treatment of complex regional pain syndrome.

Erfan Shafiee: Primary author, conception of study idea and study design, developing surveys, writing ethics application, data analysis, writing manuscript, preparing the manuscript for submission.

Joy MacDermid: Co-author, conception of study/survey idea and study/survey design, revising the manuscript for important intellectual content, final approval of the manuscript before submission.

David Walton: Co-author, conception of survey design, manuscript reviewer

Tara Packham: Co-author, conception of survey design, manuscript reviewer

Ruby Grewal: Co-author, conception of survey design, manuscript reviewer

Chapter 6: Developing Treatment Decision Aids for People Living with Complex Regional Pain Syndrome (CRPS)

Erfan Shafiee: Primary author, conception of study idea and study design, data analysis, writing manuscript, preparing the manuscript for submission.

Joy MacDermid: Co-author, conception of study idea and study design, revising the manuscript for important intellectual content, final approval of the manuscript before submission.

David Walton: Co-author, manuscript reviewer, member of the expert panel for the development of treatment decision aids

Tara Packham: Co-author, manuscript reviewer, member of the expert panel for the development of treatment decision aids

Ruby Grewal: Co-author, manuscript reviewer, member of the expert panel for the development of treatment decision aids

Chapter 7: General discussion and future direction

Erfan Shafiee: Sole author

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Chapter 1

1 Introduction

1.1 Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS), previously known as reflex sympathetic dystrophy (RSD) or causalgia, is a primary pain disorder. The hall mark symptom of CRPS is constant severe pain (disproportionate to the extent of injury) in one or more limbs, typically following an injury or trauma ^{1,2}. CRPS is characterized by pain, sensory disturbances, motor dysfunction, and autonomic dysfunction, which can manifest in various degrees of severity and duration ³. Due to the heterogeneity of symptoms and the lack of consensus on diagnostic criteria and treatment approaches, patients with CRPS often face difficult treatment decisions, which can lead to confusion, anxiety, and uncertainty ⁴.

Diagnosing CRPS is challenging and relies on clinical findings while excluding other potential causes that would better explain the signs and symptoms ⁵. Although there is no universally effective treatment, emphasizing timely detection and multidisciplinary care has shown promising outcomes ^{6,7}. By proactively identifying early signs and symptoms of CRPS, healthcare professionals can implement a comprehensive treatment strategy involving collaboration among different specialists, such as physicians, rehabilitation team, psychologists, and pain management specialists ⁸. This multidisciplinary approach acknowledges the multifaceted nature of CRPS and aims to tailor treatment to each individual's specific needs. Consequently, early detection and multidisciplinary treatment offers a more holistic approach to managing CRPS, potentially improving outcomes ⁹.

1.2 Etiology, epidemiology, and pathophysiology of CRPS

The exact pathophysiology of CRPS is not fully understood. Despite significant advances in understanding the pathophysiology of CRPS, the precise mechanisms remain unclear. It is likely that the etiology of CRPS is multifactorial, involving complex interaction among genetic and environmental factors, various mechanisms of the peripheral and central nervous systems, as

well as the immune system ². There is evidence of ongoing inflammation and abnormal activity in the peripheral and central nervous systems, which can contribute to the persistence of pain and other symptoms. Neuroplastic changes may also occur in response to the ongoing pain, leading to alterations in sensory processing and motor function ¹⁰. Although autonomic symptoms are included in the diagnostic criteria for CRPS and have been known to be one of the main causes of CRPS, recent studies have de-emphasized the importance of the sympathetic nervous system in the pathophysiology of the condition ¹⁰.

The prevalence of complex regional pain syndrome (CRPS) is difficult to estimate due to the lack of standardized diagnostic criteria and differences in study populations. The reported incidence of CRPS varies widely between 5.5 per 100,000 person-years in the United States and 26.2 per 100,000 person-years in the Netherlands ^{11,12}. The prevalence of CRPS is reported to be higher in women than in men, and the condition can occur at any age, with a peak incidence in the fourth to sixth decades of life ¹³. The incidence and prevalence of CRPS may also vary depending on the underlying cause of the condition, as CRPS can usually occur as a result of trauma, surgery, infection, or other medical conditions ¹².

1.3 Diagnostic criteria

The diagnostic criteria for Complex Regional Pain Syndrome (CRPS) have undergone several revisions over the years, reflecting the evolving understanding of the condition. The first criteria were proposed by the International Association for the Study of Pain (IASP) in 1994 ¹⁴. In 2003 a second set of criteria, termed the Budapest Criteria, were developed primarily based on empirically-derived criteria published previously, and were later revised in 2007 to improve their specificity and diagnostic accuracy ¹.

More recently, there has been a shift towards incorporating the diagnosis of CRPS into the broader category of Chronic Primary Pain (CPP) in the International Classification of Diseases (ICD)-11. In 2018, the IASP and the World Health Organization (WHO) collaborated to adapt the CRPS diagnostic criteria to the ICD-11 category of CPP, which includes a broader range of chronic pain conditions ^{15,16}. This change reflects the recognition that CRPS is a complex and multifaceted condition that can present with a wide range of symptoms and clinical

features, and highlights the need for a more comprehensive and inclusive approach to diagnosis and management.

1.4 CRPS treatment options

A wide range of treatment options have been introduced for CRPS over time with the choice of treatment depending on the severity of the condition, the patient's response to previous treatments, and the patient's preferences ^{7,17,18}.

1.4.1 Non-pharmacological treatments:

Non-pharmacological treatments for CRPS encompass a range of specific interventions, such as physical exercises, electrical/thermal modalities, movement representation techniques, desensitization/sensory re-education techniques, functional training, activities of daily living (ADL) modifications, splinting, using assistive devices, or psychological interventions. These interventions can be administered by one or more rehabilitation specialists in the field, such as physical therapists, occupational therapists, hand therapists, and psychotherapists. It is challenging to delineate each intervention to a specific discipline, as there is significant overlap and collaboration among these professionals.

Physical therapists play a vital role in CRPS management by focusing on improving physical function, reducing pain, and restoring mobility. This may involve a combination of exercises to improve range of motion and strengthen muscles, as well as the use of electrical or thermal modalities to alleviate CRPS symptoms. Physical therapists tailor treatment plans to meet the individual needs of patients, emphasizing functional goals and promoting overall physical well-being ^{17,19}.

Occupational therapy focuses on enhancing patients' ability to perform activities of daily living (ADLs) and engaging in meaningful occupations. Occupational therapists help persons with CRPS by providing activity modifications, teaching pacing techniques, setting goals, and utilizing mental and sensory exercises to reduce symptoms and improve participation. By addressing specific challenges and barriers to participation, occupational therapy aims to optimize independence and quality of life ²⁰.

Psychotherapy interventions in CRPS aim to address the psychological and emotional aspects of the condition. Cognitive-behavioral therapy (CBT), neurocognitive rehabilitation, and patient education are commonly used approaches. These interventions assist patients in developing a more accurate perception of their pain, improving coping mechanisms, and managing stress related to CRPS. By addressing the psychological impact of the condition, psychotherapy can help patients develop resilience and enhance their overall well-being ²¹.

It is essential to recognize that these rehabilitation interventions for CRPS often overlap and complement each other. Healthcare professionals from different disciplines collaborate to develop comprehensive and holistic treatment plans addressing the multifaceted nature of CRPS. By integrating these interventions and promoting interdisciplinary collaboration, healthcare providers can optimize outcomes and support individuals with CRPS in their journey toward improved functioning and well-being.

1.4.2 Pharmacological treatments:

In recent decades, a range of pharmacological interventions, including bisphosphonates, corticosteroids, ketamine, scavengers/MgSO₄, nonsteroidal anti-inflammatory drugs and selective inhibitors of cyclooxygenase-2, and anti-epileptic drugs, have been suggested as potential treatments for CRPS-I in adults. However, there is currently limited evidence on the precise effectiveness and safety profiles of these drugs for the management of CRPS ²³. Based on the findings of the most recent systematic review and meta-analysis in 2022, bisphosphonates have been found to be effective in terms of reducing pain and other symptoms (allodynia, hyperalgesia, and swelling). Ketamine was also reported to have small but positive effects on pain reduction. However, there is no strong evidence on the effectiveness of other pharmacological interventions previously proposed for CRPS management ²³.

1.4.3 Interventional treatments:

Interventional treatments for CRPS include sympathetic nerve blocks (stellate ganglion block (SGB) and lumbar sympathetic block (LSB)), neuromodulation (traditional dorsal column stimulation and dorsal root ganglion stimulation), and epidural injection (local anesthetic, clonidine, and opiate) ²⁴. Surgical treatments for CRPS are usually reserved for severe cases that

do not respond to other treatments. Based on the findings of the most recent review in 2021, sympathetic nerve blocks are known as the first-line interventional treatment for CRPS. Using opiates, local anesthetics, and/or clonidine are recommended for refractory cases. Finally, neuromodulation has been found to be effective in more chronic cases. Regarding neuromodulation technique, evidence indicated that dorsal root ganglion stimulation is more effective than traditional dorsal column stimulation ²⁵.

Overall, CRPS poses significant challenges in terms of management, and may require a combination of conservative, pharmacological, interventional, and surgical approaches. A multidisciplinary approach involving a team of healthcare professionals may be necessary to achieve the best outcomes for patients with CRPS. It is important to inform people with CRPS about various treatment options that are available and appropriate for them, considering the severity of their symptoms and the stage of the condition. Additionally, it is essential to recognize that each person's experience with CRPS is unique, leading to potential variations in outcomes following specific interventions.

1.5 Decision making for choosing the treatment options

CRPS is a challenging condition to manage, and treatment decisions can be complex and challenging and often requires careful consideration of multiple factors ⁴.

One of the major difficulties that patients with CRPS face in the decision-making process is the lack of access to reliable resources. CRPS is a relatively rare condition, and many healthcare professionals may have limited experience in managing it ²⁶. As a result, patients may struggle to find accurate information about the condition and the available treatment options. Furthermore, not all individuals with CRPS have access to adequate support, and in some cases certain healthcare professionals may require further education regarding the condition ^{27,28}. The lack of access to reliable resources can also contribute to a sense of uncertainty and anxiety for patients and may feel overwhelmed by the range of treatment options available, and may struggle to determine which option is best for them ⁶.

To address these difficulties, healthcare professionals should take a person-centered approach to the decision-making process and inform individuals with CRPS about the available

treatment options, ensuring that the patient's preferences and values are considered, and use the latest available evidence ²⁹. Additionally, efforts should be made to improve access to reliable resources in lay language for patients with CRPS, such as patient education materials, support groups, and online resources ³⁰. By providing patients with accurate and reliable information, healthcare professionals can help to reduce uncertainty and anxiety, and facilitate a more effective and efficient decision-making process. By actively involving patients in the decision-making process, healthcare professionals can foster a sense of ownership and engagement, which can significantly enhance adherence to treatment ³¹. As one of the participants mentioned in one of our interview studies, they have the feeling of “... being a part of the decision ...“ by the process of shared decision-making. This comprehensive approach not only addresses the challenges faced by patients but also contributes to improved overall treatment outcomes.

1.6 Treatment Decision Aid

Treatment decision aids (TDAs) are developed as a tool to help patients navigate decision making process, making informed decisions regarding treatment options ³², and facilitate the process of shared decision making (SDM). TDAs are patient-centered tools providing information about the available treatment options, unknown outcomes, or known outcomes that patients value differently. They are intended to assist the person in weighing the benefits and risks, and help patients consider their own preferences when creating a personalized treatment plan that meets their specific needs and goals ³³.

The Ottawa Decision Support Framework (ODSF) is a conceptual model that provides guidance for structuring, development, and implementation of TDAs, published in 1998 ³⁴. It emphasizes the importance of tailoring decision support to the individual needs and preferences of the patient and promoting patient autonomy and involvement in the decision-making process ³⁴. It consists of four main components: (1) providing information about the options, (2) clarifying values and preferences, (3) providing decision support, and (4) providing follow-up support to evaluate the effects of decision support on decisional outcomes.

The use of TDAs in the context of CRPS has the potential to improve patient outcomes by facilitating SDM between patients and healthcare professionals. In the process of SDM,

patients and healthcare professionals work together to make treatment decisions that are based on the best available evidence, the patient's preferences and values, and the healthcare professional's expertise. However, to the best of our knowledge, there is no rehabilitation treatment decision aid available for CRPS.

Despite the potential benefits of TDAs in CRPS, there are also potential challenges associated with their development and implementation. These challenges include the complexity and heterogeneity of CRPS symptoms and treatment options, the differences in patients' preferences and values, and the need for healthcare providers to be trained in SDM and the use of TDAs^{35,36}. Addressing these challenges will require collaboration between patients, healthcare providers, and researchers to develop and refine TDAs that are tailored to the specific needs and preferences of patients with CRPS³⁶.

1.7 The gap in the knowledge

Despite the growing use of TDAs in health conditions, there is a notable gap in the knowledge about their application in rehabilitation interventions for CRPS. While TDAs have shown promising results in aiding decision-making processes for various medical conditions³⁷, no evidence is available about their effectiveness and feasibility in the context of CRPS rehabilitation. Given the complex and multifaceted nature of CRPS, accessible and comprehensible scientific information plays a crucial role in empowering patients to make informed decisions regarding their treatment options. Therefore, exploring the potential of TDAs in CRPS rehabilitation is an important avenue for improving patient outcomes and promoting SDM between patients and healthcare providers.

1.8 Objectives of the dissertation

The overall objective of this Ph.D. dissertation was to develop a treatment decision aid for rehabilitation interventions for CRPS using the ODSF as a theoretical framework. This dissertation consisted of five papers, including a systematic review and meta-analysis, an overview of systematic reviews, a critical appraisal of guidelines, a survey of patients' and therapists' priorities and preferences regarding rehabilitation interventions for CRPS, and a cognitive interview for evaluating the content/face validity of the developed rehabilitation

treatment decision aid. The results of this dissertation contribute to the development of an evidence-based decision aid that can help patients make informed choices about rehabilitation interventions for CRPS and facilitate the process of SDM. The decision aid developed in this study is based on the best available evidence and was aimed to be tailored to the needs and preferences of patients and therapists.

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Chapter 2

The effectiveness of rehabilitation interventions on pain and disability for Complex Regional Pain Syndrome; A systematic review and meta-analysis

This study has been published in The Clinical Journal of Pain.

Shafiee E, MacDermid J, Packham T, Walton D, Grewal R, Farzad M. The effectiveness of rehabilitation interventions on pain and disability for complex regional pain syndrome: a systematic review and meta-analysis. *The Clinical Journal of Pain*. 2023 Feb 1;39(2):91-105.

The screenshot shows the article page for "The Effectiveness of Rehabilitation Interventions on Pain and Disability for Complex Regional Pain Syndrome: A Systematic Review and Meta-analysis" in *The Clinical Journal of Pain*. The page includes a navigation bar with "Articles & Issues", "For Authors", and "Journal Info". On the left, there are icons for "Cite", "Share", "Favorites", and "Permissions". The article title is prominently displayed, followed by the authors' names and their credentials. Below the authors' names is the "Author Information" link. The publication details are: *The Clinical Journal of Pain* 39(2):p 91-105, February 2023. | DOI: 10.1097/AJP.0000000000001089. At the bottom of the article information, there are "BUY" and "SDC" buttons, and a "Metrics" button with a bar chart icon.

Abstract

Objectives:

To summarize and critically appraise the body of evidence on conservative management of complex regional pain syndrome (CRPS), we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs).

2 The effectiveness of rehabilitation interventions on pain and disability for Complex Regional Pain Syndrome; A systematic review and meta-analysis

Abstract

Objectives: To summarize and critically appraise the body of evidence on conservative management of Complex Regional Pain Syndrome, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods: We conducted a literature search from inception to November 2021 in the following databases: Embase, Medline, CINAHL, Google Scholar, PEDRO, and Psychinfo. Two independent reviewers conducted risk of bias and quality assessment. Qualitative synthesis and meta-analysis were the methods for summarizing the findings of the RCTs. The GRADE approach was used to rate the overall quality and certainty of the evidence on each treatment outcome.

Result: Through database search, 751 records were found, and 33 RCTs were eligible for inclusion. Studies were published between 1995 to 2021. The overall risk of bias for two studies was low, eight studies was unclear, and 23 studies was high.

Low-quality evidence suggests that mirror therapy (as an addition to conventional stroke rehabilitation interventions) and graded motor imagery program (compared to routine rehabilitation interventions) may result in a large improvement in pain and disability up to 6-month follow-up in post-stroke CRPS-1 patients. Low-quality evidence suggests that pain exposure therapy and aerobic exercises as an additive treatment to PT interventions may result in a large improvement in pain up to six-month follow-up. The evidence is very uncertain about the effect of all other targeted interventions over conventional PT or sham treatments on pain and disability.

Discussion: There is an ongoing need for high-quality studies to inform conservative management choices in CRPS.

Keywords: Complex Regional Pain Syndrome; CRPS; Physical Therapy; Occupational Therapy; Conservative management; Systematic review; Meta-analysis

2.1 Introduction

In 1994, the International Association for the Study of Pain (IASP) established the diagnostic label of complex regional pain syndrome (CRPS) for the conditions previously known as reflex sympathetic dystrophy (RSD), Sudeck's atrophy, causalgia, reflex neurovascular dystrophy, algodystrophy, or algoneurodystrophy. ¹

CRPS is a painful, chronic, and disabling condition characterized by autonomic and neuro-inflammatory signs and symptoms out of proportion in magnitude or duration to any inciting event ². CRPS is a multifactorial condition accompanied by any or all sensory or motor disturbances, autonomic dysfunction, trophic changes, skin changes, restricted range of motion, or temperature changes. ³

Most recently (September 2019), the *IASP CRPS Special Interest Group* proposed pragmatic updates to the CRPS assessment instructions and adaptations in the IASP diagnostic taxonomy. ⁴ Based on these adaptations, CRPS has been classified as “chronic primary pain” within the International Classification of Diseases (ICD-11) and further divided into four diagnostic subtypes; CRPS-1, CRPS-2 (accompanied by discrete damage to the peripheral nerve), CRPS with Remission of Some Features, and CRPS Not Otherwise Specified (NOS). The detailed description and diagnostic criteria are discussed comprehensively in the IASP and World Health Organization (WHO) report. ⁵

As CRPS is a complex condition encompassing variable symptoms, the management of this condition is also complex and challenging. Conservative management is often the front-line treatment, assuming it will be effective for some individuals and avoid the potential risks of symptom exacerbation that sometimes accompanies more aggressive interventions like surgery. ⁶ A broad selection of conservative interventions are available for CRPS, including pain management, pharmacotherapy, psychological therapies, rehabilitation interventions, neurostimulation approaches, and alternative therapies. ⁷

Optimal rehabilitation of CRPS can involve multiple professionals and intervention strategies intended to mitigate symptoms and facilitate full functional recovery. Different rehabilitation management approaches are advocated across clinical studies. ^{7,8} Clinical practice

guidelines have been developed for CRPS but are not fully evidence-based or able to provide definitive clinical pathways.⁸⁻¹⁰ The most recent systematic reviews on the management of CRPS have been either conducted through a limited scope (for instance, reviewed only physical therapy interventions)¹¹ or used a very broad scope that reviewed all surgical, pharmacological, or conservative interventions without appraising the quality of evidence or conducting meta-analysis.¹²⁻¹⁴ The body of evidence on the effectiveness of different rehabilitation interventions on pain and disability, as the main concerns of the patients with CRPS, has not been recently synthesized.

The purposes of this study were to i) identify and synthesize evidence from randomized controlled trials (RCTs) on the short- and longer-term effects of different rehabilitation interventions for managing pain and disability in patients with CRPS, and ii) statistically compare the effectiveness of specific rehabilitation interventions against either no intervention/placebo or standard practice through meta-analysis of standardized mean differences where adequate data were available to do so.

2.2 Method

2.2.1 Study design:

We included randomized clinical trials in CRPS that investigated the effect of any conservative management in which pain and/or disability were a primary or secondary outcome. This study was registered in the PROSPERO database (CRD42021285374). This review has been reported in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.¹⁵

2.2.2 Eligibility criteria:

The population of interest for this study was adults 18 years or older with CRPS-1/2 or shoulder-hand syndrome (SHS), either after trauma or after neurologic conditions such as stroke. Studies were eligible if they were any type of RCTs of a non-invasive intervention delivered by a rehabilitation professional (occupational therapist, physical therapist, or psychologist) for which a recognized and accepted patient-reported outcome of either pain severity or function/disability

was used. Studies that were published as full-text articles in a peer-reviewed journal were included. RCTs that included pharmacological and surgical interventions were excluded. Studies on CRPS in children, non-randomized clinical trial studies, or conference abstracts were excluded.

2.2.3 Search strategy:

Two independent reviewers (ESh and MF) conducted a literature search from inception to October 2021 in the following databases: Embase, Medline, CINAHL, Google Scholar, Psychinfo, and Physiotherapy Evidence Database (PEDro). A forward and backward tracing approach was used to identify and retrieve further eligible reviews.

The first-pass screening was conducted through title/abstract by the same two independent authors to identify those manuscripts that were clearly not relevant to the question. The same two authors then screened the full text of retained studies against the eligibility criteria. Where there was any disagreement between the two authors, a consensus was achieved through discussion with a third author (JM).

2.2.4 Data extraction:

Two independent researchers extracted and compared data using a standardized form. A consensus was achieved through consultation with a third author (JM) in case of any discrepancies. The following data were extracted from eligible RCTs: author, year, type of CRPS, number of participants, mean age, intervention and comparison group, description of intervention characteristics, results, and main conclusion.

2.2.5 Methodological Quality and Risk of Bias Assessment:

A modified version of the Cochrane risk of bias tool for methodological quality and risk of bias assessment was used by two independent raters to score each manuscript. Any disagreement in quality assessment was resolved through discussion between the two reviewers. If the resolution was not achieved, the third reviewer (JM) helped.

The modified version of the Cochrane risk of bias tool consists of nine critical domains, including random sequence generation, allocation concealment, blinding of study participants and personnel, blinding of outcome assessment (both self-reported and investigator-administered outcomes), completeness of outcome data (attrition bias and method of analysis), selective reporting, and other biases (sample size and follow-up duration). Each domain was rated as either low, unclear, or high risk of bias, and each manuscript was then assigned an overall risk of bias rating (low, unclear, or high) through the algorithm. The detail of how to rate each domain is fully described in Cochrane Handbook for Systematic Reviews of Interventions.¹⁶

2.2.6 Evaluation of the quality and certainty of the evidence

The overall quality and certainty of evidence on each treatment outcome was evaluated by the two reviewers (ESh and MF) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.¹⁷

Considering the GRADE approach, RCTs start as high-quality evidence, and they will be downgraded once or twice based on meeting the following factors:
Study limitations, inconsistency, imprecision, and indirectness.

Factors that may increase the quality of evidence include large effect, dose-response gradient, and all plausible confounding. We did not consider publication bias in our judgement for rating the overall quality of the evidence, as the assessment of this domain has not been suggested when there are so few studies for any given intervention.^{18,19}

We considered two key components to rate the overall quality and certainty of the evidence on a particular treatment outcome: i) size of the effect estimate; ii) certainty of the evidence.

The overall quality of the evidence on each treatment outcome was rated as high, moderate, low, and very low. The detailed instruction for rating the quality of evidence is comprehensively reported in the GRADE series articles.^{17,20} If there was any disagreement between the two reviewers, the third author (JM) was invited for judgment.

2.2.7 Data synthesis:

Qualitative synthesis was used to summarize and present the findings of the studies in terms of mean age, sex, number of participants, control and intervention groups, and overall risk of bias of the included studies.

We calculated standardized mean difference (SMD) based on Hedge's *g* as a measure of effect size for the studies provided sufficient numerical data.^{21,22} Where there was more than one study for each treatment outcome, and studies had clinical homogeneity in terms of dose of the treatment (duration and frequency), follow-up time points, and study population. We pooled the effect sizes using STATA software (version 16). I^2 (I-squared) value was used to report statistical heterogeneity across RCTs, with 0% to 25% representing low heterogeneity, 26% to 50% representing medium heterogeneity, and above 50% representing high heterogeneity.²³ In the case of high heterogeneity, the random-effect model was the preferred method for meta-analysis. We used Hedge's *g* benchmark to interpret the magnitude of the effect sizes: trivial effect (SMD<0.2), small effect (SMD=0.2), medium effect (SMD=0.5), and large effect (SMD>0.8).²⁴ When sufficient numerical data was presented in the studies, we conducted subgroup analysis based on gender to compare the differences between men and women.²⁵

2.3 Result

The database searches returned 978 articles, with 746 remaining after duplicate removal. Hand searching added five more records. After title/abstract screening, 41 studies remained for full-text review, from which seven were removed due to being poster presentations, not being English, or full-text unavailability. This left a final pool of 33 studies for synthesis. Figure 1 shows the summary of the selection process in a PRISMA diagram.¹⁵

2.3.1 Description of included review

Thirty-three randomized clinical trials evaluated the effectiveness of various rehabilitation interventions for CRPS, including mirror therapy (MT),²⁶⁻³⁰ Graded motor imagery program (GMIP),³¹⁻³⁴ multimodal PT,^{35,36} transcutaneous electrical nerve stimulations (TENS),³⁷ acupuncture,³⁸⁻⁴² tactile discrimination techniques,⁴³ ultrasound of the stellate ganglion,⁴⁴⁻⁴⁶

manual lymph drainage (MLD),^{47,48} laser therapy,⁴⁹ virtual body-swapping,⁵⁰ CO2 bath therapy,⁵¹ Qigong exercises,⁵² pain exposure,^{53,54} aerobic exercises,⁵⁵ electromagnetic field treatment,⁵⁶ fluidotherapy,⁵⁷ prism adaptation,⁵⁸ autogenic exercises,⁴¹ and visual illusion.⁵⁹ The full detail of the interventions, dosages, and durations is provided in Appendix 1.

Publication dates ranged from 1995^{39,60} to 2021.^{30,58,59} There was no study specific to CRPS-2. Eight RCTs (8/34; 23%) focused specifically on post-stroke CRPS,^{26,27,29,30,38,42,55,57} 16 RCTs^{31-37,43-45,47,51,54,56,58,59} (16/34; 47%) recruited CRPS patients in their upper limb, and the other reviews included CRPS patients with mixed etiologies either in upper or lower limb. The sample size across studies was 10 to 178. The included studies used various diagnostic criteria for the diagnosis of CRPS. Seven studies^{49,50,54,57-59,61} (7/33; 21%) used Budapest criteria⁶², 14 studies^{26,27,32-34,37,43-45,47,53,55,56} (14/33; 42%) used IASP diagnostic criteria⁶³, and three studies^{30,48,51} (3/33; 9%) did not report the criteria they used for diagnosis. The other nine studies^{29,35,36,38,40-42,46,52,64} (9/33; 27%) used older criteria for the diagnosis of CRPS are presented in table 1.

2.3.2 Methodological Quality of the Included RCTs:

Table 2 presents the results of the Cochrane risk of bias assessment. The level of agreement between the two raters was high (Kappa: 0.9). The overall risk of bias was high in 23 studies (24/34; 70%), unclear in eight studies (8/34; 24%), and low in two studies (2/34; 6%). The most significant methodological limitations in most of the studies were low sample size and short follow-up periods. However, most of the studies were rated as having low risk of bias in random sequence generation^{28-33,35,37-41,45,49,52-59} (24/34; 70%) and allocation concealment^{28-34,37,38,40,41,43-45,48,49,53,55,58,59,65,66} (22/34; 64%) (Table 3).

2.3.3 Effectiveness of the interventions:

2.3.3.1 Mirror therapy:

Four studies^{26,27,29,30} with an unclear and high risk of bias evaluated the effectiveness of mirror therapy compared to routine rehabilitation interventions on pain and disability improvement in a total of 155 post-stroke and mixed etiology CRPS-1 patients.

In a study by Saha et al.³⁰ with high RoB the authors investigated the effectiveness of adding a 4-week mirror therapy (30 minutes a day for 5 days a week) to conventional stroke rehabilitation interventions compared to conventional rehabilitation interventions alone in 38 post-stroke CRPS-1 patients. The authors reported significant improvement in pain and functional activities at short-term (2-week) follow-up in the intervention group.

Cacchio et al.²⁶ in a study with unclear RoB compared a four-week mirror therapy (30 minutes for the first two weeks and one hour for the last two weeks per session) in addition to routine stroke rehabilitation interventions compared to placebo (covered mirror) plus routine stroke rehabilitation interventions in 48 persons with post-stroke CRPS. They found that adding mirror therapy to routine stroke rehabilitation interventions was more effective than covered mirror plus routine stroke rehabilitation interventions in pain and function improvement at post-treatment and six-month follow-up.

In another three-arm RCT with unclear RoB, Cacchio et al.²⁷ compared four-week mirror therapy (30 minutes daily) to mental imagery and placebo (covered mirror) in 24 persons with post-stroke CRPS-1. This study demonstrated that mirror therapy was more effective in pain reduction than the other two groups post-intervention.

Vural et al.²⁹ in a study with high RoB investigated the effectiveness of adding a 30-minute mirror therapy to a 20-session conventional stroke rehabilitation program (5d/wk, for 2 to 4h/d) compared to conventional rehabilitation interventions in 30 post-stroke CRPS-1 patients. The authors concluded that adding mirror therapy to conventional stroke rehabilitation interventions improved the upper limb function and pain severity more than conventional therapy without mirror therapy after four weeks of intervention.

Evidence summary:

The pooled estimate of the SMD for pain ($I^2=86\%$) and disability ($I^2=87\%$) improvement was 1.88 (95%CI: 0.73 to 3.02) and 1.30 (95%CI: 0.11 to 2.49), respectively, for mirror therapy intervention. (Figures 2 and 3)

Low-quality evidence (RCT evidence high; downgraded once for sample size, once for inconsistency, and once for methodological limitations; upgraded once for large effect size)

suggests that mirror therapy as an addition to conventional stroke rehabilitation interventions may result in a large improvement in pain and disability up to 6-month follow-up in post-stroke CRPS-1 patients.

2.3.3.2 Graded Motor Imagery Program (GMIP):

Four RCTs,³¹³²⁻³⁴ all with high RoB, evaluated the effectiveness of a GMIP on pain improvement in a total of 88 upper limb and mixed etiologies CRPS-1.

In a cross-over RCT by Moseley et al.,³¹ a six-week graded motor imagery program (two weeks limb laterality recognition + two weeks imagined movements + two weeks mirror-box therapy) was compared with 12-week medical management, which mainly was PT interventions in 13 patients with chronic CRPS after non-complicated wrist fractures. After 12 weeks, the control group was crossed over to GMIP. The results of this study found a significant pain improvement in favour of the GMIP group at 12-week follow-up.

In another study by Moseley et al.³² the order of applying three different GMIP was compared to each other (Recognition of hand laterality, Imagined hand movements, and Mirror movements) in 20 patients with CRPS-1 after wrist fracture. Authors³² found that the order of the MIP components affected the outcomes of pain and disability at six- and 18-week follow-up. They concluded that appropriately ordered GMIP could be more effective in pain and function improvement than inappropriately ordered GMIP. The more effective order is hand laterality recognition, imagined movements, and mirror movements.

In a study by Schreuders et al.³⁴ GMIP interventions in addition to routine PT and OT were compared to PT and OT interventions alone in 18 patients with upper limb CRPS. The authors concluded that adding GMIP to routine OT or PT interventions does not have any significant effect on pain and disability at six weeks post-intervention.

Moseley et al.³³ compared GMIP interventions to a control group (PT and ongoing medical care) in 51 patients with CRPS-1. The results indicated that patients in GMIP group demonstrated superior results in pain and disability improvement than routine PT interventions

and medical management in patients with upper limb CRPS-1 at six-month follow-up. (Figures 4 and 5)

Evidence summary:

Across GMIP studies, the pooled estimates of the SMD for pain ($I^2=0\%$) and disability ($I^2=55\%$) improvement were 1.36 (95%CI: 0.75 to 1.96) and 1.64 (95%CI: 0.53 to 2.74), respectively.

Low-quality evidence (RCT evidence high; downgraded twice for sample size, once for inconsistency, and once for methodological limitations; upgraded once for large effect) suggests that GMIP compared to routine rehabilitation interventions may result in a large improvement in pain and disability up to 6-month follow-up in patients with CRPS-1.

2.3.3.3 Acupuncture:

Four studies^{38,40,42,64} all with high RoB evaluated the effectiveness of acupuncture on pain and disability improvement in a total of 354 CRPS-1 patients.

Li et al.³⁸ investigated the effectiveness of a 30-session electro-acupuncture therapy plus massage therapy compared to routine post-stroke rehabilitation interventions in 120 post-stroke patients with the shoulder-hand syndrome. The results of this study demonstrated that electro-acupuncture therapy plus massage was superior to routine stroke rehabilitation interventions and led to significant upper limb function and pain improvement in passive shoulder movement at 12-week follow-up.

In a large RCT with 178 participants with post-stroke CRPS-1 by Zheng et al.,⁴² the authors concluded that adding one month (45 min daily) acupuncture to routine rehabilitation interventions could be more effective in pain and function improvement compared to rehabilitation interventions alone at post-treatment.

Fialka et al.⁶⁴ compared the effectiveness of classical acupuncture (5 times per week for 3 weeks) to sham acupuncture in 14 patients with CRPS-1. Both groups demonstrated pain improvement. However, the pain reduction was greater in the experimental group at three weeks post-intervention follow-up.

In a study by Korpan et al.⁴⁰ with 14 upper limb CRPS participants, the authors compared the effectiveness of classical Chinese acupuncture to sham acupuncture. They followed patients for six months. At follow-up, both groups experienced pain improvement. However, there was no significant difference between the two groups. (Figures 6 and 7)

Evidence summary:

The pooled estimate of the SMD when using acupuncture for pain ($I^2=92%$) and disability ($I^2=88%$) improvement was 0.52 (95%CI: -0.44 to 1.49) and 0.64 (95%CI: -0.05 to 1.33), respectively.

The evidence is very uncertain about the effect of acupuncture compared to sham treatment or routine rehabilitation interventions on pain and disability (RCT evidence high; downgraded once for methodological limitations, once for imprecision, and once for inconsistency).

2.3.3.4 Pain exposure:

Two studies^{53,54} with low and high RoB evaluated the effectiveness of pain exposure treatment in a total of 102 patients with upper and lower limb CRPS-1.

In a study by Barnhoorn et al.⁵⁴ with low RoB, conventional PT was compared to a five-session pain exposure physical therapy (PEPT) in 56 people with upper limb CRPS-1. The follow-up time points were three, six, and nine months after randomization. The authors found no superiority of the PEPT over conventional PT in terms of pain, range of motion, function, and skin temperature.

Hollander et al.⁵³ in a high RoB study compared the effectiveness of exposure in vivo (EXP) versus pain-contingent treatment as usual (TAU) in 46 patients with upper and lower extremity CRPS-1. The authors found that EXP was superior to TAU in reducing upper disability from pre-treatment to post-treatment and upper and lower extremity disability up to six-month follow-up. Also, EXP was superior to TAU in improving pain up to 6-month follow-up. (Figures 8 and 9)

Evidence summary:

The pooled estimate of the SMD for pain ($I^2=59\%$) and disability ($I^2=81\%$) improvement was 0.81 (95%CI: 0.12 to 1.49) and 0.59 (95%CI: -0.56 to 1.75), respectively for pain exposure treatments.

Low-quality evidence (RCT evidence high; downgraded once for sample size, once for methodological limitations, once for imprecision, and once for inconsistency; upgraded once for large effect size) suggests that pain exposure treatment may result in a large improvement in pain up to six-month follow-up.

The evidence is very uncertain about the effect of pain exposure treatment on disability (RCT evidence high; downgraded once for sample size, once for methodological limitations, once for imprecision, and once for inconsistency).

2.3.3.5 Ultrasound targeting the stellate ganglion:

The effectiveness of ultrasound applied to the stellate ganglion in pain and disability improvement was investigated in three RCTs (with unclear and high RoB)⁴⁴⁻⁴⁶ in a total of 100 participants with upper limb CRPS-1.

In a study by Askin et al.⁴⁴ with high RoB, the authors compared the application of two different dosages of ultrasound on stellate ganglion (for 5 minutes/day, for 20 sessions) to placebo ultrasound in 45 patients with upper limb CRPS-1. All three groups also received conventional PT interventions. The results of this study indicated that stellate ganglion block via ultrasound did not improve pain and hand function in patients with CRPS-1.

Furthermore, Aydemir et al.⁴⁵ in a study with unclear RoB compared the effectiveness of applying a 20-session ultrasound directed to the stellate ganglion with a placebo and lidocaine in 25 patients with upper limb CRPS. All three groups received exercises, TENS, contrast baths, and compression. The results of this study indicated that the block with ultrasound was not superior to lidocaine or placebo in improving pain and function after 20 sessions of intervention.

In another RCT by Hazneci et al.⁴⁶ with unclear RoB the authors found the inferiority of using ultrasound for stellate ganglion block compared to TENS on pain improvement in 30

military participants with CRPS. Both groups also received contrast bathing and exercise programs. The final follow-up was three weeks following the intervention. (Figures 10 and 11)

Evidence summary:

The pooled estimate of the SMD for pain ($I^2=94\%$) and disability ($I^2=42\%$) improvement were 0.46 (95%CI: -2.41 to 1.48) and 0.13 (95%CI: -2.41 to 1.48), respectively.

The evidence is very uncertain about the effect of ultrasound of the stellate ganglion compared to placebo or TENS on pain and disability (RCT evidence high; downgraded once for methodological limitations, once for imprecision, and once for inconsistency).

2.3.3.6 Fluidotherapy:

Two RCTs with high RoB evaluated the effectiveness of fluidotherapy in 52 CRPS-1 patients. In an RCT by Özcan et al.,⁵⁷ the authors evaluated the effectiveness of adding 15 sessions of fluidotherapy (5 sessions/week) to conventional stroke rehabilitation interventions compared to rehabilitation interventions alone in 30 post-stroke CRPS-1. The authors reported that both groups demonstrated improvement in terms of pain intensity and function. The only difference between the two groups was more improvement in neuropathic pain and edema in the experimental group. The SMD for pain and disability improvement was 0.86 (95%CI: 0.15 to 1.57) and 0.12 (95%CI: -0.56 to 0.80), respectively.

In another RCT by Sethy et al.⁶¹ the authors investigated the effectiveness of combining fluidotherapy (10 minutes) to stress-loading exercises (20 minutes) compared to routine OT interventions (30 minutes, 5 days/week, for 8 weeks) in 22 post-stroke CRPS-1. They found a significant difference between the two groups in terms of pain intensity, arm function, and pain-related disability, favouring the experimental group at eight weeks post-intervention. The SMD for pain and disability improvement was 1.81 (95%CI:0.84 to 2.77) and 9.53 (95%CI: 6.60 to 12.46). Due to the significant difference in the treatment dosage between these two studies, we decided not to pool the data.

Evidence summary:

The evidence is very uncertain about the effect of fluidotherapy as an additive treatment to conventional stroke rehabilitation interventions on pain and disability (RCT evidence high; downgraded once for sample size, once for methodological limitations, once for imprecision, and once for inconsistency).

2.3.3.7 Aerobic exercises:

In a study by Topcuoglu et al.⁵⁵ with high RoB the authors explored the effectiveness of adding upper extremity aerobic exercises (5 days a week, 30 minutes a day, for 4 weeks) to conventional PT in 40 people with post-stroke CRPS compared to conventional PT interventions alone. This study found a significant improvement in CRPS signs and symptoms (hyperalgesia, sweating, metacarpal joint tenderness, rest, and movement pain) in the aerobic exercise group at 4-week post-treatment.

Evidence summary:

The SMD for pain was 0.86 (95%CI: 0.23 to 1.50). Low-quality evidence (RCT evidence high; downgraded twice for sample size, once for methodological limitations, and once for imprecision; upgraded once for large effect size) suggest that aerobic exercises as an additive treatment to PT interventions may result in a large effect in pain improvement.

2.3.3.8 Manual lymphatic drainage:

Two RCTs^{47,48} with high and unclear RoB compared the effectiveness of MLD to conventional care (NSAIDs and PT)⁴⁷, and MLD to exercise therapy⁴⁸ in a total of 69 patients with upper⁴⁷ and lower limb⁴⁸ CRPS-1.

In a study by Duman et al.⁴⁷ the authors investigated the effectiveness of adding three weeks of MLD to conventional care compared to conventional care alone in a total of 34 patients with upper limb CRPS-1. Both groups also received additional two months of a home program. This study found no significant difference between the two groups in terms of pain and function improvement at a two-month follow-up.

In another study by Uher et al. ⁴⁸ the authors evaluated the effectiveness of adding MLD to the exercise program (six weeks, three times a week) in a total of 35 patients with lower limb CRPS-1 compared to exercise alone. This study demonstrated no significant benefit for adding MLD to routine exercise interventions six weeks after intervention.

Evidence summary:

The numerical data was only available for one study. ⁴⁷ The SMD for this study was 0.33 (-0.32 to 1.00) and -0.08 (95% CI: -0.58 to 0.74) for the effectiveness of MLD on pain and disability improvement, respectively.

The evidence is very uncertain about the effect of MLD as an additive treatment to routine rehabilitation interventions on pain and disability (RCT evidence high; downgraded once for methodological limitations, once for imprecision, and once for inconsistency).

2.3.3.9 Multimodal PT:

In a three-arm RCT by Oerlemans et al. 1999 ³⁵ with high RoB, the authors compared routine PT interventions plus medical management to either OT interventions plus medical management or a control intervention (known as social work) plus medical management in 135 patients with upper limb CRPS-1. The results of this study demonstrated that in short terms (3-6 months follow-up), PT and OT interventions were superior to the control group regarding pain improvement. However, no significant difference was found in long-term follow-up (12 months).

Evidence summary:

When comparing PT and OT over social work, the SMD for pain improvement was 0.27 (95% CI: -0.13 to 0.68) and 0.08 (95% CI: -0.32 to 0.49), respectively.

The evidence is very uncertain about the effect of PT and OT interventions compared to social work on pain at one-year follow-up (RCT evidence high; downgraded once for methodological limitations, once for imprecision, and once for inconsistency).

2.3.3.10 Virtual body swapping:

In a pilot RCT with high RoB by Jeon et al.⁵⁰ one session of virtual body swapping with mental rehearsal was compared to virtual body swapping alone in 10 patients with CRPS-1. The authors found no significant difference in terms of pain intensity at post-intervention in patients with upper limb, lower limb, or whole-body CRPS-1.

Evidence summary:

The evidence is very uncertain about the effect of virtual body swapping with metal rehearsal compared to virtual body swapping alone on pain (RCT evidence high; downgraded once for methodological limitations, twice for sample size once).

2.3.3.11 Tactile discrimination training:

Four various tactile discrimination trainings (TDT) were compared to each other in a study with high RoB and 10 participants with upper limb CRPS-1. Moseley et al.⁴³ found no significant difference in pain assessments at two-day follow-up after TDT.

Evidence summary:

The evidence is very uncertain about the effect of TDT on pain in the short term (two-day follow-up; RCT evidence high; downgraded once for methodological limitations, twice for sample size once).

2.3.3.12 Pulsed electromagnetic field treatment:

Durmus et al.⁵⁶ in a study with high RoB investigated the effectiveness of a 30-session (6 weeks) pulsed electromagnetic field (PEMF) treatment plus calcitonin and conventional stretching exercises compared to placebo PEMF plus calcitonin and stretching exercises in 40 distal radius fractures with CRPS. The authors found no significant difference between active and placebo groups on rest and activity pain and range of motion.

Evidence summary:

The SMD for the pain was 0.15 (95%CI: -0.45 to 0.76). The evidence is very uncertain about the effect of PEMF compared to placebo on pain (RCT evidence high; downgraded once for methodological limitations, twice for sample size, and once and for imprecision).

2.3.3.13 Laser therapy:

In a study by Dimitrijevic et al.⁴⁹ with high RoB the effectiveness of a 20-session low-level laser therapy (LLLT) plus kinesitherapy was compared to interferential therapy plus kinesitherapy in 50 people with both upper and lower limb CRPS-1. The authors found no clinically significant pain improvement in this comparison at post-treatment.

Evidence summary:

The SMD for pain at rest and pain at movement was reported separately, and it was 0.65 (95%CI:0.09 to 1.21) and 0.56 (95%CI: 0.01 to 1.12), respectively.

The evidence is very uncertain about the effect of adding laser therapy to kinesitherapy on pain (RCT evidence high; downgraded once for methodological limitations, twice for sample size once, and once for imprecision).

2.3.3.14 CO2 bath therapy:

The effectiveness of adding a 4-week CO2 bath therapy to exercise therapy was investigated in an RCT by Mucha et al.⁵¹ with high RoB. In 40 people with CRPS-1, combining CO2 bath therapy with exercise therapy was more effective than exercise alone in rest pain, movement pain, and night pain reduction.

Evidence summary:

The evidence is very uncertain about the effect of adding CO2 bath therapy to exercise therapy on pain (RCT evidence high; downgraded once for methodological limitations, twice for sample size once).

2.3.3.15 Qigong and autogenic exercises:

The effectiveness of qigong compared to sham exercises on pain improvement was investigated in an RCT by Wu et al. ⁵² with high RoB in 26 people with CRPS. Participants in the experimental group received six sessions of 40-minute qigong exercises under the supervision of two masters, followed by seven weeks at home daily (a 10-week protocol). The evaluation was conducted 6-10 weeks after enrollment. The authors concluded that qigong exercises resulted in transient pain reduction and long-term anxiety reduction. The SMD for pain improvement after qigong exercises was 0.17 (95% CI: -0.57 to 0.91).

In a study by Fialka et al. ⁴¹ with high RoB with 18 patients with upper limb CRPS-1, the authors investigated the effectiveness of adding 10 sessions of 90-minutes autogenic training to home therapy exercises compared to home therapy exercises alone. The results of this study indicated no differences in pain improvement between the two groups.

Evidence summary:

The evidence is very uncertain about the effect of qigong and autogenic exercises compared to sham and home therapy exercises on pain at 10-week post-treatment (RCT evidence high; downgraded once for methodological limitations, twice for sample size, and once for imprecision).

2.3.3.16 Transcutaneous electrical nerve stimulations (TENS):

Bilgili et al. ³⁷ in a study with high RoB investigated the effectiveness of TENS in the management of 30 patients with upper limb CRPS-1. The experimental group received 20 minutes of TENS therapy, and the control group received sham TENS therapy. Both groups also received conventional PT interventions for 15 sessions. The authors found significant improvement in pain, range of motion, edema, and functions of patients who received TENS therapy.

Evidence summary:

The SMD for pain and disability were 0.66 (95%CI: -0.05 to 1.37) and 0.32 (95%CI: -0.41 to 1.04), respectively.

The evidence is very uncertain about the effect of TENS compared to sham TENS on pain and disability (RCT evidence high; downgraded once for methodological limitations, twice for sample size, once for imprecision, and once for inconsistency).

2.3.3.17 Prism adaptation:

Halicka et al.⁵⁸ in a study with low RoB investigated the effectiveness of prism adaptation for 49 unilateral upper-limb CRPS-1 compared to sham treatment on pain. The authors found no superiority of the prism adaptation over sham treatment up to 6-month follow-up.

Evidence summary:

The SMD for pain at three- and six-month follow-up was 0.19 (95%CI: -0.35 to 0.75) and 0.17 (95%CI: -0.37 to 0.72), respectively. The evidence is very uncertain about the effect of prism adaptation compared to sham treatment on pain (RCT evidence high; downgraded once for methodological limitations, twice for sample size, once for imprecision, and once for imprecision).

2.3.3.18 Visual illusions:

In a study by Lewis et al.⁵⁹ with high RoB the authors conducted an RCT to see whether altering hand images to match the patient's desired hand appearance would improve body perception disturbance and pain. The findings of this study on 45 patients with CRPS-1 indicated that single and repeated exposures to a visual illusion of the hand that alters hand appearance to a patient's desired look could reduce pain intensity both after treatment and up to two-week follow-up.

Evidence summary:

The SMD for pain was 0.05 (95%CI: -0.56 to 0.67). The evidence is very uncertain about the effect of visual illusion on pain up to two-week follow-up (RCT evidence high; downgraded once for methodological limitations, twice for sample size, and once for imprecision).

2.4 Discussion

This study updated the most recent findings on the conservative management for CRPS. By broadening the scope of our inclusion criteria beyond just physical therapy interventions (compared to the previous systematic reviews) we could capture more interventions, including qigong exercises, fluidotherapy, prism adaptation, and visual illusions.

Although our inclusion criteria were broader than previous reviews focusing only on physically-based interventions, there are very few occupation-based or psychological papers specific to CRPS, and an ongoing gap about how commonly used interventions in the broader field of chronic pain (like graded activity, cognitive behavioral therapy, or acceptance and commitment therapy) might be implemented effectively for persons with CRPS.

In this study, we reviewed 33 RCTs with a total of 1370 participants (compared to 18 RCTs with 739 participants in the previous systematic review ¹¹). The quality of the evidence on the effectiveness of mirror therapy and GMIP has been increased from very low to low due to the larger pooled sample size and effect size compared to the previous Cochrane review. ¹¹ The current evidence favours using mirror therapy, graded motor imagery program, aerobic exercises, and pain exposure therapy for pain improvement. However, only graded motor imagery and, to a lesser extent, mirror therapy (considering the lower limit of the CI being close to the no difference line) are effective in mitigating disability. The quality of evidence based on the GRADE approach is not yet compelling, and our confidence in reporting the effectiveness of rehabilitation interventions is not high. The other rehabilitation interventions in our review (TENS, multimodal PT, acupuncture, tactile discrimination techniques, ultrasound of the stellate ganglion, MLD, laser therapy, virtual body swapping, qigong exercises, EMF, fluidotherapy, prism adaptation, and visual illusions) were not superior to sham treatments or conventional rehabilitation intervention and the evidence is very uncertain.

The diagnostic criteria for CRPS have been revised several times in the past three decades. Between the years of 1872 and 1993 this condition was known as RSD, Sudeck's atrophy, causalgia, reflex neurovascular dystrophy, algo-dystrophy, or algoneurodystrophy. ¹ Later in 1994, IASP labeled this condition as CRPS and proposed new diagnostic criteria to be

descriptive, general, and not imply any etiopathology (including any direct role for the sympathetic nervous system)⁶⁷. Considering poor specificity of those criteria and after a series of revision and scientific meetings, Budapest criteria was introduced in 2003 and widely used since 2010. The recent Valencia consensus-based adaptation of the Budapest CRPS diagnostic criteria developed in 2019, extend the Budapest criteria by clarifying one of the points regarding CRPSII; however, this would not change the classification of post-stroke shoulder hand syndrome from CRPS Not Otherwise Specified (NOS)^{4,62}.

Given that the included studies in our review span over a period of time (between 1993 and 2021), their use of various diagnostic criteria could be a source of heterogeneity in the diagnosis of CRPS patients. Considering poor specificity of the older diagnostic tools, there is a sufficient likelihood that at least some of the included participants in the primary RCTs do not meet the current CRPS diagnostic criteria and were deemed to be misdiagnosed. These patients are referred to as CRPS Not Otherwise Specified (NOS) in the current IASP diagnostic criteria⁴. Fifteen studies were conducted after 2010 of which only 46% (7/15) used Budapest criteria to confirm the diagnosis of CRPS highlighting the ongoing need for implementation of a consistent reporting standard to support both clinical translation and evidence synthesis⁶⁸.

Persistent pain in CRPS could be classified mechanistically as nociplastic pain and as chronic primary pain,^{69,70} considering the pathophysiology of CRPS (which is believed to result from the autonomic nervous system, neurogenic inflammation, and central sensitization).⁷¹ However, several pain mechanisms (nociceptive, central, neuropathic, psychosocial, and movement system) could simultaneously be associated with the perceived pain in musculoskeletal conditions such as CRPS.⁷² Considering that a specific PT modality or agents may only target a specific pain mechanism, the ineffectiveness of some singular interventions in managing pain and disability in our review may reflect a mismatch to the multifactorial nature of CRPS. There is a need for trials of targeted multimodal interventions which may better address the complexity of this syndrome.

The most recent comprehensive review supports the benefits of using TENS to relieve pain in various musculoskeletal conditions with acute and nociceptive pain.⁷³ However, the effect of using TENS to reduce pain and disability in chronic conditions like CRPS is controversial and drawing a definite conclusion is not possible.^{7,11,74} The electrode placement and dosing issues require further investigation to resolve this uncertainty.

The most evident paucity in the evidence was the low sample size in most of the studies, which could endanger the studies' precision and internal validity. Considering the fact that CRPS is not a very prevalent condition, conducting large RCTs could be a great challenge. There is a need for multi-site rehabilitation studies to move beyond our current level of evidence for CRPS interventions. CRPS is a complicated syndrome with signs and symptoms that vary person by person in terms of temporal stability, severity, onset, chronicity, and duration of symptoms. Therefore, recruiting a homogenous sample could be another significant challenge in this field. As a common and unique aspect of pain, allodynia is associated with decreased tolerance to treatment and poorer prognosis but is rarely accounted for in rehabilitation studies⁷⁵. The small samples likely preclude subgrouping or including allodynia as an exclusion criteria, but whether allodynia itself is changed by our interventions remains unknown because it is seldom measured.

Clinical guidelines and textbooks favour multimodal and individually tailored interventions for patients with CRPS to address the signs and symptoms of each individual.^{9,76} However, CRPS management is difficult, regardless of the treatment approach. The results of previous systematic reviews and meta-analyses could not draw a firm conclusion about any specific treatment approach. On the other hand, clinical guidelines mostly reflect expert panel opinions.⁷⁷ In clinical settings, clinicians mostly use PT modalities and conventional rehabilitation interventions empirically to address patients' pain, functional limitations, and symptoms due to a lack of solid evidence.⁷⁸

CRPS persistent pain, as the leading symptom being out of proportion in magnitude or duration to the inciting event, usually is associated with physical and functional dysfunction. This association may contribute to developing psychological symptoms, like depressive symptoms, fear of movement, or anxiety, potentially driving an ongoing cycle of pain, fear of movement due to pain, functional limitations, and psychological symptoms.⁷⁹⁻⁸² This is where an integrated interdisciplinary and multimodal treatment approaches including PT, OT, and psychological intervention that is individually tailored becomes important. However, the role of psychological factors in the development and progression of CRPS is still uncertain.^{80,83}

Movement representation techniques, including graded motor imagery and mirror therapy, were reported to be effective in treating CRPS pain and disability. These techniques

target both physical dysfunction and altered perception and awareness of the affected body part. Various mechanisms have been reported for the effectiveness of MT.⁸⁴ One reason could be activating the primary motor cortex and mirror neuron system by incorporating visual feedback when moving the unaffected body part.⁸⁵ The other mechanism could be the mismatch between the performed and observed movement to increase one's spatial attention toward the affected limb, leading to activating motor networks.⁸⁴ The effectiveness of mirror therapy in other neuromusculoskeletal conditions affecting unilateral limbs has been investigated, and a positive impact has been reported for mirror therapy on treatment outcome.^{86,87}

Fluidotherapy as a thermal modality was also found to be effective in improving CRPS pain. However, the clinical heterogeneity was high, and we did not include them in meta-analysis. Using thermal modalities for musculoskeletal conditions improves tissue extensibility, joint stiffness, pain threshold, muscle spasm, and facilitating tissue healing.⁵⁷ However, the role of tactile stimulation from immersion in the moving cellulose media may also influence the effects seen. Given vasomotor instability, insufficiency and painful hypoesthesia in patients with CRPS, thermal modalities may have contraindications, and clinicians should be cautious not to overstimulate hyperalgesic or allodynic areas.⁸⁸ Furthermore, applying thermal modalities and contrast baths should be done with caution not to increase the instability of the affected body part. For example, for patients with warm, reddened affected limbs, fluidotherapy and thermal modalities like ultrasound are contraindicated.⁸⁹

Pain exposure therapy and its derivative, pain exposure physical therapy (PEPT) was one of the conservative treatments found to be effective in the pain improvement of CRPS patients in our meta-analysis. In PEPT, the focus of therapists is on a therapist or self-delivered tactile stimulation and stretching, physical activities, activities of daily living, and functional disuse, whereas pain exposure therapy targets pain or fear of movement.^{90,91} The idea behind pain exposure therapy is rooted in the fear-avoidance model and the association between psychological factors and CRPS onset and progression.⁷⁹ The results of our meta-analysis indicated that pain exposure therapy had a large effect size and could effectively reduce pain. However, the confidence interval around the SMD was wide, and the lower limit of the confidence interval was close to the small effect size threshold. We should keep this point in mind that although the targeted mechanism and methods of delivery of pain exposure therapy are

distinct from other rehabilitation interventions, some commonalities between these interventions can overestimate or underestimate the true effect.⁷⁷

Although only one RCT with 40 participants was available for the effectiveness of aerobic exercises on pain in CRPS patients, this study reported a large effect size for this treatment.⁵⁵ Aerobic exercises can effectively reduce pain by impacting the central sensitization mechanisms and increasing the pain threshold. Studies have shown that alterations in functions and connectivity between different brain regions are evident in patients with CRPS.⁹² Aerobic and physical exercises have been found to be effective in inducing brain changes in terms of morphology and function, and consequently could be effective in reducing pain and disability.⁹³ Furthermore, resistance training exercises may stimulate the androgen receptors and create exercise-induced hypoalgesia through this mechanism.^{94,95}

Based on the most recent clinical guidelines,⁹ education, pain relief, physical rehabilitation and psychological interventions are the four pillars of CRPS care. Furthermore, rehabilitation interventions are considered as the first-line treatment in the management of CRPS. However, these recommendations are mostly based on the expert opinion and all type of studies other than RCTs. This issue led to a large gap between the recommendations of the systematic reviews and clinical guidelines. The findings of our review and the previous Cochrane review¹¹ highlight this gap and acknowledge this disparity between the recommendation of clinical guidelines and systematic reviews.

In this study we faced some limitations. One of the limitations of our review was lack of numerical data in some of the included studies that reduced the number of studies available for meta-analysis for each treatment outcome. The other limitation of our review is that due to low number of studies, we entered both CRPS-1 and SHS populations together for the purpose of meta-analysis. Although post-stroke SHS is named CRPS, no clear criteria for the diagnosis of SHS exist⁹⁶. Also, we only included conservative treatments (e.g., non-invasive) that can be performed by physical/occupational/hand therapists and minimally invasive techniques were not included. Moreover, we could not perform subgroup analysis based on gender as we planned, due to lack of sufficient numerical data in the primary studies. Furthermore, we could not assess publication bias due to low number of studies for any given intervention.

One of the other limitations in interpreting the results of a meta-analysis is overlap effects and commonalities within the targeted interventions in rehabilitation interventions that could lead to underestimating/overestimating the true treatment effect in the experimental group and has limited our confidence in making definite recommendations. As mentioned earlier in the discussion, there is a likelihood of heterogeneity in the diagnostic criteria across the included RCTs, however, due to the low number of studies in each treatment category, conducting subgroup analysis was not possible to see if this issue could be a source of heterogeneity.

In order to advance the evidence regarding the effectiveness of rehabilitation interventions in CRPS patients, more rigorous RCTs with higher sample sizes are required. Also, no sufficient studies available on the effectiveness of some of the interventions that has been recently investigated and found to be effective, such as fluidotherapy, aerobic exercises, and pain exposure therapy. Furthermore, no high-quality study was available specifically on patients with CRPS-2 and the evidence requires more studies in this population.

2.5 Conclusion

The results of this study found a large effect for the effectiveness of mirror therapy, graded motor imagery program, pain exposure therapy, and aerobic exercises in pain and disability improvement in CRPS-1 patients (or CRPS NOS). However, the evidence is not certain about the effectiveness of other rehabilitation interventions on pain and disability in patients with CRPS-1. There is an ongoing need for high-quality studies to inform conservative management choices in CRPS.

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2.7 List of tables

Table 2-1 Summary of the included RCTs.

Intervention	Study	Diagnostic criteria	Age: mean (+SD)	Population	Intervention	Comparison	Sample size	Outcome measures	Follow-up
GMIP	³¹ (Moseley 2004)	Bruehl 1999 ⁶³	36(14)	Wrist fractures	6-week GMIP	Medical management (mostly PT)	13	VAS (for pain and function)	2,4,6,12 weeks after 6-week MIP
	³² (Moseley 2005)	Bruehl 1999 ⁶³	38 (8)	Wrist fractures	hand laterality recognition, imagined movements, mirror movements	Compared to each other	20	NRS (for pain)	6 and 18 weeks
	³³ (Moseley 2006)	Bruehl 1999 ⁶³	-	Mixed etiology	6-week GMIP	Physical therapy and ongoing medical care	37	VAS, NRS (for function)	6 weeks and 6 months

	³⁴ (Schreuders TAR 2014)	Bruehl 1999 ⁶³	43 (7)	UL	6-week GMIP	Conventional PT and OT	18		6 weeks post treatment
MT	²⁶ (Cacchio 2009) a	Bruehl 1999 ⁶³	58 (10)	Post-stroke	4-week MT + routine stroke rehabilitation	Placebo + routine stroke rehabilitation	48	VAS, WMFT and Motor Activity Log	6 months
	²⁷ (Cacchio 2009) b	Bruehl 1999 ⁶³	62 (53-71)	Post-stroke	4-week MT/30 minutes daily	Two groups: Placebo and mental imagery	24	VAS, WMFT	Post-intervention at 4 weeks
	²⁹ (Vural 2016)	Veldman 1993 ⁹⁷	65(11)	Post-stroke	4-week MT + conventional stroke rehabilitation	Conventional stroke rehabilitation	30	VAS, motor items of the FIM	Post-intervention at 4 weeks
	³⁰ (Saha 2021)	SHS (Diagnostic criteria not reported)	58(5)	Post-stroke	4-week MT + conventional stroke rehabilitation	Conventional stroke rehabilitation	38	NPRS, FIM	2 weeks
Multi modal PT	^{35,36} (Oerlemans 1999)	Veldman 1993 ⁹⁷	53(16)	Upper limb	PT interventions	OT and Social work	135	-	-
TENS	³⁷ (Bilgili 2016)	Merskey 1994 ⁶⁷	47(14)	Upper limb	TENS + routine PT	Sham TENS + routine PT	30	VAS, DHI	
Acupuncture	³⁸ (Li 2012)	Steinbrocker 1948 ⁹⁸ SHS diagnosed by reference to the diagnostic criteria described in Chinese Rehabilitation Standards for Diagnosis	61(5)	Post-stroke	6-week Electric acupuncture plus massage	Conventional stroke rehab interventions	120	NPRS, FMA	6 weeks post-treatment and 12-week follow up

		and Treatment.							
	40 (Korpan MI 1999)	Kozin 1992 ⁹⁹	-	CRPS-1	Classical Chinese acupuncture	Sham acupuncture	14	VAS	6 months
	64 (Fialka 1993)	Kozin 1992 ⁹⁹	High	CRPS-1	Classic acupuncture	Sham acupuncture	14	VAS	Post-treatment
	42 (Zheng 2018)	SHS (Criteria in rehabilitation of post-stroke SHS)	54(6)	Post-stroke	Acupuncture + stroke rehabilitation interventions	Conventional stroke rehabilitation	178	VAS, FMA	1-month post-treatment
Tactile discrimination techniques	43 (Moseley 2009)	Bruehl 1999 ⁶³	43(11)	Upper limb	Four 30-minute TDTs	Compared with each other	10	Two Point discrimination, VAS	Two days post-treatment
Ultrasound of the stellate ganglion	44 (Askin 2014)	Bruehl 1999 ⁶³	45(22-69)	Upper limb	Group I (n = 15) 0.5 watts/cm ² ; group II (n = 15) 3 watts/cm ² on stellate ganglion + conventional PT	group III placebo US + Conventional PT	45	VAS, DASH	After 20 sessions of intervention
	45 (Aydemir 2006)	Bruehl 1999 ⁶³	21(1)	Upper limb	Stellate ganglion block with US + exercise + contrast bath	Lidocaine or sham + exercise + contrast bath	25	Functional Hand Scale	After 20 sessions of intervention
	46 (Hazneci 2005)	Kozin 1992 ⁹⁹	21(1)	Military recruits with upper limb CRPS	US + exercise + contrast bath	TENS + exercise + contrast bath	30	SPE, PPE	Three weeks post-intervention

MLD	⁴⁷ (Duman 2009)	Bruehl 1999 ⁶³	21(1)	Upper limb	3-week MLD + conventional care + 2 months home program	Conventional care + 2 months home program	34	VAS, third finger pulp-distal palmary crease distance	2 months after treatment
	⁴⁸ (Uher 2000)	(Diagnostic criteria not reported)	-	Lower limb	6-week MLD	Exercise	35	verbal rating scale	6 weeks post-intervention
Laser therapy	⁴⁹ (Dimitrijevic 2014)	'Budapest criteria' ⁶²	56(12)	Mixed	20-session laser therapy + kinesiotherapy	Interferential therapy + kinesiotherapy	50	VAS	Post-treatment
virtual body swapping	⁵⁰ (Jeon 2014)	'Budapest criteria' ⁶²	39(11)	Mixed	Virtual body swapping + mental rehearsal	mental rehearsal	10	11-point Likert scale for pain	Post-treatment
CO2 baths	⁵¹ (Mucha 2005)	acute algodystrophy of the hand (diagnostic criteria not reported)	51(20-74)	Upper limb	CO2 bath therapy + exercise (4 weeks)	Exercise	40	VAS	8 weeks post treatment
Qigong exercises	⁵² (Wu 1999)	CRPS I (diagnostic criteria not reported)	18-65	CRPS-1	10-week qigong exercises+ 3 weeks home exercises	Sham qigong exercises + home exercises	26	VAS	10-week posttreatment
Pain exposure	⁵⁴ (Barnhoorn 2015)	'Budapest criteria' ⁶²	44(17)	Upper limb	5 sessions of PEPT	Conventional PT (Dutch multidisciplinary Guideline)	56	VAS, DASH	3, 6 and 9 months after randomization
	⁵³ (den Hollander 2016)	Merskey 1994 ⁶⁷	45(11)	UL and LL	exposure in vivo (EXP)	pain-contingent treatment as usual (TAU)	46s	NPS, WAQ, RASQ	6 and 12 months

aerobic exercise	⁵⁵ (Topcuoglu, 2015)	Bruehl 1999 ⁶³	66(9)	Post-stroke	4-week Aerobic exercises + PT	Conventional PT	40	VAS, FIM	Four weeks post-intervention
EMF	⁵⁶ (Durmus 2004)	Merskey 1994 ⁶⁷	39(12)	Wrist fracture	6-week pulsed EMF + exercise	Placebo EMF + exercise	40	VAS	6 weeks post-treatment
Fluidotherapy	⁵⁷ (Sezgin Özcan 2019)	'Budapest criteria' ⁶²	63(12); (28-84)	Poststroke	15 sessions fluidotherapy + conventional stroke rehabilitation	Conventional stroke rehabilitation	30	VAS, FIM	Three weeks post-intervention
	⁶¹ (Sethy 2017)	'Budapest criteria' ⁶²	35-65	Poststroke	Stress loading (20 minutes)+ Fluidotherapy (10 minutes)	Occupational therapy	22	VAS, DASH	8 weeks post-treatment
Prism Adaptation	⁵⁸ (Halicka 2021)	'Budapest criteria' ⁶²	46(40-52)	UL	2 weeks of twice-daily home-based prism adaptation	Sham	49	NPRS	4 weeks post-treatment, 3 and 6 months
Visual illusions	⁵⁹ (Lewis 2021)	'Budapest criteria' ⁶²	52(13)	UL	5 sessions Showing an altered digital image of the affected hand for 1 minute	Unaltered image of the hand	45	NRS	2 weeks post-intervention
Autogenic trainings	⁴¹ (Fialka 1996)	Kozin 1992 ⁹⁹	64(3)	CRPS-1	10 sessions of Autogenic training + home therapy exercises	Only home therapy exercises	18	VAS	10 weeks post-treatment

Table 2-2 Risk of bias of the included RCTs based on modified Cochrane Risk of bias assessment tool.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete data	Selective reporting	Other biases		Overall risk of bias
							Sample size	Follow-up duration	
(Moseley 2004)	+	+	-	+	+/+	-	-	?	High
(Moseley 2005)	+	+	+	?	+/-	-	-	+	High
(Moseley 2006)	+	+	-	+	+/+	+	-	+	High
(Schreuders 2014)	+	+	-	+	-/-	-	-	?	High
(Cacchio 2009) a	?	?	?	+	?/+	+	-	+	Unclear
(Cacchio 2009) b	?	?	?	+	+/+	-	-	-	Unclear
(Vural 2016)	+	+	-	+	+/+	+	-	-	High
(Oerlemans 1999)	+	?	-	?	?/+	-	-	+	High
(Bilgili 2016)	+	+	+	?	+/+	+	-	-	High
(Li 2012)	+	+	-	?	+/+	+	?	+	Unclear
(Fialka 1996)	+	-	-	+	-/-	?	-	+	High
(Korpan 1999)	+	+	-	-	+/+	+	-	+	High
(Fialka 1996)	+	+	-	+	+/+	+	-	-	High

(Moseley 2009)	?	+	?	?	+/+	-	-	-	High
(Askin 2014)	-	+	+	+	+/-	+	-	-	High
(Aydemir 2006)	+	+	+	+	?/?	+	-	?	Unclear
(Hazneci 2005)	?	?	+	?	?/?	+	-	-	Unclear
(Duman 2009)	?	?	-	?	+/+	+	-	+	Unclear
(Uher 2000)	?	+	-	+	+/-	-	-	-	High
(Dimitrijevic 2014)	+	+	+	?	?/-	+	-	-	High
(Jeon 2014)	?	?	?	+	+/+	-	-	-	High
(Mucha 2005)	?	?	-	?	+/+	-	-	-	High
(Wu 1999)	+	?	-	?	+/+	+	-	+	Unclear
(Barnhoorn 2015)	+	+	-	+	+/+	+	+	+	Low
(Topcuoglu 2015)	+	+	-	+	+/+	+	-	+	High
(Durmus 2004)	+	?	+	+	+/+	+	-	-	High
(den Hollander 2016)	+	+	+	-	+/+	+	+	+	High
(Sezgin 2019)	+	+	-	+	+/+	+	+	-	High
(Halicka 2021)	+	+	+	+	+/+	+	+	+	Low
(Lewis 2021)	+	+	+	-	+/+	+	+	-	High
(Saha 2021)	+	+	-	-	+/+	+	-	-	High
(Zheng 2018)	-	?	-	-	+/+	+	+	-	High

(Sethy 2017)	+	+	-	+	+/+	+	-	-	High
-: High risk of bias; +: Low risk of bias; ?: Unclear risk of bias									

Table 2-3 A summary of the risk of bias and the level of evidence.

Treatment	Study	Risk of Bias	Level of Evidence
GMIP	³¹ (Moseley 2004)	High	Low-quality evidence
	³² (Moseley 2005)	High	
	³³ (Moseley 2006)	High	
	³⁴ (Schreuders TAR 2014)	High	
Mirror Therapy	²⁶ (Cacchio 2009) a	Unclear	Low-quality evidence
	²⁷ (Cacchio 2009) b	Unclear	
	²⁹ (Vural 2016)	High	
	³⁰ (Saha 2021)	High	
Multimodal PT	^{35,36} (Oerlemans 1999)	High	Uncertain
TENS	³⁷ (Bilgili 2016)	High	Uncertain
Acupuncture	³⁸ (Li 2012)	Unclear	Uncertain
	⁴⁰ (Korpan MI 1999)	High	
	⁶⁴ (Fialka 1993)	High	
	⁴² (Zheng 2018)	High	
Tactile discrimination techniques	⁴³ (Moseley 2009)	High	Uncertain
Ultrasound of the stellate ganglion	⁴⁴ (Askin 2014)	High	Uncertain
	⁴⁵ (Aydemir 2006)	Unclear	
	⁴⁶ (Hazneci 2005)	Unclear	
MLD	⁴⁷ (Duman 2009)	Unclear	Uncertain

	⁴⁸ (Uher 2000)	High	
Laser therapy	⁴⁹ (Dimitrijevic 2014)	High	Uncertain
virtual body swapping	⁵⁰ (Jeon 2014)	High	Uncertain
CO2 baths	⁵¹ (Mucha 2005)	High	Uncertain
Qigong exercises	⁵² (Wu 1999)	Unclear	Uncertain
Pain exposure	⁵⁴ (Barnhoorn 2015)	Low	Uncertain
	⁵³ (den Hollander 2016)	High	
Aerobic exercise	⁵⁵ (Topcuoglu, 2015)	High	Uncertain
EMF	⁵⁶ (Durmus 2004)	High	Uncertain
Fluidotherapy	⁶¹ (Sethy 2017)	High	Uncertain
	⁵⁷ (Sezgin Özcan 2019)	High	
Prism Adaptation	⁵⁸ (Halicka 2021)	Low	Uncertain
Visual illusions	⁵⁹ (Lewis 2021)	High	Uncertain
Autogenic trainings	⁴¹ (Fialka 1996)	High	Uncertain

2.8 List of figures

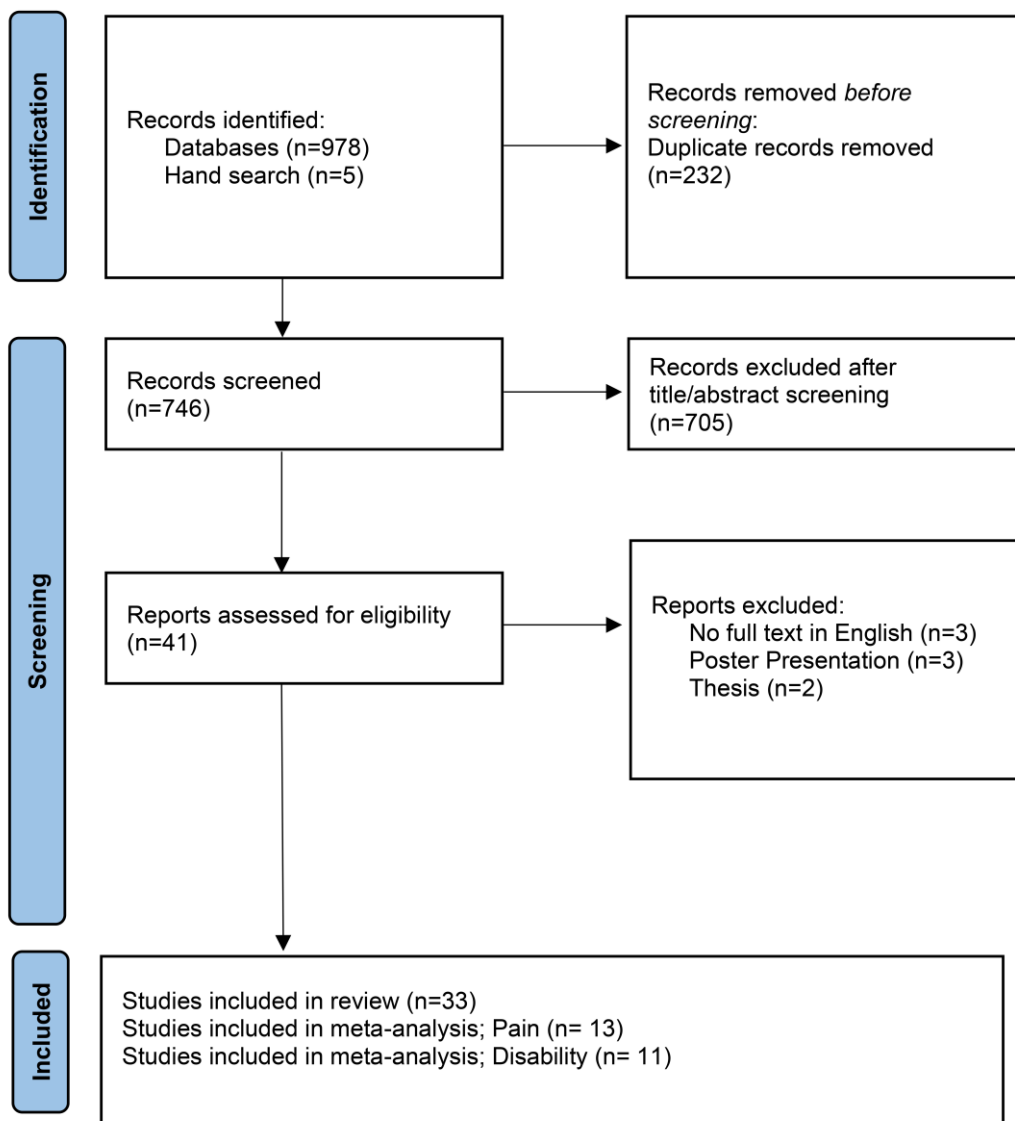


Figure 2-1 PRISMA Flow diagram.

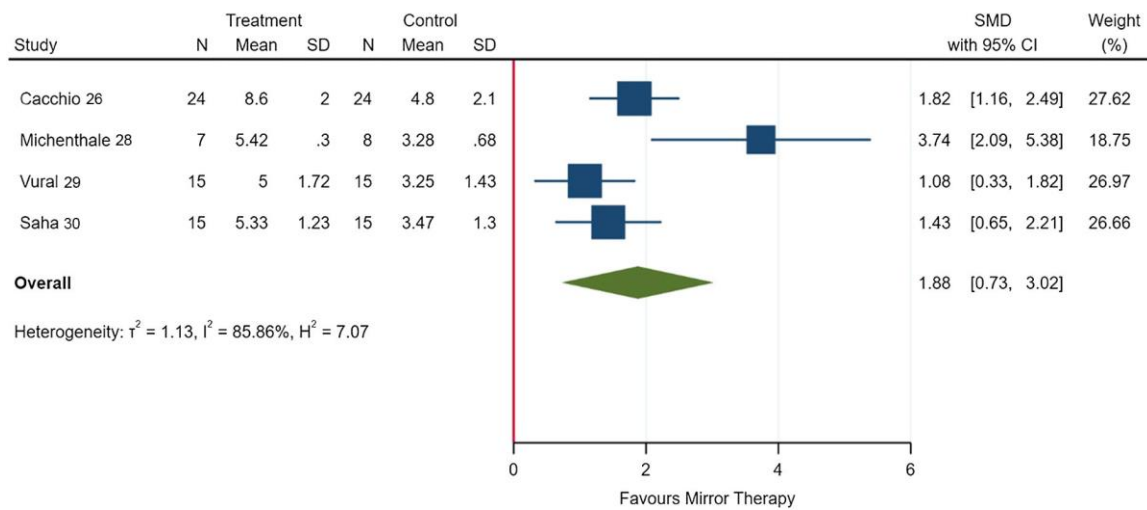


Figure 2-2 Forest plot for pain improvement after mirror therapy.

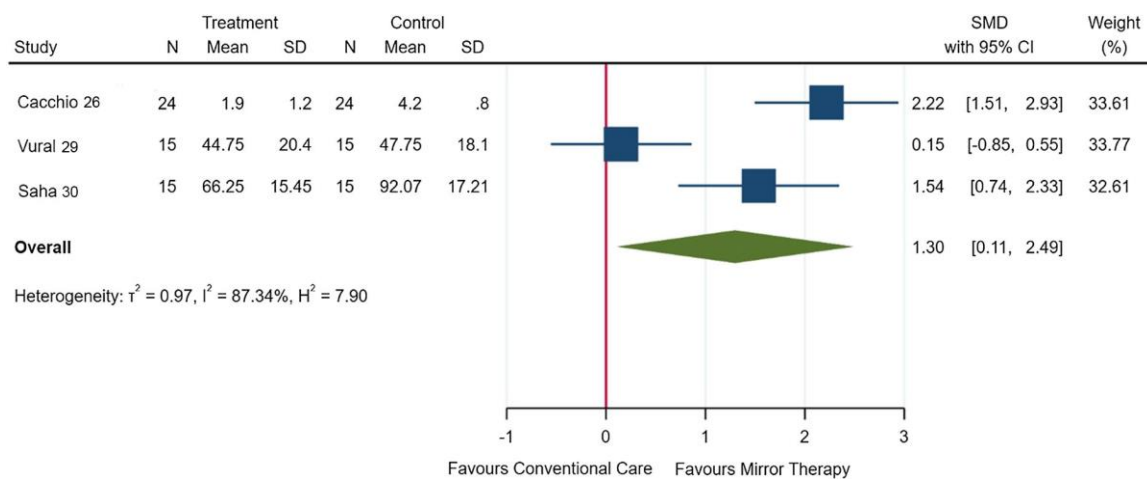


Figure 2-3 Forest plot for disability improvement after mirror therapy.

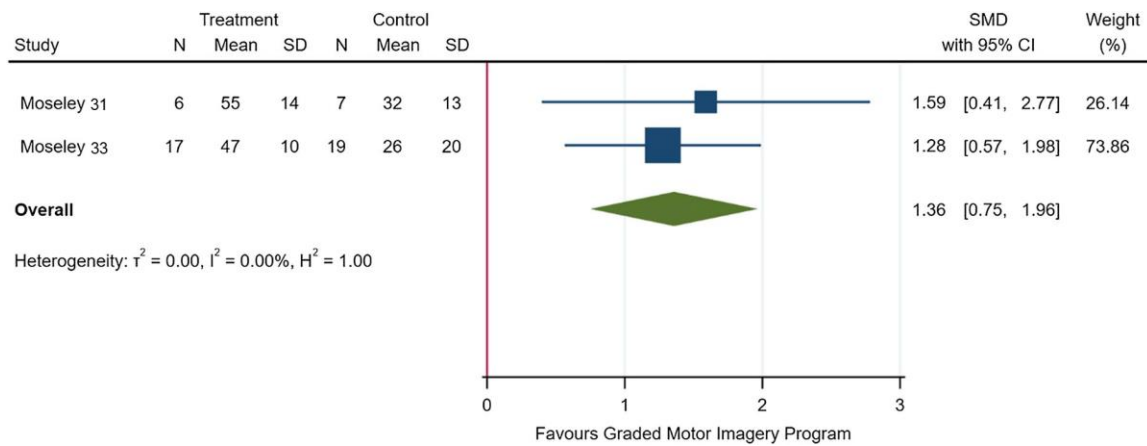


Figure 2-4 Forest plot for pain improvement after GMIP.

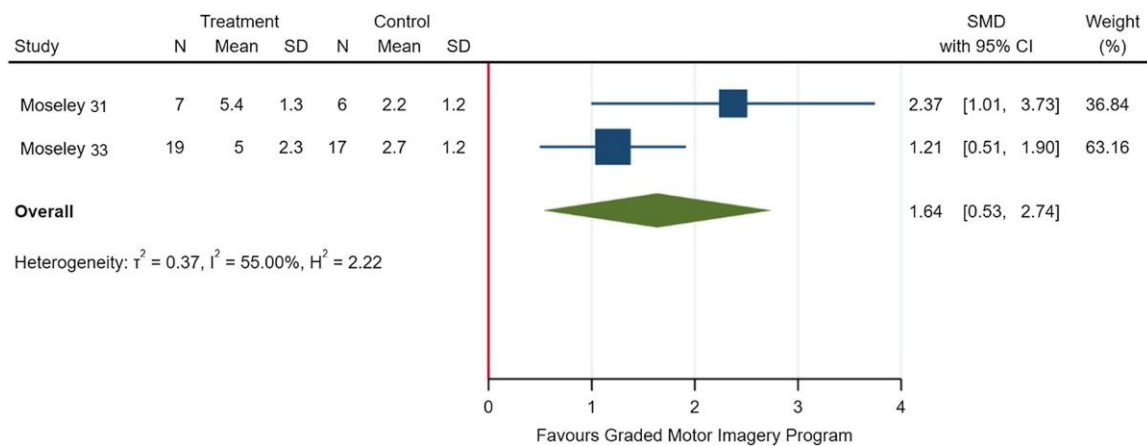


Figure 2-5 Forest plot for disability improvement after GMIP.

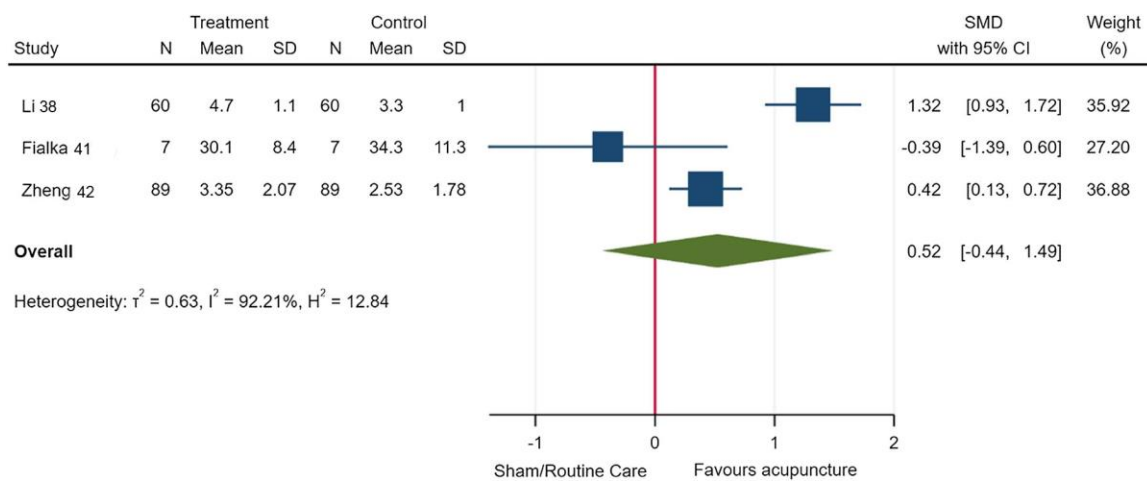


Figure 2-6 Forest plot for pain improvement after acupuncture.

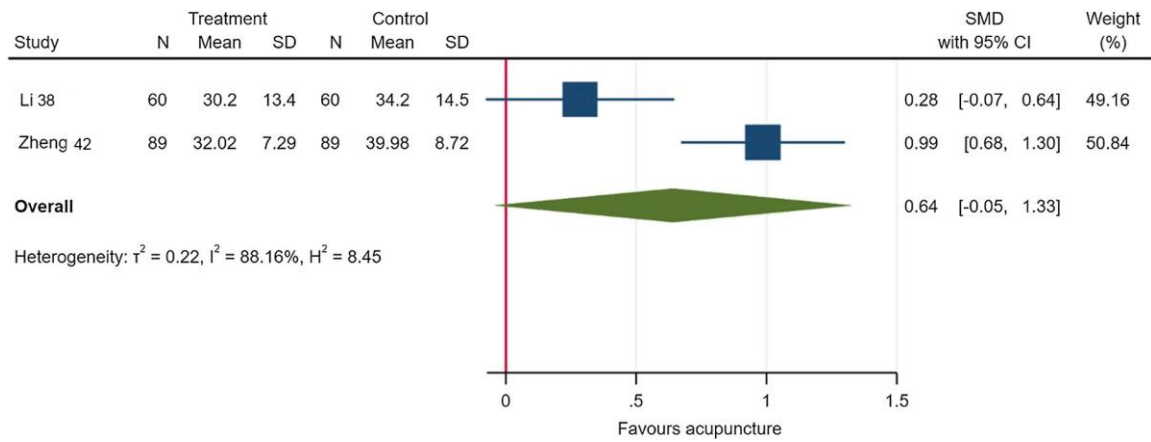


Figure 2-7 Forest plot for disability improvement after acupuncture.

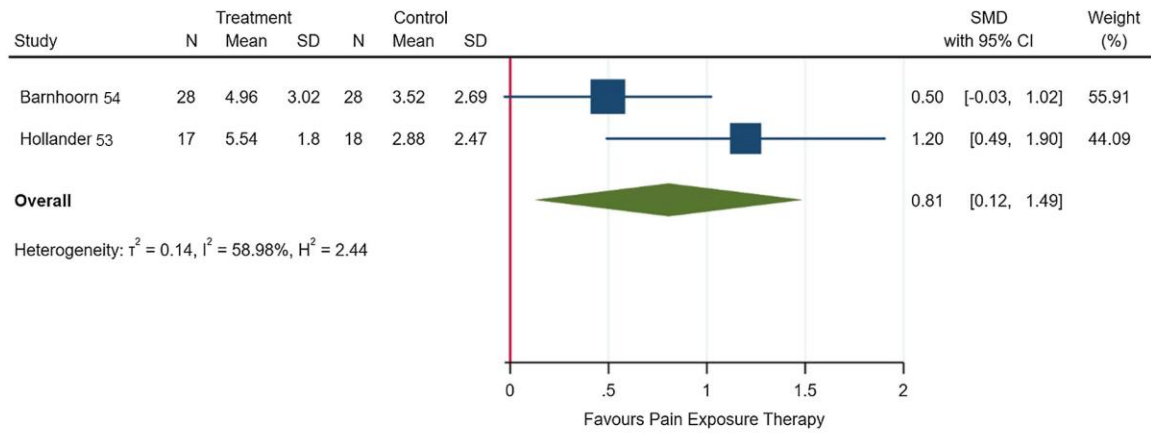


Figure 2-8 Forest plot for pain improvement after pain exposure therapy.

Figure 9.

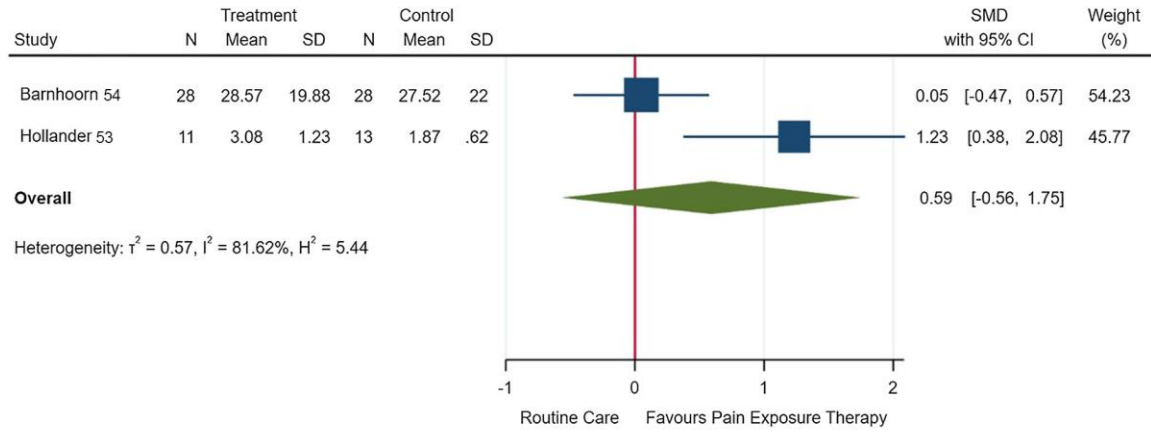


Figure 2-9 Forest plot for disability improvement after pain exposure therapy.

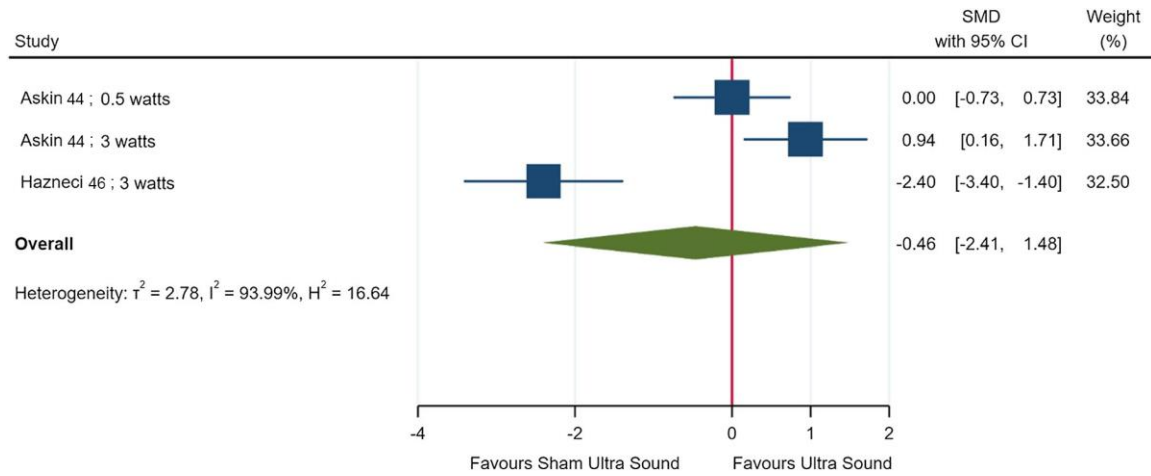


Figure 2-10 Forest plot for pain improvement after stellate ganglion block using ultrasound.

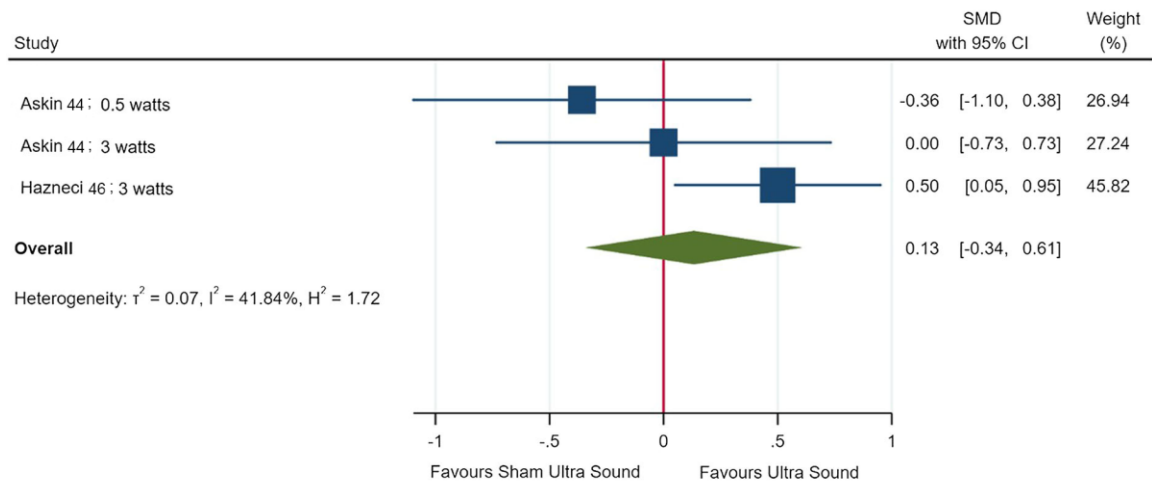


Figure 2-11 Forest plot for disability improvement after stellate ganglion block using ultrasound.

Chapter 3



Rehabilitation interventions for Complex Regional Pain Syndrome; an overview of systematic reviews

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Rehabilitation Interventions for Complex Regional Pain Syndrome: An Overview of Systematic Reviews

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3 Rehabilitation interventions for Complex Regional Pain Syndrome; an overview of systematic reviews

Abstract

Background: Complex Regional Pain Syndrome (CRPS) is a painful and disabling condition characterized by signs and symptoms that are out of proportion to the inciting event. A rising number of systematic reviews have been conducted on various conservative managements of CRPS targeting different rehabilitation interventions and objectives.

Objectives: To summarize and critically appraise the body of evidence on conservative management of the CRPS, and to provide an overall picture of the current state of the literature.

Design: Overview of systematic reviews on conservative treatments for CRPS.

Methods: We conducted a literature search from inception to January 2023 in the following databases: Embase, Medline, CINAHL, Google Scholar, Cochrane library, and Physiotherapy Evidence Database (PEDro). Two independent reviewers conducted study screening, data extraction, and methodological quality assessment (using AMSTAR-2). Qualitative synthesis was the preferred method in reporting the findings of our review. We calculated corrected covered area (CCA) index to account for the proportion of overlapping primary studies that were included in multiple reviews.

Result: We identified 214 articles and a total of nine systematic reviews of randomized controlled trials were eligible for inclusion. Pain and disability were the most common outcomes evaluated in the reviews. There were six (6/9;66%) high quality, two (2/9;22%) moderate-quality, and one critically low-quality systematic review (1/9;11%); with the quality of the included trials ranging from very low to high. There was a large overlap across primary studies that were included in the systematic reviews (CCA=23%). The findings of high-quality reviews support the effectiveness of mirror therapy and graded motor imagery programs on pain and disability improvement in CRPS patients. Large effect size was reported for the effectiveness of mirror therapy on pain and disability (SMD:1.88 (95%CI: 0.73 to 3.02) and 1.30 (95%CI: 0.11 to 2.49), respectively) and the effectiveness of GMIP on pain and disability improvement (SMD: 1.36 (95%CI: 0.75 to 1.96) and 1.64 (95%CI: 0.53 to 2.74), respectively).

Conclusion: The evidence is in favour of adopting movement representation techniques such as mirror therapy and graded motor imagery programs for the treatment of pain and disability in patients with CRPS. However, this is based on a small body of primary evidence and more research is required to generate conclusions. Overall, the evidence is not comprehensive or of sufficient quality to make definitive recommendations about the effectiveness of other rehabilitation interventions on improving pain and disability.

PROSPERO: registration No.: CRD42021230701

3.1 Introduction

Complex regional pain syndrome (CRPS) is a painful and disabling condition with associated autonomic and neuro-inflammatory signs and symptoms. It can be provoked by even minor injuries; however, its symptoms, functional limitations, and complications may persist long after the recovery of the primary impairment^{1,2}. CRPS has been classified under *chronic primary pain* in diagnostic parenting for the International Classification of Diseases (ICD-11)³.

As CRPS is a multifactorial condition, people with CRPS may experience a wide range of complications in the affected body part, such as sensory or motor disturbances, autonomic dysfunction, and limitation in function and difficulty performing activities of daily living⁴. As a result, multimodal and interdisciplinary approaches, including pharmacotherapy, conservative management, psychological interventions, surgery, and alternative therapies are required to fully manage the variable presentation of this condition⁵⁻⁷.

A number of systematic reviews (SRs) have been conducted on conservative management of CRPS targeting different rehabilitation interventions and objectives⁵. However, the overview of systematic reviews on the effectiveness of different methods of rehabilitation interventions on pain and disability, which are the main concerns of the patients with CRPS has not been updated in the past decade.

Although high-quality SRs could be considered one of the reliable sources of high-quality evidence for clinical decision making, the findings and recommendations from several SRs with various quality may be overwhelming to facilitate clinical decision making⁸.

An overview of SRs is considered a method of compiling evidence from multiple SRs to provide a broader synthesis of the current state of the literature to enlighten the evidence gap ⁹.

In the present study, we provided a summary of the evidence on the effectiveness of rehabilitation interventions on pain and disability outcomes in CRPS patients by appraising the methodological quality of the SRs of randomized clinical trials (RCTs) and reporting the quality of the evidence for each treatment.

3.2 Method

3.2.1 Study design:

In this overview of SRs, we included SRs and meta-analyses (MA) of RCTs investigating the effect on pain and disability of any conservative management of CRPS. We have registered this overview on the PROSPERO database (CRD42021230701). We used the updated guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) ¹⁰ to conduct this overview.

3.2.2 Eligibility criteria:

The eligible studies were reviews of RCTs on adults with CRPS-1 or 2, older than 18 years old, either after trauma or after neurologic conditions. The primary or secondary outcomes were pain and/or disability evaluated by self-reported outcome measures. Reviews related to CRPS in children, non-RCTs studies, or other types of review such as scoping or integrative reviews were excluded.

3.2.3 Search strategy:

Two independent reviewers (ES and MF) searched six electronic databases (Embase, Medline, CINAHL, Google Scholar, Cochrane library, and Physiotherapy Evidence Database (PEDro)) since inception to January 2023. In order to check for ongoing SRs or overview of SRs on this topic, the PROSPERO database was checked. The reference lists of eligible reviews were also checked to identify further candidate reviews that might have been missed in the database search. The search keywords, Boolean operators, and search strategy are presented in Appendix 1.

The first author (ES) and one independent reviewer (MF) conducted title/abstract checking to identify potential eligible SRs. If there was any uncertainty about the inclusion of a paper through abstract checking, the full text of that paper was checked to confirm its eligibility.

In the last step, the same two reviewers (ES and MF) screened the full text of the identified reviews to confirm if they met the eligibility criteria. Where there was any disagreement between the two authors, consensus was achieved through discussion with a third author (JCM).

3.2.4 Data extraction:

The study team developed a standardized data extraction sheet to compile data from eligible SRs, including author name, year, databases searched for each review, type of CRPS, number of included studies, risk of bias tools used for the primary studies, assessment tools for reporting the quality of evidence, results, and main conclusion.

The first author (ES) extracted the data from studies, and all of the data was double checked by the second reviewer (MF). In case of any discrepancies, consensus was achieved through consultation with the third reviewer (JCM).

3.2.5 Methodological Quality Assessment:

Two independent reviewers (ES and MF) applied AMSTAR-2 for the purpose of assessing methodological quality and risk of bias of each included systematic review. Any disagreement in quality assessment was resolved through discussion between the two reviewers: in cases where resolution was not achieved, the third reviewer would help.

AMSTAR-2 is a 16-item checklist used to critically appraise systematic reviews based on several aspects of methodological excellence ¹¹. Each item is scored as “Yes”, “No”, “Partial yes”, or “Not applicable”. The AMSTAR-2 does not generate an overall score. As noted in the AMSTAR-2 manual, “*A high score may disguise critical weaknesses in specific domains, such as an inadequate literature search or a failure to assess risk of bias (ROB) with individual studies that were included in a systematic review ...*” ¹¹. However, accounting for methodological flaws in critical domains is essential to make a final rating about the overall confidence in the results of a review.

In this review, we considered these domains as critical: a) Comprehensive literature search strategy (item 4), b) justification for the excluded studies (item 7), c) adequate description of the included studies (item 8), d) satisfactory technique for risk of bias assessment in studies (item 9), and e) considering risk of bias and quality assessment in the discussion and interpreting the results (item 13).

The following rating scheme was applied to rate the overall confidence in the results of a review: *High*= ≤ 1 non-critical weakness; *Moderate*= >1 non-critical weakness; *Low*= One critical flaw with or without non-critical weaknesses; *Critically low*= >1 critical flaw with or without non-critical weaknesses ¹¹.

3.2.6 Data synthesis:

Narrative synthesis was used to report the findings and characteristics of the SRs (rehabilitation treatments for CRPS, population, number of participants, and overall risk of bias of the included studies) to summarize the body of literature.

The details of risk of bias and quality assessment were summarized by tabulations. The findings of the reviews were grouped and reported based on the quality of SRs to yield final conclusions.

We decided not to re-score the methodological quality of the primary studies in the systematic reviews, instead relying on the scoring of the review authors. In case there was any discrepancy between the reviews in assessing the risk of bias of one RCT, we relied on the reports of the higher quality review.

In order to account for the proportion of overlapping primary studies that were included in multiple reviews, we calculated corrected covered area (CCA) index: $CCA = (N-r)/(r*c-r)$; N= number of primary studies in each review (including double counting); r= number of index publications (first-time primary studies) c=number of systematic reviews. The CCA index ranges from 0 to 100% with higher scores indicating greater overlap ¹². A CCA value less than 5 indicates a slight overlap, but values more than or equal to 15 indicate a very high overlap ¹³.

3.3 Result

Through database searching we identified 214 articles and after deduplication 205 studies were left for title/abstract checking. Handsearching also added two more records. A total of 21 studies remained for full-text review from which 12 studies were removed as they were clinical guidelines, expert-opinion, non-structured reviews, or overview of systematic reviews. Nine studies were included in the final overview¹⁴⁻²⁰. Figure 1 shows the summary of the selection process.

3.3.1 Description of included review

Nine reviews of RCTs evaluated the effectiveness of various rehabilitation interventions for CRPS. The oldest review was published in 2002¹⁹ and the newest was published in 2022²¹. There was no review specific to CRPS-2. A total of 82 RCTs were included in the systematic reviews. There were some overlaps across reviews and some RCTs were reported in multiple reviews. The overall CCA index was 23% indicating high overlap across systematic reviews (Appendix 2).

Pain and disability were the most evaluated primary outcomes in the reviews^{14-17,19,21,22}. However, three reviews did not focus specifically on any primary outcome^{18,20,23}. Only three reviews^{14,16,22} considered adverse events associated with conservative treatments for CRPS in their reports.

The risk of bias of the primary RCTs in the reviews were evaluated in eight studies^{14-19,21,22} using various risk of bias tools, including Cochrane and modified Cochrane ROB assessment tool^{14,18,21,22}, PEDro scale^{16,17}, and 15-item check list (by de Vet et al., 1997²⁴)^{15,19}. The quality of evidence for each rehabilitation intervention was also evaluated in four reviews using GRADE principles^{14,21,22} and van Tulder levels of evidence classification^{15,19} in which the quality of evidence is rated as strong, moderate, limited and no evidence. Table 1 and 2 presents the summary of the included reviews (Appendix 3).

3.3.2 Methodological Quality of the Included Reviews:

Table 3 presents the results of AMSTAR-2 methodological quality assessment. The level of agreement between the two raters was high (Kappa: 0.9).

The most common methodological flaw across systematic reviews were failing to register the review protocol prior to conducting the review and not reporting the source of funding for the included reviews. All studies met the criterion of aligning the research question with PICO. There were six (6/9; 66%) high quality systematic reviews^{14-17,21,22}. The methodological qualities of two reviews (2/9; 22%) were rated as moderate^{18,19}, and one review (1/9;11%) as critically low²⁰.

3.3.3 Findings from high-quality systematic reviews:

In a high-quality systematic review on the treatment of CRPS in adults, Cossins et al.¹⁵ in 2013 reviewed seven RCTs²⁵⁻³¹ investigating the effectiveness of electromagnetic field therapy²⁹, GMI^{25,26}, MT^{27,28}, occlusal splints³⁰, and manual lymphatic drainage³¹ in early and long-standing CRPS-1 patients. The authors found strong evidence for the effectiveness of physiotherapy/rehabilitation interventions taken together on pain improvement. When considering each treatment separately, the quality of evidence on the effectiveness of GMI on pain improvement in CRPS-1 patients after wrist fracture is strong. However, moderate quality evidence was found for the effectiveness of mirror therapy on pain improvement in early and long-standing post-stroke CRPS-1 patients. The quality of evidence for the effectiveness of occlusal splints and MLD was not reported in this review.

In a review by Theime et al.¹⁶ in 2010, the authors reviewed the efficacy of movement representation techniques for the treatment of limb pain. Theime et al.¹⁶ found significant pain reduction and disability improvement after movement representation techniques (GMI and MT) in CRPS-1 patients after wrist fractures²⁵ (12- week follow-up), upper limb CRPS-1 (six-month follow-up)³², post-stroke CRPS (12-week and 6-month follow-up)^{27,28}, and CRPS-1 and 2 in upper and lower limbs³³. The authors also conducted a MA. The results of MA of four RCTs with 108 participants indicated a large effect size in favour of movement representation techniques compared to other rehabilitation interventions (pooled SMD: -2.23 (95%CI: -3.88 to -

0.57)). Adverse event was one of the outcomes that were considered in this systematic review. Only two studies explicitly studied adverse events as one of their outcomes and no serious adverse events were reported.

In a high-quality Cochrane review, Smart et al.¹⁴ in 2016 reviewed 18 RCTs with 739 participants on the effectiveness of various physiotherapy interventions on pain and disability in CRPS-1 and 2. The physical therapy interventions were GMI^{25,26,32,34}, mirror therapy^{27,28}, routine PT and OT³⁵, virtual body swapping³⁶, tactile discrimination training (TDT)³⁷, stellate ganglion block with ultrasound³⁸⁻⁴⁰, pulsed electromagnetic field (PEMF)²⁹, laser therapy⁴¹, Co2 bath therapy⁴², electro-acupuncture therapy⁴³, manual lymphatic drainage (MLD) therapy^{31,44}.

The authors used the GRADE approach to rate the overall quality of the evidence on each outcome. Based on the results of this study very low-quality evidence was found for the effectiveness of GMIP on pain and disability improvement compared to routine care and physiotherapy interventions (Pain; MD: -21.00 (95% CI -31.17 to -10.83); Disability; MD: 2.30 (95% CI: 1.12 to 3.48)).

Very low-quality evidence was found for the effectiveness of mirror therapy compared to placebo on pain and disability improvement (Pain; MD: 3.4 (95% CI: -4.71 to -2.09); Disability; MD: -2.3 (95% CI: -2.88 to -1.72)). However, very low- to low-quality evidence was found for non-superiority of the TDT, stellate ganglion block via ultrasound, PEMFT, laser therapy, and MLD compared to routine PT interventions or placebo in short-term in patients with CRPS-1.

Two out of 18 studies in this systematic review reported adverse events associated with the treatments. One of trials reported a painful sensation caused by the pressure stimulation associated with TDT as an adverse event, and one trial reported no serious adverse event for laser and interferential therapies.

In another high-quality review by Méndez-Rebolledo et al.¹⁷ in 2017, the authors investigated the effect of GMI and mirror therapy on CRPS-1 and found six RCTs^{25-28,32,45}. The results of this systematic review indicated that although the evidence on the effectiveness of MT and GMI is not sufficient and strong, they can improve pain in patients with CRPS-1.

In a high-quality SR and MA in 2022, Shafiee et al.²¹ reviewed 33 RCTs evaluating the effectiveness of rehabilitation interventions in patients with CRPS, including mirror therapy (MT)^{27,28,33,45,46}, graded motor imagery (GMI)^{25,26,32,34}, multimodal PT^{35,47}, transcutaneous electrical nerve stimulations (TENS)⁴⁸, acupuncture^{43,49-52}, tactile discrimination techniques³⁷, ultrasound of the stellate ganglion³⁸⁻⁴⁰, manual lymph drainage (MLD)^{31,44}, laser therapy⁴¹, virtual body swapping³⁶, CO₂ bath therapy⁴², Qigong exercises⁵³, pain exposure^{54,55}, aerobic exercises⁵⁶, electromagnetic field treatment²⁹, fluid therapy^{57,58}, prism adaptation⁵⁹, autogenic exercises⁵¹ and visual illusion⁶⁰.

Based on the results of this study, low-quality evidence indicated that adding mirror therapy and graded motor imagery program to conventional stroke rehabilitation interventions or compared to routine rehabilitation interventions may result in a large improvement in pain and disability up to 6-month follow-up in post-stroke CRPS-1 patients. The pooled estimate of the SMD of mirror therapy for pain and disability was 1.88 (95%CI: 0.73 to 3.02) and 1.30 (95%CI: 0.11 to 2.49), respectively. The pooled SMD of GMIP for pain and disability improvement was 1.36 (95%CI: 0.75 to 1.96) and 1.64 (95%CI: 0.53 to 2.74), respectively.

Furthermore, low-quality evidence suggested that adding pain exposure therapy (pooled SMD: 0.81 (95%CI: 0.12 to 1.49)) and aerobic exercises (pooled SMD: 0.86 (95%CI: 0.23 to 1.50)) to PT interventions may result in a large improvement in pain up to six-month follow-up.

However, uncertain evidence was found for the effectiveness of all other targeted interventions over conventional PT or sham treatments on pain and disability.

In 2022, Smart et al.²², published an update on the Cochrane review published in 2016¹⁴ and added 16 more trials (600 participants) to the previous version. The updated version had a total of 34 RCTs with 1339 participants. A wide range of physiotherapy interventions were delivered in the primary RCTs, including “electro-physical modalities^{29,38-41,48,61-65} (ultrasound, TENS, laser, interferential therapy, pulsed electromagnetic field therapy, whirlpool baths, neuromuscular electrical stimulation, fluidotherapy, contrast baths), cortically-directed sensory-motor rehabilitation strategies^{25-28,32,36,37,45,59,66-70} (GMI, mirror therapy, virtual body swapping, tactile sensory discrimination training, prism adaptation treatment), exercise^{35,43,56} (active, active-assisted, passive, stretching, strengthening, mobilizing, functional; supervised and

unsupervised), cognitive-behavioral interventions^{54,71} ('exposure-based' strategies), MLDs and pain management advice^{31,44}.”

Although the updated version included 16 more studies, the overall conclusion was the same as the original review. The authors found very uncertain evidence with very low-quality on the effectiveness of physiotherapy interventions on pain and disability in CRPS patients. The authors also explored adverse events in the primary RCTs and found no unwanted side effects in the clinical trials.

3.3.4 Findings from moderate-quality systematic reviews:

In a moderate-quality systematic review, in 2002, Forouzanfar et al.¹⁹ found positive but not significant effect for a 15-session (five times a week for three weeks) acupuncture compared to placebo on pain improvement in patients with CRPS-1/RSD by reviewing three small RCTs⁴⁹⁻⁵¹. Three other RCTs were on the effectiveness of MLD⁴⁴ (compared to exercise therapy), PT interventions³⁵ (compared to OT and social work), and qigong exercises⁵³ (compared to sham exercises). The authors concluded that the evidence to support the effectiveness of these interventions is limited and they could not make a definite conclusion.

Duong et al.¹⁸ conducted an updated systematic review on the treatment of CRPS published between 2009-2017 in 2018. The authors identified six RCTs that advocated physical therapy interventions for CRPS. The PT interventions were pain exposure PT⁵⁵ (compared to routine PT), upper extremity aerobic exercises (compared to routine PT)⁵⁶, TENS (compared to sham TENS)⁴⁸, MT (compared to covered mirror)^{28,45}, and virtual body swapping (compared to mental rehearsal)³⁶.

The authors of this review did not use any tool to rate the overall quality of the evidence. They concluded that PT interventions could be considered as a common approach for the treatment of CRPS, however, the evidence on the long-term effect and optimal dosage is vague and requires further studies. Furthermore, they concluded that MT, TENS, and aerobic exercises were found to be effective in pain and disability improvement, but not pain exposure PT and virtual body swapping.

3.3.5 Findings from low-quality systematic reviews:

In a study by Tran ²⁰ et al. in 2010, three RCTs were identified investigating the effectiveness of rehabilitation interventions in people with CRPS, including PT (compared to OT and social work) ³⁵ and GMI ^{25,26}. The authors reported that the evidence on the effectiveness of PT and OT interventions is unclear, and the results are contradictory. They also concluded that motor imagery programs produce promising results.

3.4 Discussion

In this study we conducted an overview of systematic reviews of RCTs to provide a summary and quality of evidence on the effectiveness of various rehabilitation interventions in patients with CRPS. In this study we reviewed nine SRs and MA conducted between 2002 and 2022, comprised of 35 RCTs with high overlap in the primary studies. Most of the included systematic reviews (6/9;66%) were of high quality.

Based on the findings of our overview, most of the reviews are in favor of adopting movement representation techniques (mirror therapy and graded motor imagery techniques). However, the number of primary RCTs in this field is not compelling (<6 for each intervention), and recommendations are based on these studies. It is important to emphasize that our overview does not indicate that movement representation techniques are effective, but implies that high-quality evidence is not sufficient to make a firm conclusion. Nevertheless, low-quality evidence is not an indicator of no effect, instead it means that more research is needed to reach a definite conclusion.

Given the fact that CRPS development could be due to the multiple mechanisms leading to alterations in both peripheral and central nervous system, not only is there variation across different types of treatments, but they are intended to address different mechanisms ⁷²⁻⁷⁴.

Furthermore, given the paucity of robust evidence, choosing treatments relative to the proposed mechanism may be relevant ⁷⁵. In the same way that there is probably not a single mechanism that accounts for this syndrome, neither a single-treatment nor an all-treatment approach should be suggested for the optimal management of CRPS ⁷². The ideal treatment method is the one takes holistic approach and does not prioritize any aspect of the individual, including body

structure, impairment, and body function over the contributions of other factors, such as personal/environmental factors and participation ⁷⁶ (according to the International Classification of Functioning, Disability, and Health; ICF).

The most obvious limitation in the evidence raised by systematic reviews was the small sample size in most of the primary RCTs ^{21,22}. This may compromise the precision and internal validity of the studies and subsequently the quality of evidence. Given that CRPS is not a common condition, running large RCTs might be difficult. Multi-site rehabilitation studies could be considered a solution to address this issue and advance beyond our present level of evidence ⁷⁷.

One important consideration in presenting the results of an overview of systematic reviews is to assess and document the degree of overlap in primary studies, because ignoring this issue leads to improper assumptions about the effectiveness of a given intervention ^{12,78}. In this overview we considered all rehabilitation interventions as a single concept (conservative treatment), and calculated the value of CCA across all systematic reviews and rehabilitation interventions. However, rehabilitation treatments cover a wide range of interventions targeting multiple mechanisms in CRPS ⁷².

A high level of overlap indicates that different systematic reviews are not drawing upon different pools of evidence and therefore not necessarily contributing new information to our knowledge. Differences in publication dates, inclusion/exclusion criteria or the focus of the research question should reduce overlap. Conversely, when the research question is similar across systematic reviews one would anticipate overlap would be present since standardized methods of systematic review should lead to a similar pool of primary studies being synthesized. However, we found that systematic reviews did not always reach the same conclusion.

Considering presenting the findings of our overview based on the quality of the systematic reviews, there was not considerable difference between the reports of high-quality versus moderate/low-quality systematic reviews. However, there was an inconsistency across systematic reviews in the literature in terms of reporting the quality of evidence or recommendations and interpreting the results of the primary studies. The quality ratings and recommendations varied depending on the scales used for quality assessment.

For instance, in a high quality SR by Cossins et al. in 2013¹⁵, the authors used 15-item check list for ROB assessment, and van Tulder classification to rate the overall quality of evidence; in another high quality SR by Shafiee et al. in 2022²¹, the authors used modified version of the Cochrane ROB assessment tool and GRADE. While the 2022 study found low-quality evidence for the same intervention on the same outcome with two additional primary RCTs, the 2013 study found strong evidence for the effectiveness of GMIP on pain relief. Considering that the 2022 study, compared to 2013 study, conducted MA, included two more RCTs for, and found large effect size, was expected to have superior quality evidence, but it did not. As it is evident in this comparison, using different critical appraisal tools led to different conclusions, assuming that other characteristics of the reviews are of equal quality.

More favorable results are observed in narrative reviews in which authors reported the findings of the primary RCTs without reporting and calculating the effect size^{15,79,80}. However, the reviews that were accompanied by MA reported contradictory results compared to the narrative synthesis^{16,77}. For instance, in a SR and MA by Shafiee et al. in 2022²¹, the results of MA indicated that TENS is not superior to sham TENS treatment and evidence is very uncertain (overall effect size for pain and disability was 0.66 (95% CI: -0.05 to 1.37) and 0.32 (95% CI: -0.41 to 1.04), respectively), however, in a narrative review by Duong et al.¹⁸, TENS was recommended and reported to be effective in pain and function improvement.

One of the probable explanations might be the methodological discrepancies between these two designs. The number of studies is often less in MA due to the inadequate numerical data in primary studies⁸¹. Furthermore, MA considers standard errors in each study and implements them in calculating the effect size of each treatment⁸². The other reason might be due to the way the results of the MA were interpreted. Some authors focus on point estimates while others focus on confidence intervals which can lead to differences in interpretation. Although a point estimate of a large effect size is reported for some of the treatment outcomes in a MA which optimistically suggests a large benefit to patients, the confidence intervals around the pooled estimate sometimes crossed the no difference line, which can be interpreted as that there is potential that the treatment is not effective at all^{5,83}. More often, failing to calculate the magnitude of the effect size in narrative synthesis may have contributed to a lack of emphasis on the size of treatment effect when making recommendations

⁸⁴. Even where evidence is strong, if the effect of treatment is quite small and there are potential downsides like costs, inconvenience, discomfort with treatment or other downsides, this is ideally considered when making a recommendation about use in routine clinical practice.

One of the other important issues that should be addressed in systematic reviews and primary studies is reporting the adverse events associated with the treatments. The findings of our overview found no serious adverse event for rehabilitation interventions in patients with CRPS. In this overview we could find only three reviews ^{14,16,22} that explored adverse events in their study. However, it is not clear whether this could be due to the absence of adverse events or adverse events not being reported by the systematic reviews or primary RCTs.

As mentioned earlier, one of the most common methodological flaws across SRs was failing to register the review protocol prior to conducting the review and not reporting the source of funding for the included reviews. However, we should acknowledge that registration was not common, especially for reviews in the past. The International Prospective Register of Systematic Reviews (PROSPERO) was launched in February 2011 to improve the transparency of SRs. According to the records, the number of registered SRs was quite low in the first years after the PROSPERO was launched, and it gradually climbed (from 63 SRs per month in 2012 to 800 per month in 2017) ⁸⁵. For the older studies we should highlight that at that time, registration as well as reporting guidelines were not developed as they are now. Failure to register the review protocol may not necessarily result in bias the way it does in an RCT, and there was no evidence in our systematic review that those who failed to register the review protocol came to different conclusions.

Concerning the influence of funding sources on the results of primary studies or treatment effects as well as potential sponsorship bias, the first meta-epidemiological study in the field of physical therapy was published in 2020 ⁸⁶, and it evaluated the influence of sponsorship bias on treatment effects. According to the findings of this study, RCTs with improper or unclear influence of funders seemed to have a larger effect size than those with clear impact of industrial funding, and that sponsorship bias was relatively small and probably less noticeable. Research in the field of physical therapy is less funded than other fields. As the results of the meta-epidemiological study showed, studies that were funded in the field of PT had a higher

methodological quality. Possible explanations for this result could be that funding facilitates the rigorous administration of clinical trials through including a multidisciplinary research team with several members, larger sample sizes, and publication in high-impact journals ⁸⁶.

There were certain limitations to this study that should be considered when interpreting our findings. Since we included only systematic reviews of RCTs to focus on the higher quality study designs, our findings may have been affected by publication bias or missed evidence that would have been useful from observational studies. Next, we did not assess the methodological quality and risk of bias of the primary RCTs included in the systematic reviews, instead relying on the rating of the review authors. However, there is no consensus on whether to extract risk of bias assessment directly as stated in the systematic reviews or to re-run the quality/risk of bias assessment for the purpose of the overview ⁷⁸. Furthermore, due to limited information of the primary RCTs in some of the systematic reviews, the overall conclusion on a few interventions might be excessively broad for clinicians, since we were dependent on the detail provided in the systematic review.

It is important to note that overviews provide an important mechanism for understanding the pool of synthesized evidence on a given research question. However, when it comes to carrying out the interventions, dosage, frequency, and details of the treatments, overviews may be less useful ⁸⁷. Finally, we pooled results addressing post-traumatic CRPS Types I and II, and post-stroke CRPS without considering the potential heterogeneity of the diagnostic criteria used to set the inclusion criteria for the original RCTs.

3.5 Conclusion

Based on the findings of our overview, most systematic reviews are in favour of adopting movement representation techniques such as mirror therapy and graded motor imagery programs. However, this is based on a small body of primary evidence. More research is also needed to generate conclusions regarding the effectiveness of other rehabilitation interventions on pain and disability improvement.

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3.7 List of tables

Table 3-1 Summary of the included reviews

Author	Databases	AMSTAR 2	ROB tool	Quality of Evidence	Outcome
Forouzanfar, 2002 ¹⁹	1966-2000: Cochrane, Pubmed, Embase and MEDLINE	Moderate	15-item check list (de Vet et al., 1997)	van Tulder classification of the levels of evidence (van Tulder et al.'s, 1997): Strong, moderate, limited and no evidence. (van Tulder et al., 1997).	Pain
Tran, 2010 ²⁰	1950-April2009 Medline, Embase	Critically low	Not assessed	Not assessed	No specific primary outcome
Cossins, 2013 ¹⁵	June 2000-Feb 2012 Medline (PubMed), SCOPUS, CINAHL, and AMED bibliographic databases and the Cochrane Central Register of Controlled Trials	High	15-item check list (de Vet et al., 1997)	van Tulder classification of the levels of evidence (van Tulder et al.'s, 1997)	Pain
Thieme, 2016 ¹⁶	Inception-Aug 2014 Cochrane Central Register of	High	PEDro scale	Not assessed	pain, disability, and quality of life

	Controlled Trials, MEDLINE, EMBASE, CINAHL, AMED, PsychINFO, Physiotherapy Evidence Database, and OTseeker				
Smart, 2016 ¹⁴	Inception-Feb 2015 CENTRAL (the Cochrane Library), MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, PEDro, Web of Science, DARE and Health Technology Assessments	High	modified version of the Cochrane ROB assessment tool	GRADE	Pain and disability
Méndez- Rebolledo, 2017 ¹⁷	1990-May 2016 Cochrane Bone, Joint and Muscle Trauma Group, Cochrane pain, palliative and supportive care group, Cochrane	High	PEDro scale	Not assessed	Pain

	Library, CINAHL, PsycINFO, ERIC, Biomed Central, Lippincott, Williams and Wilkins, MEDLINE/PubMed, PubMed Central, SAGE publications, Springer, ScienceDirect, and Wiley Online				
Duong, 2018 ¹⁸	May 2009-Aug2017 MEDLINE, EMBASE, Psychinfo, and CINAHL	Moderate	Cochrane ROB assessment tool	Not assessed	No specific primary outcome
Smart, 2022 ²²	February 2015 -July 2021 CENTRAL (the Cochrane Library), MEDLINE, Embase, CINAHL, PsycINFO, LILACS, PEDro, Web of Science, DARE and Health Technology Assessments from	High	modified version of the Cochrane ROB assessment tool	GRADE	Pain, disability, adverse event, quality of life

<p>Shafiee, 2022²¹</p>	<p>Inception-November 2021</p> <p>Embase, Medline, CINAHL, Google Scholar, PEDRO, and Psychinfo</p>	<p>High</p>	<p>modified version of the Cochrane ROB assessment tool</p>	<p>Grade</p>	<p>Pain, disability, and adverse event</p>
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Table 3-2 Summary of the systematic reviews considering each treatment separately.

Treatment	Number of reviews	Conclusion
Mirror therapy	7	<p>3/7 reviews reported very low- to moderate-quality evidence for the effectiveness of mirror therapy on pain and disability improvement in post-stroke CRPS patients.</p> <p>1/7 reviews judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of mirror therapy at reducing pain and disability compared to other routine physiotherapy interventions or placebo.</p> <p>1/7 reviews reported good evidence for the effectiveness of mirror therapy on pain improvement.</p> <p>1/7 reviews did not report the quality of evidence, but reported that mirror therapy is effective in pain and function improvement in post-stroke CRPS.</p> <p>1/7 reviews reported no sufficient evidence for the effectiveness of MT on pain improvement.</p>
GMI	7	<p>2/7 reviews reported very-low quality evidence for the effectiveness of GMI on pain and disability improvement in patients with CRPS.</p> <p>1/7 reviews judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of GMI programs at reducing pain and disability compared to each other and waiting list control.</p> <p>1/7 reviews reported strong evidence for the effectiveness of GMI on pain improvement.</p>

		<p>1/7 reviews reported good evidence for the effectiveness of GMI on pain improvement.</p> <p>1/7 reviews reported no sufficient evidence for the effectiveness of GMI on pain improvement.</p> <p>1/6 reviews found promising results for the effectiveness of GMI.</p>
MLD	5	<p>2/5 reviews reported very low-quality evidence for non-superiority of the MLD compared to routine rehabilitation interventions on pain improvement.</p> <p>1/5 reviews judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of MLD combined with conventional care at reducing disability compared to conventional care alone.</p> <p>1/5 reviews reported limited evidence for the efficacy of the MLD in CRPS patients.</p> <p>1/5 reviews reported strong evidence for the effectiveness of rehabilitation interventions together (including MLD) on pain improvement.</p>
Multimodal PT	4	<p>1/4 reviews reported very low-quality evidence for the effectiveness of multimodal PT on impairment improvement at 12-month follow-up.</p> <p>1/4 reviews judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of multimodal PT at reducing pain and disability compared to OT and social work (control).</p> <p>1/4 reviews reported very low-quality evidence for non-superiority of the multimodal PT compared to other routine rehabilitation interventions on pain and disability improvement.</p> <p>1/4 reviews found contradictory results for the effectiveness of multimodal PT interventions.</p>

TENS	3	<p>1/3 reported very low-quality evidence for non-superiority of the TENS compared to sham TENS on pain and disability improvement.</p> <p>1/3 reviews judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of TENS at reducing pain and disability compared to sham TENS.</p> <p>1/3 reviews did not report the quality of evidence, but reported that TENS is effective in pain and edema improvement and has minimal functional benefits.</p>
Aerobic exercises	3	<p>1/3 reviews reported very low-quality evidence for the effectiveness of aerobic exercises on pain improvement.</p> <p>1/3 reviews judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of aerobic exercise combined with physiotherapy at reducing pain and disability compared to physiotherapy alone.</p> <p>1/3 reviews did not report the quality of evidence, but reported that aerobic exercises are effective in the treatment of CRPS-1 patients.</p>
Pain exposure physical therapy (PEPT)	3	<p>1/3 reviews reported very low-quality evidence for the effectiveness of PEPT compared to routine rehabilitation interventions for pain improvement.</p> <p>1/3 reviews judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of PEPT at reducing pain and disability compared to conventional treatment.</p> <p>1/3 reviews reported that the evidence did not support the use of PEPT.</p>
TDT	3	<p>3 reviews reported very low-quality evidence for non-superiority of the TDT to routine rehabilitation interventions.</p>

Laser therapy	3	<p>2/3 reviews found very low-quality evidence for non-superiority of the laser therapy.</p> <p>1/3 review found very low-quality evidence for small clinically insignificant effectiveness of laser therapy compared to interferential current therapy on pain improvement.</p>
stellate ganglion block with ultrasound	3	3 reviews reported very low-quality evidence for non-superiority of the stellate ganglion block with ultrasound compared to placebo in pain improvement.
Qigong exercises	2	<p>1/2 reviews reported very low-quality evidence for non-superiority of the qigong exercises compared to sham treatment on pain improvement.</p> <p>1/2 reviews found promising results for the effectiveness of Qigong exercises on pain improvement.</p>
Virtual body swapping	2	2 reviews judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of virtual body swapping at reducing pain.
Virtual reality	2	2 reviews judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of virtual reality at reducing pain and disability compared to sham virtual reality.
(Pulsed) electromagnetic field therapy (PEMF)	2	2 reviews judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of PEMFs at reducing pain and disability compared to placebo PEMF.

Co ₂ baths	2	2 reviews judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of Co ₂ baths combined with exercise at reducing pain compared to exercise alone.
Fluidotherapy	2	2 reviews judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of fluidotherapy combined with conventional rehabilitation compared to conventional rehabilitation alone at reducing pain and disability.
Acupuncture/electro acupuncture	2	2 reviews judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of acupuncture/electro acupuncture compared to sham treatment or routine rehabilitation interventions at reducing pain and disability.
Whirlpool baths	1	1 review judged the certainty of the evidence to be very low-quality and found uncertain evidence regarding the effectiveness of Whirlpool baths at reducing pain compared to neuromuscular electrical stimulation (NMES).

Table 3-3 AMSTAR-2 Rating

Questions	Forouzanfar 2002 ¹⁹	Tran 2010 ²⁰	Cossins 2013 ¹⁵	Thieme 2016 ¹⁶	Smart 2016 ¹⁴	Méndez-Rebolledo	Duong 2018 ¹⁸	Shafiee 2022 ²¹	Smart 2022 ²²
1. Research question and inclusion criteria aligned with PICO	+	+	+	+	+	+	+	+	+
2. A priori protocol used	-	-	-	+	+	-	-	+	+
3. Study design selection explained	+	+	+	+	+	+	+	+	+
4. Comprehensive search carried out	+	?	+	+	+	+	+	+	+
5. Duplicate study selection used	+	-	+	+	+	+	+	+	+
6. Duplicate data extraction used	+	-	+	+	+	+	+	+	+
7. List of excluded studies included, with justification	-	+	+	+	+	+	+	-	+
8. Included studies described in adequate detail	+	+	+	+	+	+	+	+	+
9. Satisfactory technique used for assessing risk of bias	+	-	+	+	+	+	+	+	+
10. Sources of funding of included studies reported in review	+	-	-	-	+	-	-	-	+

11. If meta-analysis, combination of data justified	N/A	N/A	N/A	+	+	N/A	N/A	+	+
12. If meta-analysis, risk of bias of included studies considered	N/A	N/A	N/A	+	-	N/A	N/A	+	-
13. Risk of bias considered in interpretation and discussion	+	-	+	+	+	+	-	+	+
14. Satisfactory explanation given for any heterogeneity	+	-	+	+	+	+	-	+	+
15. Publication bias in the included studies assessed	N/A	N/A	N/A	-	-	N/A	N/A	-	-
16. Review authors reported on any of their own conflicts of interest	-	+	+	+	+	+	+	+	+
Overall quality	Moderate	Critically Low	High	High	High	High	Moderate	High	High

- = no; + = yes; ? = partial yes; N/A = not applicable; High – no or one non-critical weakness; Moderate – more than one non-critical weakness; Low – one critical flaw with or without non-critical weaknesses; Critically low – more than one critical flaw with or without non-critical weaknesses

3.8 List of figures

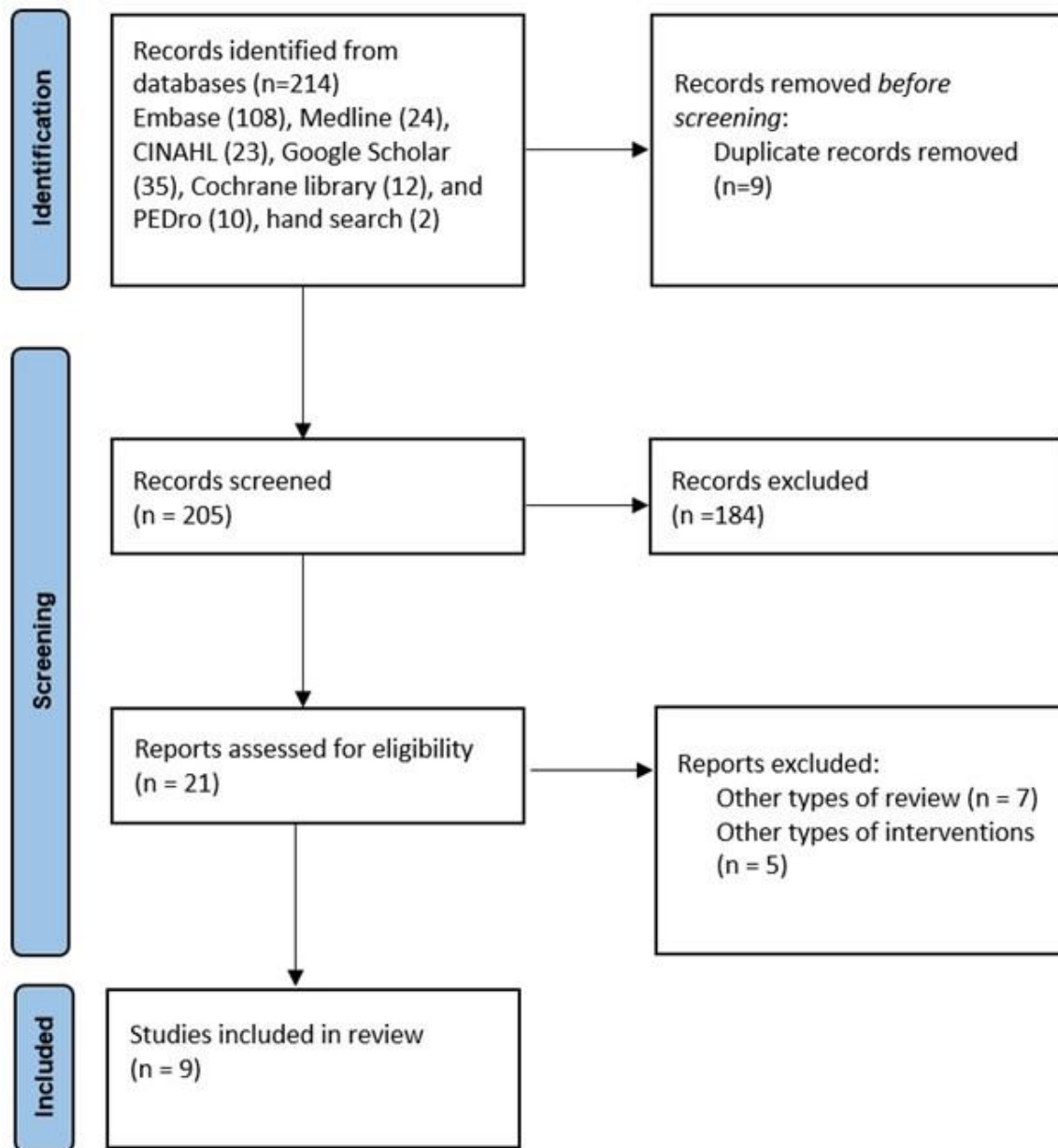


Figure 3-1 Prisma flow diagram

Chapter 4

4 A Systematic Critical Appraisal of Clinical Practice Guidelines for Non-pharmacological Conservative Management of Complex Regional Pain Syndrome (CRPS) Using the AGREE-II Instrument

Abstract

Background

Complex regional pain syndrome (CRPS) is a rare debilitating neurological condition. Rehabilitation interventions have long been the frontline treatment for the management of CRPS. Several clinical practice guidelines (CPGs) have been developed for this condition. In this study, we focused on the recommendations of CPGs for non-pharmacological conservative management of CRPS.

Aim

The aim of our study was to identify, summarize, and appraise CPGs for non-pharmacological conservative management of CRPS and to describe the best recommended practice in the management of CRPS.

Methods

We systematically searched EMBASE, MEDLINE, Google Scholar, PEDro, and Cochrane electronic databases, from inception to January 2023 to include CPGs that focused on non-pharmacological conservative management of CRPS. We used the Appraisal of Guidelines for Research and Evaluation (AGREE)-II to evaluate the quality of the CPGs. Recommendations, core concepts, aims, and treatment algorithms of the CPGs were presented in a narrative format, thematic analysis, and matrixes to summarize, categorize, and compare the findings of the guidelines.

Results

A total of nine CPGs were included in our systematic review, of which three were updates of the previous versions. Two CPGs were rated as high-quality, two as moderate-quality, and two as low-quality. The most common interventions recommended by CPGs were pain management (100% of the CPGs) followed by functional restoration (83%), stress-loading (67%), psychotherapy (67%), edema management (67%), gentle active movements (67%), vocational rehabilitation (67%), normal functional activities (67%), general PT interventions (67%), and isometric-isotonic strengthening (67%).

Conclusion

The majority of CPGs for non-pharmacological management of CRPS are based on expert opinion and clinical experience rather than peer-reviewed empirical evidence. Pain management, functional restoration, and inter/multidisciplinary care were the most recommended considerations in conservative management of CRPS. There is a need for high-quality primary research to explore the effectiveness of various conservative management on CRPS outcomes.

Keywords: Complex Regional Pain Syndrome; CRPS; Guideline; Conservative treatment; Rehabilitation; Clinical Practice Guidelines

4.1 Introduction

Complex regional pain syndrome (CRPS), which is a “chronic primary pain” condition, is a rare debilitating neurological condition that typically develops after a trauma or nerve injury. As the name implies, CRPS is a collection of difficult-to-manage signs and symptoms that are usually out of proportion to the primary impairment, or trauma ¹. CRPS has a long history of nomenclature changes, and the diagnostic criteria for this condition have been changed multiple times over the years. The underlying pathophysiology of CRPS development is still largely unknown ².

CRPS is not a common condition and various studies have reported a very low prevalence rate ². Based on the Nationwide Inpatient Sample database, the largest population-based study of CRPS in the United States in 2016 revealed that 0.07% of patients (22,533 out of 33,406,123 patients) were discharged with a diagnosis of CRPS ³. Based on the Truven

MarketScan Commercial and Medicare Supplemental databases, another study reported a higher prevalence of 1.2% (78,912 patients out of 6,575,999) ⁴.

CRPS management has always been challenging for clinicians and the evidence supporting the efficacy of the available treatments is not compelling ⁵. Rehabilitation interventions have been the frontline treatment for the management of CRPS over the past two decades.

According to the findings of the most recent systematic reviews and meta-analysis, an overall lack of high-quality clinical trials leading the authors to conclude that evidence on the effectiveness of rehabilitation (non-pharmacological conservative management) for CRPS is inconclusive ⁶. In the absence of clear empirical evidence, expert consensus tends to be favored in the development of clinical practice guidelines (CPGs) that play an important role in guiding clinicians with their decision-making.

Over the past two decades, several CPGs have been developed for pharmacological, surgical, and rehabilitation management of CRPS ^{1,7,8}, though there has yet to be a rigorous systematic synthesis of these guidelines to identify those interventions with the strongest support. In this study, we focused on the recommendations of CPGs for non-pharmacological conservative (rehabilitative) management of CRPS.

The aim of our study was to identify, summarize, and appraise the CPGs for non-pharmacological conservative management of CRPS intended to identify consistent best-available evidence for recommended practice in the treatment of CRPS.

4.2 Methods

The Preferred Reporting Items in Systematic Review and Meta-Analysis (PRISMA) statement was used to report this systematic review of CPGs ⁹. This study was registered on PROSPERO (CRD42023388177).

4.2.1 Search strategies and eligibility criteria:

We searched EMBASE, MEDLINE, Google Scholar, PEDro, and Cochrane electronic databases, since inception to January 2023. A hand search was also conducted to identify any potential CPG

that was not found in the scientific databases. Acknowledging historical shifts in terminology the search keywords and Boolean operators were: “Complex regional pain syndrome OR CRPS OR RSD OR reflex sympathetic dystrophy OR Sudeck's atrophy OR causalgia” AND “conservative OR rehabilitation OR non-pharmacolog* OR physiotherap* OR physical therap* OR hand therap* OR occupational therap* OR OT OR PT OR HT” AND “Guideline OR recommendation OR clinical practice guideline OR review OR systematic review”.

We included CPGs if they mainly focused on non-pharmacological conservative management of CRPS, or if they provided recommendations on conservative management of CRPS as a part of the guidelines. We included CPGs that were published in English, either in a peer-reviewed journal or by a panel of experts from national or multinational agencies. However, we did not set any restrictions on the date of publication or the country of origin. Two independent reviewers (ES and MF) ran the literature search and conducted title/abstract screening. In case of any uncertainty about the inclusion of guidelines by title or abstract, the full text of the guidelines was reviewed to check for eligibility.

4.2.2 Data extraction and synthesis:

The following data were extracted from the included guidelines: Guideline publishers, authors name, year of publication, country of origin, last update of the guideline, the goal of the guideline, core concepts/themes, and the details of the therapeutic pathway or algorithm. The first reviewer (ES) extracted the data from all guidelines, and it was double checked by the second reviewer (MF).

Data synthesis included extracting and classifying recommendations, providing a narrative summary, and identifying consistent recommendations across CPGs. In order to compare, categorize, and summarize the interventions recommended by the guidelines, a matrix of guideline recommendations was created, and guidelines were marked if they recommended that intervention. Even though the phrasing of each guideline varied, we merged recommendations that were conceptually comparable across guidelines. We used narrative synthesis to describe the aim, scope, main focus, and core concepts of the guidelines.

Furthermore, thematic analysis was used in order to identify the aim, scope, and theme of the recommendations across CPGs in accordance with the methods of axial coding^{10,11}. For the purpose of thematic analysis, the first author assigned a code to each recommendation when extracting data. The general characteristics of the codes to be given were agreed upon before data extraction began, including the main aim of the recommendation (e.g., symptom reduction) or the category of intervention (e.g., routine care or psychotherapy). Then, the second reviewer reread the thematic codes and refined them if required. In the final phase, a group discussion was held, and themes were finalized through consensus among all authors.

4.2.3 Quality appraisal:

We used the Appraisal of Guidelines for Research and Evaluation (AGREE)-II¹² to systematically evaluate the quality of the CPGs. The AGREE-II comprises 23 items in six domains, including Scope and Purpose (3 items), Stakeholder Involvement (3 items), Rigour of Development (8 items), Clarity of Presentation (3 items), Applicability (4 items), and Editorial Independence (2 items). Each item of the AGREE-II is scored on a 7-point Likert-type scale (1: strongly disagree to 7: strongly agree). Based on the AGREE-II user's manual¹³, the overall aggregated score is calculated using the following formula: $(\text{obtained score} - \text{minimum possible score}) / (\text{maximum possible score} - \text{minimum possible score}) * 100$. The overall quality of the guidelines was judged based on a standardized rubric.

A high-quality guideline is the one that has sufficiently covered at least three of the six domains, including “rigour of development” (scored 60% or more on each domain). A moderate-quality guideline is one with two or more domains, or three domains excluding “rigour of development”, rated sufficiently (scored 60% or more on each domain). Guidelines with one or no domain rated sufficiently (scored 60% or more on each domain) were considered low-quality^{12,14}.

In order to visually illustrate and compare the domain-level quality of guidelines, a polar bar chart was created using Vizzlo website (<https://vizzlo.com>) (Figure 2).

4.3 Results

4.4 Literature search:

Our search strategy yielded a total of 472 records. After deduplication and rigorous title/abstract checking by the two reviewers, 14 records were deemed eligible for full-text review, of which nine CPGs met the inclusion criteria^{8,15-22}. The five excluded records²³⁻²⁷ were guidelines on the diagnosis and surgical procedures for the management of CRPS (Figure 1).

4.5 Characteristics of included guidelines:

Nine CPGs that included non-pharmacological conservative management of CRPS were published between 1998 and 2022^{8,15-22}. There was only one CPG that specifically focused on non-pharmacological conservative management for CRPS²². The other guidelines provided recommendations on diagnosis, referral, rehabilitation interventions, psychotherapy, and pharmacological/surgical management of CRPS. (Table 1)

One of the records was a concise guidance adopted from the detailed guidelines published by the UK Royal College of Physicians²¹. Two of the CPGs had published an update^{20,28} on their previous versions^{17,19}; however, the recommendations were the same in both the older and updated versions. This reduces the number of analyzed CPGs to six. Three of the CPGs were published in the United States^{8,15,20}, one in Netherlands¹⁶, one in the United Kingdom²⁸ and one was a collaboration between 37 European countries²². A single guideline used exclusively peer-reviewed empirical evidence¹⁶ while the others were based mostly on expert opinions. The summary of findings for each guideline is presented in Appendices.

A total of 47 recommendations, interventions, and techniques were identified by the CPGs. The most common interventions recommended by CPGs were pain management (100% of the CPGs) followed by functional restoration (83%), stress-loading (67%), psychotherapy (67%), edema management (67%), gentle active movements (67%), vocational rehabilitation (67%), normal functional activities (67%), general PT interventions (67%), isometric-isotonic strengthening (67%).

Through thematic analysis, each of these 47 recommendations were given a specific code by the first author. A total of 12 codes (subthemes) were assigned to the recommendations in the first round. The second reviewer reread the codes and merged a few codes, resulting in a total of 7 codes (subthemes) in the second round. Through consensus between the two reviewers and a group discussion among authors in the third round, a total of three general themes were assigned to the recommendations of CPGs, including symptom reduction, functional restoration, and inter/multidisciplinary care. The details of subthemes for each recommendation and final themes are presented in Appendices.

4.6 Quality appraisal:

The agreement between the two raters in quality appraisal was high (ICC>0.90). Appraising CPGs using AGREE-II indicated that two CPGs were rated as high-quality^{16,28}, two as moderate-quality^{20,22}, and two as low-quality^{8,15}. All CPGs adequately addressed two AGREE-II domains (scope/purpose and presentation clarity) (scored >60%). Rigour of development was the lowest scoring domain, with only two guidelines^{16,28} scored 72% and 78%, while the other guidelines scored less than 40%. The only item that none of the guidelines considered was updating plan and procedure, while three guidelines (out of nine) were an update of an older version. Only two CPGs scored high on search method and literature search^{16,28}. Details of the results of the quality appraisal are presented in table 2 and Figure 2.

4.7 Summary of the CPGs findings:

CPGs elaborated different approaches to propose step by step clinical pathway for conservative management of CRPS. However, the majority of them agreed on early referral to rehabilitation as the anchor for optimal management. Two components were identified as the core of all the CPGs, including symptom reduction and functional restoration. Developing a strong therapeutic rapport with patients, keeping them motivated and engaged in therapy, and patient education were pointed as the keys to successful treatment.

The majority of the recommendations focused on pain management, functional restoration, multi/interdisciplinary care, and a gradual increase in the intensity of the interventions. In case of failing to progress through the treatment algorithm within a specific

period of time (1-3 months), more intensive interventions, pharmacotherapy, psychotherapy, behavioral therapy, or referring to specialized care for pain management were usually recommended. More details on the summary of each CPG are provided in the online appendix.

4.8 Discussion

To the best of our knowledge this study is the first systematic review of CPGs for non-pharmacological conservative management of CRPS. We found six original guidelines published between 1998 and 2022. There were only two low-quality CPGs^{12,14} that were published in 1998 and 2002. The other CPGs were of high- and moderate-quality. The majority of CPGs were based on expert opinions.

In the absence of compelling empirical evidence, it is impossible to report the anticipated effectiveness of most interventions reported in the CPGs, and most guidelines were developed by national professional associations or experts, meaning some recommendations might not be applicable to other nations or cultural contexts²⁹.

Chronic pain conditions, notably CRPS, are typically associated with physical and psychosocial suffering, both of which aggravate the course of disease¹². Persistent pain experienced by people with CRPS can lead to avoidance behavior, fear of movement, decreased mobility, pain catastrophizing, altered functional status, and psychological abnormalities. Some authors have opined that this chain of events results in a “vicious pain cycle” that amplifies and prolongs suffering and disability³⁰.

According to the conventional protocols, the focus of chronic pain management was on the sensory processing of pain instead of considering chronic pain as a multidimensional condition. Therefore, using opioids, NSAIDs, nerve blocks, and spinal cord stimulation was more common for the treatment of chronic pain³¹. Over the past two decades, with the upsurge in implementing non-pharmacological conservative management and rehabilitation interventions, chronic pain conditions have been optimally managed by multidisciplinary interventions to break the vicious pain cycle and address emotional burdens as well as pain, impairment, and physical limitations^{32,33}.

In most CRPS CPGs, rehabilitation interventions were introduced as the mainstay and core of CRPS management^{8,15,19,20}. Since one of the defining characteristics of CRPS is the variability of presentations between patients as well as the wide range of signs and symptoms experienced by a given patient⁷, CPGs were mostly in favour of implementing multimodal and multidisciplinary care for the conservative management of CRPS^{34,35}. However, empirical evidence is limited to single treatments rather than the multimodal therapies as a whole.

Since CRPS affects multiple aspects of a person's health, patients with CRPS typically have functional limitations that prevent them from working or participating in social activities. Due to the multifactorial and enigmatic nature of CRPS onset and development, a successful treatment approach should be one that covers multiple dimensions and mechanisms of this complex condition and patient's health³⁶. Neither a single-treatment nor an all-treatment approach should be suggested for the optimal management of CRPS. According to the recommendations of the previous empirical studies⁷, the ideal treatment method is the one that takes a holistic approach and does not prioritize impairment or body function/structures over the contributions of environmental and personal factors³⁷. Improving participation in activities of daily living and therapy should also be regarded one of the therapeutic targets, as it has been in some CPGs through multimodal and interdisciplinary care²². Vocational rehabilitation, recreation therapy, ergonomics, goal setting, and sleep hygiene are some of the examples of considering participation at the latter stages of the treatment algorithm.

Increasing patient motivation to increase patient engagement and adherence to treatment^{8,15,19,20} was also one of the factors that was recommended. However, no specific strategy has been proposed to increase patient motivation. Although no evidence was found for patient motivation as a treatment approach, three guidelines emphasized patient motivation as one of the pillars of successful treatment^{8,15,19,20}.

In order to appraise the quality of CPGs, we used the AGREE-II instrument, which was published in 2009³⁷. We should note that CPGs that were published prior to 2009^{8,15} have been judged against a tool that was developed later, and might have been underrated in quality appraisal, while the CPGs that were published after 2009 received higher ratings for quality assessment. However, the findings of low-quality guidelines do not differ from those of

moderate- and high-quality guidelines.

"Rigor of Development" was one of the AGREE-II domains that was given priority over other domains in assigning an overall rating for a CPG. This domain investigates literature search, evidence-based recommendations, and the link between recommendations and evidence. Since there were only two guidelines^{16,28} that integrated evidence-based findings with expert opinion, the other guidelines were rated poorly (less than 40%) in this domain.

A number of disparities were evident when comparing the findings of CPGs with the most recent systematic reviews and meta-analysis on conservative management of CRPS^{5,6}. In the most recent systematic review by Shafiee et. al.⁶ the highest quality evidence (moderate-quality) was in favour of employing movement representation techniques, such as mirror therapy and graded motor imagery programs. In contrast, movement representation techniques were only recommended in two of the CPGs¹⁷⁻²¹ reviewed here. Notwithstanding the evidence, electrical stimulations were recommended in 4/6 of the CPGs¹⁵⁻²¹, while systematic reviews and meta-analyses have previously found this is not an effective intervention^{5,6}. Pain management and functional restoration, on the other hand, were the most commonly proposed intervention plans in CPGs; however, specific therapeutic interventions, dosage of treatment, and a detailed strategy to address these outcomes were not provided.

Lack of high-quality evidence is one of the main paucities of the literature on non-pharmacological conservative management for CRPS^{5,6}. A number of potential causes have been identified for this paucity.

One of them could be that CRPS is not a common condition and most of the RCTs are of low-quality due to small sample sizes in clinical research studies. Furthermore, CRPS is characterized by fluctuating signs and symptoms and that it most likely requires a more personalized approach to care. Therefore, due to the heterogeneity of CRPS, recruiting a homogenous sample of patients could be challenging. Moreover, CRPS diagnosis has been challenging and diagnostic criteria have been changed several times over the past two decades, which could lead to the misdiagnosis or overdiagnosis of CRPS patients³⁸. One of the gaps in CPGs and literature is that no specific guideline or high-quality study is available specifically for CRPS-II.

4.9 Conclusion

Pain management, functional restoration, and multi/interdisciplinary care are favored in the majority of CPGs for non-pharmacological conservative management of CRPS, which are mostly based on expert opinion. More intense interventions, stronger drugs for pain relief, more intensive psychotherapy, or the use of more aggressive pain management techniques are recommended in case of failing to progress through the treatment algorithm. For more evidence-based suggestions regarding the efficacy of conservative treatment for CRPS, more high-quality primary studies are required.

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4.11 List of tables

Table 4-1 An overview of the clinical practice guidelines

Author/Publisher, Year	Country of origin	Quality (AGREE-II)	Aim/Scope
Stanton-Hicks, 1998 ¹	USA	Low	Present an orderly approach for the treatment of chronic CRPS-I and -II
Stanton-Hicks, 2001 ²	USA	Low	Incorporating interdisciplinary approaches and refining the linear approach of timing and sequencing of the treatments proposed in the previous guideline.
Perez S, 2010 ³	Netherlands	High	Developing evidence-based multidisciplinary guidelines for treatment of CRPS-I from studies published between 1980 to June 2005.
Goebel, 2011, 2012, 2018 ⁴⁻⁶	UK	High	Guidelines for diagnosis, referral, and management of CRPS developed by an expert panel and based on experts' opinion
Norman 2013,2022 ^{7,8}	USA	Moderate	Developed by a collaboration of expert practitioners and adapted from three expert consensus meetings:

			Malibu (1987), Minneapolis (2001), Budapest (2004).
Goebel, 2019 ⁹	A collaboration of 37 countries in Europe	Moderate	Developed by a collaboration between the experts of European Pain Federation and CRPS patients. Presenting 17 standards in eight areas for use by healthcare providers, commissioners, and policymakers for the purpose of identification and appropriate resource allocation.

Table 4-2 Appraisal of Guidelines Research and Evaluation of the guidelines AGREE.

Agree-II domains	Stanton-Hicks, 1998 ¹		Stanton-Hicks, 2001 ²		Perez S, 2010 ³		Goebel A, 2011,2012, and 2018 ⁴⁻⁶		Norman, 2013, 2022 ^{7,8}		Goebel, 2019 ⁹	
	1	2	1	2	1	2	1	2	1	2	1	2
Scope/Purpose	64		58		78		81		83		83	
Objectives	6	4	5	5	6	6	6	6	6	6	6	6
Questions	4	4	3	3	5	5	6	6	6	6	6	6
Population	6	5	6	5	6	6	7	6	6	6	6	6
Stakeholder involvement	31		31		53		64		42		64	
Group membership	6	6	6	6	7	7	6	7	7	6	7	7
Target population references and view	1	1	1	1	1	1	1	1	1	1	1	1
Target users	2	1	2	1	4	5	7	7	3	3	7	6

Rigour of development	5		5		72		78		32		6	
Search methods.	1	1	1	1	6	7	7	7	3	3	2	1
Evidence selection criteria	1	1	1	1	6	6	7	7	3	3	1	1
Strength and limitations of the evidence	1	1	1	1	6	6	5	6	3	3	1	1
Formulation of recommendations	1	1	1	1	6	7	7	6	5	3	3	2
Consideration of benefits and harms	4	3	4	3	5	5	7	6	4	3	2	2
Link between recommendations and evidence	1	1	1	1	5	5	6	6	5	5	1	1
External review	1	1	1	1	6	7	6	6	1	1	1	1
Updating procedure	1	1	1	1	1	1	1	1	1	1	1	1
Clarity of presentation	67		69		78		89		69		88	
Specific and unambiguous recommendations	3	4	5	5	6	6	6	7	5	6	6	6
Management options	6	6	5	6	6	6	6	7	5	5	5	6
Identifiable key recommendations	5	6	5	5	6	4	6	6	5	5	5	6
Applicability	10		6		38		77		35		91	
Facilitators and barriers to application	3	2	3	2	4	3	6	6	3	3	2	2
Implementation advice/tools	1	1	1	1	3	3	5	5	4	3	3	2
Resource implications	1	1	1	1	3	3	5	5	3	3	3	2

Monitoring/auditing criteria	2	2	1	1	3	4	7	6	3	3	2	2
Editorial independence	0		33		50		50		100		100	
Funding body	1	1	5	5	1	1	7	7	7	7	7	7
Competing interest	1	1	1	1	7	7	1	1	7	7	7	7
Overall Quality	Low		Low		High		High		Moderate		Moderate	

4.12 List of figures

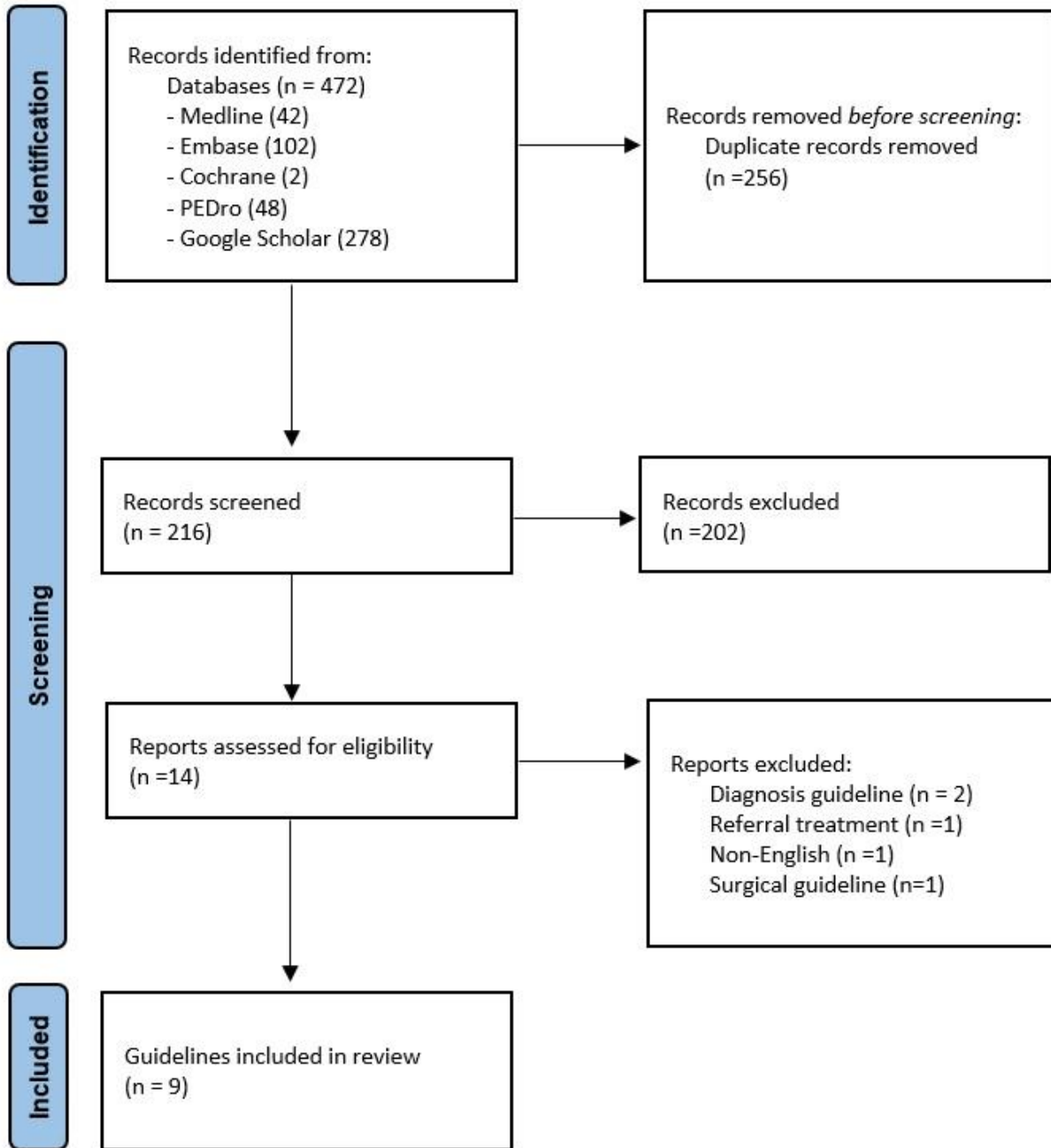


Figure 4-1 Prisma flow diagram of the included guidelines

Clinical Practice Guidelines for CRPS

Comparing the quality of the CPGs using AGREE-II

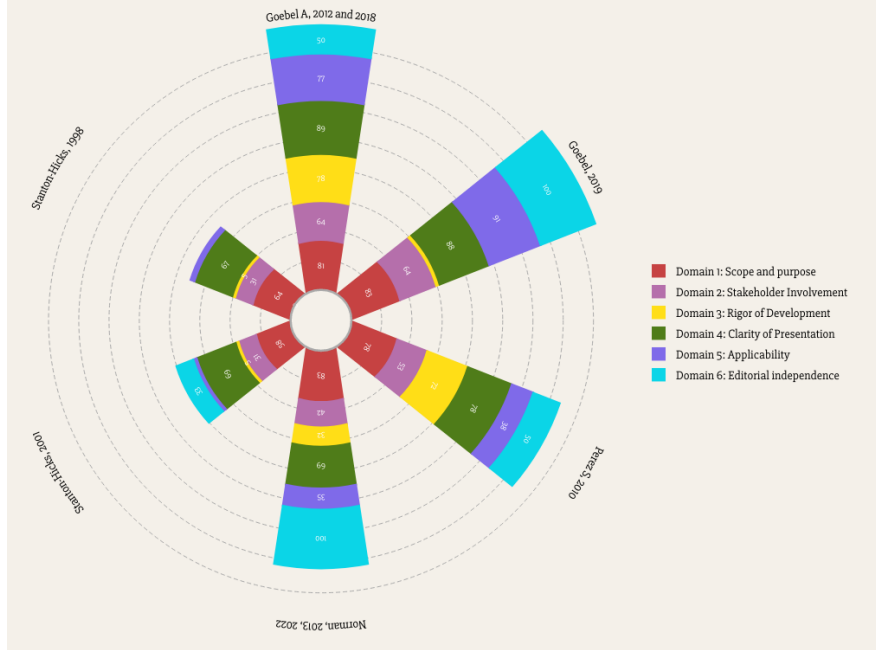


Figure 4-2 Agree-II scores for CPGs

Chapter 5

5 A Survey of Patient and Therapist Preferences and Priorities for Conservative Management of Complex Regional Pain Syndrome

Abstract

Background: A wide range of conservative management has been evaluated and recommended in the evidence and clinical practice guidelines for Complex Regional Pain Syndrome (CRPS). However, there is no consensus on the best and optimal practice for the conservative management of CRPS.

Aim: To identify and compare priorities and preferences of CRPS patients with those of therapists treating CRPS patients, regarding conservative management of CRPS.

Methods: Two surveys were created by a group of physical/occupational therapy professors and clinicians for persons with CRPS and therapists treating CRPS patients. The surveys asked patients and therapists about their preferences and priorities regarding treatments, outcomes, and decision-making process. The surveys were distributed internationally to patients and therapists through social media. Descriptive statistics were used to present and compare the findings of the surveys.

Results: A total of 79 responses (33 patients and 46 therapists) were received. The mean age was 59 (42-70) for patients and 38 (25-71) for therapists.

The most important outcomes for patients were CRPS-related pain reduction (97%), improvement in function (94%) and stiffness improvement (78%). The most effective treatments from patients' perspectives were self-management (59%), general functional activities (56%), pain education (56%), and stretching and strengthening exercises (56%). Patients prioritized three reasons as the most important ones for choosing rehabilitation interventions as their treatment options: does not involve surgery (68%), coverage by insurance/benefits (66%), and ability to stop rehabilitation interventions at any time (66%). Most of the patients (79%)

preferred shared decision-making to make the final decision for their treatment.

Therapists prioritized pain reduction (95%), function improvement (91%), and hypersensitivity (84%) as the most important outcomes. The most desirable and preferred treatment options were general functional activities (89%), pain education (84%), and self-management (70%). As with patients, most of the therapists (77%) agreed on shared decision-making as the optimal way to make the final decision for the treatment of CRPS.

Conclusion: People living with CRPS often lack the information required to make informed decisions about their treatment. Both patients and therapists valued pain reduction and functional improvement as important outcomes and treatment targets. The majority of patients and therapists selected shared decision-making as the optimal approach to selecting a rehabilitation intervention.

Key words: CRPS, Priority, Preference, Conservative treatment, Rehabilitation interventions, Physical therapy, Occupational therapy, Survey

5.1 Introduction

Managing Complex Regional Pain Syndrome (CRPS) has always been challenging for clinicians in a variety of ways, including diagnosis, management, and predicting the condition's prognosis¹. Since CRPS is characterized by fluctuating signs and symptoms, treatment is complex and usually requires a more individualized approach to care². Depending on the severity of the presenting signs and symptoms, a wide range of treatment options are available across and within disciplines, such as pharmacotherapy, psychotherapy, surgery, nerve blocks, or rehabilitation interventions. However, there is no agreement among clinicians, researchers, and patients on the best approach to CRPS management^{3,4}.

Rehabilitation interventions and conservative management are the anchors of the treatment plan for patients with mild to moderate CRPS. However, no high-quality empirical evidence exists to support the effectiveness of any particular intervention^{5,6}. In the absence of high-quality evidence, clinical practice guidelines (CPGs) play an important role in guiding clinicians' decision-making. Most CRPS CPGs are based on clinical expertise and lived experience expertise. These guidelines, developed by groups of clinical experts and interest

groups, are mostly based on expert opinion rather than robust research findings. Therefore, most of the recommendations were based on the clinical experience of the experts. The majority of the CPGs recommended implementing inter/multidisciplinary care, pain management, functional restoration, movement representation techniques, and a gradual increase in the intensity of the interventions as the key to successful management for CRPS⁶⁻⁹. However, there is no common step-by-step guide to conservative management for CRPS, and researchers and therapists have yet to reach a consensus on an optimal routine practice for CRPS.

The crux of the optimal management of CRPS has led patients to struggle with decision-making for their condition¹⁰. Considering that CRPS is not a common condition and is heterogeneous in signs and symptoms, the treatment is usually more symptom-based and varies among patients and providers¹. Another potential reason for lacking a common treatment pathway for rehabilitation interventions for CRPS could be a lack of high-quality empirical evidence, which makes it difficult to provide CRPS patients with a definite treatment pathway. In this situation patients usually become confused and make uninformed decisions regarding their condition due to a lack of agreement among clinicians, evidence, and online resources^{11,12}.

The purpose of this survey was to determine the priorities and preferences of therapists (physical/occupational/hand therapists) and CRPS patients regarding CRPS rehabilitation interventions. These two surveys investigated therapists' and patients' perspectives on key outcomes, rehabilitation interventions, and decision-making process.

5.2 Methods

The Western University Health Science Research Ethics Board (HSREB-119735) and Lawson Health Research Board (R-22-049) approved this project. The research team for this study designed two complimentary surveys: one for patients and the other for therapists treating CRPS patients. Each survey included a variety of question formats, including fixed-response and free-text responses.

Each survey had five sections: 1) demographic information, 2) the importance of possible outcomes, 3) patient or therapist experiences with the effectiveness of available rehabilitation interventions, 4) reasons for choosing and declining rehabilitation interventions (for patients) and

frequency of recommending rehabilitation interventions (for therapists), and 5) their perspectives on the decision-making process. The demographic questions for the therapist survey were drawn on the standardized demographic questions provided by ASHT¹³.

The rehabilitation interventions were extracted from recommendations of systematic reviews, clinical practice guidelines, and the experiences of the research team. The full copy of the surveys is presented in the supplementary material.

Questions on the possible treatment outcomes, effectiveness of the available treatment, reasons for choosing and declining rehabilitation interventions (for patients) and frequency of recommending treatments (for therapists) were rated on a 5-point Likert scale. At the end of each section, patients and therapists could add their own ideas in a free-text response option.

For the decision-making section, therapists were given one question with three response options, and patients were given three questions with three, four, and five response options. The reason for this difference was that the additional two questions for patients inquired about their support for decision-making and their previous experience with decision-making.

Therapists were asked an open-ended question at the end of the survey to express their opinion, preferences, or considerations in the management of CRPS, which were not considered in the survey. It aimed to capture valuable insights that might not have been covered by the structured survey, allowing for a more comprehensive understanding of therapist perspectives.

5.2.1 Inclusion criteria

Therapists in the field of physical/occupational/hand therapy who had the experience of delivering conservative treatment to patients with CRPS for at least two years, and those who were able to read and write in English were eligible to complete the survey.

Patients with CRPS, older than 18 years old, diagnosed with CRPS in either upper limb, lower limb, or both, experiencing CRPS signs and symptoms for at least three months, and those who were able to read and write in English were eligible to participate in this study.

5.2.2 Survey distribution

The surveys were created on the University of Western Ontario's Qualtrics platform ([MySurveys - Western University \(uwo.ca\)](https://www.qualtrics.com/my-surveys/)). The surveys' links and invitation posters were posted on social media (LinkedIn, Instagram, Facebook, and Twitter) by the research team inviting eligible participants. Invitation posters including the QR code and link to the surveys were also sent to the physical/occupational/hand therapy and pain associations in Canada, and other therapists in the researchers' networks. Furthermore, an invitation email (with the link and QR code of the survey) was sent to the therapists that the research team knew who might be willing to participate in our study. In order to recruit patients with CRPS, the research team reached out to national and international CRPS associations and support groups. Participants were provided with a letter of information and consent upon clicking on the link or scanning the QR code and could complete the survey online.

5.2.3 Data analysis

Survey responses were exported from Qualtrics platform in the SPSS format. We used SPSS software version 28 (IBM, New York, NY) for the purpose of data analysis. Quantitative data were analyzed using descriptive statistics. Demographic information for both therapists and patients were summarized and provided in Tables 1 and 2. The full details of the data are available in the online Supplementary material. Data was graphed using bar charts was used to visualize the survey responses and compare the response patterns between therapists and patients. The responses of therapists to the free-text question express their opinion on what has not been provided in the survey, were summarized using direct quotes and presented in a table (Table 3). In order to make comparison easier, we transformed the 5-point Likert scale to 3-point Likert scale. For example, we merged "extremely important"/"very important" and "slightly important"/"not important" response options together. The third response option, moderately important, was presented exactly as it was reported in the surveys.

5.3 Results

A total of 79 responses (46 therapists and 33 patients) were received. The mean age for therapists was 38 (25-71) and 59 (42-70) for patients. The location of practice for the majority of the

therapists were Canada (22/46; 48%), Iran (11/46; 25%), and United States (3/46; 6%). The other therapists were located in United Kingdoms, United Arab Emirates, Brazil, Argentina, Australia, Kuwait, and Italy. Patients were from Canada (11/33; 34%), United States (10/33; 31%), Australia (5/33; 16%), and Iran (3/33; 9%).

5.3.1 Patients' demographic information:

Most of the patients were female (23/33; 69%) and the majority of them (20/33; 63%) were living with someone else who could support them if needed (partner/ parents/ another family member/ roommate). The majority of the patients were not working (21/33; 63%), since they were either retired, unemployed, or unable to work. The duration of having CRPS symptoms for 72% (24/33) of the patients was more than one year. Patients experienced CRPS signs and symptoms mostly in one hand/arm (13/33; 41%) and one leg (8/33; 25%), and the other patients had symptoms in both hands/arms, both legs, and whole body. More details of the demographic data for patients are presented in Table 1.

5.3.2 Therapists' demographic information:

The majority of the therapists were occupational therapists (57%), and 54% of the respondents were also practicing as a hand therapist. Fifty-five percent of the respondents were senior therapists with more than 10 years experience in practice. The number of CRPS patients visiting each year was between 1-10 patients for 74% (32/46) of the therapists. The practice setting for most of the therapists (31/46; 70%) was outpatient clinics (either therapist-owned or hospital-based). More details of the demographic data for therapists are presented in Table 2.

5.3.3 Important potential treatment outcomes:

Based on patients' perspectives CRPS-related pain reduction (97%), function improvement (94%), and stiffness improvement (78%) were the most important potential outcomes. Based on the therapists' perspectives, the most important potential outcomes for CRPS rehabilitation management were function improvement (95%), CRPS-related pain reduction (91%), hypersensitivity to a non-noxious stimulus (84%), and movement restrictions improvement

(84%). The frequency for the other important outcomes is presented in Figure 1 and online Supplementary materials.

Patients recommended another six important outcomes in the open-text section, including *“difficulty in sleeping”, “bathing”, and “self-care”, “sexual functions”, “eliminating or at least Reducing symptoms of Complications of CRPS” and “vision changes, dental problems, various hearing issues”*.

Therapists, however, added eight more priority outcomes to the provided list, including *“fear avoidance behavior”, “mental health”, “patients fear of movement or causing harm (reduction)”, “reduction of life stressors”, “laterality”, “psychological symptom”, “preventing deformity”, and “psychological wellbeing”*.

5.3.4 Desirability and effectiveness of the rehabilitation interventions:

Based on the patients’ perspectives, the most effective rehabilitation interventions were self-management (59%), general functional activities (56%), pain education (56%), and stretching and strengthening exercises (56%). Biofeedback and contrast baths were the two interventions that were unknown for 50 and 37 percent of the patients, respectively. The most desirable treatment for therapists were general functional activities (89%), pain education (84%), self-management (70%), stretching and strengthening exercises (61%), and graded motor imagery (61%); The frequency for the other interventions is presented in Figures 2a and 2b and online Supplementary materials.

The other treatment options recommended by patients were *“interferential therapy helps similar to TENS; also paced cycling is the best type of exercise”, “visual imagery-imagining”, “occupational therapy, ADL education”, “laser therapy”, “manual lymphatic drainage”, “Creams/Patches for pain - Bio freeze, CBD/Lidocaine compounds”, “core strengthening”, and “weight bearing”*. One of the patients stated that *“cold and hot pack are very painful”*.

Therapists added six more treatments to the list, including *“yoga”, “continuous passive motion (CPM)”, “graded exposure therapy”, “visualization”, “functional electrical stimulation”, “creating a comfortable space where the patient feel safe”, “electroacupuncture”, and “positioning”*.

5.3.5 Frequency of rehabilitation intervention recommendations by therapists

Pain education (95%), general functional activities (91%), self-management (77%), swelling control (68%), desensitization/sensory re-education (64%), and stretching/strengthening exercises (64%) were the most frequent rehabilitation interventions recommended by therapists. Therapists were less likely to recommend acupuncture, TENS, and bio-feedback.

The other frequent rehabilitation interventions recommended by therapists in the free-text question were CPM, weight-bearing (movement in closed chain, compression, composite fisting), lymphatic massage therapy osteopathy, visualization, electroacupuncture, and positioning (Figure 3).

5.3.6 Reasons for choosing and not choosing rehabilitation interventions:

The most important reasons for patients to choose rehabilitation interventions were not being an invasive approach (does not involve surgery) (68%), coverage by the insurance/benefit (66%), ability to stop rehabilitation interventions at any time (66%), no major risk or side effects (62%), and being recommended by their doctor (62%).

The majority of patients identified two reasons for not choosing rehabilitation interventions, including not providing long-lasting relief (63%) and being expensive (50%). The other factors did not seem important for patients not to choose rehabilitation interventions. More details on the frequency of the reasons for choosing and not choosing rehabilitation interventions are presented in figure 3 and the online supplementary materials.

5.3.7 Decision-making:

More than half of the patients believed that they were not provided with the information on risk and benefits of the available treatment (57%) and on different type of treatment (56%). Additionally, 46% reported that they were not confident in making an informed-decision and 44% disclosed that making treatment choices was not easy for them. Indeed, lack of information

about the risks and side effects of the rehabilitation interventions were reported to be one of the reasons that made it difficult for 62% of the patients to make choices about their treatment. The other factors were not being confident in the trustworthiness of the information they obtain from multiple resources (56%), and lack of information about what each treatment does (53%). More details on the frequency of patients' perspectives for decision making are presented in figure 4 and online supplementary materials.

The majority of the patients (79%) and therapists (77%) agreed on shared decision-making, in which the therapist recommends options and the patient and therapist make a shared decision together, as being the optimal way to make the final decision.

5.4 Discussion

We conducted an international survey study to explore the priorities and preferences of patients with CRPS and practicing therapists regarding rehabilitation interventions for CRPS. The findings of our survey indicated that the priorities and preferences of CRPS patients and therapist for rehabilitation interventions have a considerable overlap. Pain reduction, function improvement, reducing hypersensitivity, and stiffness improvement were identified as the most important outcomes for both patients and therapists. In contrast, they were less concerned about the changes in skin/nails textures, abnormal sweating, and hair growth. The rehabilitation interventions rated by both patients and therapists as most effective and desirable were general functional activities, pain education, and self-management. Therapists also recommended these three interventions more frequently than other options.

In 2013, there was consensus work with patients, clinicians, researchers, industry representatives done to inform the development of the core outcome measurement set for CRPS^{14,15}. The main outcomes that were recommended by that group were pain, disease severity, participation and physical function, emotional and psychological function, self-efficacy, catastrophizing and patient's global impression of change. In our survey results, both patients and therapists identified pain reduction and function improvement as crucial outcomes for CRPS. These align with the outcomes suggested in the 2013 study, emphasizing the significance of managing pain and enhancing physical abilities for individuals with CRPS. Furthermore, our

survey respondents also highlighted the importance of reducing hypersensitivity and improving stiffness, which were not explicitly mentioned in the 2013 study. These outcomes may reflect the specific concerns and experiences of the individuals surveyed, indicating their desire for interventions targeting these symptoms

Published guidelines for CRPS recommend patient education to be one of the pillars of treatment ^{4,6}. In line with the recommendations of the guidelines, the results of our survey indicated that patients consider education as one of the most effective treatments and therapists rate it as one of the most desirable interventions that they usually recommend. Likewise, educational approaches were the most commonly employed therapy modalities reported in the 2019 survey of practitioners for CRPS rehabilitation ¹⁰. In addition to the existing evidence supporting patient education as a key component of treatment for CRPS, there is a need to explore the specific effectiveness of Pain Neuroscience Education (PNE) in the CRPS population ⁵. While PNE has been studied and utilized in the broader context of chronic pain management, research on its application and efficacy specifically for individuals with CRPS is limited and only a few numbers of case studies are available.

Therapists and patients held similar views regarding the desirability and effectiveness of TENS and acupuncture treatments as less popular options. This is concordant with the most recent systematic review and meta-analysis ^{3,5} which found no superior effect for TENS compared with sham TENS on pain and disability improvement. However, using TENS for pain reduction, improving ROM, and edema had previously been recommended in the clinical practice guidelines for CRPS ^{4,6,16}.

Contrast bath and bio-feedback were not familiar options for half of the patients. Furthermore, one of the patients in the free-text response noted that a contrast bath is a painful experience for her and did not recommend it at all. Patients' intolerance to thermal and mechanical stimulation is one possible cause of the discomfort they feel during thermal modalities ^{17,18}. The reluctance of therapists to suggest hot/cold strategies was also documented in an survey of the practitioners which quoted a participant stating *“Never cold therapy as most of my patients have extreme cold hyperalgesia”* ¹⁰.

Although there is no clear step-by-step pathway for the management of CRPS, most of the interventions recommended in the clinical practice guidelines and research studies focus on pain reduction and function improvement, the two main concerns of patients with CRPS^{3,5}. The most recent systematic review of the CRPS guidelines identified three common themes: pain reduction, function improvement, and multi/interdisciplinary treatment. These three themes correspond well with the preferences and priorities expressed by therapists and patients identified in our survey study. The core concept of the preferences and priorities for both patients and therapists were increasing knowledge and awareness to inform self-management, reducing pain, and starting activities and exercises.

Patients and therapists raised valuable information in the free-text spaces. Therapists considered psychological outcomes, including fear avoidance behaviors, reduction of life stressors, psychological wellbeing, and mental health, while patients raised ADL-based issues which could be regarded as increasing their participation in daily life routines, including bathing, sleeping, sexual activities, and self-care.

Therapists and patients provided suggestions for interventions in the free-text questions, including more passive approaches like electrical stimulation, continuous passive motion (CPM), massage, or positioning. These findings diverge from the previous survey study conducted with practitioners, where passive therapies were not commonly recommended and received criticism in open-ended questions¹⁰. This discrepancy may be attributed to the geographical distribution of participants in our survey. The majority of patients in our study were from the United States and Canada (>60%), while most therapists were from Canada and Iran (>60%). This difference in location may reflect a variation in the prioritization of technology or passive approaches compared to the sample of the other survey study¹⁰, which had a higher proportion from England, Australia, and New Zealand (>60%).

There were other more personalized interventions recommended by our respondents that went beyond routine care, including core strengthening with horses; using companion animal (dog) to modulate body temperature, breathing, heart rate; creams/patches for pain, bio freeze, CBD/Lidocaine compounds; rest and distraction; or self-management apps.

Based on the findings of our survey, patients with CRPS revealed that they are not confident that they can make an informed decision for their rehabilitation interventions. Barriers to informed decision-making foregrounded a lack of sufficient and trustworthy information about their treatment options and the risk and benefits of each treatment. Therefore, making an informed decision was reported as challenging; most therefore preferred shared decision-making. Therapists also agreed on shared decision-making as the best way to make final decisions. One of the potential benefits of shared decision-making was mentioned to be affect decision quality, which in turn can affect illness behavior, health outcomes, emotions, and resource utilization^{19,20}. The other benefits of using shared decision-making process were facilitating the integration of both evidence-based information and patients' preferences during consultations; It leads to enhanced patient understanding, accurate perception of risks, improved communication between patients and clinicians, and reduced conflicts in decision-making, feelings of being uninformed, and unnecessary use of tests and treatments²¹.

Our research team believes that developing a treatment decision aid could be a step forward in informing patients with CRPS about their treatment options for the conservative management of this condition and facilitating the decision-making process, given the complexity of CRPS, the lack of reliable resources based on the empirical evidence in lay language, and the lack of a routine treatment pathway for rehabilitation interventions.

Our survey study had some limitations. First, since this study was a part of a Ph.D. thesis and due to time constraints, we did not include CRPS patients in the process of creating survey questions to leverage their lived experience perspectives and this could increase the potential of selection bias. By excluding the perspectives of CRPS patients during the survey question development, their unique insights and experiences related to the condition may not have been adequately captured. This can result in a biased representation of the patient population and potentially limit the generalizability of the study findings

Second, although our surveys were distributed internationally, most of the survey respondents were from Canada, the US and Iran: and this might limit the external validity of the findings of our survey, since some of the questions about decision making and living situations could be cultural-dependent. And lastly, our surveys were designed by a group of researchers and therapists and neither a pilot study nor formal validation was conducted prior to distribution.

Without testing the surveys in a smaller, representative sample or conducting formal validation procedures, there is a higher risk of errors, inaccuracies, or shortcomings in the survey instrument itself. This can compromise the reliability and validity of the collected data and may undermine the overall robustness and trustworthiness of the study results.

5.5 Conclusion

There is a considerable overlap in the preferences of therapists and CRPS patients for CRPS rehabilitation interventions, highlighting areas of agreement supporting implementation and uptake. Pain management, functional improvement, and hypersensitivity were identified as key outcomes by both therapists and patients, with general functional activities, pain education, and self-management identified as the most successful and desirable therapies. Both patients and therapists prefer shared decision making to develop an intervention plan to achieve the desired outcomes. The development of accessible treatment decision aids for CRPS patients as trustworthy resources may help to address the identified barriers to current decision-making processes for persons with CRPS.

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5.7 List of tables

Table 5-1 Demographic information of the therapists

Demographic information		No. (%)
Sex	Male	22 (48%)
	Female	24 (52%)
Location of practice	Canada	22 (47%)
	Iran	11(25%)
	US	3 (6%)
	UK	2 (4%)
	UAE	2 (4%)
	Brazil	2 (4%)
	Argentina	1 (2%)
	Australia	1 (2%)
	Russia	1 (2%)
	Kuwait	1 (2%)
	Italy	1 (2%)
Geographic setting of your primary practice	Urban	32 (70%)
	Suburban	7 (15%)

	Rural	5 (10%)
	Other	2 (5%)
Profession	Occupational Therapist	26 (57%)
	Physical Therapist	17 (36%)
	Other	3 (7%)
Practicing as a Hand Therapist	Yes	25 (54%)
	No	21 (46%)
Years in experience	0-5 years	15 (32%)
	6-10 years	7 (15%)
	11-20 years	14 (30%)
	21-30 years	10 (23%)
No. CRPS patients visiting each year	0-10 patients	34 (74%)
	10-20 patients	7 (15%)
	More than 20 patients	5 (11%)
Current practice setting	Therapist-owned outpatient clinic	17 (38%)
	Hospital-based outpatient clinic	15 (32%)
	Private practice	9 (20%)
	Research	6 (14%)

	Academic-based hospital clinic setting	4 (9%)
	Hospital-based inpatient setting	2 (4%)
	Home health care system	2 (4%)

Table 5-2 Demographic information of the patients

Demographic information		No. (%)
Sex	Male	10 (31%)
	Female	23 (69%)
Country of living	Australia	5 (16%)
	Canada	11 (34%)
	Iran	3 (9%)
	US	10 (31%)
	Others	4 (9%)
Living situation	Living alone (Do not have any support available at home)	9 (28%)
	Living with someone else who can support me if needed (partner/ parents/ another family member/ roommate)	20 (63%)

	Living with someone else who is dependent on me (dependent children; dependent partner/spouse)	4 (9%)
Work status	Working full time	5 (15%)
	Working part-time	3 (9%)
	Homemaker	1 (3%)
	Retired	12 (34%)
	Unemployed	1 (3%)
	Unable to work	8 (25%)
	On worker's comp	2 (6%)
	Currently on sick leave	1 (3%)
Highest level of education completed	High school	2 (6%)
	College and vocational schools	10 (31%)
	Undergraduate studies	11 (34%)
	Graduate studies	7 (19%)
	Prefer not to say	3 (9%)
How long have you had symptoms?	1-3 months	2 (6%)
	3-6 months	1 (3%)
	6-12 months	6 (19%)

	More than 1 year	24 (72%)
In which part of your body do you experience the symptoms?	One hand/arm	13 (41%)
	Two hands/arms	2 (6%)
	One leg	8 (25%)
	Two legs	2 (3%)
	Whole body	8 (25%)

5.8 List of figures

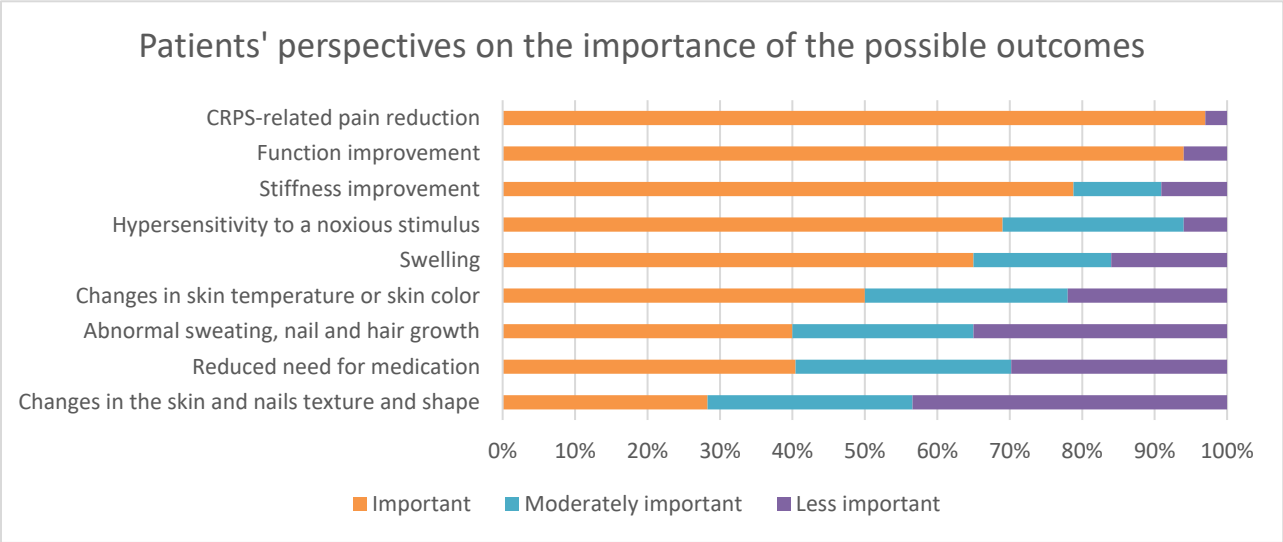


Figure 5-1a

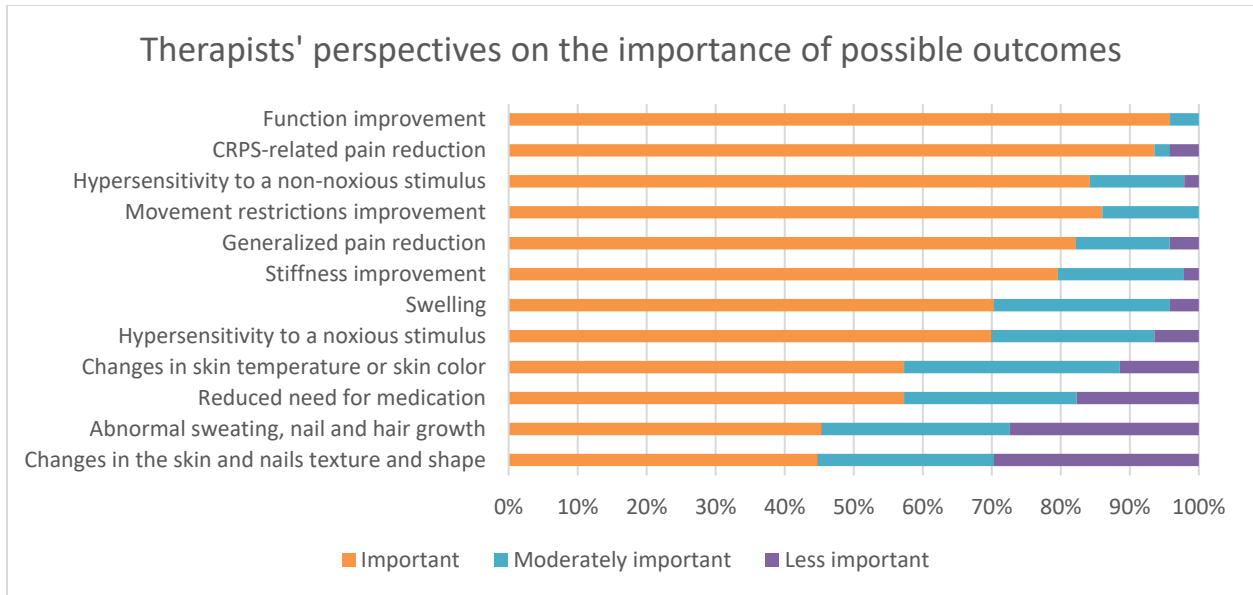


Figure 5-1b

Figure 5-1 Patients' (1a) and therapists' (1b) perspectives on the importance of possible outcomes.

Patients' perspectives on the effectiveness of the rehabilitation interventions

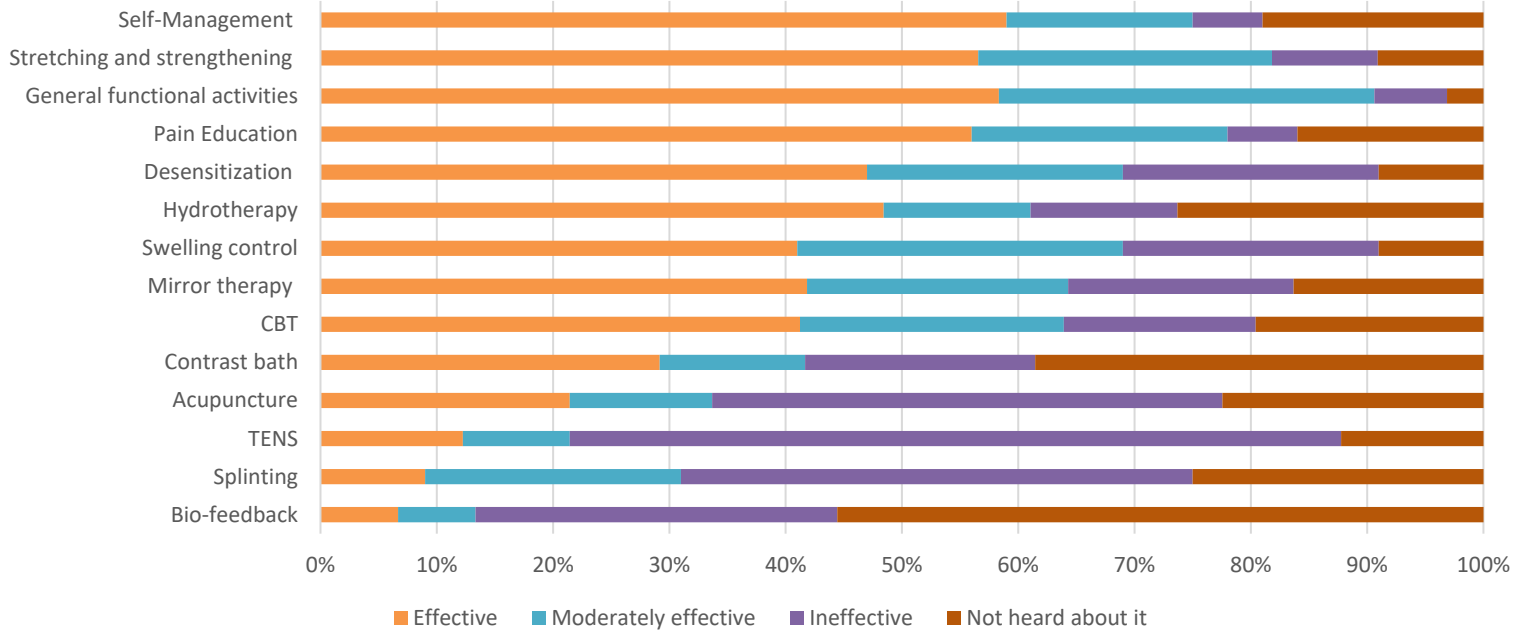


Figure 5-2a

Therapists' perspectives on the desirability of the rehabilitation interventions

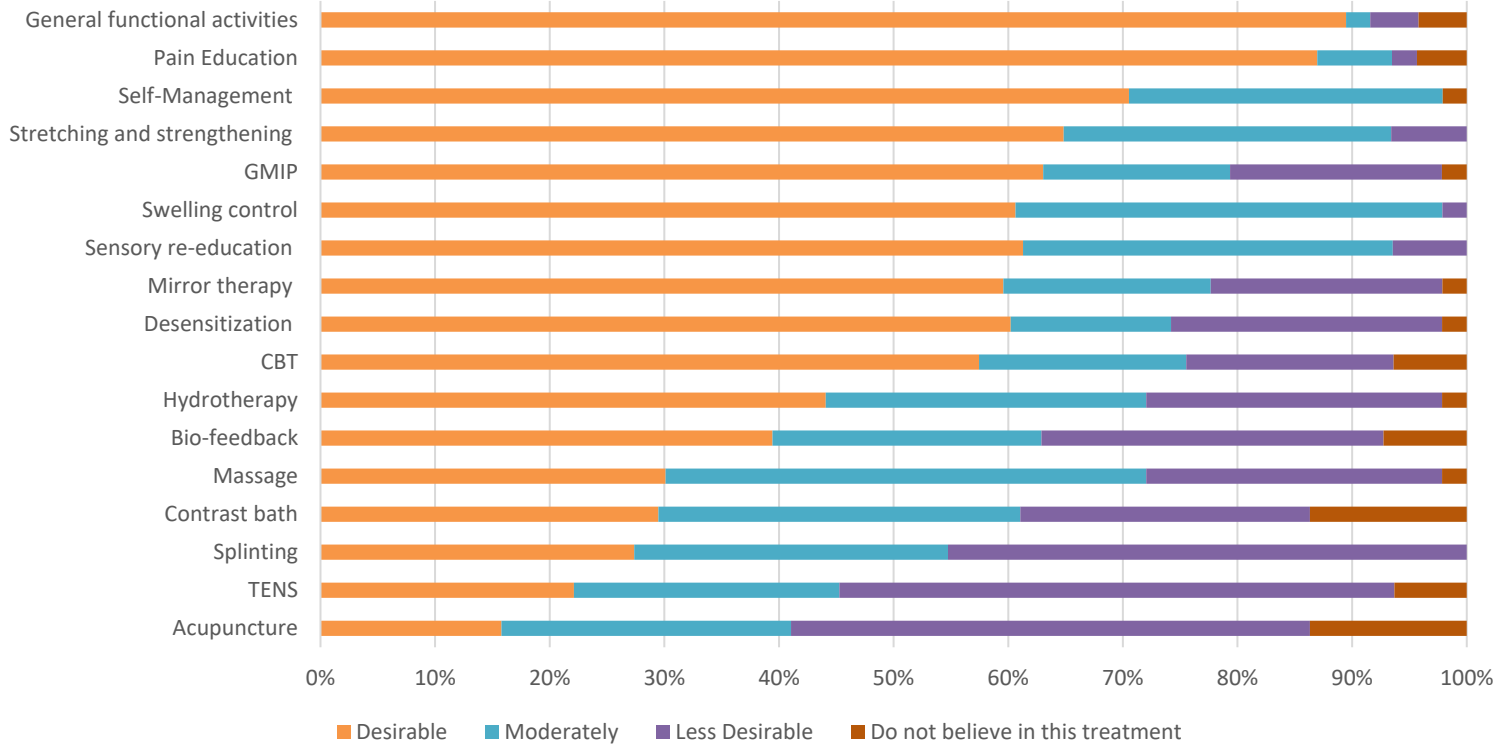


Figure 5-2b

Figure 5-2 Patients' (2a) and therapists' (2b) perspectives on the effective and desirable treatments.

Frequency of rehabilitation intervention recommendations by therapists

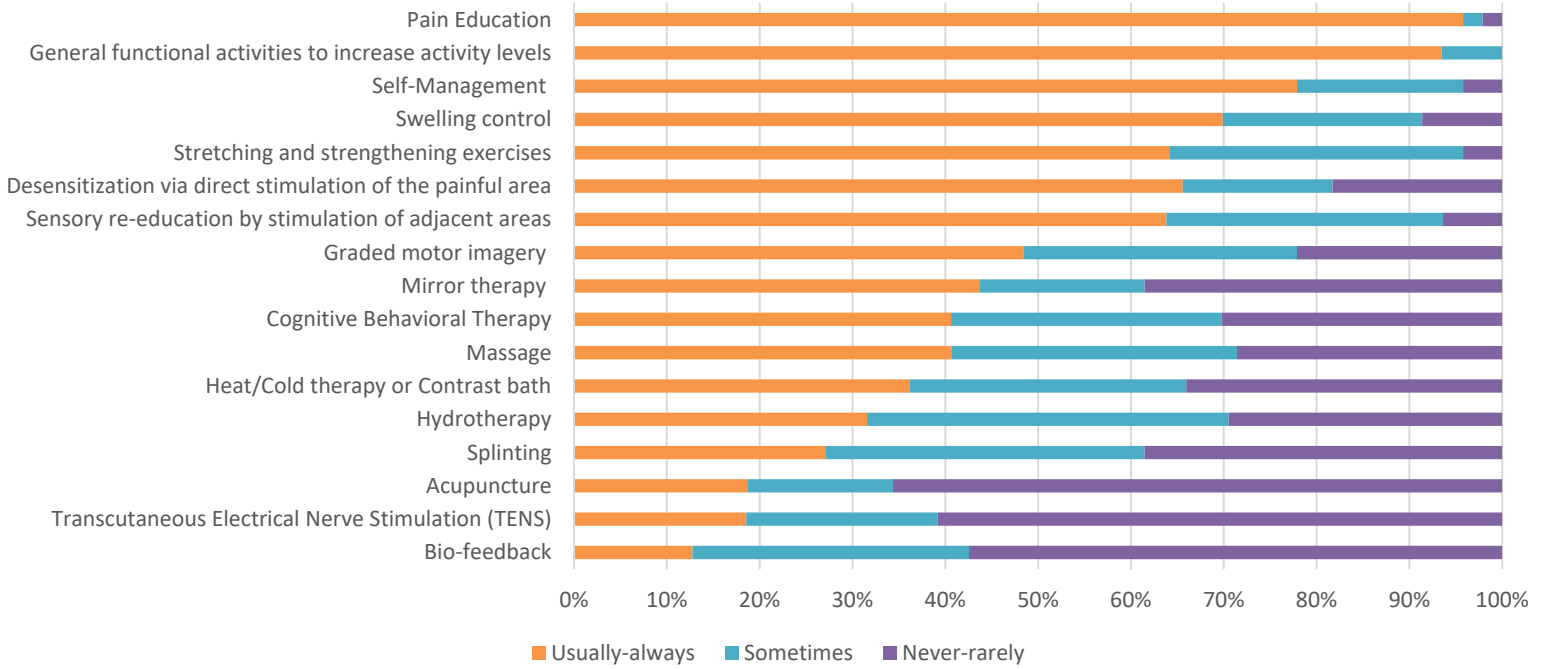


Figure 5-3 Frequency of rehabilitation intervention recommendations by therapists

Patients' perspectives on the reasons for choosing rehabilitation interventions

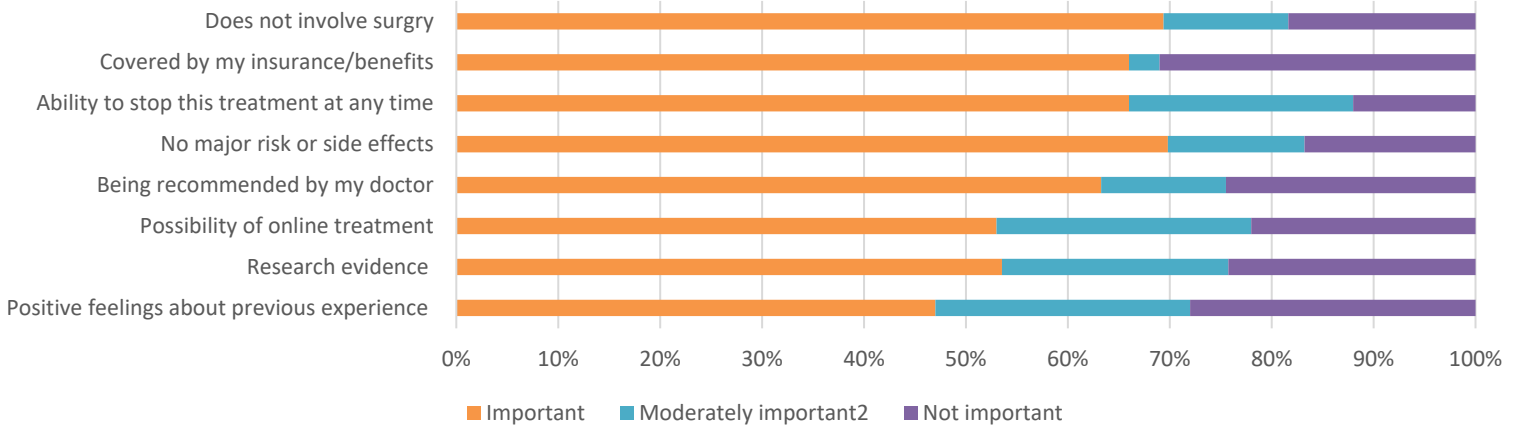


Figure 5-4a

Patients' perspectives for not choosing rehabilitation interventions

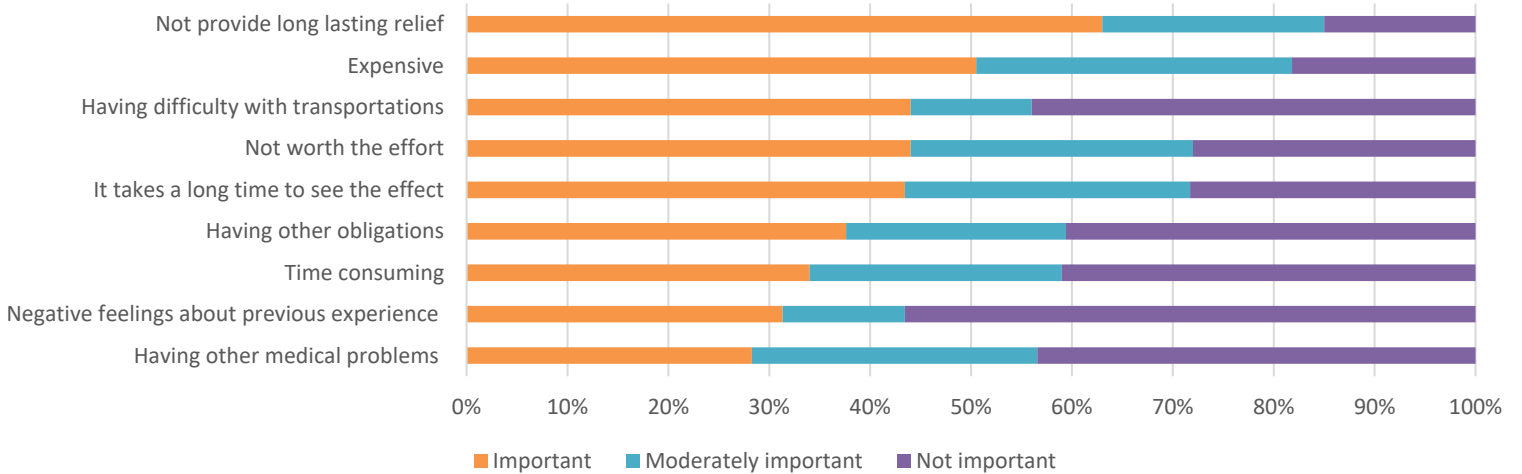
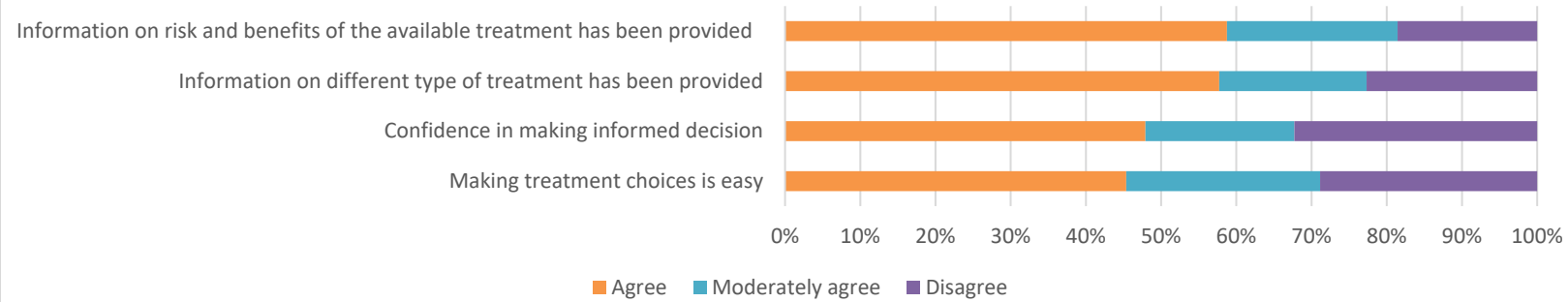


Figure 5-4b

Figure 5-4 Patients' perspectives for choosing (3a) and not choosing (3b) rehabilitation interventions.

Patients' experience of making choices about treatment options



How much do the followings make it difficult for you to make choices about your treatment?

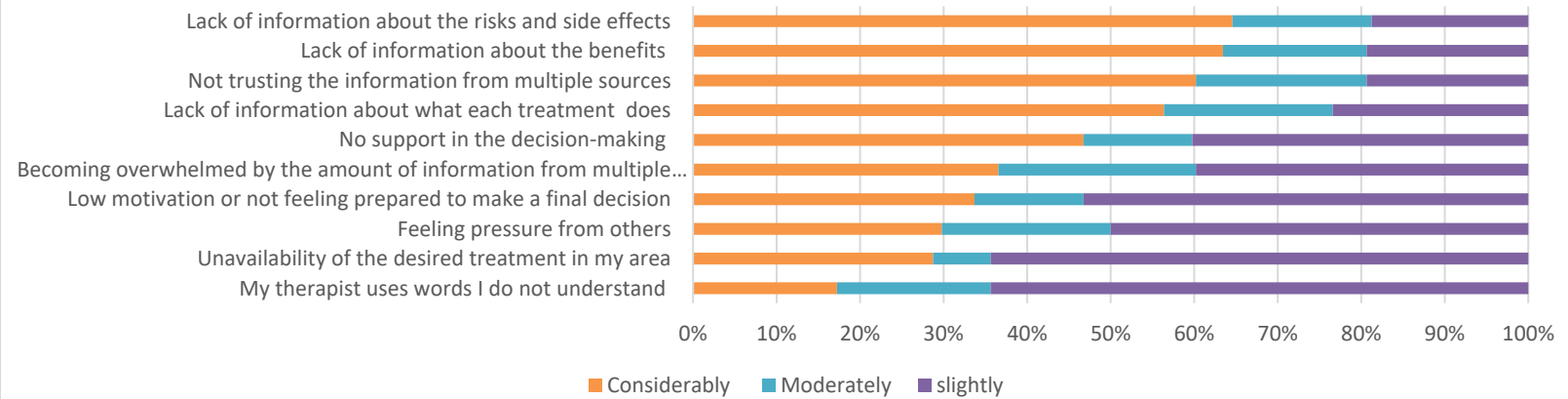


Figure 5-5 Patients' perspectives on decision making process

Chapter 6

6 Developing Rehabilitation Treatment Decision Aid (TDA) for People Living with Complex Regional Pain Syndrome (CRPS); *“I am finally a part of the decision”*

6.1 Introduction

Complex regional pain syndrome (CRPS) is a chronic and debilitating pain condition that can significantly impact a person's quality of life. CRPS is characterized by persistent pain, swelling, changes in skin color/temperature/texture, as well as motor dysfunction ¹. The pathophysiology of CRPS is not fully understood. A wide range of treatment options are available for CRPS, including medications, non-pharmacological approaches (movement therapies, activation therapies and psychological therapies), and interventional and surgical treatments (sympathetic nerve blocks, spinal cord stimulation, and intrathecal drug delivery) ².

Managing CRPS can be challenging due to the wide range of signs and symptoms that patients may experience, making it difficult to establish a standardized treatment approach ³. Treatment decisions for CRPS often require careful consideration of factors such as patient characteristics, symptom severity, and potential side effects of interventions ⁴. Due to the heterogeneity of the disease presentation and limited understanding of its underlying mechanisms, healthcare providers may face difficulty in providing optimal care to people with CRPS ⁵. Therefore, comprehensive assessments, involving a multidisciplinary team and tailored to patient needs, may be necessary to effectively manage the condition ^{6,7}.

Treatment decision aids (TDAs) are designed to provide information about the benefits and risks of different treatment options, helping patients and clinicians make more informed decisions ^{8,9}. Additionally, TDAs can help patients clarify their values and preferences and select the treatment option that best aligns with their goals and preferences ^{10,11}.

TDAs have been developed for a range of medical conditions, including chronic pain, and have been shown to be effective in improving patient outcomes. A systematic review and

meta-analysis of 28 randomized controlled trials of TDAs for a range of medical conditions found that TDAs were associated with improved knowledge, more realistic expectations about treatment outcomes, and increased patient involvement in treatment decision-making¹². TDAs have also been shown to improve patient satisfaction with care and reduce decisional conflict, which is the uncertainty and doubt that patients may experience when making difficult treatment decisions^{12,13}.

Despite the potential advantages of TDAs, there is a considerable gap in the literature concerning the development of TDAs specifically tailored to the management of CRPS. Furthermore, the wide array of treatment options available for CRPS makes it essential for patients and clinicians to have access to accurate and comprehensive information about different treatment options to allow them to select the one that best meets their needs and expectations.

Developing TDAs for CRPS is a complex and challenging process that requires input from patients, clinicians, and researchers. The Ottawa Decision Support Framework (ODSF) is a valuable tool that can guide the development of TDAs by providing a structured approach. The development of TDAs typically involves several stages, including identifying the information needs of patients and clinicians, searching available empirical evidence, developing and pilot testing the TDA, and evaluating its effectiveness¹⁴. The development of TDAs for CRPS also requires careful consideration of the specific features of the condition, such as the chronic nature of the pain and the impact on physical and psychological functioning. Patient and clinician involvement, as recommended by the ODSF, can help to identify gaps in knowledge and information and ensure that the TDA addresses the desired outcomes of persons with CRPS and minimizes the overuse of interventions that well-informed patients do not value¹¹.

The objectives of this study were to 1) developing an evidence-based TDA for rehabilitation interventions for CRPS by incorporating the preferences of both patients and therapists; 2) assessing the face and content coverage of the developed TDA through a cognitive interview with patients and therapists.

6.2 Material and methods

6.2.1 Development of the TDA

The initial TDA was created based on the Ottawa Decision Support Framework¹⁴ (ODSF) using information synthesized from various sources, including: 1) a systematic review and meta-analysis of randomized clinical trials for CRPS rehabilitation interventions, 2) an overview of systematic reviews for CRPS rehabilitation interventions, 3) appraising the clinical practice guidelines for CRPS rehabilitation, 4) an international survey that explored the priorities and preferences of patients and therapists, 5) a focus group with experts. This information was used to develop a TDA that contained relevant information on the benefits and risks associated with different rehabilitation interventions for CRPS. The TDA also included information about CRPS itself, such as its diagnosis, prognosis, and guiding patients through the decision-making process.

6.2.2 Validation study design

The Western University Health Science Research Ethics Board (HSREB-122748) and Lawson Health Research Board (ReDA-13394) approved this project.

As a validation step, we employed a descriptive qualitative approach using the principles of cognitive interviewing to investigate how participants interpreted particular words, phrases, and constructs on the TDA. The cognitive interviewing approach involved conducting semi-structured interviews using a "think aloud" approach and probing techniques¹⁵. We employed the think aloud approach to encourage participants to verbalize their thoughts while reading the TDA, allowing the interviewer to understand how participants interpret and understand each item. Additionally, probing techniques were used to elicit further information on how the participant arrived at their response or to clarify any confusion or uncertainty. The initial TDA was revised based on feedback received from the interviews and further consultation with experts in the field of chronic pain and rehabilitation. The final TDA was then developed for use in clinical practice.

6.2.3 Participants

Convenience sampling method was used to include participants who were diagnosed with CRPS, older than 18 years, and had received or were about to receive rehabilitation interventions for their condition. In addition, healthcare providers (pain specialists and occupational/physical/hand therapists) who were experienced in treating CRPS patients were also invited for the interview. The patient sample was recruited from CRPS support groups on social media (Twitter and Facebook). Health care providers were invited from the Hand and Upper Limb Center Clinical Research Lab (HULC-CRL) and pain clinic at the St. Joseph's Health Care in London, Canada. We aimed to interview 5-10 patients with CRPS and 5 healthcare providers who provide treatment for CRPS. Enrollment continued until data sufficiency was achieved ¹⁶.

6.2.4 Data Collection:

The interviews were conducted online using the WebEx platform in a private and quiet room to ensure the privacy of the patients. Prior to the interviews, participants were given the rehabilitation decision aid, an overview of the interview, and an online informed consent form. The interviews were conducted by the first author (ES) and followed an interview guide, developed by the research team, that included questions about the participants' experiences with the TDA, their thoughts on the usefulness, clarity, and comprehensiveness of the items and statements of the TDA. Patients were encouraged to provide us with any suggestion to further improve the content of the TDA. To ensure the accuracy of the data collected, the interviews were audio-recorded and transcribed verbatim. The transcripts were then checked for accuracy by comparing the transcripts to the audio-recordings and any identifying information was removed to maintain participant confidentiality.

6.2.5 Data Analysis:

Demographic information for patients (age, sex, living status, working status), symptom characteristics (if symptoms started following an injury, duration of their symptoms, and the location of the CRPS symptoms) and providers' demographics (age, sex, specialty, and years of working experience) were collected and are presented in Table 1.

After conducting the semi-structured interviews, the interviewer (ES) transcribed and analyzed the original audio recordings. Then, a descriptive content analysis method was used to provide a rich and comprehensive portrayal of the participants' views on the usefulness, clarity, and comprehensiveness of the items and statements in the rehabilitation decision aid ¹⁷. The analysis process allowed us to categorize and classify statements extracted from the scripts. The results of the interviews were analyzed to consider face validity and content coverage ^{18,19} of the rehabilitation treatment decision aid. We assessed face validity of the TDA by asking participants' feedback on its visual design, layout, mode of presentation (online or paper copy) and overall relevance to the target population. By incorporating the perspectives of the participants, we aimed to ensure that the decision aid appeared visually appealing, user-friendly, and aligned with the specific needs and preferences of people with CRPS. Content coverage was evaluated through the analysis of the interview results, participants' feedback, suggestions for improvement, as well as identifying areas of strength and weakness related to the content of the decision aid. This approach helped us identify gaps in information, clarify any ambiguities, and strengthen the overall content coverage of the decision aid.

ES, was responsible for conducting the interviews and analyzing the data. He is a PhD candidate in physical therapy with a prior foundation in occupational therapy. However, it is important to acknowledge that the sole involvement of ES in the process poses a potential risk of biases. These biases may include confirmation bias, observer bias, or discipline bias, given that ES is responsible for conducting, transcribing, and analyzing the interviews without the direct input of other researchers or analysts. By acknowledging and reflecting on the interviewer's positionality throughout the analysis process, we aimed to enhance the transparency and rigor of our interpretations. It allowed us to critically engage with the data, considering both the participants' perspectives and the potential influence of the interviewer's disciplinary and ideological background.

6.3 Results

6.3.1 Development of the TDA

The initial version of the rehabilitation treatment decision aid for CRPS was drafted by the first author (ES) based on synthesized data from literature reviews and clinical practice guidelines for CRPS. The first draft consisted of 10 sections: 1) Explanation of CRPS, 2) CRPS diagnosis, 3) Main rehabilitation interventions (occupational therapy, physical therapy, and psychological interventions), 4) Pros and cons of rehabilitation interventions, programs, and modalities, 5) Four key points to remember, 6) Reflection on patient priorities, 7) Prioritizing patient preferences, 8) Assessing patient inclination toward decision-making, 9) Fact-checking CRPS information, and 10) Making decisions about the next steps.

After running several expert panel meetings, including committee members of the Ph.D. thesis, physical therapists, and a group meeting with graduate students, the first draft was revised based on their feedback and suggestions. The experts primarily provided input on the content and categorization of the interventions. Initially, the first draft categorized rehabilitation interventions delivered by occupational therapists, physical therapists, and psychotherapists separately. However, experts recommended presenting the interventions without any categorization due to significant overlap among the interventions delivered by different disciplines. This was done to avoid misinterpretation, confusion, and conflicts. The expert panel also suggested including a section dedicated to potential areas/outcomes that could be affected by CRPS, allowing patients to acknowledge and choose the ones relevant to them. One expert recommended that the decision aid should be divided into two separate sections: an educational section and a decision aid section. Another suggestion was to link the rehabilitation interventions to the potential outcomes they have been found effective in improving. Additionally, it was suggested to add the possibility of receiving online interventions to the pros section for each treatment. Some changes were proposed to make the wording and phrasing of the decision aid easier to read and to use lay language.

6.3.2 Validation of the developed TDA

The revised decision aid consisted of two sections: an educational section and a decision aid section. The educational section provides patients with the concept of a decision aid, the definition and diagnosis of CRPS, and a simple explanation of the available rehabilitation interventions. The decision aid section included various subsections: identifying important outcomes, evaluating the effectiveness of interventions on specific outcomes, weighing the pros and cons of each rehabilitation intervention, highlighting key points to remember, reflecting on priorities and preferences, fact-checking information about CRPS, and determining the patients' leaning towards making a final decision.

The revised version of the rehabilitation treatment decision aid was then provided to patients with CRPS (lived experience experts) and therapists having the experience of working with CRPS patients.

We interviewed five patients with CRPS and five therapists (two occupational therapists, two physical therapists, and one hand therapist). All patients had CRPS symptoms for more than one year (ranging from 2 to 15 years). Two were diagnosed with whole body CRPS, one with CRPS in one knee and leg, one with both upper limbs, and one in one hand. All patients were female, and the mean age was 49 years old. Two therapists had 5 years experience and the other three had more than 10 years clinical experience.

6.3.3 Cognitive interview results

Overall findings of the cognitive interview based on the feedback provided by the participants indicated that the decision aid was generally perceived as comprehensive, balanced, and informative, offering valuable insights into the treatment options available for people with CRPS. Patients reported that they initially received limited information and treatment options after being diagnosed with CRPS. They emphasized that there was a lack of an evidence-based tool in lay language to help people with CRPS to make an informed, shared decision about the rehabilitation interventions available to them and the importance of receiving comprehensive information about various therapies and rehabilitation options.

Considering the structure of the interview guide questions, the interviews yielded six overarching

topical categories related to the structure and content of the TDA. The details of the topics are elaborated on in the following sections with quoted statements from participants.

6.3.3.1 Initial impression with the current TDA

All participants had a positive initial impression when they first saw the decision aid. Patients agreed with the suggestions provided, considering them in line with their doctors' recommendations. Participants also emphasized the value of having a written plan. All patients expressed that they initially received limited information on the available rehabilitation treatment options after being diagnosed with CRPS and 4/5 patients emphasized the importance of trust in reliable and evidence-based information sources.

“ ... I think the biggest thing is handling the barriers to sort of acceptance of different treatments. Especially because there is a lot of pseudoscience around some of them. Things like acupuncture or other things that I tried in the past there wasn't good research on it. So, if you wanna be able to say, here's an option, and the research and evidence itself is mixed, how are you gonna convince somebody it's something to try? ... ” Pt#2; 41-year-old woman with whole body CRPS for 16 years.

All patients expressed that they did not have previous experience with any structured rehabilitation treatment decision aid. They usually obtained their information from a simple internet search. One of the patients mentioned that she always looked for research evidence to obtain information about her condition.

“I think a lot of people are not like me. I did tons and tons of research and I read medical articles from journals, and I did all of that, and I think that I had a better understanding sometimes than even my doctor did.” Pt#2; 41-year-old woman with whole body CRPS for 16 years.

One of the patients expressed that she did not trust health care providers and the information she obtained from different people before. Despite previous negative experiences with health information, patient participants endorsed the helpful potential of a decision aid to foster communication:

“... I will be perfectly honest with you. I sort of rolled my eyes and the reason I did is that because I've been through so much, I'm like, oh God. Having to trust somebody to give me information. Even when it was early on, I didn't trust the people who were supposed to be helping me because they weren't helping me. And so, depending on the source of where the decision aid would've come from, at that time, I would've been like, okay! That's nice! Thank you! And I'll just put that over here in my recycling bin ... I think getting over the hump of having providers who are trustworthy, having information that is accurate helps a lot.” pt#1, 50-year-old female, with CRPS in two arms for two years.

Healthcare providers also raised concerns about the absence of reliable resources in lay language for patients with CRPS. They recognized the potential of the developed TDA as a valuable starting point for new patients, allowing them to gain a clearer understanding of the available interventions for their condition:

“As an OT, I often see patients with CRPS who struggle to find reliable resources in simple language. It's a frustrating situation for them... they are usually confused and overwhelmed by the complex information out there. That's why I believe the developed TDA can be a game-changer, providing them with a clear and better picture and overview of the available interventions. It has the potential to guide them for making informed decisions for their treatment journey“ therapist #2, OT, with more than 10 years experience.

6.3.3.2 Overall balance, language, comprehensibility, clarity, and readability of the TDA

Overall, all patients and therapists commended the decision aid for its clarity, readability, and straightforward language. Participants found the language used in the decision aid easy to understand and suitable for people with different educational backgrounds. No major revisions or simplifications to the language were suggested. Two participants (patient #2 and therapist #3) however, did identify two terms as being vague in the “potential outcome” section. The patient mentioned that “performing activities independently” could be misinterpreted, as the aim of rehabilitation interventions is not just being independent: *“ ... I noticed there's sort of the tendency to say like, perform daily activities independently. It's not, not always about*

independence, it's also about being able to just do them better than you were able to before. Because I live a fairly independent life. I'm raising, you know, a kid who just turned five. My husband works. It's not that I can't do things independently, it's just I struggle to do them. So it's being able to do them better. Um, so I think sometimes tending to make the question seem like the person is really disabled means that people who are less disabled don't feel included. So I don't know if there's a way to make the language more inclusive ...” Pt#2; 41-year-old woman with whole body CRPS for 16 years.

Therapist #3 mentioned that the term “participation” is a professional term commonly used within the field of therapy and is not easily comprehensible outside of the therapeutic context. However, other participants found the TDA easy to understand and appreciated its comprehensiveness without being overwhelming.

“...I think the verbiage is clear and concise. I don't think it's difficult. I don't think it's difficult to read at all. I think this is very inclusive to everyone ...” pt#4, 41-year-old female, with CRPS in one leg for two years.

“... I liked reading it the first time, reading the second time, and then I read it the third time. It was still clear; I was able to go through it. I didn't feel like I was stumbling through. I think you were clear on the language. I liked how it was outlined. I liked the fact that it wasn't complex, but it wasn't dumbing down on the language. It was like you made the point and explained it, it was at a good reading level, so it wasn't overwhelming ...” Pt #3, 47-year-old female with CRPS symptoms in one leg for over a year.

6.3.3.3 Missing rehabilitation interventions

Participants mentioned additional rehabilitation techniques not listed in the decision aid and recommended acknowledging that the decision aid does not cover all possible techniques but focuses on the most effective ones for CRPS. The additional rehabilitation interventions suggested by the patients and therapists were virtual reality, cupping therapy, acupuncture, specialized hand therapy, and speech therapy for swallowing and speech challenges. One of the patients also reported having a service dog that is being trained by the treatment team.

“... I've used virtual reality glasses and it was something that wasn't mentioned as a rehabilitation technique here. But you can't list everything for everyone because you only have a certain amount of space. But you wanna be upfront with individuals too, to let them know that you're providing like the top things that have been effective. But again, these may or may not work for every single patient, but they've been most effective for most CRPS patients ...” pt#5, 47-year-old female, with CRPS in two arms and back for more than one year.

“... We sometimes refer our patients to speech therapists because of their problems with speech and sometimes swallowing. They have really important roles in teamwork ...” therapist #1, PT, with more than five years experience.

6.3.3.4 Rehabilitation interventions – pros and cons of treatment options

One of the sections of the TDA that all patients and most of the therapists expressed caught their attention, was the section explaining the potential pros and cons of the specific interventions.

“... I loved the pros and cons. That was probably the best thing for me because going in I'd like for somebody to tell me the benefits and what's gonna work and what's not gonna work, so that I can make an informed decision ...” pt#1, 50-year-old female, with CRPS in two arms for two years.

“... The most prominent and relevant section of the decision aid was pros and cons section. you know, I think this is where people can decide and weight and finalize their decision ... ” therapist #2, OT, with more than 10 years experience.

6.3.3.5 Key points to remember

Patient #4 and therapist #3 suggested adding the importance of joining support groups as a key point for people with CRPS. They emphasized the benefits of sharing experiences and seeking advice from others going through similar challenges. Additionally, participants suggested acknowledging the variability of preferences and outcomes based on individual circumstances in the key points to remember section. They highlighted the need for flexibility in treatment options.

“... Finding a support group has been really helpful. I'm part of several support groups online on social media ... to hear other people's journeys with their specific treatment plans, doctors in their area ... we talk a lot about regional areas, US patients, what doctors like, hey, I've heard of this therapy. Do you know of a doctor that's close to the area? So that's been really good to be part of these ... sometimes because we're having a bad flare, it's good to have somebody else that's going through the same thing as you. I think that's been a key tool for me to use throughout my ongoing therapy with CRPS is definitely being part of a support group and be a part of as many of them as you can ... ” pt#4, 41-year-old female, with CRPS in one leg for two years.

Two patients and two therapists highlighted the importance of a multidisciplinary treatment team and coordinated care among healthcare professionals. They found it beneficial when different specialists communicated and checked each other's notes to ensure consistent and effective treatment.

“... I was fortunate to have a really good multi-disciplinary team that they talked to each other, and so having that relationship with them and my primary care doctor, that was the most successful thing for me ... So, I didn't have to feel overloaded with keeping up with everything. ... I couldn't keep track of it in my head because I was so overwhelmed, and I was taking so many medications. I was so tired ... But when she got together that multidisciplinary team, and then I was actually informed, and they sat down, and they talked to me about my options and I felt like I was actually a part of the decision ...” pt#1, 50-year-old female, with CRPS in two arms for two years.

6.3.3.6 General suggestions and recommendations

Participants provided feedback on the decision aid's format, suggesting improvements such as including key points to remember at the beginning, compiling all information in one document with a table of contents, and incorporating videos or clickable links for better explanations of certain treatments. One of the patients and two of the therapists proposed an online tool as an alternative to a paper copy or pamphlet to have videos or clickable links to provide better explanations of certain treatments. They found it difficult for people who have not been exposed to some of the interventions to imagine and fully understand how a specific intervention is being performed.

“... I almost think that that should be some sort of, you know, video or clickable link. That doesn't tell me what that is. I do think that it would be beneficial to have a video or even an explanation, anything. So maybe an online tool will be needed for this one instead of having a paper copy or a pamphlet, something like that ...” Pt#2; 41-year-old woman with whole body CRPS for 16 years.

“... I'm not sure if this tool is going to be an online tool or just will be in paper format, but I think that having it online, website or like an application to have some videos for introducing the interventions in short videos would provide patients with a better picture of what they should expect ...” therapist #5, OT, with more than 5 years experience.

Most patients (3/5) and two therapists (2/5) recommended moving the “key points to remember” to the beginning of the TDA. The reason for this idea was to inform patients of the important points before providing them with the treatment options.

One of the patients and one occupational therapist raised an issue regarding “check the fact section” and they believed that this section is redundant. Patient #2 mentioned:

“... Check the fact section you might not need. Mostly because if the person has paid attention to it, they're gonna know the answers and if they haven't, they're not gonna know. They're not gonna care anyway. If somebody says, I'm not sure, well, what does that even mean? Who's going to answer the question for them? And does it really change the outcome of the decision aid? Probably not. Sometimes when people see those things, they're like, oh God, I didn't read it well enough. They're, they're testing me, they're mad at me because I don't know the answer, which isn't really the goal of what you're doing ...”

“... I believe that check the fact section is redundant and it is not adding any value to the decision aid. I think it is digressing the overall aim of the decision aid. So, I think you should remove this section ...” therapist #2, OT, with more than 10 years experience.

6.4 Discussion

The aim of this study was to develop and validate an evidence-based rehabilitation treatment decision aid for people with CRPS based on the ODSF. To the best of our knowledge, this is the first structured, evidence-based rehabilitation treatment decision aid developed for CRPS.

The development process of this tool was comprehensive and incorporated multiple sources of information. Firstly, the latest available evidence in the literature was extensively reviewed to ensure that the decision aid was grounded in current research and best practices. This approach allowed for the inclusion of up-to-date and relevant information that would aid people with CRPS in making informed treatment choices and ensure that they access the best available evidence in a lay language.

Additionally, experts in the field of CRPS and rehabilitation were consulted throughout the development phase. Their expertise and insights played a crucial role in shaping the content and structure of the decision aid. By involving specialists, the tool was able to incorporate a comprehensive range of perspectives and address the diverse needs and preferences of people with CRPS.

Furthermore, the integration of patient feedback was a fundamental aspect of the tool's development. Patient perspectives and priorities were sought through various methods such as interviews and surveys. By actively involving patients, their unique experiences and insights were incorporated into the decision aid, ensuring its relevance and usability in real-world scenarios. Patient feedback served as a valuable guide in developing and refining the tool and making it more patient-centered.

The overall findings and content analysis of our study revealed several important themes that informed the refinement of the decision aid. Participants expressed that they initially received limited information and treatment options after being diagnosed with CRPS. They emphasized the importance of receiving comprehensive information about various therapies and rehabilitation options to avoid stress, anxiety, confusion, and being overwhelmed with the situation. They found the diagnosis of CRPS stressful and not having reliable resources to learn about all the available options for their treatment worsened the situation for them. This feedback

emphasizes the significance of tailoring the decision aid to address individual differences and promoting a realistic understanding of treatment outcomes ¹¹⁻¹³.

One of the barriers to accepting treatments by patients was stated mixed or limited evidence and uncertainty about the effectiveness of rehabilitation interventions. Therefore, addressing skepticism and uncertainty when presenting treatment options is one of the important considerations when a patient is diagnosed with CRPS. This issue also underscores the need for open communication and providing people with CRPS with a balanced view of the benefits and limitations of different treatments.

Another significant theme that emerged was the emphasis on individualized treatment and realistic expectations. Participants appreciated the acknowledgment that there is no guaranteed cure for CRPS and that treatment outcomes can vary among people. They suggested incorporating this information earlier in the decision aid to help manage expectations. By addressing this concern, the decision aid can foster realistic expectations and empower people to actively engage in their treatment process. This issue was also reported to be one of the important factors for the effectiveness of decision aids ²¹.

Receiving multidisciplinary and coordinated care is highlighted in clinical practice guidelines for CRPS ²². Considering the complexity and heterogeneity of CRPS signs and symptoms, the treatment of CRPS is mostly symptom-based and it is individualized for each participant ⁷. This raises the importance of incorporating different disciplines (including occupational/physical/therapist, pain specialist, neurologist, psychologist, and other professionals as relevant) in the management of CRPS to fully address various symptoms of patients ²³⁻²⁶. This point was also emphasized by almost all of the participants and they found it crucial for consistent and effective treatment.

Our study also had some limitations that is important to acknowledge that may affect the generalizability and validity of the findings. Firstly, one limitation of this study was the potential for severity bias in the sample. The inclusion of two people with whole body CRPS and one with bilateral upper extremity involvement may not represent the full spectrum of CRPS presentations. This could limit the generalizability of the findings to individuals with less severe or localized CRPS. Additionally, there is a potential for gender bias, as our patient participants

were only female. This gender bias may limit the applicability of the findings to male individuals with CRPS.

Another limitation of this study is the uncertainty surrounding data sufficiency in the interview part. While efforts were made to include a sufficient number of participants to achieve saturation/sufficiency, it is important to acknowledge the possibility that saturation may not have been fully reached. The criteria used to establish data saturation were based on iterative analysis and discussion among the research team. However, it is acknowledged that different researchers or additional participants might have contributed further perspectives and insights.

Another potential bias/limitation of our study could be the insider status of the interviewer relative to the participating therapists from hospital. The interviewer was affiliated with St. Joseph's Hospital. This insider status may have influenced the responses provided by the participating therapists as they might have been hesitant to express negative opinions or critique aspects of the decision aid due to the potential for professional and social repercussions. This limitation may affect the depth and breadth of perspectives obtained.

The overall findings of our study identified the importance of addressing information needs, managing expectations, addressing skepticism, and promoting multidisciplinary care in the management of CRPS. The findings and recommendations from this study contribute to the ongoing improvement and refinement of the decision aid to better serve people with CRPS. A significant constraint in our study was the limited time available due to the deadlines for the first author's Ph.D. defense. The time constraint impacted various aspects of the study, including data collection and the potential for a more extensive sample size. However, despite this limitation, we made efforts to ensure rigor and comprehensiveness in our research within the available timeframe. Additionally, future studies could incorporate ongoing feedback from patients and healthcare providers to further refine the decision aid, ensuring its continuous improvement and relevance in supporting treatment decision-making for people with CRPS.

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6.6 List of tables

Table 6-1 Demographic information of the participants in the cognitive interview

		Therapists (n)	Patients with CRPS mean (\pm SD); n
Age		40 (\pm 8)	49 (\pm 4)
Sex	Female	1	5
	male	4	0

Working experience (Therapists)	Less than 5 years	2	NA
	More than 5 years	3	
Duration of CRPS symptoms		NA	+1 year (2-15)

Chapter 7

7 General Discussion and Future Directions

7.1 Overview of this dissertation

The objective of this dissertation was to develop a decision aid for rehabilitation interventions addressing pain and disability in persons with Complex Regional Pain Syndrome (CRPS) based on the Ottawa Decision Support Framework (ODSF). The developed decision aid was based on the most recent available evidence (up to January 2023) and intended to be adapted to the preferences and needs of patients and therapists. This chapter explores the study's implications and the potential for future research to explore the effectiveness of implementing the decision aid in patients' clinical outcome.

Employing the ODSF as a well-established framework¹ for the development of the rehabilitation treatment decision aid (TDA), we could use a structured approach to decision-making, incorporating the best available evidence, the preferences of patients and therapists, and the clinical judgment of healthcare providers. The TDA was intended to help patients and healthcare providers make more informed decisions about the best course of action for rehabilitation interventions addressing the individual experience of CRPS; and to include patients in the decision-making process. People with CRPS often face challenging decisions regarding their treatment due to the variety of symptoms and the absence of agreement on diagnostic criteria and treatment approaches. This lack of clarity can cause patients to feel confused, anxious, and uncertain. While decision aids have demonstrated positive outcomes in assisting decision-making for various medical conditions, their effectiveness and feasibility in the context of CRPS rehabilitation have not been studied or proven. To the best of our knowledge, this is the first structured, evidence-based rehabilitation treatment decision aid developed for CRPS

Conducting a literature review, we identified information on the different rehabilitation interventions available for CRPS, their potential benefits and risks, and the level of evidence supporting their use^{2,3}. The decision aid also included information on the patient's and health

care provider's preferences and values, extracted from the survey study we conducted, which were used to tailor the pathway of the TDA to the individual's needs, preferences, and values.

In order to validate the TDA that was developed by our research team, we conducted cognitive interviews with persons with lived experience of CRPS and health care providers to CRPS patients. Employing a cognitive interview approach⁴, we were able to assess the clarity and comprehensibility of the decision aid's content and to identify any areas of confusion or misunderstanding among the patients and health care providers. Using the feedback obtained from cognitive interviews we were able to refine and improve the decision aid, ensuring that it is understandable and relevant to its target users and covers all relevant aspects.

7.2 Clinical and research implications

The ODSF is a theoretical framework that emphasizes the importance of tailoring decision support to the individual needs and preferences of the patient and promoting patient autonomy and involvement in the decision-making process¹. A decision aid for rehabilitation interventions for CRPS using the ODSF could have several clinical and research implications, including:

Improved patient outcomes: Decision aids can help patients make more informed decisions about their healthcare options, leading to better treatment outcomes. In the case of CRPS, a decision aid could help patients understand the benefits and risks of different rehabilitation interventions, linking patient expectations to the known effects/outcomes, and leading to more appropriate and effective treatment choices.

Increased patient involvement in decision-making: The TDA emphasizes the importance of involving patients in healthcare decisions. A decision aid for CRPS rehabilitation interventions could empower patients by providing them with information and helping them make choices that align with their preferences and values. Additionally, it is helpful in reducing patient's burden of finding reliable information about their treatment choices. Participants in our study reported the diagnosis of CRPS was overwhelming for them, and they valued trusted advice. Confusion around identifying the available treatment options could exacerbate the anxiety, uncertainty, and mental burden for patients.

Standardized decision-making: The ODSF provides a standardized approach to developing decision aids, ensuring that the aid is evidence-based and reflects best practices. This could lead to more consistent and effective decision-making across healthcare settings. For instance, since upper extremity CRPS is commonly treated in hand therapy clinics influenced by occupational therapy, while lower extremity CRPS is typically treated in general physical therapy clinics, having a shared decision aid could introduce greater uniformity in the types of treatments considered and provided.

Evaluation of the effectiveness of the decision aid: A decision aid for CRPS rehabilitation interventions can be evaluated to determine its effectiveness in helping patients and healthcare professionals make informed decisions about treatment options. Future research can assess the impact of the decision aid on patient outcomes, including satisfaction with care, quality of life, and adherence to treatment. Our research team encourages other researchers and clinicians in the field of CRPS management to use the rehabilitation decision aid we have developed to further refine the tool and in this population.

Identification of patient preferences and values: A research study using a decision aid for CRPS rehabilitation interventions can identify patient preferences and values related to different treatment options. This information can help healthcare professionals better understand patient needs and make more patient-centered treatment decisions. Engaging patients actively in the decision-making process has been shown to improve adherence to treatment and patient satisfaction.

Assessment of the impact of the decision aid on healthcare utilization: A decision aid for CRPS rehabilitation interventions can be evaluated to determine its impact on healthcare utilization. Future research studies can assess the effect of the rehabilitation decision aid on healthcare resource utilization for patients, such as the number of clinic visits or therapeutic sessions to obtain information about the available treatment options for their condition.

Identification of factors influencing decision-making: A research study using a decision aid for CRPS rehabilitation interventions can identify individual level, intervention level and system level factors influencing decision-making by patients and healthcare professionals. This

information can help to develop strategies to promote shared decision-making and improve the use of evidence-based treatment options.

Overall, a rehabilitation treatment decision aid for CRPS can be a valuable tool for improving patient outcomes, enhancing patient-centered care, and providing opportunities for research to advance the understanding and management of CRPS.

7.3 Limitations

This PhD dissertation had several limitations that should be considered when interpreting the findings and considering the implications of the results.

Firstly, development of a TDA is a complex process that requires a significant amount of time and resources. Given the limited four-year timeframe of the PhD thesis, it was not feasible to conduct testing and validation of the TDA within a clinical practice setting. However, for future research, we highly recommend that researchers pursue a validation study to assess the effectiveness of the developed rehabilitation TDA in real-world clinical settings.

Secondly, the study's recruitment of patients was limited due to several factors. Despite efforts to recruit a larger sample size, the number of patients who participated in the cognitive interview was smaller than intended. This may have impacted the generalizability of the findings and the representativeness of the sample. In addition, the recruitment of patients was also limited due to the COVID-19 pandemic, which made it difficult to conduct face-to-face interviews and assessments.

We also recruited a large number of therapists and patients from different parts of the world. While this could be viewed as a strength of the thesis, as it provides diverse perspectives on rehabilitation interventions for CRPS, it could also be seen as a potential limitation. The advantage might be that we have input from patients and therapists from different cultures and societies, while the disadvantage could be that TDAs, and their recommendations could vary across different cultures. This issue could decrease the usability of our TDA, and we strongly recommend future researchers to consider adaptations when using for their patients in different countries, if required.

Finally, another limitation of the study was that we did not evaluate the decision aid's effectiveness in the clinical setting. Although the decision aid was based on the most recent available evidence and was designed to be adaptable to the preferences and needs of patients and therapists, it is unclear whether it will be effective in clinical practice. The decision aid will need to be tested in a clinical setting to determine its effectiveness and impact on patient outcomes.

In conclusion, while this study provides a valuable contribution to the development of a decision aid for rehabilitation interventions for CRPS, several limitations should be considered when interpreting the results. Future studies should focus on addressing these limitations, including evaluating the decision aid's effectiveness in a clinical setting, recruiting a larger and more diverse sample of patients, and revising the items of the current TDA if indicated by such work.

7.4 Suggestions for the future research

We highly recommend conducting further research to thoroughly evaluate the effectiveness of the rehabilitation TDA developed by our research team. This would involve investigating various aspects related to shared decision-making, patient involvement, and patient satisfaction with the decision-making process. The following research endeavors would contribute to a deeper understanding of the TDA's effectiveness, feasibility, and impact on the care provided to patients with CRPS.

One potential next step would be to prioritize a study aimed at assessing the impact of the TDA on shared decision-making. This study could involve a randomized controlled trial design, where patients with CRPS are randomly assigned to either the group utilizing the TDA or a control group receiving standard care. Outcome measures such as the level of shared decision-making, patient engagement, and decisional conflict could be evaluated to determine the effectiveness of the TDA in facilitating shared decision-making and increasing patient involvement in decision-making.

Furthermore, it would be valuable to investigate the integration of the TDA into routine clinical practice. This could be achieved by conducting a feasibility study or implementation research, which examines the practical aspects of incorporating the decision aid into the existing

routine patient care. This research could identify any barriers or facilitators to the adoption of the TDA by healthcare providers and patients with CRPS. Factors such as usability, acceptability, and workflow integration could be explored to gain insights into the successful implementation of the TDA in real-world clinical settings.

Considering the importance of patient satisfaction, another research avenue could focus on assessing patient satisfaction with the decision-making process when using the TDA. This could involve qualitative interviews or surveys to gather patient perspectives on their experiences with the TDA, their level of satisfaction, and perceived benefits or drawbacks. Understanding the impact of the TDA on patient satisfaction would provide valuable insights into its effectiveness and potential improvements.

7.5 References

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Appendices

8 Appendices

8.1 Summary of the Stanton-Hicks, et al., 1998 guideline

Author, Year	Summary of the findings
Stanton-Hicks, et al., 1998 ¹	<p>A consensus treatment guideline to present an orderly approach for the treatment of chronic CRPS I and II</p> <p><i>Central theme</i> → Functional restoration</p> <p><i>Two essential components</i> → Self-management and functional rehabilitation</p> <p><i>Main focus</i> → Specific exercise therapy to restore function after musculoskeletal injury.</p> <p><i>Core concepts</i> → Motivation, Mobilization, and Desensitization*. *Desensitization → By application of pharmacological and interventional techniques to address certain signs and symptoms, and relieving pain.</p> <p style="text-align: center;">This guideline includes four steps:</p> <ol style="list-style-type: none">1. Developing therapeutic alliance and rapport.2. Incorporating motivation, mobilization, and desensitization.3. Isometric strengthening and stress-loading.4. Completing functional recovery. <p>Complications:</p>

1. Depressive and anxiety symptoms, inappropriate anger, and personality disorders → Pharmacotherapy, psychotherapy, and behavioral management
2. Severe pain → Aggressive treatment of the nociceptive or neuropathic generator
3. Severe cutaneous allodynia → Cutaneous desensitization and Proprioceptive stimulation
4. Dependent edema → Elevation, active ROM, antiedema garments, pumps, and diuretics
5. Contractures → Frequent gentle work, dynamic splinting, and serial splinting

Lower extremity CRPS

- hydrotherapy through a graduated weight-bearing program.
- modified scrub-loading (e.g., PABS board) techniques
- Balanced walking as much as tolerated.

Last stages of the algorithm

- Self-management and minimizing dependence on invasive and technical modalities

8.2 Summary of the Stanton-Hicks; 2002 guideline

Author, Year	Summary of the findings
Stanton-Hicks; 2002 2	<p>“Rehabilitation is the mainstay of CRPS treatment”.</p> <p>Rationale → Incorporating interdisciplinary approaches and refining the linear approach of timing and sequencing of the treatments proposed in the previous guideline.</p> <p>The goal of treatment → Minimization of pain and optimization of function through rehabilitation, pain management, and psychological therapy.</p> <p>** In case of not responding to treatment within 12-16 weeks → more interventional therapies. **</p> <p>Successive steps in the pathway → Achieving gentle active ROM, stress loading, scrubbing techniques, isotonic strengthening, general aerobic conditioning, and postural normalization.</p> <p>Key to successful treatment → keep patients motivated and engaged.</p> <p>Failure to progress in each stage → stronger drugs for pain relief, more intensive psychotherapy, or the use of more aggressive pain management techniques, such as regional anesthesia or SCS.</p> <p style="text-align: center;">This guideline includes three stages:</p> <ol style="list-style-type: none"> 1. Developing a strong therapeutic alliance and rapport for a successful occupational and physical therapy intervention. 2. Increase patients’ flexibility with the use of gentle active ROM. 3. Normalizing use of the affected limb, assessment of ergonomics, posture, and required modifications at home and

	<p>the workplace, and complementary recreation therapy and vocational rehabilitation.</p> <p>In case of concomitant Myofascial pain syndrome (MFPS) associated with the affected region → stretching, strengthening, postural correction, electrical stimulation, and muscle relaxants.</p> <p>Edema control → elevation, retrograde massage, Jobst compression pump, sympathetic blocks, diuretics.</p>
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Table 5: Summary of the Perez S, et al., 2010 guideline	
Author, Year	Summary of the findings
Perez S, et al., 2010 ³	<p>Developing evidence-based multidisciplinary guidelines for treatment of CRPS-I from studies published between 1980 to June 2005.</p> <p>→“Physiotherapy”, without elaborating on what this physiotherapy entails, is usually recommended as a supplementary treatment for patients with CRPS-I.</p> <p>Key to successful recovery → Functional recovery</p> <p style="text-align: center;">Recommendations based on the level of evidence:</p> <ol style="list-style-type: none"> 1. Level-2 evidence → Physiotherapy (in general) for upper limb CRPS-I is likely to have positive impact on this condition and patients’ coping skills. 2. Level-3 evidence → Physiotherapy interventions might be effective for the treatment of chronic CRPS-I. 3. Level-4 evidence → Physiotherapy should be included in routine treatment of CRPS-I. 4. Level 4 evidence → Insufficient evidence for the effectiveness of TENS in the treatment of CRPS-I.

	<p>5. Level-3 evidence → OT could be effective in functional and activity limitation improvement.</p> <p>6. Level-4 evidence → No evidence on the effectiveness of multidisciplinary treatment of CRPS-I.</p>
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8.3 Summary of the Goebel A, et al., 2012-2018 guideline

Author, Year	Summary of the findings
Goebel A, et al., 2012 ⁴⁻⁶	<p>Extracted and adapted from the UK guidelines for diagnosis, referral, and management of CRPS developed by an expert panel and based on experts' opinion.</p> <p>Main focus →</p> <ul style="list-style-type: none"> - CRPS diagnostic criteria (Budapest criteria), - Differential diagnosis for CRPS, - Psychological risk factors, - Four pillars of treatment for CRPS <p>Four pillars of treatment for CRPS:</p> <ul style="list-style-type: none"> - Patient information and education - Pain relief - Physical and vocational rehabilitation - Psychological interventions <p>General Recommendations:</p> <ul style="list-style-type: none"> - Early diagnosis to prevent secondary physical limitations and psychological consequences of undiagnosed chronic pain. - To avoid symptoms' progression → Early referral to PT and start of gentle active movements. - Referring more severe cases to pain management specialist and rehabilitation programs. - Paying attention to integrated interdisciplinary treatment approach. - Providing patient education about CRPS. - Complex CRPS → Having access to specialist interdisciplinary rehabilitation programs. - Close teamwork between specialist rehabilitation teams and pain management services. - Access to rehabilitation medicine cares in the context of a cognitive behavioral approach involving both the patient and their family. - Features of the rehabilitation program → Being goal orientated and actively engage patients and their family in goal setting to make patients responsible for the rate of progress. - Early access to vocational assessment.

Rehabilitation Treatment Algorithm:

CRPS patients with mild/moderate symptoms

- Patient education + routine treatment*
- Successful treatment and an ongoing improvement should be evident within 4 weeks

➔ Failing to respond to routine treatment or for patients with moderate/severe symptoms and/or dystonia

- Referring to multidisciplinary pain clinics and more specific treatments⁺

*Routine treatment ➔ Routine treatments referred to: patient education and support, desensitization, general exercises and strengthening, functional activities, mirror visual feedback, gait re-education, TENS, postural control, pacing, prioritizing and planning activities, goal setting, relaxation techniques, coping skills, hydrotherapy, sleep hygiene, oedema control strategies, vocational support, facilitating self-management of condition, splinting (use with caution for a short period of time and usually in acute cases)

+ specific treatments ➔ graded motor imagery, self-administered tactile and thermal desensitization (to normalize touch perception), correcting body perception disturbance (looking, touching and thinking about the affected body part), mental visualization (to normalize altered size and form perception of the affected body part), functional movement techniques (improving motor control and awareness of affected limb position), stress loading, conflict allodynia re-education (reducing fear of physical contact with others in community settings), management of CRPS-related dystonia.

8.4 Summary of the Harden R Norman, et al., 2013 guideline

Author, Year	Summary of the findings
Harden R Norman, et al., 2013, 2019 ^{7,8}	<p>Developed by a collaboration of expert practitioners (evidence-based + expert opinion). Adapted from three expert consensus meetings: Malibu (1987), Minneapolis (2001), Budapest (2004).</p> <p>Main focus → Functional restoration</p> <p>Overall Rehabilitation Treatment Algorithm in 4 steps:</p> <ol style="list-style-type: none"> 1. Mirror visual feedback (MVF), Graded Motor Imagery (GMI), Reactivation, Contrast Baths, Desensitization, and Exposure Therapy 2. Edema Control, Flexibility (active), Isometric Strengthening, Correction of Postural Abnormalities, and Diagnosis and Treatment of Secondary Myofascial Pain 3. Stress Loading, Isotonic Strengthening, ROM (gentle, passive), General Aerobic Conditioning, Postural Normalization, and Balanced Use 4. Ergonomics, Movement Therapies, Normalization of Use, and Vocational/Functional Rehabilitation <p>** Failing to start or progressing through the treatment algorithm → More or stronger medications, more intensive psychotherapies, and/or more interventional therapies</p> <p>Core principles of Malibu experts:</p> <p>Patient motivation, desensitization, reactivation facilitated by pain relief, pharmacological and/or interventional treatments, and cognitive behavioral psychotherapeutic techniques</p> <p>Core principles of Minneapolis experts:</p>

Concurrent pathways of rehabilitation, pain management, and psychological treatment, while emphasizing on functional restoration, rather than analgesic modalities and time constraints.

Psychological intervention treatment algorithm

1. Patient and Family Education about CRPS
2. Psychological Evaluation
3. Psychological Pain Management Intervention
4. Focused cognitive behavioral therapy targeting these issues

OT roles in conservative management of CRPS→

- *Overall Goal →*
- ✓ Minimizing pain and edema while maximizing functional use of the affected body part.
- ✓ Adjusting therapeutical interventions based on therapeutic response while sustaining patients' enthusiasm and encouragement in the rehabilitation process.
- *Therapeutic leaders* in the functional restoration process with considering biopsychosocial principles
- *Evaluation* of the affected body area functional status: Active ROM (goniometer); edema (circumferential measurement or volumeter), coordination/dexterity, skin/vasomotor changes, pain/ sensation, and use of the affected body part in activities of daily living (ADL)
- *Interventional focus →*
 - a) Early phases of the movement (activation of premotor and primary motor cortices) using GMI and MVF.
 - b) Minimizing edema
 - c) Normalizing sensation
 - d) Promoting normal positioning
 - e) Decreasing muscle guarding
 - f) Increasing functional use of the extremity
 - g) Splinting (in severe cases)
- Beginning *gentle active movements*
- *Edema management* (specialized garments and manual edema mobilization)
- *Desensitization techniques* (Superficial or surface techniques)
- *Stress-loading program* (Two principles: scrubbing and carrying)
- *General use of the affected body part in ADL*
- *Increasing functional use of the extremity.*
- *Participating in active ROM, coordination/dexterity, and strengthening tasks.*

- *Proprioceptive neuromuscular facilitation (PNF) patterns* to improve strength and balance while increasing ADL performance.
- *Collaborating with vocational counselor* to set return-to-work goals.

PT roles in conservative management of CRPS →

- Overall PT exercise program goal → gradual increase of strength and flexibility, mainly through weight-bearing while paying attention to pacing, rest breaks, and relaxation techniques.
- Critical role in *functional restoration*.
- *Complementing* occupational, vocational, and recreational therapy.
- *Gentle progressive exercise program* → increasing ROM, flexibility, and strength
- *Improving functional tasks* → gait training (lower extremity), collaborating on OT, recreational, and vocational goals.
- *Applying therapeutical interventions* according to patients' tolerance and paying attention to insensate area.
- *Aggressive PT* leads to → severe pain, edema, distress, fatigue, exacerbating inflammation and sympathetic response.
- *Avoid* using assistive or ROM devices, prolonged use of ice, and inactivity.
- *Informing patients* of the pain experience in case of too much or too little exercise and help them find the "happy medium".
- *Helping patients* toward functional active lifestyle.
- *Emphasizing on* maintaining normal posture and movement pattern to avoid changes to adjacent joints and muscles.
- *activation of cortical networks* → GMI and MVF
- *Instructing patients* to avoid physical stressors
- *Graded exposure therapy to exercises* (educational program explaining the "fear-avoidance mode) + tailored exercise program → pain and disability improvement
- *Pain exposure therapy* (A time-contingent approach incorporating regular PT techniques to perform progressive-loading exercises tailored to specific body functions)
- *Mat exercises* → A non-weight-bearing approach for the extremity and postural muscles strengthening.
- *Teaching neuromuscular proprioception exercises* → to master proper movement patterns.
- *Re-establishing body awareness by behavioral programs* → A pain-contingent approach including graded sensory motor returning exercises for pain reduction and tactile discrimination sense improvement.

- *Aggressive treatment of myofascial pain syndrome of the supporting joint*
- *Aquatic therapy*
- *Hands-on techniques* → massage, myofascial release, electrostimulation modalities, contrast baths

Recreational therapy roles in conservative management of CRPS →

- *Goal* → Using enjoyable activities for increasing body movement in the affected body part by regaining the patients' ability and freedom to follow their own leisure lifestyle choices.
- *Techniques* → modifications, adaptive equipment, and creative problem solving
- *Complementing OT and PT goals* by advanced planning.
- *Developing new leisure skills while reintroducing the patient to stable community involvement.*
- *Overcoming Kinesiophobia and promoting increased movement* with the use of creative tactics by providing patients decision-making freedom and fun.

Vocational Rehabilitation (VR) roles in conservative management of CRPS →

- *Goal* → Preparing patients to return to work and gaining ultimate functional restoration.
- *Return to work assessment* → Assessing data from medical, occupational, educational, financial, and labor market fields.
- *Addressing benefits of work and accommodations + job modifications + pain management techniques*
- *Planning for return-to-work*
- *Assessing the possibility of returning to the original job, alternatives of either a modified version of the previous job or an alternate job with the same employer, or a new job placement.*

Collaboration with OTs for the assessment of the return-to-work goals.

8.5 Summary of the Andreas Goebel, 2019 guidelines

Author, Year	Summary of the findings
Andreas Goebel, 2019 ⁹	<p>Developed by a collaboration between the experts of European Pain Federation and CRPS patients, including 17 standards in 8 areas →</p> <p>Covered areas: Diagnosis, multidisciplinary care, assessment, care pathways, information and education, pain management, physical rehabilitation, and distress management.</p> <p>Diagnosis →</p> <ol style="list-style-type: none"> 1. Using Budapest criteria for diagnosis. 2. No use of diagnostic tests, except for excluding other diagnoses. <p>Multidisciplinary care →</p> <ol style="list-style-type: none"> 3. Severity of CRPS as the indicator of the need for multidisciplinary care for more severe and complex cases. <p>Assessment →</p> <ol style="list-style-type: none"> 4. A thorough evaluation identifying any triggers for the CRPS, the severity of pain and how it affects the ability to function, engagement in ADL, participation in extracurricular activities, quality of life, sleep, and mood regulation. <p>Care pathway →</p> <ol style="list-style-type: none"> 5. Referring to specialized care in case of no improvement in pain and function within two months after starting treatment, despite good adherence to treatment. 6. Cues for referral to super-specialized care → CRPS spread, fixed dystonia, myoclonus, skin ulcerations or infections or malignant oedema in the affected limb, and extreme psychological distress.

	<p>7. Advanced CRPS treatments, such as multidisciplinary psychologically informed rehabilitation pain management programs (PMP), must be made available in specialized care facilities.</p> <p><i>Information and education</i> →</p> <p>8. Providing adequate information to patients, their dependents, or carers, regarding CRPS causation, natural course, signs and symptoms, outcomes, and treatment options by therapeutic disciplines.</p> <p><i>Pain management</i> →</p> <p>9. Accessing pharmacological treatments appropriate to CRPS or other similar neuropathic pain conditions.</p> <p>10. Pain management must be accompanied by a tailored rehabilitation plan. 11. Stopping guidelines and medication reduction plan in case of demonstrating adverse events or non-efficiency.</p> <p>12. Reassessment of patients due to the alteration of the clinical picture of CRPS.</p> <p><i>Physical rehabilitation</i> →</p> <p>13. Early and frequent assessment in terms of affected limb function, general body function, and home/work/school activity participation, as appropriate. Vocational rehabilitation should be offered, as needed.</p> <p>14. Early referral to OTs and PTs.</p> <p>15. Available training on basic approaches of CRPS pain management for OTs and PTs.</p> <p><i>Distress management</i> →</p> <p>16. Depression, anxiety, post-traumatic stress, pain-related fear and avoidance should be assessed as distress factors.</p> <p>17. Evidence-based psychological treatment should be available to CRPS patients, as needed.</p>
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8.6 Overlap across studies in terms of treatment goals and potential outcomes

Treatments/Goal/Techniques	Stanton-Hicks, 1998	Stanton-Hicks, 2001	Perez, 2010	Goebel A, 2012/18	Norman, 2013	Goebel, 2019	Overall
Pain management	X	X	X	X	X	X	100%
Functional restoration	X	X	X	X	X		83%
Stress-loading	X	X		X	X		67%
Psychotherapy	X	X			X	X	67%
Edema management	X	X		X	X		67%
Gentle active movements	X	X		X	X		67%
Vocational rehabilitation		X		X	X	X	67%
Normal functional activities		X		X	X	X	67%
Physiotherapy in general			X	X	X	X	67%
Isometric/isotonic strengthening	X	X		X	X		67%
Electrical stimulation		X		X	X		50%
Self-management	X	X		X			50%
Exercise therapy/aerobic exercises	X			X	X		50%
Motivation and engagement	X	X			X		50%
Desensitization	X			X	X		50%
Behavioral management/therapy	X			X	X		50%
Splinting	X			X	X		50%
Hydrotherapy	X			X	X		50%

Recreation therapy		X		X	X		50%
Postural correction		X		X	X		50%
Relaxation techniques		X		X	X		50%
Occupational therapy			X		X	X	50%
Education				X	X	X	50%
Proprioceptive stimulation/PNF	X				X		33%
Scrubbing techniques	X	X					33%
Ergonomics		X			X		33%
Multidisciplinary care			X	X		X	50%
Mirror therapy				X	X		33%
Gait re-education/ training				X	X		33%
Pacing				X	X		33%
Coping skills			X	X			33%
Graded motor imagery				X	X		33%
Dystonia management				X		X	33%
Stretching		X					17%
Goal setting/prioritizing /planning activities				X			17%
Sleep hygiene				X			17%
Correcting body perception disturbance				X			17%
Mental visualization				X			17%
Allodynia re-education				X			17%
Contrast Baths					X		17%
Exposure Therapy					X		17%
Reactivation					X		17%

Pain exposure therapy					X		17%
Mat exercises					X		17%
Massage					X		17%
Myofascial release					X		17%
Mobilization	X						17%

8.7 Thematic analysis for conservative management for CRPS

Treatments/Goal/Techniques	Subthemes	Themes
Pain management	Pain reduction	Symptom reduction
Functional restoration	Func Res	Functional restoration
Stress-loading	Func Res	Symptom reduction
Psychotherapy	Psycho Ther	Inter/multidisciplinary care
Edema management	Symp Red	Symptom reduction
Gentle active movements	Exercise	Functional restoration
Vocational rehabilitation	Return to routine life	Inter/multidisciplinary care
Normal functional activities	Exercise	Functional restoration
Physiotherapy in general	Routine rehab care	Inter/multidisciplinary care
Isometric/isotonic strengthening	Exercise	Functional restoration
Electrical stimulation	Routine rehab care	Inter/multidisciplinary care
Self-management	Patient education and consultation	Inter/multidisciplinary care
Exercise therapy/aerobic exercises	Exercise	Functional restoration
Motivation and engagement	Patient education and consultation	Inter/multidisciplinary care
Desensitization	Symp Red	Symptom reduction
Behavioral management/therapy	Behavioral therapy	Inter/multidisciplinary care
Splinting	Symp/Func	Symptom reduction
Hydrotherapy	Func Res	Functional restoration
Recreation therapy	Return to routine life	Inter/multidisciplinary care
Postural correction	Routine rehab care	Functional restoration
Relaxation techniques	Symp/Func	Inter/multidisciplinary care

Occupational therapy	Routine Rehab care	Inter/multidisciplinary care
Education	Patient education and consultation	Inter/multidisciplinary care
Proprioceptive stimulation/PNF	Routine rehab care	Inter/multidisciplinary care
Scrubbing techniques	Symp Red	Symptom reduction
Ergonomics	Return to routine life	Inter/multidisciplinary care
Multidisciplinary care	Symp/Func	Inter/multidisciplinary care
Mirror therapy	Symp/Func	Symptom reduction
Gait re-education/ training	Func Res	Functional restoration
Pacing	Func Res	Functional restoration
Coping skills	Return to routine life	Inter/multidisciplinary care
Graded motor imagery	Symp/Func	Functional restoration
Dystonia management	Symp Red	Symptom reduction
Stretching	Exercise	Functional restoration
Goal setting/prioritizing /planning activities	Return to routine life	Inter/multidisciplinary care
Sleep hygiene	Return to routine life	Inter/multidisciplinary care
Correcting body perception disturbance	Symp/Func	Inter/multidisciplinary care
Mental visualization	Func Res	Inter/multidisciplinary care
Allodynia re-education	Symp Red	Symptom reductions
Contrast Baths	Symp Red	Symptom reduction
Exposure Therapy	Symp Red	Inter/multidisciplinary care
Reactivation	Return to routine life	Functional restoration
Pain exposure therapy	Pain reduction	Symptom reduction
Mat exercises	Exercise	Functional restoration

Massage	Routine rehab care	Inter/multidisciplinary care
Myofascial release	Pain management	Symptom reduction
Mobilization	Func	Functional restoration

8.8 Search strategy for the clinical practice guidelines

- 1 peripheral neuropathy/ or Complex regional pain syndrome.mp. or pain/ or complex regional pain syndrome/ or myofascial pain/ or causalgia/
- 2 CRPS.mp.
- 3 reflex sympathetic dystrophy.mp. or complex regional pain syndrome type I/
- 4 complex regional pain syndrome type I/ or RSD.mp.
- 5 Sudeck's atrophy.mp.
- 6 causalgia.mp. or complex regional pain syndrome type II/
- 7 conservative treatment/ or conservative.mp.
- 8 rehabilitation.mp.
- 9 non-pharmacological.mp.
- 10 physiotherapy/ or physicaltherapy.mp.
- 11 occupational therapy/ or hand therapy.mp.
- 12 Guideline.mp. or practice guideline/
- 13 recommendation.mp. or practice guideline/
- 14 1 or 2 or 3 or 4 or 5 or 6

15 7 or 8 or 9 or 10 or 11

16 12 or 13

17 14 and 15 and 16

8.9 Rehabilitation Treatment Decision Aid

8.9.1 What is a Rehabilitation Treatment Decision Aid?

A treatment decision aid (TDA) is a tool that can facilitate collaboration between patients and clinicians in making decision regarding the available rehabilitation interventions for Complex Regional Pain Syndrome (CRPS). TAD helps patients in assessing the possible advantages and disadvantages of different interventions, and allowing them to consider their own preferences to create a treatment plan that meets their specific needs and objectives.

8.9.2 Complex Regional Pain Syndrome: Key Facts

- 🔑 A Chronic Pain Condition
- 🔑 The exact cause of CRPS is still unknown
- 🔑 Happens due to the malfunction of the nervous system
- 🔑 CRPS is a complex of symptoms →

Severe pain in an arm, hand, leg and/or foot (the affected limb(s))

Strong reaction to touch or cold/hot weather

Difficulties doing daily activities

Changes in body hair and/or nails

Changes in sweating (can be more or less than usual, or in unusual spots)

Swelling (that isn't going away, or that comes and goes for no reason)

Stiffness

Changes in skin's temperature or in the colour and texture of the skin of the affected limb

8.9.3 CRPS Diagnosis

- **No specific timeline for CRPS diagnosis.**
- **Who can confirm the diagnosis of CRPS for me?**
Your family doctor/physician
Your surgeon if you have had surgery
- **You may be referred to other specialists →**
In some cases, your doctor may refer you to a specialist, such as a pain management specialist or a neurologist, for further evaluation and treatment.

8.9.4 Rehabilitation Treatment

In this section we will explain rehabilitation interventions that are recommended and being used for the management of CRPS:

- **Mirror therapy:** Placing a mirror between your affected limb (for example, the arm or leg affected by CRPS) and your unaffected limb. By doing simple exercises or movements with your unaffected limb while looking in the mirror, you can "trick" your brain into thinking that your affected limb is moving too.
- **Graded Motor Imagery** involves a series of mental exercises, such as imagining moving the affected limb, recognizing pictures of body parts, and differentiating between left and right limbs. By doing these exercises in a structured way, it can help improve the brain's connection to the affected limb.
- **Stress loading** involves gradually increasing the amount of weight or resistance placed on a specific muscle or joint, which puts stress on the tissue and signals the body to build stronger muscles and bones.
- **Heat/Cold therapy or Contrast bath:** A series of quick and repeated immersions in warm and cold water to help reduce inflammation and pain.
- **Sensory re-education/desensitization:** Touching or rubbing the skin with different textures and materials:
 - a) directly in the area affected by your condition to feel more normal or
 - b) on nearby skin to help retrain the feeling
- **General functional activities** to increase activity levels (daily activities that are important to you e.g. getting dressed, preparing meals)
- **Swelling control** like massage, compression stockings, or hands-on treatments to reduce the swelling of your affected limb.
- **Splinting or bracing:** Devices that are put on your hands or limbs to help you move, or to help you rest.
- **Biofeedback:** A type of therapy that uses sensors attached to your body to help you become more aware of your body, relax you and relieve pain.

- **Transcutaneous Electrical Nerve Stimulation (TENS):** A device that sends small electrical current to body parts for pain relief.
- **Hydrotherapy:** Water therapy; Moving and exercising in water, essentially in a pool, used for pain relief and treatment; can be whole body or just one limb.
- **Acupuncture:** Inserting thin needles into targeted areas of the body for pain relief.
- **Pain education/Self-management:** Pain education involves educating you about your pain, its causes, and ways to manage it, such as through relaxation techniques, exercise, and proper medication use. Self-management involves learning how to manage your symptoms and strategies to cope with pain, improving daily activities, and promoting overall physical and emotional well-being.
- **Cognitive Behavioral Therapy** is a type of talk therapy with your therapist that helps you become aware of inaccurate or negative thinking about your symptoms.

8.9.5 Key Points to Remember

1. **Everyone's experience with CRPS is different:** What works for one person may not work for another. By working closely with your healthcare team and following their recommendations, find a treatment plan that works for you the most.
2. **Be patient:** Rehabilitation interventions for CRPS can take time to be effective, so it's important to be patient and stick to your treatment plan.
3. **Stay active:** Staying active is essential for managing CRPS. Your therapist will work with you to develop an exercise program that is safe and effective for your specific needs.
4. **Work with a multidisciplinary team:** CRPS is a complex condition that often requires a team approach to treatment. Working with several different health professionals (for example, a doctor plus a physiotherapist plus a psychologist) can help you to develop the best treatment plan to help your body, your mind and your emotions.

8.9.6 Making decisions about treatment

First, it is important to identify which outcomes are most important to you: Please mark the top five important outcomes for you. (Hint: what area do you want to see change in the most?)

- | | |
|------------------------|--|
| ○ Pain reduction | ○ Emotional factors and psychological factors such as sadness, anger, stress, anxiety, or depressive symptoms. |
| ○ Function improvement | ○ Sleep quality |
| ○ Swelling | ○ Sexual activities |
| ○ Stiffness | ○ Fatigue and energy level |
| ○ Hypersensitivity | ○ Return to work/school |
| ○ Range of motion | ○ Engaging in social activities |
| ○ Strength | |

- Reduction of medication use
- Ability to perform daily activities
- Muscle atrophy

- **OR Please mention the outcomes that are important to you and have not been mentioned in the list above.**
- It is important to discuss your treatment options with your healthcare provider to help you make an informed decision.
- The following treatment options are recommended by experts, published guidelines, and evidence from individual research studies. We have listed them under the specific outcomes they should help to change. We will also describe them a bit more on the following pages. However, it is important to note that some of these treatments may not be easily available where you live.

Interventions	Pain Reduction	Function Improvement	Other Symptoms Reduction
Mirror Therapy	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
Graded Motor Imagery	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
Pain education/Self-management	<input checked="" type="checkbox"/>		
Modalities (e.g. TENS, hydrotherapy, contrast bath, acupuncture, splinting)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> Stiffness improvement
General functional activities	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> Stiffness improvement
Strengthening and stretching exercises	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> Stiffness improvement
Stress loading	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> Stiffness improvement

Hydrotherapy/contrast bath		☑	☑ Edema improvement
Sensory re-education/desensitization			☑ Reducing Hypersensitivity
Retrograde Massage			☑ Edema improvement
Splinting			☑ Preventing or correcting deformities

8.9.7 Types of rehabilitation programs:

In this section we will provide you with a short description and discuss the pros and cons of each type of treatment:

1. Mirror Therapy; Graded Motor Imagery;

✓ **Pros:**

- There are several studies that show mirror therapy and graded motor imagery can reduce pain and improve function
- Can be done at home, reducing the need for frequent visits to a therapist
- It is not expensive and very easy to use
- Can be done online

✓ **Cons:**

- Can be time-consuming: It may take several weeks or months to see significant improvement

2. Pain education/Self-management

✓ **Pros:**

- Facilitates pain management.
- Helps you understand the causes of your pain and how it has affected your body
- Causes the feeling of having more control over your symptoms

- Can improve your mental health condition, which has been affected by your condition
- Reduces the fear of movement due to pain and encourages you to start light activities
- Being recommended by therapists and patients who have the experience of receiving pain education and tried self-management based on the published survey studies
- Can be done online
- ✓ **Cons:**
 - May not be effective in patients with severe symptoms
 - Requires motivation to follow the sessions over a period of time
 - May not provide immediate relief and it may take several weeks or months to see significant improvement
 - They should be used with other rehabilitation interventions, and should be taught by specialists
 - Limited research evidence in CRPS population

3. General functional activities; Strengthening and stretching exercises; Stress loading

- ✓ **Pros:**
 - Can reduce fear of movement, swelling, stiffness and pain
 - It is as active approach and can be done at home, reducing the need for frequent visits to a therapist
 - Can improve function, mobility, and flexibility
 - Can increase independence
 - Can be done online
- ✓ **Cons:**
 - It can be painful and unpleasant at the beginning.
 - May not be effective in patients with severe symptoms and fear of movement.
 - Stress loading → May exacerbate your symptoms if it not performed correctly

4. Sensory re-education/desensitization

- ✓ **Pros:**
 - Reducing sensitivity to touch
 - You can see the results almost quickly (within few weeks)
 - Improving sensory perception and reduced fear of being touched
 - Improving function as a result of engaging in more activities
 - Can be done online

✓ **Cons:**

- It can be painful and unpleasant at the beginning
- It can increase pain and discomfort if it is not implemented by an expert in a correct way
- Limited research evidence in CRPS population

Modalities

Transcutaneous electrical nerve stimulation (TENS); Hydrotherapy; Contrast bath;
Acupuncture; Splinting

✓ **Pros:**

- Generally, they can provide immediate pain relief.
- TENS → can help reduce pain and improve circulation in the affected limb.
- Splinting → can be useful in preventing possible deformities and contractures.
- Hydrotherapy/contrast bath → Improving flexibility, function, and mobility; Reducing stress and anxiety; Reducing swelling

✓ **Cons:**

- They can be a painful and unpleasant experience for some patients
- Limited research evidence
- Cannot be done online
- Controversy among therapists about the effectiveness of modalities
- Needed to be performed by an expert
- Acupuncture → can have some side effects such as bleeding, bruising, or infection if it not applied by an expert
- Splinting → Immobilization could exacerbate your symptoms and stiffness
- Splinting → Skin breakdown or irritation in some patients with sensitive skins
- Hydrotherapy and contrast bath → Controlling the appropriate water temperature could be difficult

Psychological Interventions✓ **Pros:**

- Can improve your awareness about your pain functional limitations

- Can improve your mental health by relaxation techniques, teaching some coping skills, and reducing your anxiety or depressive symptoms
 - Can increase your motivation and adherence to treatment to stick to your intervention plan
- ✓ **Cons:**
- It is a time-consuming process and needs multiple sessions over an extended period of time
 - Not all patients accept to receive psychological interventions because of the stigma of mental health issues in some cultures
 - Needs to be delivered by specialists
 - Limited research evidence in CRPS population

8.9.8 Priorities for Rehabilitation

In this section we would like you to reflect on the issues that matter most to you. We would like you to think about your priorities and preferences for the care that you want to receive. In the following section, please rate how important are the following factors to you.

	Not important at all (1)	Slightly Important (2)	Moderately Important (3)	Important (4)	Extremely important (5)
Receiving online treatment					
Receiving in-person treatment					
Learn ways to live better with the pain and symptoms you have					
Avoid invasive treatments like surgery or injections					
The results and recommendations of the research evidence					

The ability to you to have access to a rehabilitation clinic for your treatment? By access, we mean the ability to attend regularly, considering factors such as location, transportation, and flexibility of schedule.					
Avoid visiting multiple experts in different fields for my condition					
Avoid receiving psychological interventions					

8.9.9 Check the facts

Do all people with CRPS get better with rehabilitation interventions?

- Yes
- No
- I'm not sure

Are rehabilitation interventions kind of treatments that work for everyone with CRPS?

- Yes
- No
- I'm not sure

Can rehabilitation interventions help relieve your symptoms over the long term completely?

- Yes
- No
- I'm not sure

8.9.10 Where are you leaning now?

Now that you've thought about the facts, your feelings, and your preferences, you may have a general idea of where you stand on this decision. Show which way you are leaning right now.

1	Visiting one expert in the field of rehabilitation.
---	---

2	Visiting more than one expert in the field of rehabilitation
3	Not interested in receiving rehabilitation interventions.
4	Undecided

8.9.11 Decide what's next

Do you understand the rehabilitation intervention options available to you?

- Yes
- No
- I'm not sure

Are you clear about which benefits and risks matter most to you?

- Yes
- No
- I'm not sure

Do you have enough support and advice from others to make a choice?

- Yes
- No
- I'm not sure

How sure do you feel right now about your decision?

- Not sure at all
- Somewhat sure
- Very sure

Check what you need to do before you make this decision.

- I'm ready to take action
- I want to discuss the options with others
- I want to learn more about my options

In the box below, you can write down your questions, concerns, and preferences about rehabilitation treatments for your condition so that you and your therapist can talk more about it.

8.10 Letter of Information and consent for Survey Study (Patients)

Letter of Information and Consent: Patients with CRPS

PLEASE READ THE STUDY INFORMATION BELOW AND BE ADVISED THAT TAKING THE SURVEY MEANS YOU HAVE READ THE INFORMATION AND CONSENTED TO PARTICIPATE.

Study Title: A survey of patient/therapist preferences and priorities for conservative treatment of complex regional pain syndrome.

Principal Investigator: Dr. Joy MacDermid, PT PhD

Co-Investigators: Erfan Shafiee, PhD Candidate; Dr. Ruby Grewal, MD; Dr. Tara Packham, OT PhD; Dr. David Walton, PT PhD

Introduction

Complex regional pain syndrome (CRPS) is a disabling and painful condition associated with changes in sensory, motor, and autonomic systems. An integrated interdisciplinary treatment approach has been proposed for CRPS, targeting pain reduction, physical rehabilitation, psychological interventions, and patient information and education to enhance self-management.

Providing patients with clear information regarding diagnosis and treatment options can improve the active engagement of patients in treatment procedures to achieve the most favorable recovery. Helping patients understand their priorities, values, and preferences leads to more participation in the decision-making process. Based on an international consensus, shared decision making (the interaction and collaboration between patients and clinicians in the process of making decision for a condition) gives rise to better treatment outcomes, increased adherence to treatment, increased compliance with the decisions, and increased patients engagement in the treatment process. Therefore, the findings of this study can help us to understand and find the gaps between patients' and

therapists' preferences and priorities in the treatment of CRPS.

Purpose of this Study

This survey aims to understand and find the gaps between patient and therapist priorities and preferences in the conservative treatment of CRPS. It also investigates patients' awareness of CRPS conservative treatment, treatment effectiveness, and treatment outcomes.

Purposes of the study:

1. To understand patients' preferences, priorities, and awareness of available conservative treatments and treatment outcomes for CRPS.
2. To understand patients' experience about their shared decision making in the treatment of CRPS.
3. To understand therapists' preferences and priorities for the conservative treatment of CRPS.
4. To find the gaps between patients' and therapists' priorities and preferences regarding decision making for CRPS conservative treatment.

Study Procedure

You are being invited to participate in this survey because you have been diagnosed with Complex Regional Pain Syndrome (CRPS). If you agree to participate, you will be completing a survey either in paper format (if you are at the SJHC Hand and Upper Limb Clinic) or online (using Qualtrics), which will take around 15-30 minutes. The survey includes four different types of question including, demographic information, patient's awareness, treatment options, and decision making and support regarding your chronic pain condition (CRPS). After data gathering, if we find any response with more than 70% incomplete data, it will be excluded from our analysis

Possible Risks and Harms

There are no anticipated risks or harms associated with participating in this study except for the possibility of fatigue or discomfort while completing the survey. If any question makes you feel uncomfortable, you can skip that question or leave the study at any time.

Although we take all preventative measures to avoid a privacy breach, there might always be a risk of such a break. All data collected will remain confidential and accessible only to the research team of this study.

Possible Benefits

There is no direct benefit in participating in this study. However, the final aim of our project is to develop a patient decision aid for people with CRPS to decide for their conservative treatment more open-minded and make an informed decision. Therefore, the results of this study could have benefits to the society and improve the healthcare services available to you.

Voluntary Participation

Participating in this study is completely voluntary. You may refuse to participate in the study or refuse to answer any questions. Leaving the study will have no effect on your future care. If you have concerns contact the principal investigator, Dr. Joy MacDermid or research assistants, Katrina Munro, or Christina Ziebart.

Confidentiality

All data collected, including age, gender, and survey responses will remain confidential and accessible only to the research team of this study. While we will do our best to protect your information, there is no guarantee that we will be able to do so. The survey is completed on Western University's Qualtrics platform and is served on a server in Ireland. All data collected will be exported from Qualtrics and will be stored on a secure hospital network on a password-protected computer. In accordance with the Lawson policies, data will be kept for 15 years. Representatives of the University of Western Ontario Health Sciences Research Ethics Board and Lawson Quality Assurance and Education Program may contact you or require access to your study-related records to monitor the conduct of research and to ensure that proper policies and guidelines are

being followed. In accordance with Lawson policy, the study investigators will retain your information and study data for 15 years.

Compensation

You will not be compensated for participation in this research.

Contact for Further Information

If you require any further information regarding this research study or your participation in the study you may contact our research team member: Joy MacDermid; Erfan Shafiee; David Walton; Ruby Grewal; Tara Packham; Katrina. If you have any questions about your rights as a research participant or the conduct of this study, please contact: St. Joseph's Health Care London Patient Relations Consultant.

8.11 Letter of Information and Consent for Survey Study (Therapists)

Letter of Information and Consent: Therapists treating patients with CRPS

PLEASE READ THE STUDY INFORMATION BELOW AND BE ADVISED THAT TAKING THE SURVEY MEANS YOU HAVE READ THE INFORMATION AND CONSENTED TO PARTICIPATE.

Study title: A survey of patient/therapist preferences and priorities for conservative treatment of complex regional pain syndrome.

Principal Investigator: Dr. Joy MacDermid, PT PhD

Co-Investigators: Erfan Shafiee, PhD Candidate; Dr. Ruby Grewal, MD; Dr. Tara Packham, OT PhD; Dr. David Walton, PT PhD

Introduction

Complex regional pain syndrome (CRPS) is a disabling and painful condition associated

with changes in sensory, motor, and autonomic systems. An integrated interdisciplinary treatment approach has been proposed for CRPS, targeting pain reduction, physical rehabilitation, psychological interventions, and patient information and education to enhance self-management.

Providing patients with clear information regarding diagnosis and treatment options can improve the active engagement of patients in treatment procedures to achieve the most favorable recovery. Helping patients understand their priorities, values, and preferences leads to more participation in the decision-making process. Based on an international consensus, shared decision making (the interaction and collaboration between patients and clinicians in the process of making decision for a condition) gives rise to better treatment outcomes, increased adherence to treatment, increased compliance with the decisions, and increased patients engagement in the treatment process. Therefore, the findings of this study can help us to understand and find the gaps between patients' and therapists' preferences and priorities in the treatment of CRPS.

Purpose of this Study

This survey aims to understand and find the gaps between patient and therapist priorities and preferences in the conservative treatment of CRPS. It also investigates patients' awareness of CRPS conservative treatment, treatment effectiveness, and treatment outcomes.

Purposes of the study:

1. To understand patients' preferences, priorities, and awareness of available conservative treatments and treatment outcomes for CRPS.
2. To understand patients' experience about their shared decision making in the treatment of CRPS.
3. To understand therapists' preferences and priorities for the conservative treatment of CRPS.
4. To find the gaps between patients' and therapists' priorities and preferences regarding decision making for CRPS conservative treatment.

Study Procedure

You are being invited to participate in this survey because you are a therapist who treats patients with Complex Regional Pain Syndrome (CRPS). If you agree to participate, you will be completing a survey online (using Qualtrics), which will take around 15-30 minutes. The survey includes four different types of question including, demographic information, treatment options and outcomes, and final decision-making and support regarding your preferences in treating patients with CRPS. After data gathering, if we find any response with more than 70% incomplete data, it will be excluded from our analysis.

Possible Risks and Harms

There are no anticipated risks or harms associated with participating in this study except for the possibility of fatigue or discomfort while completing the survey. If any question makes you feel uncomfortable, you can skip that question or leave the study at any time.

Although we take all preventative measures to avoid a privacy breach, there might always be a risk of such a break. All data collected will remain confidential and accessible only to the research team of this study.

Possible Benefits

There is no direct benefit in participating in this study. However, we the final aim of our project is to develop a patient decision aid for people with CRPS to decide for their conservative treatment more open-minded and make an informed decision. Therefore, the results of this study could have benefits to the society and improve the healthcare services available to the people with CRPS.

Voluntary Participation

Participating in this study is completely voluntary. You may refuse to participate in the study or refuse to answer any questions. If you have concerns contact the principal investigator, Dr. Joy MacDermid or research assistants, Katrina Munro, or Christina Ziebart.

Confidentiality

All data collected, including age, gender, and survey responses will remain confidential and accessible only to the research team of this study. While we will do our best to protect your information, there is no guarantee that we will be able to do so. The survey is completed on Western University's Qualtrics platform and is served on a server in Ireland. All data collected will be exported from Qualtrics and will be stored on a secure hospital network on a password-protected computer. In accordance with the Lawson policies, data will be kept for 15 years. Representatives of the University of Western Ontario Health Sciences Research Ethics Board and Lawson Quality Assurance and Education Program may contact you or require access to your study-related records to monitor the conduct of research and to ensure that proper policies and guidelines are being followed. In accordance with Lawson policy, the study investigators will retain your information and study data for 15 years.

Compensation

You will not be compensated for participation in this research.

Contact for Further Information

If you require any further information regarding this research study or your participation in the study you may contact our research team member: Joy MacDermid; Erfan Shafiee; David Walton; Ruby Grewal; Tara Packham; Katrina. If you have any questions about your rights as a research participant or the conduct of this study, please contact: St. Joseph's Health Care London Patient Relations Consultant.

8.12 Letter of Information and Consent for Cognitive Interview (Patients)

Project Title: Content validity of the rehabilitation treatment decision aid for CRPS patients.

Investigators

Dr. Joy MacDermid, PT Ph.D. (Principal Investigator)

Department of Physical Therapy, Western University

Erfan Shafiee, PT Ph.D. Candidate (Co-investigator)

Department of Physical Therapy, Western University

Ruby Grewal, MD (Co-investigator)

Department of Physical Therapy, Western University

What is the purpose of this study?

The following study is a PhD thesis project at University of Western Ontario (UWO). This PhD thesis focused on creating a tool (Rehabilitation Treatment Decision Aid) to assist patients and healthcare providers in making informed decisions about rehabilitation interventions for a condition called Complex Regional Pain Syndrome (CRPS). The decision aid developed in this study is an important contribution to the field of CRPS rehabilitation interventions. It has the potential to help patients and healthcare providers make more informed decisions about treatment options, ultimately improving patient outcomes and reducing the burden of CRPS. The decision aid was designed to be tailored to the needs and preferences of individual patients, and it is based on the best available evidence. This is particularly important, as CRPS is a complex condition with a range of possible interventions, and there is often uncertainty around which interventions are most effective for individual patients.

We invite you to participate in this study because you have been diagnosed with CRPS. The form you will fill out, will help us figure out if the decision aid we made is valid, useful, and easy to understand.

In addition, the study includes a second component that involves conducting interviews with participants. It's important to note that participation in the interviews is optional and participants have the choice to participate or not.

STUDY OBJECTIVES

The objectives of this study will be to

- 1) assess the face and content validity of the developed treatment decision aid (TDA)

through a cognitive interview with patients and therapists.

- 2) Identify any areas of confusion or misunderstanding in the questions in the TDA.
- 3) Collect feedback from patients and healthcare providers on the decision aid, including suggestions for improvements or additional information.

Recruitment

We will require to have approximately 20 people who have the following criteria:

1. Diagnosed with CRPS,
2. Can speak, read/write in English
3. Consent to participate in this study

Study Procedures

This study is a survey about the content validity of the rehabilitation treatment decision aid that has been developed by our research team. If you are willing to participate, you can complete the form which asks about the clarity and relevance of each item of the decision aid . You are always welcome to ask any questions you might have about your participation in this study, via email addresses or phone numbers that are provided at the end of this letter.

If you choose to take part in the interview section of the study, you will find a box at the end of the online survey where you can input your email address. Following this, the research team will contact you in the future.

Participation in the Study:

Participation in this study is completely voluntary and you can download the pdf version of the letter of information and consent form for your own records. By giving consent,

you do not waive any of your legal rights. You have the option to refuse participation or decline to answer any questions.

What are the benefits of this study?

There are no direct benefits to you associated with your participation in this study

However, your study participation could benefit future patients to make informed decision about their treatment. Treatment decision aids inform patients and clinicians about treatment benefits and risks. Decision aids can also help patients identify their values and preferences and choose the best treatment. Despite the potential advantages of TDAs, there is a considerable gap in the literature concerning the development of TDAs specifically tailored to the management of CRPS.

Are there any risks or discomfort associated with this study?

Although we always make the best efforts to keep the study files and documents safe in locked cabinets or in password-protected computers, there is always a potential for a privacy breach. However, identifying information will be kept separate from the study data.

How many people are in this study?

There will be approximately 20 people in this study, however, for qualitative research, data collection will stop when we reach theoretical saturation, meaning we are not learning any new information from the participants.

Is there any compensation if I participate?

The survey part of the study does not offer any compensation.

Will my results be kept confidential?

No personal information will be collected from you. All survey responses will be kept confidential. Your identity will remain anonymous, and your responses will be used for research purposes only. We will not share any individual responses with anyone outside

of the research team. If you are willing to participate in the interview component of the study, you will be asked to enter your email address at the end of the survey. We will not share your email address with anyone outside of the research team. All data collected will be exported from Lawson REDCap and will be stored on a secure hospital network on a password-protected computer and data will be kept for 15 years.

Publication

If you wish to receive a copy of the research outcomes, we will provide it to you after its publication.

Whom you may contact to find out more about this study?

You will be given a copy of this letter. If you have questions about taking part in this study, you can directly contact:

Dr. Joy MacDermid, Principal Investigator, Katrina Munro, Study Research Assistant, Erfan Shafiee, Student Investigator.

If you have any other questions about your rights as a research participant or about the conduct of the study, you may contact: St Joseph’s Health Care London Patient Relations Consultant.

Consent to Participate In the project titled: Content validity of the rehabilitation treatment decision aid for CRPS patients.

This study has been explained to me, and any questions I had have been answered. I know that I may leave the study at any time. I agree to take part in this study.

Print Participants Name

Signature

Date

My signature means that I have explained the study to the participant named above. I have answered all their questions.

Person obtaining consent

Signature

Date

8.13 Letter of Information and Consent for Cognitive Interview (Therapists)

Project Title: Content validity of the rehabilitation treatment decision aid for CRPS patients.

Investigators

Dr. Joy MacDermid, PT Ph.D. (Principal Investigator)

Department of Physical Therapy, Western University

Erfan Shafiee, PT Ph.D. Candidate (Co-investigator)

Department of Physical Therapy, Western University

Ruby Grewal, MD (Co-investigator)

Department of Physical Therapy, Western University

What is the purpose of this study?

The following study is a PhD thesis project at University of Western Ontario (UWO). This PhD thesis focused on creating a tool (Rehabilitation Treatment Decision Aid) to assist patients and healthcare providers in making informed decisions about rehabilitation interventions for a condition called Complex Regional Pain Syndrome (CRPS). The decision aid developed in this study is an important contribution to the field of CRPS rehabilitation interventions. It has the potential to help patients and healthcare providers make more informed decisions about treatment options, ultimately improving patient outcomes and reducing the burden of CRPS. The decision aid was designed to be tailored to the needs and preferences of individual patients, and it is based on the best available evidence. This is particularly important, as CRPS is a complex condition with a range of

possible interventions, and there is often uncertainty around which interventions are most effective for individual patients.

We invite you to participate in this study because you are a healthcare provider (surgeon, nurse, pain physician, or therapist) treating patients with CRPS. The form you will fill out with us, will help us figure out if the decision aid we made is valid, useful, and easy to understand.

In addition, the study includes a second component that involves conducting interviews with participants. It's important to note that participation in the interviews is optional and participants have the choice to participate or not.

STUDY OBJECTIVES

The objectives of this study will be to

1) assess the face and content validity of the developed treatment decision aid (TDA)

through a cognitive interview with patients and

therapists.

2) Identify any areas of confusion or misunderstanding in the questions in the TDA.

3) Collect feedback from patients and healthcare providers on the decision aid, including suggestions for improvements or additional information.

Recruitment

We will require to have approximately 20 healthcare providers:

1. Working as a surgeon, nurse, pain physician, or therapist and treating patients with CRPS,

2. Can speak, read/write in English

3. Consent to participate in this study

Study Procedures

This study is a survey about the content validity of the rehabilitation treatment decision aid that has been developed by our research team. If you are willing to participate, you can complete the form which asks about the clarity and relevance of each item of the decision aid . You are always welcome to ask any questions you might have about your participation in this study, via email addresses or phone numbers that are provided at the end of this letter.

If you choose to take part in the interview section of the study, you will find a box at the end of the online survey where you can input your email address. Following this, the research team will contact you in the future.

Participation in the Study:

Participation in this study is completely voluntary and you can download the pdf version of the letter of information and consent form for your own records. By giving consent, you do not waive any of your legal rights. You have the option to refuse participation or decline to answer any questions.

What are the benefits of this study?

There are no direct benefits to you associated with your participation in this study

However, your study participation could benefit future patients to make informed decision about their treatment. Treatment decision aids inform patients and clinicians about treatment benefits and risks. Decision aids can also help patients identify their values and preferences and choose the best treatment. Despite the potential advantages of TDAs, there is a considerable gap in the literature concerning the development of TDAs specifically tailored to the management of CRPS.

Are there any risks or discomfort associated with this study?

Although we always make the best efforts to keep the study files and documents safe in locked cabinets or in password-protected computers, there is always a potential for a

privacy breach. However, identifying information will be kept separate from the study data.

How many people are in this study?

There will be approximately 20 people in this study, however, for qualitative research, data collection will stop when we reach theoretical saturation, meaning we are not learning any new information from the participants.

Is there any compensation if I participate?

The survey part of the study does not offer any compensation.

Will my results be kept confidential?

No personal information will be collected from you. All survey responses will be kept confidential. Your identity will remain anonymous, and your responses will be used for research purposes only. We will not share any individual responses with anyone outside of the research team. If you are willing to participate in the interview component of the study, you will be asked to enter your email address at the end of the survey. We will not share your email address with anyone outside of the research team. All data collected will be exported from Lawson REDCap and will be stored on a secure hospital network on a password-protected computer and data will be kept for 15 years.

Publication

If you wish to receive a copy of the research outcomes, we will provide it to you after its publication.

Whom you may contact to find out more about this study?

You will be given a copy of this letter. If you have questions about taking part in this study, you can directly contact:

Dr. Joy MacDermid, Principal Investigator, Katrina Munro, Study Research Assistant, Erfan Shafiee, Student Investigator.

If you have any other questions about your rights as a research participant or about the conduct of the study, you may contact: St Joseph's Health Care London Patient Relations Consultant.

Consent to Participate In the project titled: Content validity of the rehabilitation treatment decision aid for CRPS patients.

Completion of the survey will be taken as your implied consent.

Curriculum Vitae

Name Erfan Shafiee

Education

Sep 2019- now

PhD candidate, School of Physical Therapy, Department of Health and Rehabilitation Sciences, University of Western Ontario (UWO), London, Canada.

Thesis: *Developing Patient Decision Aids for Conservative Treatment of CRPS.*

Sep 2017-June 2019

Master of Science, Occupational Therapy, Tehran University of Medical Sciences, University of Social Welfare and Rehabilitation Sciences (USWR), Tehran, Iran

Thesis: *The important predictor factors of long-term results following Zone II flexor tendon injury, considering ICF components”.*

Sep 2013- Aug 2017

B.Sc. Occupational Therapy, University of Social welfare and rehabilitation Sciences (USWR), Tehran, Iran

Thesis: *Principles of Splinting in patients with hand Arthritis*

Honors and Awards /Appreciation

- 2023 Canadian MSK Rehab Research Network: \$1000 Trainee Travel Awards.
- 2019 Financial funding package and scholarship, \$80,000.00 (for four years).
University of Western Ontario, PhD of Physical Therapy, Health and Rehabilitation Science Graduate Program.
- 2019 Grant awardees for the 14th IFSSH & 11th IFSHT Triennial Congress with combined FESSH Congress, Berlin, Germany, Jun 2019

Working experience

2023-2024

Postdoctoral Fellow, School of Rehabilitation Therapy, Queen's University, Kingston, ON, Canada

2022-2023

Research Assistant; Hand and Upper Limb Clinic (HULC), Saint Joseph Hospital (SJHC), London, ON, Canada.

2019-2023

Teaching Assistant; School of Occupational Therapy; University of Western Ontario, ON, Canada.

2015-2019

Orfitologist and splint fabricator at Iran Hand Rehabilitation center, Tehran, Iran

2016-2019

Occupational Therapist (Hand Therapist) at Iran Hand Rehabilitation Center, Tehran, Iran

Publications (n=26; 8 First author; 11 Co-author; 7 Senior author)

26. **Shafiee E**, MacDermid J, Packham T, Grewal R, Farzad M, Bobos P, Walton D. Rehabilitation Interventions for Complex Regional Pain Syndrome; An Overview of Systematic Reviews. *The Clinical Journal of Pain*. 2023.

25. **Shafiee E**, MacDermid J, Packham T, et al. The Effectiveness of Rehabilitation Interventions on Pain and Disability for Complex Regional Pain Syndrome A Systematic Review and Meta-analysis. *Clinical Journal of Pain*. 2023. DOI: 10.1097/AJP.0000000000001089

24. Modarresi S, Farzad M, **Shafiee E**, Modarresi G, Maleki M, Bakhshi E, Hosseini SA, Walton DM. Cross-cultural Adaptation and Psychometric Evaluation of the Persian Version of the Satisfaction and Recovery Index (SRI): Structural Validity, Construct Validity, Internal Consistency, and Test-retest Reliability. *The Archives of Bone and Joint Surgery*. 2023 Jan 1;11(1):53-63. Doi: 10.22038/ABJS.2022.61697.3019

23. Farzad M, Abdolrazaghi H, Smaeel Beygi A, **Shafiee E**, Macdermid JC, Layeghi F. Outcomes at 3 Months of a Place and Active Hold Method of Flexor Tendon

Rehabilitation Following Zone II Injury. *The Journal of Hand Surgery (Asian-Pacific Volume)*. 2022 Apr 31;27(02):352-8. <http://doi.org/10.1142/S2424835522500254>.

22. Modarresi S, Farzad M, Modarresi G, Bakhshi E, Hosseini SA, **Shafiee E**, Maleki M, MacDermid JC, Walton DM. Psychometric Evaluation of the Persian Version of the Traumatic Injuries Distress Scale. *Critical Reviews™ in Physical and Rehabilitation Medicine*. 2022;34. DOI: 10.1615/CritRevPhysRehabilMed.2022040332 .

21. Farzad M, MacDermid JC, Packham T, Khodabandeh B, Vahedi M, **Shafiee E**. Factors associated with disability and pain intensity in patients with complex regional pain syndrome. *Disability and Rehabilitation*. 2021 Dec 3:1-9. DOI: <https://doi.org/10.1080/09638288.2021.2009045>

20. Mahdavi M, Farzad M, Mehta SP, MacDermid JC, Vahedi M, Hosseini SA, **Shafiee E**, Farhoud AR. Severity of persistent pain and disability can accurately screen for presence of pain catastrophizing and fear of performing wrist movements in individuals with distal radius fracture. *Musculoskeletal Science and Practice*. 2022 Feb 1;57:102474. DOI: <https://doi.org/10.1016/j.msksp.2021.102474>

19. Farzad M, MacDermid JC, Ring DC, **Shafiee E**. A Scoping Review of the Evidence regarding Assessment and Management of Psychological Features of Shoulder Pain. *Rehabilitation Research and Practice*. 2021 Sep 30;2021. DOI: <https://doi.org/10.1155/2021/7211201>

18. **Shafiee E**, MacDermid J, Farzad M, Karbalaei M. A systematic review and meta-analysis of Patient-Rated Wrist (and Hand) Evaluation (PRWE/PRWHE) measurement properties, translation, and/or cross-cultural adaptation. *Disability and Rehabilitation*. 2021 Sep 7:1-5. DOI: <https://doi.org/10.1080/09638288.2021.1970250>

17. **Shafiee E**, Farzad M, Khodabandeh B, Smaeil Beigy A, Backonja M. Psychometric properties of the Persian version of the neuropathic pain questionnaire. *Disability and Rehabilitation*. 2021 Jul 22:1-5. DOI: <https://doi.org/10.1080/09638288.2021.1955301>

16. **Shafiee E**, MacDermid J, Walton D, et al. "Psychometric properties and cross-cultural adaptation of the Patient-Rated Tennis Elbow Evaluation (PRTEE); a systematic review and meta-analysis." *Disability and Rehabilitation* (2021): 1-16. DOI: <https://doi.org/10.1080/09638288.2021.1938248>
15. **Shafiee E**, Farzad M, MacDermid J, et al. Determinants of Pain and Disability After Carpal Tunnel Release. Systematic Review. *Journal of Hand Surgery (European Volume)*. 2021; 46(2), 1-141. DOI: <https://doi.org/10.1177/17531934211015605>
14. Khodabandeh B, **Shafiee E**, Farzad M, Esmaeelbeygi A. Psychometric properties of the Persian version of the ID-Pain questionnaire. *The Archives of Bone and Joint Surgery*. 2021. DOI: <https://doi.org/10.22038/ABJS.2021.53348.2647>
13. Farzad M, Lu Z, MacDermid JC, Kachooei AR, Shafiee E. Measurement properties of the Michigan hand outcomes questionnaire: Rasch analysis of responses from a traumatic hand injury population. *Disability and Rehabilitation*. 2021 Feb 23:1-9. DOI: <https://doi.org/10.1080/09638288.2021.1894246>
12. Farzad M, MacDermid J, Mehta S, Grewal R, **Shafiee E**. Early Post-immobilization Pain at Rest, Movement Evoked Pain, and their Ratio as Potential Predictors of Pain and Disability at Six- and 12-Months after Distal Radius Fracture. *Archives of Physiotherapy*. Accepted for publication. Feb 2021. DOI: <https://doi.org/10.1186/s40945-021-00101-6>.
11. S Modarresi, G Modarresi, M Farzad, **E Shafiee**, M Maleki, MacDermid J, M Walton. Translation and cross-cultural adaptation of the Traumatic Injuries Distress Scale to Persian. *Journal of Advanced Medical Sciences and Applied Technologies*. Feb 2021. DOI: <https://doi.org/10.30476/JAMSAT.2021.89502.1017> .
10. Farzad M, MacDermid J, **Shafiee E** et al. Clinimetric Testing of the Persian version of the Patient-Rated Tennis Elbow Evaluation (PRTEE) and the Disabilities of the Arm, Shoulder, and Hand (DASH) Questionnaires in Patients with Lateral Elbow Tendinopathy. *Disabil Rehabil*. 2020. DOI: <https://doi.org/10.1080/09638288.2020.1844318> .

9. **Shafiee E**, Farzad M, Karbalaeei M. A Systematic Review of Self-Reported Outcome Measures Assessing Disability Following Hand and Upper Extremity Conditions in Persian Population. *The Archives of Bone and Joint Surgery*. 2020 Sep 10. DOI: <https://doi.org/10.22038/ABJS.2020.48859.2423> ;
8. Shirzadi A, Farzad M, Farhoud AR, **Shafiee E**. Application of continuous passive motion in patients with distal radius fractures: A randomized clinical trial. *Hand Surgery and Rehabilitation*. 2020 Aug 16. DOI: <https://doi.org/10.1016/j.hansur.2020.08.001> .
7. Farzad M, MacDermid JC, Lu Z, **Shafiee E**. Validation of Persian version of patient rated wrist/hand evaluation: confirmatory factor analysis and Rasch analysis. *Archives of Rehabilitation Research and Clinical Translation*. 2020 Aug 1:100076. DOI: <https://doi.org/10.1016/j.arrct.2020.100076> .
6. Farzad M, **Shafiee E**, Farhoud AR, Falahati Y, Alirezaloo N. Hand therapy in Iran during the pandemic of covid-19: Scraping Social media (Instagram). *Journal of Advanced Medical Sciences and Applied Technologies*. 2020 Jul 29. DOI: <https://doi.org/10.30476/JAMSAT.2020.87290.1016> .
5. **Shafiee E**, Farzad M, Macdermid J, Smaeel Beygi A, Vafaei A, Farhoud A. Cross-cultural adaptation and measurement properties of the Patient-Rated Tennis Elbow Evaluation for the Persian language. *Hand Therapy*. 2020 Jun;25(2):56-62. DOI: <https://doi.org/10.1177/1758998320910177> .
4. Mahmoodi R, Farzad M, Kachooei A, Layeghi F, **Shafiee E**. Effect of Rehabilitation Interventions on Sensation, Function, and Pain of the Patients with Carpal Tunnel Release. *Iranian Rehabilitation Journal*. 2019 Sep 10;17(3):263-70. DOI: <https://doi.org/10.32598/irj.17.3.263> .
3. Farzad M, MacDermid JC, Asgary A, **Shafiee E**, Azizi H. The patient-rated wrist and hand evaluation was successfully translated to Persian. *Journal of Hand Therapy*. 2019 Oct 1;32(4):515-8. DOI: <https://doi.org/10.1016/j.jht.2018.09.002> .

2. Farzad M, Arazpour M, **Shafiee E**, Layeghi F, A Schwartz D. Proximal Interphalangeal Joint Flexion Contracture Treatment by Serial Casting Method and the Use of Thermoplastic Tape. Iranian Rehabilitation Journal. 2019 Mar 10;17(1):75-80. DOI: <https://doi.org/10.32598/irj.17.1.75> .

1. Farzad M, **Shafiee E**, Arazpour M. Design and construction of the static progressive flexion orthosis. Journal of Hand Therapy. 2018 Jul 1;31(3):421-4. DOI: <https://doi.org/10.1016/j.jht.2017.10.010> .